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Differential Diagnosis in Internal Medicine

From Symptom to Diagnosis

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Preface

The present book, *Differential Diagnosis in Internal Medicine*, first appeared as a German edition in 1952 and since then has been translated into 10 other languages. Over the past 50 years 19 German editions have been published, and now the 19th edition of the work, which has become the classic differential diagnosis textbook, is available in English for the first time.

This book encompasses differential diagnosis across the spectrum of internal medicine, covering dermatology, neurology, and rheumatology, and provides the very latest knowledge including pathophysiological aspects. In contrast to encyclopedically structured textbooks, this book traces the path from symptom to diagnosis, just as the physician encounters the situation in the hospital and in the office.

With this pragmatic approach—starting from the symptom(s)—the physician will usually succeed in substantiating the suspected diagnosis. Using this method, Siegenthaler's *Differential Diagnosis in Internal Medicine* guides the reader through the differential diagnostic challenges in the entire field of internal medicine, including dermatology, neurology, and rheumatology. The book incorporates many relevant and instructive illustrations, tables, graphics, and algorithms, all contributing to the process of narrowing down a definitive diagnosis.

The book is intended for medical students, physicians in clinical practice, generalists, and specialists in internal medicine, dermatology, neurology, and rheumatology, and also for all those concerned with the fundamental subjects of medicine, who wish to gain a competent knowledge of internal medicine.

My thanks are due to all of the colleagues who worked with me on the book, and also to Thieme Publishing Group, in particular Thieme Publishers Stuttgart. I hope that, with the launch of the English edition, this classic textbook of differential diagnosis in internal medicine will now also find its place in the English-speaking world.

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Foreword

I first met Professor Walter Siegenthaler in the 1970s while he was at the University of Zürich, where both he and his late wife, the superb clinician Doctor Gertrud Siegenthaler-Zuber, were admired for their many accomplishments and dedication to the advancement of medicine. At that time, Professor Siegenthaler helped me establish a program to bring cardiologists from the Baylor College of Medicine and the Methodist Hospital in Houston, Texas, to Switzerland to study the pioneering balloon angioplasty work of Andreas Gruentzig. Subsequently, he honored us by serving as a Visiting Professor at Baylor, exemplifying the best of Swiss medicine. Now, 30 years later, Professor Siegenthaler remains at the leading edge of medicine, as this expertly realized book in your hands attests.

Differential diagnosis is the fundamental methodology of modern clinical medicine: we note the patient's symptoms; we develop hypotheses for the affliction and propose treatment; and we adjust treatment based on the patient's response. Thus, differential diagnosis requires the physician to be observant, knowledgeable, thoughtful, thorough, and organized, qualities that could also be used to describe the conceptualization and execution of the following pages. In the last few decades, we have seen stunning advances in the level of clinical care and diagnostic procedures available across the spectrum of human diseases. The sophistication of contemporary nosology is truly impressive.

On the other hand, the rapid turnover of medical information can prove daunting to many clinicians, and the application of the latest evidence to our daily interactions with patients may seem unclear or too complex. Siegenthaler's *Differential Diagnosis in Internal Medicine* reminds us to approach diagnostic problems in a practical, systematic, and critical manner, remembering that each patient's circumstance is unique and that it is every doctor's responsibility to exercise his or her best educated judgment to present rational choices about the most probable diagnoses and optimal treatment courses. Occam's Razor, which advises us that the simplest explanation is usually the correct one, all things being equal, is an important precept in diagnostic medicine, yet doctors must also be flexible and adaptable to the eccentricities of every case. Thus, physicians should not expect to see a zebra when confronted with a horse, but they should be able to recognize the zebra on the rare occasion that it makes an appearance.

I believe that the scholarship, clinical skill, and practical wisdom that Professor Siegenthaler and his colleagues share with us in this text are indispensable resources for the medical community. The wealth of illustrative photographs, informative tables, and up-to-date discussion of issues in internal medicine will prove very useful in daily clinical practice.

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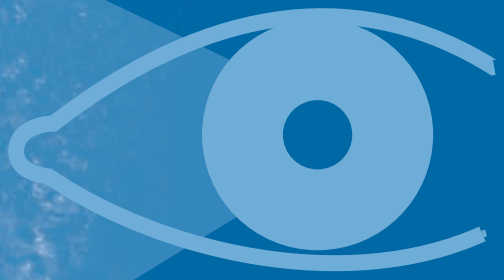
General Differential Diagnosis



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M. Battegay, B. Martina, and E. Battegay

2 History, Physical Examination, and Important Subjective Complaints

E. Battegay, S. Hunziker, and G.A. Spinas

3 Skin and External Appearance

S. Lautenschlager, E. Battegay, and G.A. Spinas

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1 General Aspects of Diagnosis and Differential Diagnosis

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1.1 Elements of the Differential Diagnosis

Disease and Differential Diagnosis

Decision-making on the Basis of Diagnosis. The physician endeavors to organize the subjective complaints and the objective findings of a patient in order to receive further indications to proceed (διαγιγνώσκω: to examine, to carefully consider, to differentiate, to become distinctively acquainted with, to decide). This approach is frequently chosen because a diagnosis in the conventional sense is not always easy to make, as more than one diagnosis can often be possible at the same time. Therefore, an important first step is to create a list of problems with a detailed description.

Dynamics of Reaching a Diagnosis. The diagnosis is of utmost importance not only for the prognosis but also for the introduction of an appropriate therapy. An established diagnosis always needs to be reassessed. Secondary diseases, complications, and side-effects can supervene. Each diagnosis continues to be a differential diagnosis, since the particular symptoms, even during the course of a disease, have to be continually reevaluated, carefully considered, and differentiated. For a proper evaluation of the symptoms and risk factors, knowledge of their clinical meaning is crucial. Consequently, the purpose of differential diagnosis is to point out what diseases can occur, when specific symptoms appear, and what risk factors with the utmost probability accompany specific diseases. In most cases, there are numerous possibilities and additional factors (frequency of disease, patient's age, secondary symptoms) that have to be taken into account. Exclusively listing all the possibilities would not be beneficial.

> Typical clinical pictures are not as frequent because of early detection of many diseases and appropriate therapies. The typical course of diseases has also become less frequent. In addition, one has to allow for biological variability.

Table 1.**1** Triage

	Time interval	Decision	Correct decision
Physician	Seconds	Disease severity	> 64 %
	Minutes	Emergency admission	95 %
	Minutes	Hospitalization	62 %
	Hours	Hospitalization	99 %

Data from the Emergency Department of the University Hospital Basel, Switzerland, B. Martina, 2000

Etiology and Course. Different aspects must be considered in order to judge a clinical picture. The study of the causes of disease, the etiology, has eclipsed the approach of nosology even in terms of therapeutic measures. Therefore the nosological entity "pneumonia" only describes a complexity of symptoms and starting point for the purpose of etiological differentiation (e. g., pneumococci, mycoplasma, chlamydiae, legionellae, viruses). Depending on the immunity and age of a patient, the course of the disease can be different even with identical pathogens, e. g., drastically different complication rates. Another example is that specific microorganisms may lead to so-called opportunistic infections in immunosuppressed patients, whereas in immunocompetent patients they do not. Where a patient is in fact examined (private practice, outpatient clinic, emergency department) also plays a significant role for the differential diagnosis.

Pathogenesis. The knowledge of *pathogenesis* must suffice in many cases in order to define a clinical picture. Pathogenic differentiation of various forms of hypertension is necessary for therapeutic and prognostic reasons. Despite research in etiology and pathophysiology we often proceed in a descriptive manner.

Criteria, Scores, Algorithms. Diagnoses as conceptual entities and bases for therapeutic measures are partially replaced by a system of criteria, which automatically leads to the next diagnostic or therapeutic step. This procedure is absolutely essential in specific situations, such as in emergency and intensive care medicine. Therefore, apnea requires immediate artificial respiration independent from etiology and pathogenesis. The identification of apnea is not a diagnosis in the narrower sense, but a state that calls for a certain therapeutic action.

Triage Decisions, Emergency Situations. Most triage decisions are not based on a definite diagnosis. Experienced general practitioners make split-second judgements based on posture, gait, facial expression, expression of the eyes, eye contact, circumstances including attire and accompanying persons, calm or uneasy appearance, perspiration, facial color, as well as breathing, and any changes in known patients. Medical split-second judgements are correct in more than 64 % of cases (Tab. 1.**1**). The clinical initial evaluation incorporates the very first visual, auditive, olfactory, affective, and intuitive impressions.

Judgements based on an evaluation made in a few minutes are very often correct. However, they must also be reassessed and adjusted according to the dynamic of the disease.

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The emergency evaluation plays an important role in the medical field. The evaluation of vital signs such as temperature, respiratory rate, blood pressure, and pulse is essential. It may be necessary to observe the patient for several hours in order to make the correct triage decision concerning hospitalization. The criteria for nonemergency situations are summarized in Tab. 1.**2**. Impaired consciousness and suicidal tendency are among high-risk criteria.

Table 1.**2** Criteria for a nonemergency situation are normal vital signs and absence of a high risk indicator

1. Normal vital signs	2. None of the following high risk factors
– Temperature 35–38.5°C – Respiratory rate 12–20/min – Blood pressure 90/60–160/110 mmHg – Pulse rate 60–100/min	– Severe pain – Chest or abdominal pain – Younger than 16 years – Unable to walk or arrival by ambulance – Impaired consciousness – Suicidal tedency

Verification of Diagnosis. Establishing an accurate diagnosis is usually an essential prerequisite for treatment of a patient. In order to continually reassess a diagnosis, the physician is obliged to maintain a self-critical attitude, e. g., in order to reexamine the effect of an adopted therapeutic regimen. This is especially important when increasingly "atypical" progression occurs or the chosen therapy is ineffective. Pattern recognition is essential to diagnostic reasoning.

Diagnosis and Individual Expression of Disease. The picture of a disease is one-sided and incomplete unless the symptoms are coupled with the ill person. Each person molds the disease and its expression by his or her individualism. A must for the physician is to respect the patient's experience in terms of perception of the disease. Specific perceptions can be the key to the diagnosis. Only when patients feel they are being understood can they be persuaded to go through stressful diagnostic processes ("shared decision-making"). Hence, the physician must comprehend the uniqueness of a patient's disease. The possibility that a patient called on him/her because of a so-called "hidden agenda" must also be borne in mind (see Chapter 2).

Diagnosis and Therapeutic Consequences. It is the job of the physician to take responsibility concerning the correct preliminary measures for each patient. The patient is entitled to interpret the disease in such a way that it correlates with personal circumstances. In view of multiple modern diagnostic methods and increasing healthcare costs, one is forced to carefully consider whether or not the effort in examining the patient and the patient's stressful situation is to be followed by therapeutic consequences.

Individually Adapted Diagnosis. A differential diagnosis indicates only the components which are needed by a physician in order to arrive at the *individually adapted diagnosis* for a particular case. Obtaining an overall picture of the patient's state of health is only possible through a combination of thorough medical knowledge and appropriate attention to the patient.

Risk Factors. In the past two decades knowledge of diagnosis, and especially risk factors, has drastically changed. Nevertheless, risk factors are frequently not recognized during hospitalizations or are not treated with priority (blood pressure, cholesterol, smoking, sedentary behavior). These risk factors, however, are essential in terms of long-term prognosis, such as in coronary heart disease.

Practical Procedure for Establishing a Diagnosis

The diagnosis is based on four essential aspects:
- ➤ medical history
- ➤ state of health
- ➤ laboratory and other investigations
- ➤ monitoring.

In case of an unsolved disease, the number of possible remaining diagnoses can be reduced drastically via history-taking and clinical examination. The additional morphological, physical, chemical, and biological examinations allow the isolation of the most probable diagnosis. Monitoring is a critical quality control of the previous diagnostic process, as well as of the subsequent therapeutic decisions.

History. Clinical experience plays an important role when collecting medical history data. The initial conversation between a patient and a physician gives the opportunity to obtain a general idea of the patient's personality, the kind of disease, and the degree of severity.

Despite the availability of laboratory and diagnostic devices, the medical history is still the most important part of the diagnostic process. If time limits the medical history (e. g., in case of an emergency), it must be done in detail thereafter. Accordingly, sufficient time must be allocated for the medical history when patients are examined. In the age of electronic medical histories, it is important to critically review patients' records. Especially with more complex clinical problems and multi-

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morbidity the history is the key to initiate appropriate diagnostic studies and therapies.

Thoroughly questioning the patient often shows that previous examinations may have focused only on specific organs. The findings may never have been examined within the scope of an overall evaluation.

Health Status (Physical Examination). The health status of a patient can be without pathological findings, even in cases of serious (nonsurgical) diseases. A careful examination of the patient, in calm surroundings, supplies the expert with important information and satisfies the patient's expectations. In patients with acute intermittent findings (e. g., pericardial friction rub, mild exanthems, signs of paralysis in early stage of myasthenia, paroxysmal arrhythmias, evening ankle edema, nocturnal pulmonary edema, etc.), an attempt should be made to examine the patient when the symptoms are present.

Examinations Involving Laboratory Analysis and Apparatus. In recent years, special laboratory techniques have greatly contributed to diagnostic procedures, e. g., D-Dimer (thrombosis), troponin (myocardial infarction), or brain natriuretic peptide (BNP) (heart failure) analysis. Despite the availability of these tests, the past medical history still represents a vital part of the diagnosis. In patients with sepsis, for example, the BNP value can be elevated. Therefore, it is important to know the specificity and sensitivity in laboratory workups. Imaging studies have also become more important. The computed tomography (CT) scan is one of the most important tools in case of a *fever of unknown origin*. Nevertheless, it is important not only to know the strengths, but also the limitations of any examination equipment. For example, transthoracic echocardiography with normal findings cannot rule out pathology of the mitral valves.

Monitoring. Monitoring is another important diagnostic element. A diagnosis must always be reevaluated with regard to its certainty, e. g., on every ward round or consultation the status of the main symptoms should be considered: do they remain identical?

> A diagnosis is therefore always preliminary—differential diagnostic thinking is an ongoing process.

Cardinal Symptoms. In differential diagnosis we proceed from a single dominant symptom, or group of symptoms (syndromes) or main symptoms, and try to classify as much as possible on the basis of the current research, in order to obtain a clinical picture. In most cases, a differential diagnosis is considered when a *cardinal symptom* indicates the direction of further measures. This leading symptom can emerge from the medical history (e. g., symptomatic epigastric pain), from clinical findings (e. g., enlargement of the spleen), as well as from laboratory work results (e. g., blood tests). So-called problem-oriented patient care is practiced in a similar manner. The aim of this book is to analyze the most common leading symptoms. Patients need to be presented, whether on ward rounds or when in conference, with these in mind.

Case Report. A clear clinical thought process becomes evident during the case presentation or when a second opinion is consulted. A good case report is essential and must be clearly structured.

In the first sentence, the following must be mentioned: name, age, situation (emergency, referral, check up, etc.), the chief complaint(s) (what is the current problem or in case of multiple symptoms, what do both doctor and patient view as being the main problem).

Only at this point should the present disease be discussed with regard to the details (e. g., characteristics of the pain), followed by the personal history, systemic history, medication, psycho-social history, etc. Too often, a case report starts with a detailed description of the present disease and its symptoms, which may have begun weeks or months ago, and thus cannot be classified.

Correct Evaluation of Evident Findings and the Differential Diagnosis

Process of Clinical Judgement. The correct evaluation of findings is crucial for the diagnosis. Positive and negative predictive values play important roles in this context. Nevertheless, personal intuition with regard to the individual patient remains an important factor.

Pathognomonic symptoms or combinations of symptoms are rare, but must be recognized when present. Except in the most obvious cases, we are subject to continuous uncertainty in *everyday clinical life*—we must use the available resources to decide on the most probable diagnosis for our individual patients and select the most effective treatment. It is assumed that with additional clinical experience the correct *clinical judgement* will automatically be made. In this we are supported by studies that critically analyze individual investigative steps and diagnostic processes. Guidelines which critically assess current research and place it in context are often helpful ("critical appraisal").

Probability-based Decision Analysis. In cases of ambiguous and usually complex situations, the physician can decrease the probability of error when diagnosing or excluding a disease using reasoning based on decision analysis. He or she analyses the probability of a disease

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diagnosis on the basis of the findings (post-test probability), whereby both the *sensitivity* (probability of test being positive when disease is present) and *specificity* (probability of test being negative when disease is not present) of the test must be given, as well as considering the pretest probability (current probability). The pretest probability is a crucial parameter.

Evidence-based Medicine. Working with guidelines for confirmed diagnoses and treatments is especially important. These instruments are part of evidence-based medicine (EBM) and represent optimal and rational care for patients.

EBM involves critical appraisal of scientific information. The clinical experience of the physician is thereby considered and is an integral part in decision-making. Study of the literature plays an important role.

Metaanalysis. A special instrument for analysis of information collected is found in systematic reviews, in particular so-called metaanalyses. By using various statistical methods, the results of individual studies are consolidated to a pooled estimate. The individual studies are weighted by size and range of results. Criteria exist for the assessment of systematic reviews as well as of scientific evidence of medical measures and classifications (Tab. 1.**3**). Similar criteria are considered for evaluating individual studies.

The methods of EBM are helpful and support the physician in finding his or her way through the ever-growing mountain of information, within a reasonable amount of time. Diagnostic and therapeutic problems, as well as questions regarding prognosis and etiology of a disease, can be approached using this technique: how and according to which criteria is a new diagnostic test to be judged, for example, or what effects are expected from a new drug? (Tab. 1.**4**). EBM is one of the fundamentals of quality assurance and thus the basis for optimal medical care. Access to the relevant articles and guidelines can be obtained through libraries, journals, and especially through medical databases.

Table 1.**3** The most important criteria in assessing a study and overview (metaanalysis)

1. Are the study results valuable?
   - Accurately described clinical problem?
   - Are the inclusion and exclusion criteria listed in detail?
2. What are the study results?
   - Are the results plausible?
   - How accurate are the results (confidence interval)?
3. Are the results useful in treating my patient?
   - Can the results be communicated to the patients I am currently treating?
   - Were all relevant endpoints in the analysis considered?
   - Do the positive effects of measures prevail over the harmful effects?

Diagnostic Process. The path *from unspecified disease to definitive diagnosis* is only rarely a linear one by which data are first collected and then analyzed according to established criteria. Additional examinations are to be conducted as indicated, whereupon everything is re-evaluated in order to make a definite diagnosis. Frequently, only a few minutes into a medical discussion, first *working hypotheses* are formulated that ultimately direct further history-taking and examination (Fig. 1.**2**).

Test Results, Specificity, Sensitivity

Test results taken from healthy persons are always spread over a Gaussian distribution. The normal range is arbitrarily defined by the so-called cut-off, such that 95 % of test persons are included and 5 % of healthy persons have values either too low or too high (Fig. 1.**1**). The curve with test results of ill persons overlaps the curve with the test results of the healthy persons. Depending on the cut-off, a number of false-positive results in healthy persons but also false-negative results in ill persons do occur. The quality of the test is then evaluated by the physician according to the rate of correctly positive results (sensitivity) and the rate of correctly negative results (specificity). For screening purposes, preferably a sensitive test is used with possibly no false-negative results. If, however, a disease is to be excluded, a test should be used with a specificity as high as possible.

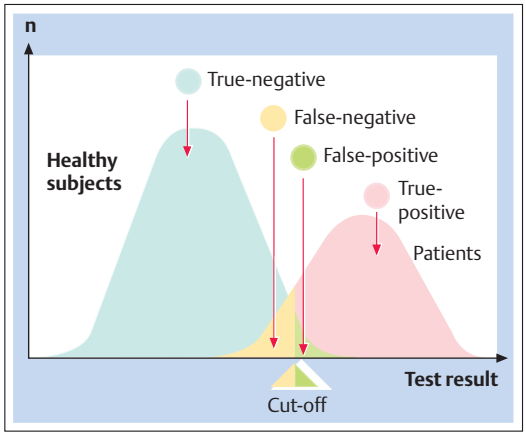

Fig. 1.**1** Distribution of test results in healthy and ill persons (Gaussian curves, after R. Speich).

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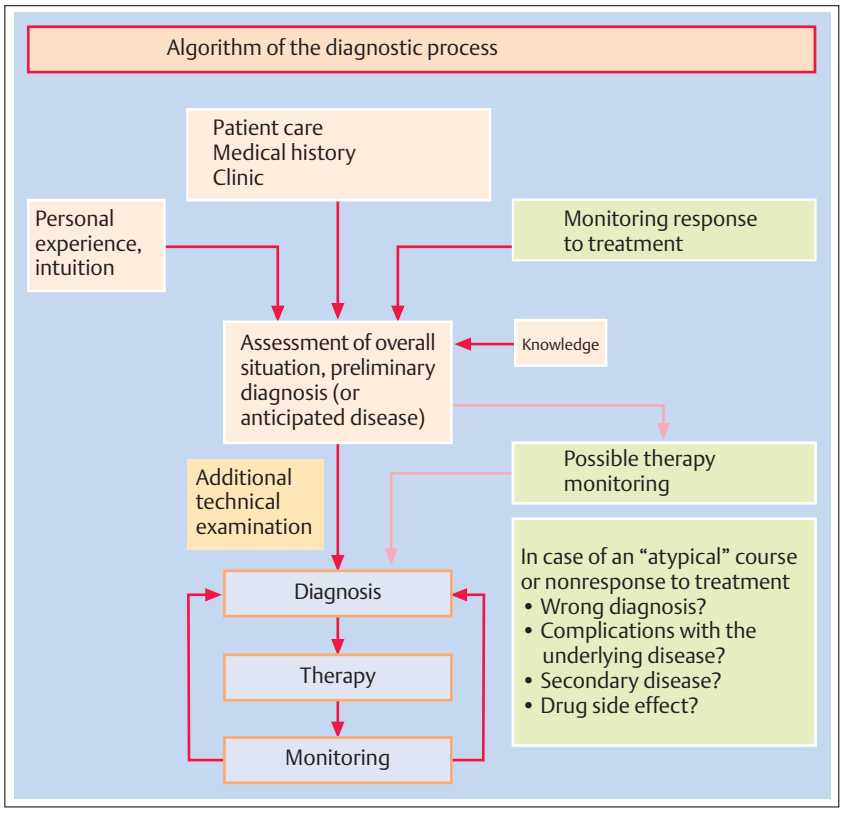

Fig. 1.2 Schematic flowchart of the diagnostic process.

Table 1.4 Guidelines for quality assurance of scientific evidence-based medicine and classification of recommendations for interventions

Class	Quality rating of evidence-based medicine
I	Evidence based on at least one adequately randomized controlled trial
II	Evidence based on at least one adequately randomized trial
II-1	Evidence based on one controlled, non randomized trial with adequate design
II-2	Evidence based on cohort studies or case-control studies with adequate design, possibly conducted by multiple research centers or research groups
II-3	Evidence based on comparison studies which compared the population at different time segments or different locations with or without intervention
III	Opinions from respected experts according to clinical experience, descriptive studies, or reports from expert committee
A	Good evidence to recommend action
B	Sufficient evidence to recommend action
C	Insufficient evidence to recommend or not to recommend action. Recommendation for intervention may be justified based on certain conditions
D	Sufficient evidence not to recommend action
E (= I)	Good evidence not to recommend action

Patient care with intuitive empathy can simplify the complex, multilayered diagnostic process. Especially in emergency situations, the experienced physician will more rapidly initiate additional examinations and arrive at a diagnosis than the inexperienced one, who on the contrary, will follow a very time-consuming, prescribed routine for history-taking and examinations in order to avoid mistakes or omissions.

Especially in emergency departments two simple questions arise:
- How ill is the patient?
- Is immediate diagnostic and/or therapeutic action necessary?

Because patients are usually hospitalized in a dynamic and seriously ill condition (i. e., are emergency patients), these questions must be continuously considered in order to make the correct triage decision.

Preliminary Diagnosis and Immediate Therapeutic Consequences. The first impression is on the one hand crucial, but on the other hand can be dangerous if not continually challenged by results of ongoing examinations. It is essential to recognize serious disease as early as possible, and to quickly initiate the appropriate measures, which are often vital to the prognosis. During the diagnostic process it is therefore often necessary to introduce therapeutic measures without a firm diagnosis,

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and independent of the specific etiology. *Treatment on the basis of a preliminary diagnosis* is often acceptable for most common diseases. *Monitoring* by a self-critical, experienced physician is the safest, simplest, and the least harmful way to clarify the clinical picture.

Important rules are to be observed at all times during the diagnostic process (Tab. 1.**5**).

In cases of new symptoms or an "atypical" course of disease, the diagnosis should be challenged. The following possibilities must be considered:

- The first diagnosis was wrong
- The diagnosis was correct, a complication supervened
- The diagnosis was correct, a secondary independent disease supervened
- The diagnosis was correct, side effects from therapy occurred
- The diagnosis was correct and the course of the disease is indeed atypical

Table 1.**5** Important diagnostic rules

- Medical history and physical examination are vital
- Serious, life-threatening diseases must be diagnosed early. Is the patient seriously ill? Is immediate action necessary?
- Common diseases are common (Sutton law)
- Pathognomonic symptoms and signs for a specific disease are rare
- No over-hasty preclusions of possible diagnoses
- Few situations are definitive, always be prepared to revise your opinion

Due to the fact that the population's lifespan has greatly increased and many people suffer from chronic diseases, these critical assessments are crucial for diagnostic and clinical activity. According to the World Health Organization, people will increasingly suffer from diseases and risk factors of a chronic nature. The possibilities mentioned above therefore help to address the differential diagnosis in complex situations, especially with multi-morbidity.

How to Handle Errors in the Medical Field

Errors. Physicians and healthcare workers are trained in terms of "*Primum nil nocere/First, do no harm.*" When differentiating the causes of iatrogenic damage, one differentiates between complications and actual mistakes or errors. Complications are inherent to a diagnostic method or therapy and cannot always be avoided. This includes side effects of prescribed medications. Errors are classified as follows:

- ➤ Doing the right thing wrongly (technical incompetence)
- ➤ Doing the wrong thing for a given situation (error)
- ➤ Doing something that is not necessary (inappropriateness)
- ➤ Neglecting something that must be done (negligence).

Models. Traditional models for handling errors in the medical field are: emphasis on training, dependence on professionalism and professional ethics, apportioning of blame and punishment, selective inspection, searching for outliers, reaction instead of prevention, elimination of superficial causes, little-to-no collective learning effect, as well as the attempt to eliminate human error. Tab. 1.**6** indicates characteristics of a more up-to-date model for handling errors in the medical field. Although systemic errors are not always present, they must be sought as a prophylactic measure.

Most malpractice lawsuits in the US arise from chest pain, wounds and fractures, and abdominal pain. Reasons for the bad rating of an emergency department's performance are a deficit of communication (50%), uncertainty concerning responsibility, and actual or alleged mistakes.

Table 1.**6** Characteristics of a model for handling errors in the medical field

- Systematic compilation of errors, damage and near damage (critical incident reporting)
- Definition of prospective problems
- Systematic monitoring of processes in medical care
- Recording of process variations
- Analysis of variance → change of process
- Systemic analysis and modification
- Search for root causes
- Collective learning effect
- Acknowledgement of the human factor

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Factors That Can Lead to False Diagnoses

Physician-specific Problems

Insufficient History and Clinical Examination. A diagnostic accuracy of 70% is reached through meticulous history-taking and examination; misleading results are rare (< 5%). Laboratory analyses and imaging studies alone achieve a guarantee of only 30% and misleading results occur in 10% of these cases. Insufficient history and examination due to lack of time, lack of knowledge, or lack of communication can therefore never be compensated by further investigation.

Disregarding the Prevalence of Clinical Pictures. It is dangerous to compare a present patient with a recent, rare and interesting case from personal experience, perhaps out of fear of not recognizing a rare disease.

> "Common diseases are common, and rare diseases are rare." Our diagnostic efforts must therefore concentrate primarily on the most probable diseases.

The simplest explanation is often the best one, and one should try to assign the complaints and medical findings of a patient to a single clinical picture. The situation can be more complex in elderly patients.

Unavailable or Inadequate Knowledge. Current knowledge can become obsolete or false within a few years. Constant postgraduate training is required (case examination, journals, books, continuing medical education, internet).

Physician's Characteristics. A physician needs an enormous amount of self-criticism in order not to run the risk of overestimation of his/her own capabilities. Professional and personal contact among colleagues on a regular basis (quality circle meeting) is essential.

Insufficient Judgement. This is an expression of inadequate logical and structural procedures from the time of medical findings to the diagnosis (logical thinking). Failure to distinguish between medical findings and interpretation, or unknowingly neglecting new results which do not fit the diagnosis (preconceived notion), are common mistakes.

A negative echocardiograph finding, for example, must not lead to the rejection of a diagnosis of bacterial endocarditis as suggested by a classic history and clinical findings (according to the Duke criteria). This would mean the omission of conclusive diagnostic procedures, such as blood cultures, and empirical therapy possibilities.

Preexisting secondary diseases may obscure symptoms of an otherwise classic diagnosis, e. g., angina pectoris as the chief symptom of coronary heart disease is frequently absent in a diabetic person.

Possible Errors of a Technical Nature. The great number of available laboratory tests and technical examinations means that it is necessary that the physician interpreting the results in the clinical context be up to date on their diagnostic significance.

Furthermore, the assumed prevalence of a disease is always considered when assessing test results (pretest probability). Whereas a slightly elevated serum alkaline phosphatase level in a patient with lymphoma may indicate liver involvement, the same value in a screened asymptomatic patient is in all likelihood a false-positive.

Patient-specific Problems

Incorrect, Biased or Inaccurate Statements (made consciously or unconsciously). These statements are based upon forgetfulness, anxiety (e. g., fear of a serious disease and the corresponding report from the doctor), or fear of consequences in regard to official matters such as suitability for military service, ability to drive a motor vehicle, liability, etc. They may also occur in cases involving addicts (alcohol, nicotine, analgesics, illicit drugs), statements of sexual orientation, and consequences pursuant to insurance laws. Another rare phenomenon which can lead to false diagnosis is Münchausen syndrome. The syndrome was named after the tale of Baron von Münchausen. Such patients feign more or less plausible, self-induced symptoms and repeatedly present to physicians and hospitals to secure numerous diagnostic tests and therapeutic interventions.

Preconceptions. These are conditioned from prior medical findings and from reading popular medical journals. They are frequently observed in patients with a smattering of medical knowledge, and satisfy the need of causality.

Inappropriate Behavior. This is characterized by a lack of cooperation, excessive demands, and fear of disease.

Dissimulation for Various Reasons. There are many reasons for this condition.

Masking of Symptoms and Findings of a Disease. Typical examples of masking of symptoms are painless acute abdomen in schizophrenic patients or in relation to medications which are being taken, e. g., by drug addicts.

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1.2 Factors That Can Influence the Differential Diagnostic Thought Process

Prevalence of Diseases

Most Common Symptoms in the Private Practice of an Internist. Differential diagnosis is based on the knowledge as to which symptoms and diseases are common. According to an American study involving over 300 million cases of consultations in private practices of internists, the most common complaints are: abdominal pain, thoracic pain, back pain, headaches, fatigue, coughing and catarrhal symptoms, as well as leg pain, skin symptoms, and vertigo. Very similar data are found among European outpatient clinics where abdominal pain, thoracic pain, and back pain are the reasons why people most often seek the help of a physician.

Differential diagnosis also takes into account the frequency of diseases according to the overall situation (Tab. 1.**7**). Patient groups in clinics and private practices differ slightly, especially in the case of emergencies.

Nonspecific Symptoms. Nonspecific symptoms are common. The initial clinical evaluation should define the types of symptom, perhaps even the exact diagnosis, the need for further clarification and treatment, and urgency. The initial clinical evaluation is managed more successfully when the physician displays empathy. (Clinic in Greek: to allocate a camp, to incline). The history and physical examination often suffice to make a diagnosis in many patients with nonspecific symptoms. The history contributes considerably more than the physical examination to the diagnosis. Unnecessary diagnostic examinations are not only expensive but often also lead to anxiety in patients.

The initial clinical examination is important for the most commonly needed evaluation, which is the differentiation between organic and non-organic causes. The positive predictive value was found to be 93 % for nonorganic abdominal pain and 98 % for chest pain where the physician felt confident in his judgement (Martina et al., 1997). Hence, nonorganic and important organic causes of diseases were rarely missed or predicted as false-positives. Typical psychovegetative signs are shown in Tab. 1.**8**.

Morbidity and Mortality. It is important to differentiate between *morbidity* and *mortality*. Figs. 1.**3** and 1.**4** show the most frequent causes of death in men and women living in Switzerland. These numbers are similar in the rest of the Western world.

Table 1.**7** Most frequent reasons for consultations of outpatients as well as inpatients at the Emergency Department, Basel, Switzerland

Outpatient	Inpatient
1. Pain 2. Psychosomatic/psychiatric symptoms 3. Upper respiratory tract infection, including influenza 4. Intoxication 5. Syncope/collapse 6. Abdominal pain 7. Gastroenteritis	1. Stroke, transient ischemic attack 2. Falling and syncope 3. Acute coronary heart disease 4. Heart failure and chronic coronary heart disease 5. Pneumonia 6. Chronic obstructive pulmonary disease and dyspnea

Table 1.**8** Typical signs in psychovegetative syndromes

Functional headache	Tension headache, vertigo, feeling of emptiness, lack of concentration (cephalea vasomotorica)
Functional cardiovascular disease	Arrhythmias, hypertonic and hypotonic regulatory disorders, precordial pain and palpitation (Effort syndrome, Da Costa syndrome, soldier heart)
Functional breathing disorders	Hyperventilation (hyperventilation tetany), constriction of the throat, dyspnea, breathing restricted as if wearing a corset, not being able to breathe deeply, sigh breathing, dry cough
Functional gastrointestinal disturbances	Uncharacteristic abdominal pain, nausea, obstipation, diarrhea, tenesmus, meteorism, flatulence (irritable colon)
Changing functional disorders	Sensitivity to weather change, paresthesia, insomnia, fatigue, temperature, regulatory disorders, pruritus, sweating, hyperreflexia, dermographia, disorders of the musculoskeletal system, sexual dysfunction

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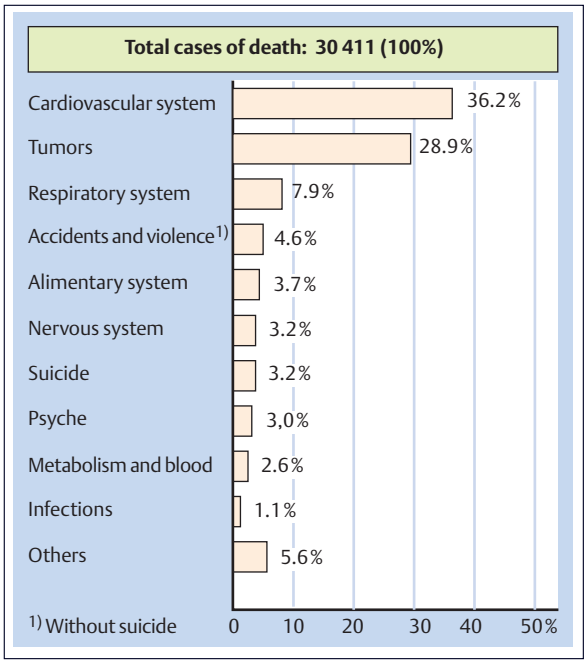

Fig. 1.**3** Most frequent causes of death in men in 2000. (Source: Swiss Federal Statistic Office)

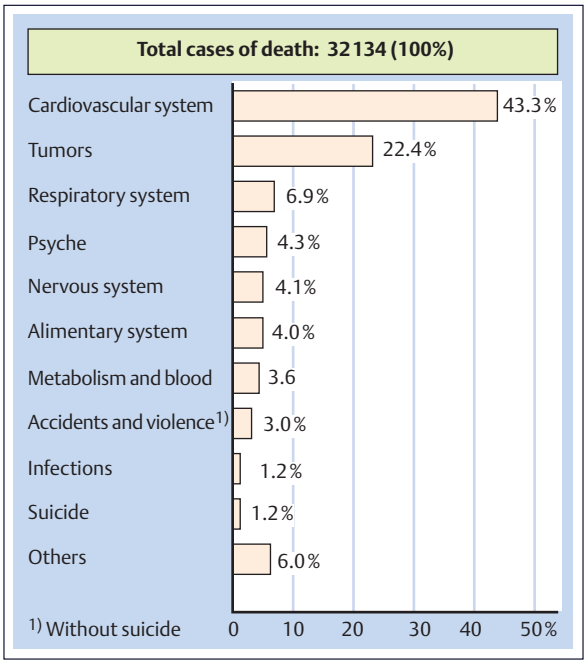

Fig. 1.**4** Most frequent causes of death in women 2000. (Source: Swiss Federal Statistic Office)

Age

Age Distribution. The influence of age must always be considered. Knowledge of age distribution provides valuable clues for the diagnosis (Fig. 1.**5**). For example, after the age of 45 *multiple sclerosis* is diagnosed more reluctantly. On the other hand, *pernicious anemia* is a disease that does not usually appear until around the fifth or sixth decade of life. *Polymyalgia rheumatica* is not usually observed until after the age of 50. Incidence of the so-called *geriatric complaints* is increasing rather rapidly, thus geriatric aspects play a significant role in medicine today.

Geriatric Aspects. Approximately 3.3 million people lived in Switzerland around 1900. Today there are about 7 million inhabitants. The number of people > 65 years of age has more than doubled within this time period. Soon every sixth person in the country will be > 65 (Fig. 1.**5**) and similarly in other European countries. Geriatric complaints are primarily diseases of arteriosclerotic nature such as cardiovascular diseases, malignant tumors and infections, which are particularly serious (e. g., pneumonia or urinary tract infections). Arthrosis, specifically of the spine and the hip joints, also plays a significant role.

Gender

Some diseases occur more frequently in males than in females. This is especially true for occupational diseases (Tab. 1.**9**) as well as diseases caused by smoking (bronchial carcinoma, chronic bronchitis, coronary heart disease, peripheral arterial occlusive disease) or alcohol (liver cirrhosis). Because on their anatomic configuration, women are susceptible to reoccurring urinary tract infections, pyelonephritis and iron deficiency due to menorrhea. Toxic shock syndrome is a rare, life-threatening bacterial infection caused by toxins produced by staphylococcus bacteria and has been associated with the use of superabsorbent tampons.

Lifestyle

Lifestyle is very important to people today. Some positive habits are healthy nutrition (Mediterranean diet) and fitness; harmful habits include addictive behaviors. The influence of *alcohol* especially on the liver, blood pressure, and nervous system is well known. *Smoking*, which is particularly on the rise in adolescents, is re-

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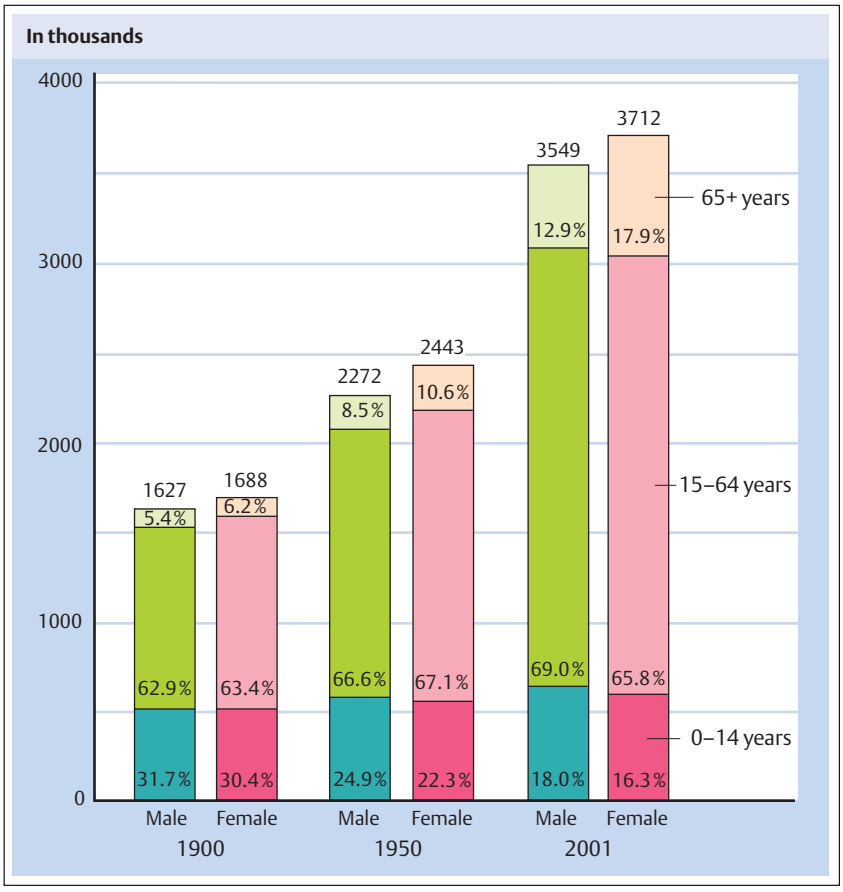

Fig. 1.**5** Resident population in 1900, 1950, and 2001. (Source: Swiss Federal Statistic Office)

sponsible for the emergence of vascular diseases (coronary heart disease, peripheral arterial occlusive disease, Buerger disease) as well as pulmonary diseases (bronchial carcinoma, chronic bronchitis, lung emphysema). Ninety percent of men who die due to bronchial carcinoma are smokers. In addition to bronchial carcinoma, the larger part of malignant tumors in the oral cavity, larynx, and esophagus is caused by smoking. Tumors of the urinary bladder, the kidneys, and the pancreas are more frequent among smokers. The medical history of patients with chronic interstitial nephritis often reveals acetophenacetin use over decades. A risk for carcinoma of the renal pelvis and the ureter is present in these patients. Cervical carcinoma is increasingly observed in young and sexually active women (human papillomavirus) who began sexual intercourse at an early age. People with highly promiscuous behaviour are more at risk for sexually transmitted infections such as human immunodeficiency virus (HIV), syphilis, gonorrhea, as well as viral hepatitis. In drug addicts hepatitis C infection is commonly observed.

Eating Habits

Eating habits are at least partly responsible for many diseases. To a large extent, obesity is closely associated with disease. Diabetes mellitus type 2, arthrosis, and hypertension are more frequently observed in obese persons. Obesity is one of the risk factors in the development of arteriosclerosis and its consequences. Also the influence of eating habits with regard to malignant tumors is suggested. Overweight women, for example, have a 2- to 4-fold higher probability of contracting uterine carcinoma. Colonic carcinoma is more prevalent among people who consume large amounts of meat than among vegetarians. Generally, it is also more frequently observed with low-fiber and high-fat diets.

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Season, Time of Day, and Weather

Certain diseases are clearly dependent on the *season*:

- Food-associated infectious diseases in particular, e. g., salmonellosis, occur more frequently in warm seasons.
- The seasonal emergence of allergic coryza depends on airborne pollens (spring/summer).
- Respiratory infections occur more frequently during the winter months and cause higher morbidity and mortality in the elderly population, especially in a humid climate and after sudden changes of weather (influenza, respiratory syncitial virus [RSV]).

Circadian Rhythms. Chronic polyarthritis is a disease with an explicit circadian rhythm and reaches maximum activity in the early morning and a minimum of activity in the afternoon. Accordingly, a correlation with the circadian cortisone output and neutrophil count has been identified.

Geographic Distribution

Tropical Diseases, Tourism. The geographic distribution of diseases must often be considered. It is especially obvious in *infectious diseases* (tropical diseases), where climatic and hygienic conditions exert influence. The physician is obliged to consider "exotic" diseases in the differential diagnosis of patients with a history of travel (tourism). In addition, even similar clinical pictures (e. g., malaria) result in a different disease course depending on the country of infection (differences in resistance).

Geographical Differences in Prevalence of Diseases. It is partly unknown why there is clustering or absence of certain diseases in specific areas (high incidence of stomach carcinoma or absence of pernicious anemia in Japan). Besides environment and nutrition, genetic factors probably play a significant role. That is why the frequency of tumors varies significantly by region. Per 100 000 inhabitants, each year there are a total of 320 new incidences of tumor in the US and 1340 in India. However, colonic cancer occurs in the US in 20–30 people per 100 000 and in Japan in only five people per 100 000 inhabitants per year.

Ethnic Groups

The patient's ethnic background can be of importance for the diagnosis. Thalassemia occurs primarily in populations bordering the Mediterranean. Sickle cell anemia is present nearly exclusively in black populations. Other important diseases of the Mediterranean are glucose-6-phosphate dehydrogenase deficiency and Mediterranean fever. In Ashkenazi Jews, Gaucher disease, Tay–Sachs disease, Niemann–Pick disease, abetalipoproteinemia, and factor XI deficiency are prevalent as are adrenogenital syndrome and pseudocholinesterase deficiency in Inuit people.

Profession and Leisure

Occupational Disease. The profession of a patient can provide diagnostic clues (Tab. 1.**9**). *Occupational diseases* are defined by a clear correlation between occupational activity and disease. *Work-related diseases* are those which emerge, are exacerbated, and reoccur associated with a profession.

Diseases Due to Leisure Pursuits. Besides occupational diseases, *leisure pursuits* are to be considered. Diseases are often observed due to sporting activities, e. g., arthrosis due to jogging or anemia as a consequence of renal and enteral blood loss. "Whirlpool dermatitis" is a new epidemic dermatosis associated with leisure. It commences after bathing in bacterially contaminated water, such as in a whirlpool, and has an incubation period of 8–48 hours. This clinical picture is characterized by a pruritic maculopapular, partially pustular rash, but also includes general symptoms such as fever, pharyngitis, conjunctivitis, and lymphadenopathy. *Pseudomonas aeruginosa* can be contracted from efflorescences. The disease heals spontaneously after 1–2 weeks. The incidence of malignant melanoma is increasing, especially in countries with intensive solar radiation (e. g., Australia). Serious sunburn, especially in childhood, clearly predisposes to malignant melanoma.

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Table 1.**9** Professions that predispose to occupational diseases (according to the Department of Occupational Medicine of the Swiss Accident Insurance Company)

Profession	Disease
Battery factory (car batteries)	Lead poisoning
Aluminum industry	Fluorosis
Previous exposure to fine particulate matter of asbestos	Asbestosis, pleural plaques, pleura mesothelium, and peritoneal mesothelioma, bronchial carcinoma
Baker/confectioner, miller	Rhinitis, bronchial asthma (flour dust, baking additives), protein contact dermatitis, eczema
Construction	Rash (cement, epoxy resins), vibration-induced vasospastic syndrome, osteopathy, arthropathy through vibrations and pneumatic tools, noise-induced hearing loss
Cotton industry/ spinning company	Byssinosis, noise-induced hearing loss
Mining, underground mining (tunnel, gallery), gravel mine, stone industry	Silicosis, noise-induced hearing loss, hyperthermia
Chemical industry	Contact eczema, toxic–irritative bronchial asthma
Hairdresser	Allergic and toxic–irritative contact dermatitis, bronchial asthma (persulfate)
Printing	Allergic contact eczema, toxic contact dermatitis (organic dissolver), occupational asthma (rubber arabicum)
Electroplating	Occupational dermatosis, bronchial asthma, cyanide intoxication
Gardener/florist	Allergic rhinitis, bronchial asthma, contact eczema
Healthcare (physician, healthcare professional, laboratory technician, and cleaning personnel)	Infectious diseases (particularly blood-transmitted infections such as hepatitis B and C, HIV infection), latex allergy (contact urticaria, rhinitis/asthma, anaphylactic reaction), allergic and toxic–irritative contact dermatitis
Foundry	Metal fume fever (foundry fever), bronchitis, pneumoconiosis due to dust particles, asbestos-related, vibration-induced diseases
Rubber industry	Allergic contact eczema, latex allergy, tumors of the urinary tract (2-naphthylamine) due to previous exposure
Hard metal manufacturing and development	Bronchial asthma, alveolitis/giant cell interstitial pneumonitis (cobalt)
Woodworking, carpentry	Bronchial asthma (wood dust, isocyanate, varnish), contact eczema, carcinoma of the paranasal sinuses (beech wood and oak wood dust), noise-induced hearing loss
Insulation work with asbestos (construction, freight car industry, sanitary installation, electrical installation)	Prior exposure to asbestos dust particles, see above
Insulation work (with insulating foam or insulating material)	Bronchial asthma (isocyanate), fiberglass dermatitis
Cheesemaker	Bronchial asthma, exogen-allergic alveolitis (cheese-washer's lung), irritative dermatitis
Plastics industry	Bronchial asthma, exogen-allergic alveolitis (isocyanate, acid anhydrides), allergic contact eczema (epoxide), styrol intoxication (polyester)
Agriculture	Bronchial asthma, exogen-allergic alveolitis (farmer's lung), chronic bronchitis, inhalation fever ("organic dust toxic syndrome"), silo-filler's disease (nitrogen oxides), infectious diseases (brucellosis, erysipeloid, leptospirosis, aphthous fever, ornithosis), allergic and toxic irritative eczema
Leather industry/tannery	Bronchial asthma (animal hair, dye), contact eczema (chromate), anthrax
Painter/varnisher	Bronchial asthma (isocyanate), allergic contact eczema/toxic contact dermatitis, acute dissolvent intoxication

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Table 1.**9** (Continued)

Profession	Disease
Metal industry	Allergic contact eczema/toxic contact dermatitis (cooling lubricant emulsion), metal fume fever (zinc oxide), acute intoxication due to organic dissolver, welder's "arc eye" (keratoconjunctivitis photoelectrica), noise-induced hearing loss
Butcher	Toxic and allergic contact dermatitis, infectious diseases, (brucellosis, erysipeloid)
Porcelain industry/ceramic	Silicosis
Welder	Welder's "arc eye" (keratoconjunctivitis photoelectrica), metal fume fever (zinc oxide)
Explosives industry	Angina pectoris (nitroglycole, nitroglycerine), contact eczema
Road construction	Actinic skin diseases, phototoxic reactions
Diver, working with air pressure	Decompression sickness (caisson disease), barotrauma
Keyboard operation (typewriter, PC)	Tendoperiostosis/tendosynovitis
Forestry	Vibration diseases (vibration-induced vasoplastic syndrome, osteopathy, arthropathy), noise-induced hearing loss, infections due to tick bites (borreliosis, early summer meningoencephalitis)

Precluding or Promoting Diseases

From medical experience, certain diseases rarely occur simultaneously, whereas others are associated with each other. Patients with chronic alcohol abuse seldom develop liver cirrhosis and chronic pancreatitis at the same time. Similarly, there are practically no incidences of malaria in patients with sickle cell anemia. Diseases of one organ can be the initial manifestation of an overall dysfunctional organism (e. g., endocrinopathy) or a systemic disease that endangers practically all organs (e. g., collagen diseases, vascular diseases). Thus upon emergence of symptoms, other possible manifestations and locations should be carefully considered (e. g., a kidney stone in conjunction with parathyroid adenoma).

1.3 Differential Diagnosis by Groups of Diseases

When differentiating a clinical picture, very often it is initially impossible to identify the real diagnosis, namely the nosological entity. Until relevant findings are present, one has to be content with the classification into one of the *groups of diseases*. In all unclear cases, consideration is almost always given to this at the beginning of the differential diagnostic process.

Degenerative Conditions

These are characterized by slowly progressing irreversible changes in blood vessels and connective tissue. Arteriosclerosis, which causes damage in organs (heart, brain, kidneys) and peripheral arteries, and arthrosis are the clinical pictures most often observed in medical practice today, particularly in elderly people.

Infectious Diseases

Inflammation is characterized classically by surgical *rubor* (reddening), *calor* (heat), *tumor* (swelling), *dolor* (pain) and *functio laesa* (loss of function). Fever, blood count, elevated C-reactive protein, and elevated erythrocyte sedimentation rate are often associated with infections. However, absence of these symptoms does not exclude the possibility of an infection (e. g., viral infection). Importantly, other diseases may be considered (e. g., collagen diseases, tumors).

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Table 1.**10** Examples of autoimmune diseases

Organ involvement	Clinical picture
Gastrointestinal tract	Pernicious anemia, celiac disease/sprue, colitis ulcerosa, Crohn disease
Blood	Immune thrombopenia (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia, paroxysmal nocturnal hemoglobinuria, secondary cryoglobulinemia
Kidneys	Postinfectious glomerulonephritis, IgA nephropathy, Goodpasture syndrome, syndromes characterized by purpura, arthritis, nephropathy, periarteritis nodosa
Endocrine system	Autoimmune thyroiditis (Hashimoto), Basedow disease, Addison disease, diabetes mellitus (type 1), idiopathic hypoparathyroidism, polyglandular deficiency syndrome (Schmidt syndrome), infertility caused by antibodies, premature ovarian failure
Central nervous system	Myasthenia gravis, mononeuritis multiplex, multiple sclerosis (?), Guillain–Barré syndrome, amyotrophic lateral sclerosis, uveitis
Joints, muscles, connective tissue	Chronic polyarthritis, visceral lupus erythematosus, Sjögren syndrome, scleroderma (including CREST), thromboangitis obliterans, Bechterew disease, Behçet disease, polymyalgia rheumatica, arteritis temporalis
Skin	Cutaneous lupus erythematosus, chronic diskoid lupus erythematosus, alopecia areata, vitiligo, pemphigus vulgaris, dermatitis herpetiformis Duhring, Schoenlein–Henoch purpura
Lungs	Wegener granulomatosis, Churg–Strauss syndrome
Liver	Autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis

Immune Mediated Diseases

- *Collagenosis* and *vasculitis* are included in this group of diseases (systemic lupus erythematosus, dermatomyositis, sclerodermia, polymyositis, periarteritis nodosa, Wegener granulomatosis, allergic vasculitis, etc.).
- These diseases can be recognized clinically by the simultaneous involvement of multiple organs. Skin efflorescences and arthropathies are often the leading clinical symptoms. At the same time changes in kidneys, lungs, muscles, and heart are evident.
- *Immune complexes*, the result of different antigens (e.g., bacteria, viruses, body's substances such as DNA, ribonucleoproteins, and medication) play a significant role, although this is currently only partially understood. Laboratory test results normally reveal a median elevated erythrocyte sedimentation rate, anemia, and other hematologic changes.
- In practically all diseases of this kind *antinuclear antibodies* can be found.

Several diseases in which autoantibodies play an important role are listed in Tab. 1.**10**.

Tumors

Suspicion of Tumors. Symptoms with slow onset, fatigue, diffuse weight loss, and diffuse general symptoms in middle and advanced age are a cause for suspicion of tumors. Local symptoms can be absent for a long period of time. It is important to know the difference in frequency of tumors according to gender (Figs. 1.**6** and 1.**7**). Body temperature can be in a subfebrile range. The erythrocyte sedimentation rate may be elevated. Anemia and an elevated platelet count can also occur.

Diagnostic information is obtained from radiological examinations including CT scans, biopsy or cytological analysis of bone marrow, aspirated fluids, changes to organs, and sputum. Evidence of tumor cells is conclusive.

Incidence and Mortality. The incidence of several tumors in men has drastically changed, as shown in Fig. 1.**8**.

Tumor Markers. Screening for tumor markers is not suitable because of low sensitivity and specificity. A notable exception is the prostate-specific antigen (PSA). Some markers however are used for follow-up after therapy and for staging classifications.

➤ α-fetoprotein	Hepatocellular carcinoma
➤ α-fetoprotein	Ovarian tumors
➤ β-HCG, LDH	Nonseminomatous testicular cancer
➤ β-HCG, LDH	Testicular seminoma
➤ β_2-Microglobulin	Multiple myeloma
➤ CA 15–3	Breast cancer
➤ CA 19–9	Colon carcinoma
➤ CA 125	Ovarian carcinoma
➤ CEA	Colon and rectum carcinoma
➤ CRP, LDH	Malignant lymphoma
➤ PSA	Prostate cancer

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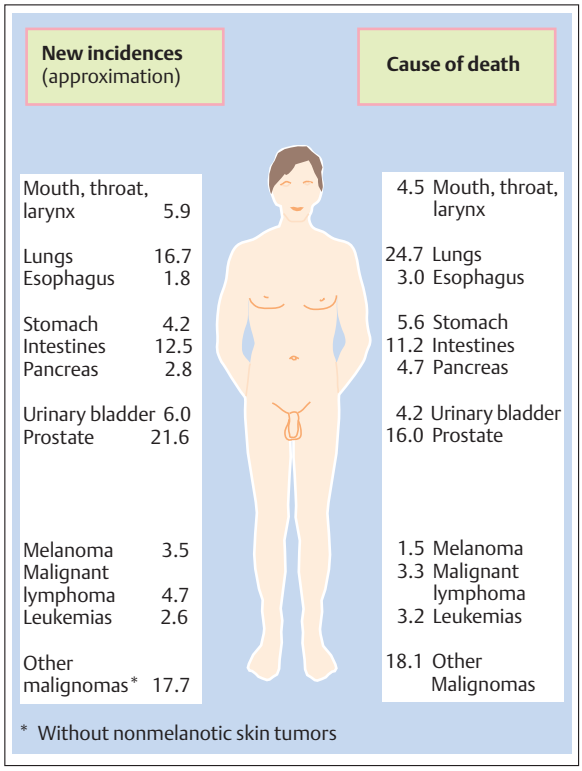

Fig. 1.**6** Percentage for each tumor location of total new incidences and total cancer deaths in males, 1989–1993. (Source: Association of Swiss Cancer Registries, Swiss Federal Statistical Office.)

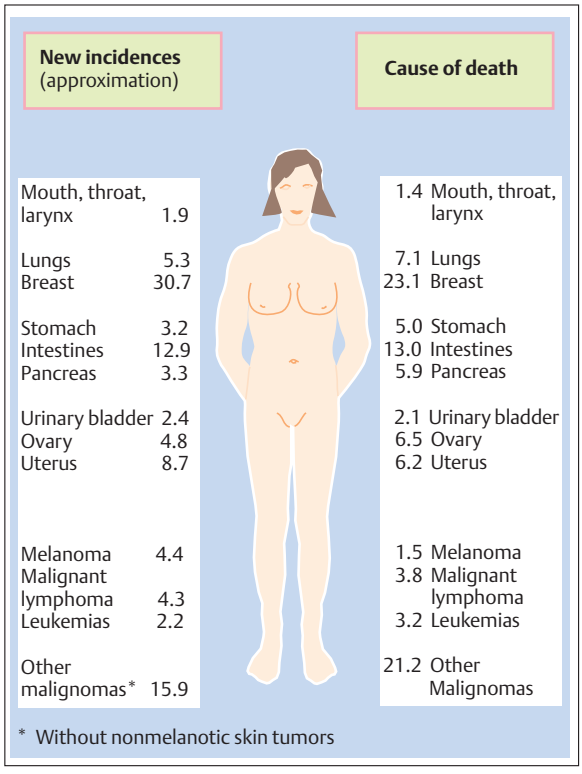

Fig. 1.**7** Percentage for each tumor location of total new incidences and total cancer deaths in females, 1989–1993. (Source: Association of Swiss Cancer Registries, Swiss Federal Statistical Office.)

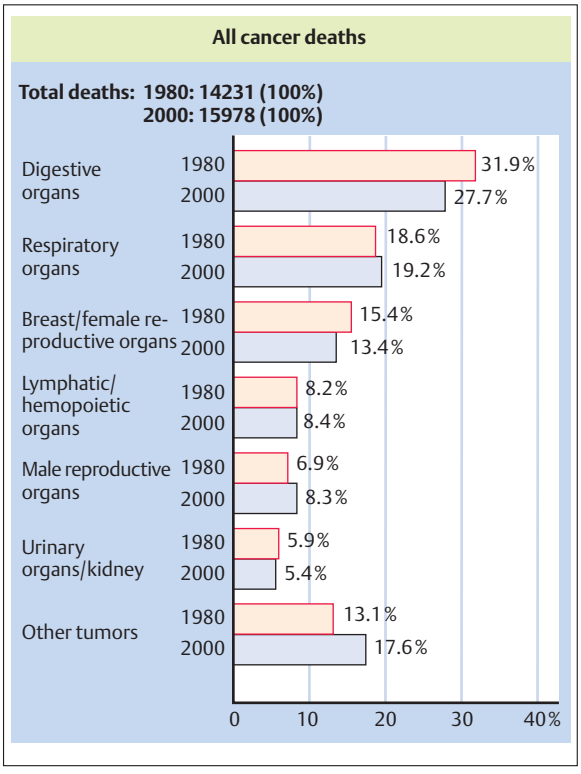

Fig. 1.**8** Deaths due to cancer in Switzerland, in 1980 and 2000. (Source: Swiss Federal Statistical Office.)

➤ SCC Cervical, lung, and rectal carcinoma.

Occult tumors may lead to particular clinical pictures and conditions. An important subgroup of the so-called paraneoplastic syndrome is formed by the paraendocrine syndromes (Tab. 1.**11**). Tumorous tissue from nonendocrine organs can become hormonally active. This kind of hormone production is typically not subject to any physiological control mechanism and does not disappear until the tumor is removed.

Paraneoplastic syndromes can precede discovery of the tumor and should therefore give rise to a comprehensive examination.

Conditions that Predispose to Malignant Tumors. A distinction between five main in groups is considered in the etiology of human tumors:

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Table 1.**11** Paraneoplastic syndromes

Clinical signs	Most common types of tumors
General paraneoplastic syndromes	
Anemia	various tumors
Eosinophilia	malignant lymphomas, leukemias, metastatic tumors
Leukocytosis	various tumors
Thrombocytosis	various tumors
Thrombocytopenia	large hemangiomas, lymphoproliferative diseases
Hypercoagulability	bronchial, stomach, intestinal, pancreatic, breast, uterus carcinoma; malignant lymphomas
Disseminated intravascular coagulation	metastatic carcinomas, leukemias, lymphomas
Erythema nodosum	lymphomas, leukemias, carcinomas
Hyperpigmentation	carcinoma of the gastrointestinal tract, malignant melanoma
Urticaria	malignant lymphoma, polycythemia vera mastocytosis
Myopathies	bronchial, stomach, ovarian carcinoma
Neuropathies	bronchial, breast, gastric carcinoma
Encephalomyelopathies	lung tumors, ovarian carcinoma, endometrial carcinoma, Hodgkin disease
Paraproteinemia	malignant lymphomas, chronic lymphatic leukemia
Glomerulonephritis	malignant lymphomas, leukemias, carcinomas (lung, breast, kidney etc.)
Thrombotic endocarditis	adenocarcinoma (stomach, lungs, pancreas)
Fever	sarcomas, hypernephroma, gastrointestinal tumors, hepatoma, leukemias
Acropachy	intrathoracic tumors, mainly bronchial carcinoma
Osteoarthropathy	
Paraendocrine syndromes	
Cushing syndrome	small-cell bronchial carcinoma, island cell tumors of the pancreas, thymoma, medullar thyroid carcinoma, carcinoid
Hirsutism	ovarial, adrenal tumors (androgenic)
Feminization	adenomas and carcinomas of the adrenal gland (estrogen)
Pubertas praecox, gynecomastia	hepatocellular, testicular and mediastinal teratomas, chorioncarcinomas, lung tumors
Hypoglycemia	large sarcomas, hepatoma, gastrointestinal carcinomas, carcinoid
Hypercalcemia	bone metastases, multiple myeloma, malignant lymphoma as well as bronchial carcinoma (epithelioma), tumors in otolaryngeal region, cervical carcinoma
Hyperthyreoidosis	choriocarcinoma, bladder moles, lung tumors
Polyglobulin	renal carcinoma, cerebellar hemangioblastomas (erythropoietin)
Schwartz–Bartter syndrome	bronchial, pancreas, duodenal carcinoma (ADH)

- Direct or indirect heredity (approximately 5% of tumors):
  - retinoblastomas, nevoid basal cell, multiple endocrine adenomatosis, familial colon polyposis, breast cancer
  - neurofibromatosis, tuberous sclerosis, multiple exostoses, albinism, Fanconi syndrome, Wiskott–Aldrich syndrome (development of secondary tumors)
- Environmental factors (at least 60%):
  - eating habits (high-fat, low-fiber, nitrosamine, mycotoxin)
  - tobacco consumption (responsible for 40% of carcinomas in men), particularly in the mouth, larynx, lungs
  - alcohol (carcinomas in the esophagus and liver)
  - profession (trigger factor in approximately 5% of all tumors) (Tab. 1.**9**)
  - promiscuity: human papillomavirus, which can lead to cervical carcinoma in younger women, HIV-associated tumors
  - ultraviolet light (melanoma), radioisotope, radiation
  - medication (cytostatic drugs, hormones)

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- Viruses:
  - HIV infections (Kaposi sarcoma, malignant lymphomas)
  - Epstein–Barr virus (Burkitt lymphoma)
  - hepatitis B and C virus (hepatoma)
- Unknown causes (approximately 35%)
- Various conditions (rare):
  - cholelithiasis, liver cirrhosis, Crohn disease, colitis ulcerosa, pernicious anemia
  - dermatomyositis
  - struma nodosa, lupus vulgaris, Paget disease, acromegaly
  - cryptorchidism.

Metabolic Diseases

Pathological metabolites or abnormal amounts of physiological substances in the blood, urine, or body tissue can be identified with different types of diseases, e. g., porphyria characterized by porphyrin, ochronosis caused by homogentisic acid, gout caused by uric acid, hyperlipoproteinemia characterized by cholesterol and triglycerides.

Genetic-related Enzymopathy. Today more than 150 diseases with enzymatic disorders involving genetic defects (enzymopathy) are known. They are also referred to as "inborn errors of metabolism." The majority are autosomally recessive inherited diseases.

A mutant gene results in a decreased or nonproduction of an enzymatic or nonenzymatic protein. The enzyme in question is an integral part of a particular step of metabolism in biosynthesis or catabolism. To some extent, the metabolic pathway is blocked and alternative pathways are therefore required, which frequently cannot prevent a metabolic deficiency because of poor capacity. Due to these effects, various mechanisms in enzymopathies can be detected:

- In some diseases, insufficient quantities of biologically important substances are produced, e. g., the production of melanin is suppressed in albinism due to the absence of tyrosinase, or type 1 diabetes mellitus results from lack of insulin.
- Pathological products that accumulate because of a lack of enzymatic degradation are renally excreted and may lead to kidney stones, e. g., oxaluria, xanthinuria, and cystinuria.
- Abnormal metabolites are accumulated, e. g., glycogen-storage diseases, mucopolysaccharidosis, and galactosemia.
- Through accumulation of intermediate products a toxic effect develops, e. g., alkaptonuria, characterized by homogentisic acid, or galactosemia, characterized by galactose-1-phosphate.
- Normal metabolic steroids accumulate in the adrenogenital syndrome due to 17-hydroxylase deficiency.
- Faulty collagen structure causes normal collagen to be unstable as in Ehlers–Danlos syndrome.

Dysfunction of the Endocrine System

The clinical picture of secretory organ disease is often characterized by dysfunctional secretion rather than by the diseased organ itself. Hormones and their metabolites can increasingly be quantitatively determined, which in turn provides important information on the type of disease (e. g., in the case of diabetes mellitus).

Mental Disorders

An assessment of mental state is one of the daily diagnostic tasks of the physician. The recognition of typical psychopathological syndromes partially allows the physician to identify physical diseases (e. g., delirium tremens and Korsakow syndrome found in chronic alcoholism accompanying pneumonias, or after surgery).

This factor does not apply for either *endogenous psychoses* (schizophrenia, manic-depressive psychosis) or for *vegetative complaints*. In these cases, often it is not the patient who complains, but rather his/her intellectual or affective behavior is noted by others.

Functionally Vegetative Complaints. When diagnosing "functionally" vegetative complaints (also psychosomatic disorders or psychovegetative syndrome), it is essential to rule out somatic disease. Generally, functional diseases belong to by far the biggest group of psychic disorders, either as a stand-alone disease or as a result of other illnesses. Uniform characterization of the psychosomatic patient is not possible. Functional vegetative diseases, however, often present as follows:

- with a chronic course
- with erractic change of the affected organs
- triggered by stress situations.

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Usually, we differentiate between the various somatic subgroups of psychovegetative syndromes (e. g., disorders in the area of the head, the cardiovascular system, respiration, the gastrointestinal tract: Tab. 1.**8**). There is hardly a more difficult diagnosis to make than that of a functional disorder. The talent of caring for a patient with empathy is not universal and is difficult to learn.

Psychosomatic Disorders. Bronchial asthma, obesity, and anorexia, as well as frequent anxiety attacks are considered as psychosomatic disorders. An increasingly common complex of symptoms, which is difficult to distinguish from depression, is chronic fatigue syndrome (Tab. 1.**12**).

Exogenous Psychoses. Mental disorder in the group of "exogenous psychoses" is an accompanying symptom of somatic disease. Bleuler distinguished between four main groups of somatic-related disorders:

- *Psychoorganic syndrome (POS).* As a result of diffuse brain damage (arteriosclerosis, cerebral injury, Korsakow syndrome), the patients examined have typical attentiveness dysfunction and disorientation as well as a lack of concentration. Furthermore, inability to think, perseveration, and emotional lability are characteristic.
- *Local psychosyndrome.* Although the brain is locally diseased, a disturbance of memory or impaired consciousness does not typically occur, but rather erratic mood changes are observed.
- *Endocrine psychosyndrome.* Mental disorders can occur in endocrine diseases. The clinical picture is the same as in local psychosyndrome.

Table 1.**12** Revised CDC Criteria for chronic fatigue syndrome†

A case of chronic fatigue syndrome is defined by the presence of:

1. Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset, is not the result of ongoing exertion, and is not alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities, *and*
2. **Four or more** of the following symptoms that persist or recur during six or more consecutive months of illness and that do not predate the fatigue:
   - Self-reported impairment in short term memory or concentration
   - Sore throat
   - Tender cervical or axillary nodes
   - Muscle pain
   - Multijoint pain without redness or swelling
   - Headaches of a new pattern or severity
   - Unrefreshing sleep

Post-exertional malaise lasting ≥24 hours

† Adapted from Fukuda, K, et al., 1994

- *Acute exogenous reaction type.* In acute, severe, general diseases, as well as in acute brain diseases, typical mental symptoms (such as sudden amentia, disorientation, indistinct enunciation, restlessness, and apathy, as well as hallucinations and delusional ideas), may develop. Typical subgroups of the acute exogenous reaction type are delirium (hallucinations), and twilight state, as well as various levels of impaired consciousness (somnolence, sopor, coma). It is often difficult to differentiate between the acute exogenous reaction type of psychosis and neurotic disorders or schizophrenia.

Hereditary Diseases

Human chromosomes consist of 22 autosomal pairs and 2 sex chromosomes (male: XY, female: XX), a total of 46 chromosomes. For diagnosis, chromosomes from human cells are individually analyzed using fluorescent staining (karyotype).

Structural Aberrations. Chromosomal aberrations can be either inherited or transmitted (mutagenic chemical substances, X-rays, radioactivity). Chromosomal abnormalities can be detected prenatally by cytogenic methods.

Chromosome Anomalies

Numerical Aberration. Trisomy (47 chromosomes), the most common chromosome disorder, is found mostly in trisomy 21 (Down syndrome; occurs in 1:650) and in sex chromosomal trisomies, with a longer life expectancy than for Down syndrome. Among the most common sex chromosomal abnormalties are: Klinefelter syndrome (47,XXY; occurs in 1:500) and the usually clinically inconspicuous, Triplo X syndrome that affects females (47,XXX; occurs in 1:1000), and Turner syndrome (45,X0; occurs in 1:10000), which is a sex chromosomal monosomy.

Simple Mendelian Genetics

This type of heredity is achieved by transmission of a single mutant gene.

Autosomal Dominant Inheritance. Symptoms occur in heterozygous carriers, who have one chromosome with a mutant gene and the other chromosome with a normal gene. The risk factor for progeny from patients with manifest disease is 50%. Not all carriers must manifest the disease (difference between the expressivity of disease and penetrance of genes). Severe, dominant inherited abnormalities are in most cases caused by new

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mutations, and disappear with the death of the carrier prior to having descendants.

Autosomal Recessive Inheritance. Symptoms only occur when the patient is homozygous (i.e., the same allele on both of his/her homologous chromosomes). The risk of repetition for other siblings with manifest disease is 25%, for heterozygous healthy bearers 50%, and for healthy siblings 25%.

X-chromosomal Inheritance. The X chromosome carries the mutant gene. In most cases, women are only asymptomatic vectors (carriers), but 50% of their male offspring fall ill.

Recessive inherited diseases are often diagnosed in early childhood, autosomal dominant hereditary diseases usually not until adulthood. Dominant inherited mutations tend to affect physical characteristics, while recessive mutations more often lead to metabolic disorders (Chapter 2).

Currently the exact location of the responsible gene, and, to an increasing degree, the biological mechanism of the disease, is known for many of the monogenously inherited diseases. In some cases, therapeutic interventions have been undertaken to counteract defects based on this knowledge.

Multifactorial Heredity

The interaction of several, sometimes unknown, genes and environmental factors appears to be responsible for various familial diseases. This type of inheritance is more common than monogenous inheritance. First degree relatives have approximately a 5% risk of becoming ill.

Allergies

Allergies are characterized by an abnormal immune reaction against substances (allergens), that do not affect healthy individuals. We distinguish between humoral allergies caused by circulating antibodies (type I, II, III) and cell-mediated allergies (type IV).

Type-I Allergy. The so-called *type-I allergy* represents a dramatic anaphylactic reaction. This type of allergy is characterized by occurrence of symptoms within minutes, or hours, of allergen exposure (inhalation, orally, per injection, percutaneously). Besides pruritus, urticaria, and angioedema, dyspnea as well as diarrhea, colic, and severe shock symptoms can also occur.

As a result of a specific antigen (protein, polysaccharide, hapten) IgE-sensitive mast cells release biologically active substances, e.g., histamine or SRS-A (slow reacting substance of anaphylaxis). These, and other mediators, then rapidly lead to the aforementioned symptoms. In most cases, but not always, a time correlation with antigen exposure can be identified (nutrition, medications, insect bites, etc.). A prick or scratch test (or an intracutaneous test) can help diagnostically. In these examinations diluted antigens are applied via scarification or subcutaneous injection. A welt that appears after 10–20 minutes indicates a positive result.

Currently, the presence of specific IgE antibodies can be determined quantitatively by RAST (Radio-Allergo-Sorbent Test). This safe method allows the identification of IgE antibodies against foods, insecticides, pollen, dust, etc. Frequently, eosinophils and an increase in serum IgE can be detected in these patients; a rapid erythrocyte sedimentation rate or a leukocytosis is usually absent.

Type-II Allergy. In *type-II allergy* circulating antibodies can lead to cell lysis (e.g., allergic hemolytic anemia, transfusion reactions).

Type-III Allergy. *Type-III allergies* comprise the so-called immune complex diseases. Different antigens (medications, bacterias, viruses, tumor cells, possibly endogenous tissues) together with the respective antibodies form circulating immune complexes that can be deposited in the basal membranes of arteries and glomeruli. Usually, these patients present a relatively similar clinical picture, which is typically characterized by arthralgia, various types of skin changes, and glomerulonephritis. Less frequent symptoms are pleurisy, pericarditis, and allergic alveolitis. Examples of immune complex diseases are: Farmer's lung, poststreptococcus glomerulonephritis, glomerulonephritis associated with endocarditis, and different types of tumors, such as colon carcinoma, bronchial tumors, and hypernephroma.

Type-IV Allergy. In association with *type-IV allergy*, sensitized T-lymphocytes can lead to allergic reactions, especially of the skin. This allergy is observed as contact eczemas and exanthemas. The onset from time of allergy contact until the emergence of symptoms can be up to 10 days.

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Intoxications

No generally valid clinical criterion is known for the differentiation of exogenous and endogenous intoxications as a disease group.

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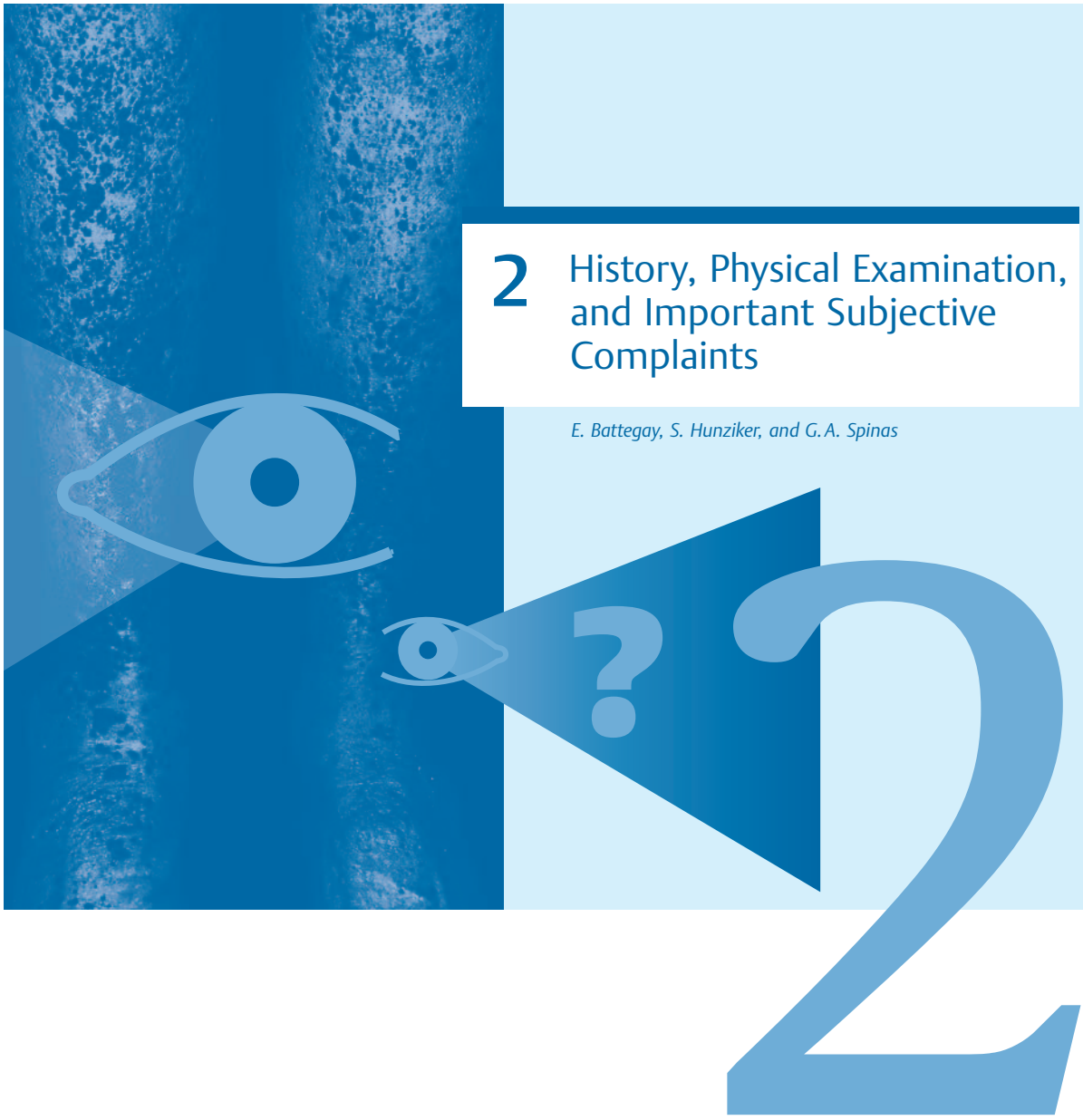

2 History, Physical Examination, and Important Subjective Complaints

E. Battegay, S. Hunziker, and G.A. Spinas

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2.1 Medical History

Greeting and Interview Setting

The interview setting should be as pleasant as possible for the patient. The patient and the examiner should make frequent eye contact and the discussion should not be disturbed by extraneous noise.

Beginning the Interview: the Patient's Perspective. The interview should begin with an open question so that the patient can describe the chief complaint in his or her own words. The patient's own perception of illness is most important at this stage. Active listening involves waiting for the patient to speak, repeating (echoing) the patient's words to elicit further details, and summarizing what the patient has said to ensure mutual understanding.

Components of the Clinical Interview

History of Present Illness. The physician-centered part of the interview begins now, but leading questions should still be avoided. Six aspects of the patient's complaint should be explored:

1. Localization of symptoms (origin and radiation, if any).
2. Temporal pattern: onset, duration, sequence of symptoms (if multiple), periodicity, and symptom-free intervals.
3. Quality: the patient should describe the symptoms in greater detail. The use of medical terms ("heart pain," etc.) is potentially misleading. The patient should be asked to describe the symptoms subjectively, yet precisely. Not all patients can find the right words for what they feel.
4. Intensity: severity and extent, or physically measurable quantity/volume (e. g., fever or vomiting).
5. Accompanying symptoms.
6. Aggravating and ameliorating circumstances.

Further Information. Further components of the history include:

- Past medical/surgical history
  - previous illnesses, operations, and hospitalizations
- Family history
  - for example, diabetes mellitus, arterial hypertension, tumors, cardiovascular diseases, renal diseases, pulmonary diseases, mental illness, epilepsy
- Psychosocial history
  - review of systems: dysfunction of other organ systems, medication use, and use of other substances and intoxicants (tobacco, alcohol, illicit drugs)
- Neurological history (neurological review of systems)
  - cognitive function: disturbances of memory and concentration, language disturbances (e. g., word-finding difficulty), highest level of intellectual function (educational/occupational), mood and behavior (usually best determined by asking another person)
  - cranial nerves: visual acuity, diplopia, tingling or numbness on the face, disturbances of hearing, dizziness, dysphagia, dysarthria
  - limbs: tingling or numbness in the arms or legs, weakness/loss of strength, loss of fine motor control (e. g., change of handwriting), gait impairment and falls, involuntary movements, cramps
  - other: headache, pain elsewhere in the body, ictal disturbances, autonomic dysfunction (abnormalities of micturition, sexual function, defecation, sweating), changes in the sleep–wake cycle.

2.2 Physical Examination

Lymph Nodes

Palpation. The lymph nodes (cervical, nuchal, submandibular, supra- and infraclavicular, axillary, and inguinal) are examined by palpation. The examiner should note the following:

- consistency (hard or soft)
- mobility
- tenderness
- size (normally < 1 cm).

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Thyroid Gland

Inspection and palpation of the thyroid gland, with the head in the normal position, can detect goiter with 40–80% sensitivity and 90–100% specificity. The sensitivity falls to 10%, however, if the goiter is only visible when the head is inclined backward (grade I goiter; see Tab. 2.**1**).

Table 2.**1** Clinical classification of goiter by size

Goiter	Clinical features
Grade I	palpable, but visible only with the head inclined backward
Grade II	visible with normal head posture
Grade III	visible from a distance

Cardiovascular System

Inspection. The examiner should pay attention to the following:

- Central cyanosis (underside of the tongue), jaundice (color of the sclerae), shape of the chest (*pectus excavatum, pectus carinatum,* flat chest, precordial prominence, i. e., enlargement of the left anterior rib cage), scoliosis.
- *Peripheral venous pressure* is tested by raising the upper body to a 45° angle. If the neck veins are filled to more than 3 cm above the sternal angle in this position, the venous pressure is elevated.
- If the test just described yields no evidence of right heart dysfunction (normal pressure), a further test is performed for hepatojugular reflux (HJR) to rule out latent right heart failure. Positive HJR is a valuable sign of elevated right heart pressure (and possibly elevated left atrial pressure), with 50–80% sensitivity and greater than 95% specificity.
- *Peripheral venous pulsations* (internal jugular vein, external jugular vein): the examiner should note the temporal relationship of the venous pulsations to the peak of the carotid impulse. A *paradoxical* rise of venous pressure is one that occurs during inspiration.
- *Other visible pulsations* (carotid artery, movements of the chest wall). Abnormally large fluctuations of intrathoracic pressure (e. g., in a severe asthma attack, or in massive upper airway obstruction) can result in paradoxical pulse, i. e., accentuation of the normal drop of systolic blood pressure in inspiration to more than 15 mmHg.

Palpation. With the patient supine, the examiner should palpate the heart and peripheral vessels (pulse examination) as well as the movements of the chest wall. The peripheral vessels to be palpated are the carotid and subclavian arteries, the abdominal aorta, and the femoral and popliteal arteries.

- *Carotid artery:* rate of rise of pressure (normal, slow, abnormally rapid, variable), one or two peaks of impulse, paradoxical (weaker in inspiration).
- *Other peripheral vessels:* evaluation of pulse (frequency, rhythm, weakness or absence of pulse).
- *Movements of the chest wall:* present or absent? If present: site (left or right ventricle), amplitude, duration.

Percussion of the heart to determine its size is a relatively sensitive method for detecting cardiomegaly.

Auscultation. The examiner listens for the heart sounds (brief, audible tones) and murmurs (turbulences):

- first heart sound, second heart sound, abnormal heart sounds
- systolic and diastolic murmurs.

Chest and Lungs

Inspection

- Shape of chest
  - symmetry, possible presence of kyphoscoliosis, *pectus excavatum* or *pectus carinatum* (pigeon-breast)
  - a barrel chest is due to overinflation of the lungs, e. g., in emphysema. The signs of barrel chest are: rib cage fixed in inspiratory position, horizontally lying ribs, manubrium raised to the lower border of the larynx, "emphysema cushion" in the supraclavicular fossa
- Auxiliary muscles of respiration
  - of greatest importance is the sternocleidomastoid muscle
  - activated when the lungs are markedly overinflated
  - additional support from the diaphragm (flat diaphragm, inspiratory insufficiency)
- Braking of expiration by the lips
  - a maneuver that prevents airway collapse

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- Propping up in the sitting position with the arms and shoulder girdle
  - improved function of the auxiliary muscles of respiration
- Respiratory rate (normal 8–20/min)
  - tachypnea (> 20/min): a nonspecific finding in many cardiorespiratory illnesses, pulmonary fibrosis, pneumonia (note: the term hyperventilation denotes metabolically excessive ventilation as demonstrated by its effect on pCO_2 and pH, without reference to the frequency or depth of respiration)
  - bradypnea (< 8/min): e. g., in opiate intoxication
- Respiratory cycle
  - duration of inspiration vs. expiration at a ratio of 2:3
  - obstructive airway disease prolongs the expiratory phase (COPD, asthma)
- Respiratory excursions
  - inspiratory excursions of the chest: two-thirds due to diaphragmatic contraction when the individual is supine, one-third when sitting or standing
  - expiration: passive at rest, can be forced by contraction of the abdominal muscles
  - symmetry (to palpation): altered in chest wall processes, pleural fibrosis, deficient inflation of the lung (atelectasis, tumor, or antalgic guarding)
  - synchrony: simultaneous outward movement of both sides of the chest
  - paradoxical movements: abnormal movements of segments of the chest wall in serial rib fractures (flail chest)
  - paradoxical respiration: movement of chest and abdomen in opposite directions in the supine patient
- Types of respiration
  - *orthopnea*: dyspnea when lying down
  - *platypnea*: dyspnea when the upper body is upright (e. g., congenital anomalies with right-to-left shunting)
  - *Kussmaul respiration*: abnormally deep and slow respirations in metabolic acidosis (ketoacidosis, renal failure)
  - *sighing*: individual, deep respirations (normally occurs a few times per hour)
  - *Cheyne–Stokes respiration*: periodic variation of respiratory depth with respiratory pauses (brief intervals of apnea)
  - *Biot respiration*: chaotic, irregular breathing (e. g., in processes affecting the medulla or medication-induced respiratory depression)
  - *gasping*: rapid, shallow, snapping inspiratory movements interspersed with apneic pauses (deep intoxications, agonal respiration)
- Clubbing and hourglass nails
  - in chronic hypoxemia (especially pulmonary fibrosis, cystic fibrosis) or idiopathic
- Cyanosis
  - bluish discoloration of skin and mucous membranes, blood with at least 5 g/dl unsaturated hemoglobin
  - *central cyanosis:* even the arterial blood is unsaturated (because of pulmonary disease), as can be seen, e. g., by inspection of the undersurface of the tongue
  - *peripheral cyanosis:* slow acral circulation, resulting in elevated consumption of oxygen in capillary blood (due to heart failure or cold), visible, e. g., in the lips; central compartments, however, are not unsaturated (the undersurface of the tongue is pink).

Palpation

Palpation is more useful than inspection for the detection of asymmetrical respiratory movements.

- Lymph nodes, trachea, skin
  - examination of the chest includes palpation of the supraclavicular, infraclavicular, and axillary lymph nodes
  - verification of the midline position of the trachea in the neck
  - feeling for crepitus beneath the skin, a sign of subcutaneous emphysema
- Vocal fremitus
  - vocal fremitus is stronger than normal if the pulmonary tissue between the bronchi and the chest wall is abnormally dense (pulmonary infiltration, typically found in lobar pneumonia)
  - vocal fremitus is weaker than normal or even absent if its transmission is impaired (pleural effusion or fibrosis, atelectasis, pneumothorax)
  - in women and children, the voice may normally be of such a high frequency that its vibrations are not transmitted to the chest wall and, therefore, no vocal fremitus is palpable
- Auxiliary muscles of respiration
  - the activity of these muscles can be palpated at the scalene and sternocleidomastoid muscles.

Percussion

Percussion is the examination of the air content of a body compartment by listening to the tone produced by a tap on its outer surface. It yields useful information to a depth of about 5 cm. It enables demarcation of the lungs from the surrounding solid organs. Pathological processes at least 5 cm in diameter can be objectively detected by comparing the findings in the two lungs. Normal percussive findings, however, do not rule out pulmonary pathology. The sensitivity of percussion varies from 100 % for large pleural effusions to 26 % for consolidations and practically nil for intraparenchymal processes.

When performing percussion, the examiner should pay attention to the following:

- Sound quality
  - *sonorous*: normal

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- *hypersonorous*: indicates greater than normal air content, e. g., over a bulla, emphysema, or pneumothorax
- *damped (hyposonorous):* indicates less than normal air content, e. g., over the liver, pneumonia, atelectasis, pleural effusion

➤ Localization and excursion of the lower border of the lung
- determined by percussion from above downward until the level of damping is reached (mid-inspiratory level)
- the lung border in inspiration is localized by the same method in deep inspiration
- the lung border in expiration is then localized after complete expiration by percussion from below upward, until a sonorous level is reached
- the distance between the inspiratory and expiratory borders is the respiratory excursion, which normally measures 4–6 cm
- a low-lying and relatively immobile diaphragm is evidence of overinflation of the lungs, e. g., in emphysema.

Similarly, the examiner percusses from above downward in the midclavicular line to locate the upper border of the liver.

Auscultation

Breath Sounds. The sounds of normal breathing are created by turbulent air flow in the pharynx, trachea, and larger bronchi. A soft, blowing sound is heard upon inspiration, and a vague and poorly demarcated sound is heard upon expiration.
The examiner should make note of the following:

➤ Poorly audible or inaudible breath sounds
- a sign of impaired ventilation of the underlying pulmonary tissue (atelectasis, effusion, bulla, pneumothorax, respiratory guarding) or of overinflation of the lung (e. g., emphysema)

➤ "Bronchial (or tubular) breathing"
- this is a loud, hissing sound heard upon both inspiration and expiration directly over the trachea or the vertebra prominens
- pulmonary tissue containing air dampens the higher auditory frequencies, so that bronchial breathing is not normally heard
- bronchial breathing is heard over areas of pulmonary infiltration with patent bronchi (e. g., in lobar pneumonia)
- it is also heard in pneumonia (patients also have fever and cough), but not in all cases (sensitivity only 14%)
- "compressive" breath sounds heard over the thin edge of a pleural effusion resemble bronchial breathing

➤ Bronchophony
- sibilant sounds, like those in a whispered "sixty-six" or "seventy-seven," are heard more intensely and at higher frequency over an area of infiltration
- pathological bronchophony has the same clinical significance as bronchial breathing (the combination of bronchophony, fever, and cough indicates pneumonia)

Adventitious Sounds. In addition to the breath sounds described above, adventitious sounds may be heard and may be either continuous or discontinuous:

➤ Continuous adventitious sounds
- These are known as *obstructive sounds*: they are "musical" vibrations such as rhonchi, dry rales, and sibilant rales (wheezes) and are well heard, e. g., in bronchial asthma.
- They are usually easier to hear upon expiration than upon inspiration.
- These mono- or polyphonic tones of varying frequency are caused by oscillations of the bronchial wall as air passes through sites of airway narrowing (due to secretions, bronchospasm, mucosal edema, tumor, or dynamic compression in emphysema, which mainly occurs during forced expiration).
- The intensity (volume) of these sounds is no indication of the severity of the obstruction! In very severe bronchospasm (status asthmaticus), too little air flows to generate any adventitious sounds ("silent chest").
- Continuous adventitious sounds accompanying nonforced respiration indicate the presence of obstructive pulmonary disease (specificity > 90%).

➤ Discontinuous adventitious sounds (rales or crackles)
- brief, well-demarcated sounds lasting up to 20 ms
- generated by the bursting of menisci of secretions in the alveoli or in the smaller, midsized, or larger airways (causing fine, intermediate, and coarse rales, respectively); they are usually heard during inspiration. (Note: the term "rales" is more commonly used in the USA, "crackles" in the UK)
- When the surrounding pulmonary tissue is infiltrated, the higher frequencies are conducted to the surface with less attenuation, so that the rales are heard as being near the ear. When the surrounding tissue is normally aerated, they are heard as distant from the ear.
- Discontinuous adventitious sounds arise in left heart failure with interstitial or alveolar edema, in pneumonia, and in pulmonary fibrosis (high-frequency crepitant rales, sclerosiphony). They resemble the sound of a hook-and-loop fastener (Velcro) being opened.
- The specificity and sensitivity of these sounds depends on the etiology of disease (Tab. 2.**2**). For example, the absence of discontinuous adventitious sounds is evidence against idiopathic pulmonary

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Table 2.2 Sensitivity and specificity of breath and adventitious sounds

Clinical finding	Diagnosis	Sensitivity (%)	Specificity (%)
Bronchial breathing	pneumonia	14	90
Discontinuous adventitious sounds			
➤ in asbestos workers	asbestosis	80	80
	sarcoidosis	5–20	?
➤ in heart disease	left heart failure	20–60	80–90
➤ with fever and cough	pneumonia	20–60	50–90
Continuous adventitious sounds			
	chronic airway obstruction	13–50	> 90
➤ during a methacholine test	asthma	40	> 90
Attenuated breath sounds			
➤ combined with fever and cough	pneumonia	15–49	> 90

fibrosis (sensitivity > 80%), but not when the underlying cause of fibrosis is sarcoidosis (sensitivity 14%).
- In bedridden, elderly patients who are sat up for auscultation, rales may be audible only during the first few breaths, and then disappear. In general, adventitious sounds due to secretions can often be coughed away.

➤ Pleural rub
- a rasping, grating sound that is usually heard at the end of an expiration, but may also be heard at the end of an inspiration
- It is often accompanied by pain in acute illnesses, but is usually painless in chronic illnesses.
- It is caused by pathological changes of the visceral and parietal pleura, which are not separated by a layer of fluid.

➤ Stridor
- a prolonged, abnormal sound due to airway stenosis, audible without a stethoscope
- Inspiratory stridor is usually due to extrathoracic airway stenosis and implies a narrowing to approximately 5 mm.

Abdomen

Inspection

The abdomen is inspected for any abnormality of shape (distention, abdominal obesity), localized protrusions, or abdominal wall hernias, which may be visible either at rest or upon coughing (epigastric, inguinal, scrotal, umbilical, or incisional hernias). Further diagnostic clues can be obtained from skin changes (e. g., scars, exanthems, petechiae, striae) and abnormalities of the abdominal hair (e. g., loss of abdominal hair in hepatic disease). Portal hypertension may produce abnormal prominence of the abdominal veins, ranging in severity up to caput medusae.

Palpation

If palpation of the abdomen is painful and elicits guarding (involuntary contraction of the abdominal muscles to ward off pain whenever the abdominal wall is lightly depressed) the parietal peritoneum may be involved by either local or diffuse peritonitis. The specificity of this finding for peritonitis is 75–99%. Rebound pain (i. e., increased pain or defensive movements when the lightly depressed abdominal wall is suddenly released) is also a sign of peritonitis; if unaccompanied by guarding, it implies exclusive involvement of the visceral peritoneum. Nonperitoneal pain on palpation is of diagnostic value only if it corresponds to the spontaneous pain reported by the patient (i. e., if the patient "recognizes" the pain). Provoked pain with no spontaneous equivalent is rarely of diagnostic significance. The same is true of pain restricted to a single point or pain that worsens upon contraction of the abdominal wall muscles. These pains are usually caused by processes affecting the abdominal wall rather than the intraperitoneal organs.

Liver. When palpating the liver, the examiner should make note of the following:
➤ *liver edge:* sharp or rounded contour, medium-hard or soft consistency
➤ *if the liver is enlarged:* symmetrical or asymmetrical enlargement of the hepatic lobes, contour of the hepatic surface
➤ the distance between the level of the diaphragm, as detected by percussion, and the palpated lower edge of the liver should be *measured* in the right midclavicular line in deep inspiration (normal distance,

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8–10 cm; if 12 cm or greater, hepatomegaly is definitely present).

Spleen. The spleen is palpated in deep inspiration in a line extending perpendicularly downward from the lower border of the rib cage to the lower pole of the spleen.

Kidneys. The kidneys are palpated with the patient supine and with the abdominal muscles as relaxed as possible. A normal kidney in normal anatomical position is not palpable, nor is it painful when lightly compressed between the examiner's hands. Palpation is supplemented by percussion, which is normally not painful.

Bladder. The bladder is palpated bimanually with the patient supine and with the abdominal muscles as relaxed as possible. It should also be percussed if an enlarged bladder is suspected. Percussion is performed along the vertical axis in the midline, from above downward. Normally, a damped tone is first heard about two finger-breadths above the symphysis pubis.

Prostate Gland. The left and right prostatic lobes are palpated with the index finger during the digital rectal examination. The examiner should note the size, symmetry, smoothness, and consistency of the surface of the prostate gland, any tenderness to compression, and its demarcation from the surrounding tissues. A normal prostate gland is chestnut-sized, symmetrical, smooth, of the same elastic consistency throughout, nontender, and well demarcated on all sides (except for the cranial surface, which cannot be palpated). Special attention should be paid to local hardening and asymmetrical prominences because prostatic carcinoma is usually found in the "outer shell" of the gland.

A normal finding on palpation does not rule out early prostatic carcinoma. During the digital rectal examination, the examiner should not only palpate the prostate gland, but also examine the anus and rectal mucosa.

Hernias. These can be brought out by having the patient stand and cough. The contents of the hernia sac are usually freely mobile and enter the sac through its patent opening when the patient coughs (e. g., in inguinal, femoral, abdominal wall, and incisional hernias). They can be palpated or observed either as a mass striking the abdominal wall when the patient coughs (e. g., in inguinal or femoral hernia) or as an actual protrusion of the wall (e. g., in abdominal wall or incisional hernia).

Musculoskeletal System

Spinal Column. The examination of the spine is summarized in Tab. 2.**3**.

Joints. The joints are inspected for their position, excursion when the patient walks, and any axial deviation, atrophy, or deformation. Certain joints have characteris-

Table 2.**3** Examination of the spine

Inspection – Posture, curvature of the spine (physiological or diminished lumbar and cervical lordosis, accentuated thoracic kyphosis), flat back, scoliosis (compensatory, not structural or fixed in the bony structure of the back) – Symmetry of the axial skeleton and of the triangles of the waist (empty spaces between the lateral contour of the trunk and medial contour of the arm), position of the shoulder (elevated/depressed), position of the pelvis (horizontal or slanted), difference of leg length, abnormal head posture, skin changes (wounds, psoriasis) – Gait (antalgic limp, Trendelenburg gait, Duchenne gait), toe/heel walking, stair climbing (impaired in local or generalized weakness)
Mobility testing – Cervical spine: maximal inclination (chin to chest), maximal reclination (head back, looking vertically upward), lateral bending, rotation of the head – Thoracolumbar spine: flexion, extension, lateral bending, rotation (torsion of the trunk with fixed pelvis), pain on straightening, distance from fingertips to floor, lumbar Schober test (ability to straighten lumbar spine)
Palpation – Paravertebral musculature (spasm), spinous processes (step formation), interspinous ligaments (tenderness) – Tenderness to percussion (local, e. g., in intervertebral disk disease, spondylitis, fracture; generalized, e. g., in osteoporosis, low pain threshold), pain on shaking – Tenderness to pressure at Valleix points – Tenderness to pressure on the iliac crest, trochanteric bursa, or pes anserinus
Neurological examination (see below) – Sensorimotor function: sensation to touch (dermatomal findings in radicular processes), pain, saddle anesthesia (e. g., in cauda equina syndrome, combined with bladder, bowel, and erectile dysfunction), testing of muscle strength – Intrinsic muscle reflexes – Signs associated with nerve stretching (Lasègue, Bragard, inverse Lasègue)

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tic pressure points that are painful in particular diseases (e. g., lateral humeral epicondylitis). Further important findings include temperature (e. g., localized warmth), swelling, effusion, and tenderness. The mobility of a joint can be expressed in degrees, as measured from the neutral position (the zero-neutral method, see also textbooks of orthopedics).

Neurological Examination

The routine neurological examination is best performed in "craniocaudal" sequence:

- Mental status
  - orientation: place, time, situation, person
  - concentration/distractibility during the interview: if the patient has trouble concentrating or is easily distracted, ask him/her to spell "WORLD" backward or subtract 7 from 100 five times
  - memory: how precisely can the patient report his or her own history? If imprecise, give the patient a list of 3–10 words to remember, and ask for them again 10 minutes later
  - motivation/drive: slowing? if so, then have the patient say as many words as possible starting with "S" in the space of one minute (normal, at least 15–20)
  - language: word-finding difficulty, etc.
  - mood and behavior during the interview
- Cranial nerves
  - testing of visual fields, visual acuity
  - eye background, pupillary width, and light response
  - ocular pursuit movements (in all six directions!) and saccades (horizontal, vertical)
  - facial expression at rest and with voluntary muscle contraction: furrowing of forehead, eye closure, showing the teeth
  - sensation to touch and pain on the face (forehead, cheek, chin)
  - innervation of the palatal veil (uvula midline?), voice (hypophonia? hoarseness?), mobility of tongue (protrusion, side-to-side movement)
- Limbs
  - postural testing of upper and lower limbs
  - rapid alternating movements of fingers (e. g., piano playing) and toes, diadochokinesis, finger–nose and knee–heel–shin tests
  - testing of strength, proximally (arm abduction above the horizontal, hip flexion), distally (finger spreading, dorsiflexion of feet and toes), and "in between" (flexion/extension at elbows and knees)
  - muscle tone: passive movement of the elbows, wrists, and knees
  - sensation to touch, pain, temperature (can be tested with a cool metal object, e. g., reflex hammer or bowl), proximally and distally on the upper and lower limbs
  - vibration sense (on both malleoli and on the wrists)
  - position sense (in the fingers and toes)
  - coin recognition in the hands
  - reflexes: intrinsic muscle reflexes (biceps, triceps, brachioradialis, quadriceps, triceps surae), plantar reflex (testing for the Babinski sign)
- Stance and gait
  - standing with eyes open and closed (Romberg test), hopping on one foot or both (to detect mild weakness of the proximal leg muscles)
  - gait: spontaneous, on tiptoe/on the heels, heel-to-toe ("tightrope") walking with eyes open and closed

The patient's mental status can usually be gauged during the taking of the medical history. Documentation of findings is important (e. g., "The patient is awake, significantly slowed, gives an imprecise history").

Coin recognition and eye movements are tested for neurological screening because these activities require the use of multiple neural systems that must all be intact to ensure normal function.

Motor deficits (paresis) can be graded according to the scale of the Medical Research Council (UK) as follows:

- M5: normal strength
- M4: movement against resistance is possible
- M3: movement against gravity is possible
- M2: movement is possible only when the opposition of gravity is removed
- M1: muscle contraction can be seen, but no movement is possible
- M0: no muscle contraction.

Impaired fine motor control of the hands, or a hand tremor, can be detected by having the patient give a sample of his or her handwriting. Videotaping is used to document involuntary movements or gait disturbances and to follow their course over time.

The elicitability and briskness of the intrinsic muscle reflexes should be tested and documented, both in absolute terms and by comparison of the two sides: – absent; + weak; ++ intermediate briskness; +++ brisk; ++++ abnormally brisk, i. e., with reflex zone expansion or clonus.

The neurological examination should, of course, be performed in still greater detail if the patient's history suggests the presence of neurological disease, or if the routine examination reveals any positive findings.

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2.3 The Asymptomatic Patient (Checkup)

Costs and Benefits. Periodic health examinations and the doctor's checkup are common reasons for medical consultation and have their own list of differential diagnoses. The persons presenting for these examinations are usually in good health. Since the ultimate purpose of the consultation is disease prevention, the extent of the examination is determined by a rational consideration of costs and benefits. Every checkup should yield an assessment of the individual's medical risks, otherwise known as "case finding." This is a special type of exercise in differential diagnosis.

Advantages and Disadvantages. Disease prevention and screening ought to reduce mortality or improve the quality of life. The degree of risk reduction that can be achieved depends on the patient's risk profile. The disadvantages of prevention and screening include the complications of potentially unnecessary diagnostic tests and treatments, and the additional psychological burden they place on healthy individuals. Falsely positive findings, truly positive but innocuous findings, or the identification of slowly progressive, oligosymptomatic diseases at an early stage can produce fear and worry, in addition to the potential adverse effects of further tests that are only questionably indicated. Persons at elevated risk of disease, e. g., the elderly, who have a higher mortality and, generally speaking, a lower life expectancy, stand to benefit more from a targeted preventive examination or screening. Screening is also useful for persons with a known genetic load (family history of a specific, genetically transmitted illness). Finally, the financial costs of screening programs must be scrutinized on a societal level, so that the total cost of health care can still be met.

Table 2.**4** Common motivations for seeking a checkup

- Fear of disease, particularly of:
  - cancer
  - HIV infection
  - dyslipidemia
- Particular symptoms (elicited by direct questioning)
- Diseases in the family or among friends or acquaintances
- Change of job, planned travel to another country, or emigration

Hidden Agendas. Patients will often have a specific motivation for desiring a "routine checkup" that they will not disclose until the examiner asks about it. The unexpressed motivation ("hidden agenda") usually concerns psychosocial problems and stress situations, or a fear of specific diseases, e. g., of cancer, because of nonspecific symptoms or a positive family history, or of human immuno-deficiency virus (HIV) infection, because of risky behavior. It is thus mandatory for the examiner to keep a broad differential diagnosis in mind and, above all, to ask the patient about the reason for the consultation, and about any health-related fears that may not be spontaneously expressed. The most common reasons why patients present for a checkup are listed in Tab. 2.**4**.

Disease Prevention in Healthy Persons

The most important preventive measures are patient counseling, patient education, and vaccination. These should be performed in all patients. Before counseling the patient, the physician should assess his or her risk profile (see Tab. 2.**5**).

Table 2.**5** Disease prevention in healthy persons

Risk profile	Counseling
Smoking	Smoking cessation
Unhealthy eating habits	Healthy eating habits
Inactive, sedentary lifestyle	Physical activity (particularly when the patient is at risk of heart disease)
Risky sexual behavior	Safe sexual behavior
Excessive alcohol consumption (CAGE questionnaire)	Programs for reduction of alcohol intake
Inadequate dental hygiene	Regular dental hygiene
Uncontrolled use of medications	Discontinuation of unnecessary medications
Traffic safety	Safety belt, motorcycle/bicycle helmet

Vaccinations

Vaccinations are often neglected in adults, even though the illnesses they prevent mainly affect adults. In Switzerland, for example, about 1100 adults die each year of invasive pneumococcal infection, and about 400 die in the annual influenza epidemic. The use of currently available vaccination strategies could lower these figures considerably.

Influenza Vaccination. Influenza vaccine is produced from highly purified and inactivated virus particles. It contains the viral components that are most commonly

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present in each individual epidemic. The efficacy of vaccination lies between 70% and 80% in young, immune-competent adults, and between 40% and 60% in the elderly. The vaccination of persons over age 65 reduces the rates of pneumonia and hospitalization by 50%. Other persons at risk who can benefit from vaccination include residents of retirement homes, patients with chronic heart or lung disease, chronic renal failure, or diabetes, and immunocompromised persons. The current recommendation is for all persons over age 65 and all persons in these high-risk groups to be vaccinated.

Vaccination Against Pneumococci. The 23-valent polysaccharide vaccine covers more than 90% of the pneumococcal strains present in Europe. Its primary benefit is the prevention of pneumococcal sepsis and the resulting mortality. Antipneumococcal vaccination should be offered to all persons over age 65, with booster vaccination every 5 years. All persons with functional or anatomical asplenia should also be vaccinated.

Screening and Differential Diagnosis in Apparently Healthy Persons

Periodic Health Exams

This term refers to regularly scheduled, evidence-based preventive examinations. The evidence for most screening tests is incomplete at present. Thus, precise determination of the individual risk profile is important, particularly in asymptomatic persons.

Obesity. Obesity is associated with elevated morbidity and mortality. Regular measurement of height and weight with calculation of the body mass index (BMI = weight in kg divided by the square of the height in m) is indicated in all adults. Furthermore, obese persons (BMI $> 30\ kg/m^2$) should be counseled for weight loss (diet, physical activity, behavior therapy where appropriate, motivation). There is insufficient evidence for any recommendation about the frequency of BMI measurement. Randomized studies show that weight loss can be achieved in the short term, but long-term results are disappointing. There is insufficient evidence that counseling and behavior-therapeutic measures promote long-term weight reduction.

Arterial Hypertension. Measurement of the arterial blood pressure with a sphygmomanometer at least every two years is recommended for all persons over age 20 (grade A recommendation) on the basis of well-founded evidence that the detection of arterial hypertension and the initiation of appropriate treatment in the asymptomatic stage reduces morbidity and mortality from cardiovascular disease. Patients found to be hypertensive should also be counseled about weight reduction, regular physical activity, avoidance of excessive salt and alcohol intake, and smoking cessation. They should also be educated and advised about other potential cardiovascular risk factors and end-organ damage.

Hypercholesterolemia. Measurement of serum cholesterol levels every 5 years is recommended (grade A recommendation) for all men over age 35 and women over age 45 without other risk factors for coronary artery disease. Several large studies have shown that the risk of cardiovascular disease in persons with high cholesterol levels or low high-density lipoprotein (HDL) cholesterol levels can be lowered by 30% over 5–7 years by the use of cholesterol-reducing drugs. A screening test for dyslipidemia is recommended for younger adults as well if they have other cardiovascular risk factors (grade B recommendation). There is insufficient evidence at present to recommend lipid screening in children, adolescents, or young adults without other cardiovascular risk factors (grade C recommendation).

Screening consists of the determination of total cholesterol and HDL cholesterol levels. There is insufficient evidence to recommend the measurement of triglyceride levels. The optimal interval between screening tests has not yet been determined either. It would seem reasonable to measure cholesterol levels every 5 years, more frequently if the levels are elevated, and less frequently in persons with repeatedly normal levels and no other cardiovascular risk factors. No upper age limit for screening has been set to date. In principle, it seems reasonable to screen elderly persons who have not yet been tested, but current data suggest that repeated lipid screening in persons over age 65 without evident atherosclerosis is less useful. The likelihood of detecting atherogenic hyperlipidemia in such cases is low. In general, such patients should be counseled about cardiovascular risk reduction.

Coronary Heart Disease. Routine screening for coronary artery stenosis or coronary heart disease with electrocardiography (ECG), ergometry (stress testing), or imaging studies is not recommended in persons whose estimated coronary risk is low or nil (grade D recommendation). Certain ECG changes (e. g., ST depression, T wave inversion, pathologic Q waves, left axis deviation) do indicate the presence of coronary atherosclerosis, but these are nonspecific findings seen in only 1–4% of asymptomatic persons with coronary heart disease. A prospective study has shown that only 3–15% of persons with such changes will go on to develop symptomatic coronary heart disease. Though stress testing demonstrably yields more reliable results, its higher cost makes it a poor screening test. At present, there is in-

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sufficient evidence for a recommendation even in persons at elevated risk for coronary heart disease (grade I recommendation).

Breast Cancer. Regular (annual or biannual) mammography is recommended for all women aged 50–70. Several randomized studies have shown that screening of this type lowers the mortality from breast cancer by 17–35%. Manual examination is generally performed in addition to mammography. The evidence for a benefit from screening is less strong in women between 40 and 49 or over 70 years of age, so that recommendations are difficult in these age groups. A decision regarding mammographic screening should be made individually by each woman and her doctor in view of her risk profile and after discussion of the possible benefits and disadvantages such as false positive findings.

Interestingly, a recent study in women aged 50–59 revealed no reduction of mortality from annual mammography combined with manual examination of the breasts, compared to manual examination alone. These data and recent metaanalyses highlighting many methodological errors in screening procedures have reopened the debate about mammographic screening for breast cancer.

Perhaps women with a history of breast cancer in first-degree relatives should be screened at an earlier age. The probability of detecting a carcinoma by mammography is known to rise with age, particularly in women with a positive family history. The sensitivity of mammography, which also increases with age, has been found to be the same in women with and without a positive family history. There is no evidence showing that mammographic screening of younger women with a positive family history lowers mortality. Thus, no definitive judgment is possible at present.

Self-examination is less sensitive than mammography for the detection of carcinoma. There is no evidence for or against breast examination by manual palpation alone, or for or against patient education and instruction in self-examination, as screening methods for breast cancer.

Cervical Carcinoma. Screening for cervical carcinoma with a Papanicolaou (Pap) smear every 3 years is recommended for all sexually active women (grade A recommendation) and should be started no later than 3 years after sexual activity begins, or at age 21. Many cohort and case-control studies have shown that screening reduces the incidence of invasive cervical carcinoma by 20–30%. Routine screening is no longer recommended after age 65 if earlier Pap smears were all normal and if the patient is not at elevated risk for cervical carcinoma (grade D recommendation). In such cases, screening can do more harm than good. The same holds for routine Pap smears after total hysterectomy. There is as yet insufficient evidence to recommend the routine use of other screening procedures such as liquid-based cytology, testing for human papilloma virus (HPV), cervicography, and colposcopy.

Ovarian Carcinoma. Routine screening for ovarian carcinoma by the measurement of tumor markers (CA-125), regular gynecological examination, or pelvic ultrasonography is not recommended in the current guidelines. In a Norwegian retrospective study, sera from women who later went on to develop ovarian carcinoma were compared with sera from women who did not; the predictive sensitivity of CA-125 was found to be only 30–35%, and its specificity was low, so that there were many false-positive results. The use of CA-125 as a screening test would therefore lead to many unnecessary follow-up studies, some of them quite invasive, e. g., laparoscopy. This would generate considerable worry and risk among the women studied, as well as occasional complications and high costs. The evidence thus does not support screening for ovarian carcinoma in asymptomatic women, even those at elevated risk for the disease.

Colorectal Carcinoma. Colorectal carcinoma usually develops from a precursor lesion (adenoma) over the course of several years. The high incidence and prevalence of the disease, the fact that it is initially asymptomatic, and the improved survival with early detection all make colorectal carcinoma an ideal candidate for a screening test. Screening is currently recommended in all persons aged 50 and over (grade A recommendation). There are two screening methods: stool testing for occult blood and colonoscopy. Though sigmoidoscopy is often performed as a screening test for colorectal carcinoma in the USA, it is rarely used in Europe, where colonoscopy is preferred. Large-scale, randomized studies have shown a reduction of mortality through testing for occult blood, though it remains unclear to what extent mortality was additionally reduced by the large number of colonoscopies performed afterward. The quality of the evidence for colonoscopy as a sole screening method is still debated, because this question was only studied indirectly. It nonetheless seems to be at least as cost-effective as other screening methods. Thus, the optimal screening method, e. g., testing for occult blood in the stool, with or without sigmoidoscopy or colonoscopy, remains an open question.

More recently introduced screening methods, e. g., computed tomographic (CT) colonoscopy, have not yet been sufficiently studied for an evidence-based recommendation.

Lung Cancer. Routine screening for lung cancer with conventional radiographs or sputum cytology is not recommended in asymptomatic adults. The utility of both methods has been studied in smokers and nonsmokers. While carcinoma of the lung was indeed detected at an earlier stage, no reduction of mortality was achieved. At present, large-scale randomized studies are underway to determine the efficacy of screening with spiral CT.

Pancreatic Carcinoma. Screening for pancreatic carcinoma with abdominal palpation and an imaging study (ultrasonography, CT, or MRI) is not recommended in

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asymptomatic patients (grade D recommendation). Nor is the measurement of tumor markers (CA 19–9) suitable as a screening test. In a large study, more than 10 000 asymptomatic persons were screened by ultrasonography, with or without the additional measurement of CA 19–9 and elastase-1. Pancreatic carcinoma was found in only 1 of 200 individuals with positive test results. Nor is there any convincing evidence that early detection of pancreatic carcinoma reduces morbidity or mortality.

Case Finding

Case finding is the identification of specific risk factors for disease in individual patients. For the reasons discussed above, valid general recommendations for screening tests are hard to formulate. Only a few such tests can be unequivocally declared to be indicated or not indicated. Many are currently recommended on the basis of less than fully convincing evidence (grade C recommendation). The decision whether to use such tests in the individual patient is largely based on his or her risk profile.

Diabetes Mellitus. It is not clear whether the early recognition of type 2 diabetes with screening tests confers any benefit (grade I recommendation). The routine measurement of plasma glucose or HbA_{1c} concentration is insufficiently sensitive (21–75 % and 15–93 %, respectively) to be recommended in all patients. Nonetheless, the American Diabetes Association recommends screening for diabetes mellitus with plasma glucose (but not HbA_{1c}) measurement every 3 years in all patients aged 45 or over. Furthermore, screening followed by treatment (if indicated) is demonstrably beneficial in a number of high-risk groups, e. g., obese patients whose BMI exceeds 27 kg/m^2; persons with hyperlipidemia, arterial hypertension, polycystic ovaries, or a positive family history for diabetes; and members of certain ethnic groups (blacks, Asian-Americans) (grade B recommendation).

Thyroid Disease. The utility of routine thyroid function tests in the absence of symptoms of thyroid dysfunction is currently debated. Screening would seem to be beneficial because the symptoms of hyper- and hypothyroidism are nonspecific, yet the cost-effectiveness of screening has not been demonstrated.

Thyroid dysfunction, particularly hypothyroidism, is very common in women over 50 years of age, so one might imagine that screening would be useful in this group; yet the United States Preventive Services Task Force (USPSTF) does not recommend screening in either children or adults (grade I recommendation). Other professional societies, such as the American Academy of Family Physicians, the American Association of Clinical Endocrinologists, and the American College of Physicians, do recommend regular screening. The American Thyroid Association recommends periodic thyroid stimulating hormone (TSH) measurement every 5 years from age 35 onward. TSH measurement is a good screening test because of its high sensitivity and specificity. The utility of treating subclinical hypothyroidism was debated for many years, but it is now clear that many patients with subclinical hypothyroidism are already symptomatic, and that thyroxine substitution leads to clinical improvement and often also prevents the later development of overt hypothyroidism.

Prostatic Carcinoma. At present, the measurement of prostate-specific antigen (PSA) combined with digital rectal examination and followed by transrectal ultrasonography and biopsy (if indicated) is considered the most suitable method for the early detection of prostatic carcinoma, despite less than optimal sensitivity and specificity. The prevalence of prostatic carcinoma at autopsy is very high, and tumors smaller than 1 cm^3 often do not elevate the PSA level. Thus, carcinomas are sometimes discovered incidentally in the follow-up of an elevated PSA level that is actually due to prostatic hyperplasia. There are no data at present to support the contention that early treatment of prostatic carcinoma in the asymptomatic phase prolongs the patient's life or improves his or her quality of life. Even a positive finding on screening will not necessarily be followed by treatment: for example, the preferred management of a small, well-differentiated prostatic carcinoma may be further observation. Because prostatic carcinoma often has a very long asymptomatic phase, progresses slowly, and takes a variable course, the interpretation of clinical studies is likely to be hampered by leadtime and length bias. The USPSTF currently makes no recommendation for or against routine screening (grade I recommendation).

Hidden Agendas

Covert Motivation. Patients will often say they just want a checkup when their visit to the doctor is actually motivated by something else. The unstated motivation is called the "hidden agenda." The patient may have expectations, feelings, and fears that are not spontaneously communicated to the physician. The hidden agenda may be traceable to a psychiatric disorder requiring treatment, such as depression or anxiety disorder, or it may have to do with nonpsychiatric symptoms of many different kinds. Thus, the patient's reason for coming for a checkup will not necessarily coincide with the medical purposes of the various screening tests to be performed. The physician must realize this in order to deliver good medical advice and ensure patient

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satisfaction. On average, patients need only about 90 seconds to reveal their chief complaint. Allowing them enough time to do so is essential for the development of a good doctor–patient relationship.

Signs of a Hidden Agenda. Only 25 % of patients who present for a checkup understand the concept of screening tests for the early detection of as yet asymptomatic diseases. More than half of them, however, wish to discuss specific questions or concerns. Directed questioning will reveal mental problems of some type in 45 %. Thus, presentation for checkup itself constitutes a clinical situation with its own differential diagnosis. A small study has shown that these supposedly healthy patients often have symptoms, and psychosocial problems are common. Possible signs of an as yet undiscovered hidden agenda are:

- frequent changes of physician
- frequent consultations despite unchanged symptoms
- disproportionate functional impairment caused by relatively mild symptoms
- dissatisfaction with medical care
- a "difficult" patient
- various clues to the real reason for the consultation, e. g., presentation of a smoker for a checkup shortly after a near relative's death from lung cancer.

Addressing the Hidden Agenda. It is medically important to recognize and address a possible hidden agenda, be it a specific fear (e. g., when a near relative has just been found to have a specific disease) or, for example, the patient's desire for an HIV test. Recognition lets the physician dispense with unnecessary testing and enhances patient satisfaction. It also reduces the likelihood of false-positive test results and erroneous diagnoses, which might in turn lead to further, possibly dangerous tests, and to greater worry on the patient's part.

2.4 Important Subjective Complaints

Appetite

Causes of Anorexia. Loss of appetite (anorexia) has many causes:

- Anorexia is often *psychogenic* (stress, problems at home or at work). The severity of psychogenic anorexia ranges from a mere lack of desire to eat to total refusal of food (anorexia nervosa).
- *Gastrointestinal disease* often causes anorexia, e. g., carcinoma of the stomach (often combined with a specific aversion to meat), colon carcinoma, early hepatitis, and other liver diseases.
- Other causes include severe infection, decompensated heart failure, poorly controlled diabetes mellitus, Addison disease, hyperparathyroidism, chronic alcoholism, drug dependency, renal failure, radiotherapy, and various medications (cytostatic agents, appetite suppressants, digitalis).

A hearty appetite is usually taken as a sign of health, but it may be a sign of disease. Increased hunger may be due to hyperthyroidism, early diabetes mellitus, or malabsorption syndrome. A markedly increased appetite (polyphagia) often turns out to be psychogenic.

Amenorrhea

Pregnancy is the most common cause of amenorrhea and must therefore be ruled out before any other tests are performed. The defining criteria for amenorrhea requiring medical evaluation are listed in Tab. 2.**6**.

Table 2.**6** The definition of amenorrhea

1. No menstrual bleeding by age 14 and developmental delay with regard to height and/or secondary sexual characteristics (primary amenorrhea)
2. No menstrual bleeding by age 16 without evidence of developmental delay (primary amenorrhea)
3. Amenorrhea subsequent to normal menstruation (secondary amenorrhea) lasting longer than 3 normal menstrual cycles or longer than 6 months

Primary amenorrhea often has genetic or anatomical causes. Any cause of secondary amenorrhea can also produce primary amenorrhea. The most common causes of primary amenorrhea are listed in Tab. 2.**7**.

Secondary amenorrhea is usually due to pregnancy. Hypothalamic disturbances induced by mental stress, dieting, an altered daily routine, vigorous athletics, or an urgent desire for children can also cause secondary amenorrhea, usually on a transient basis. Other causes are listed in Tab. 2.**8**.

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Table 2.**7** Common causes of primary amenorrhea

- Chromosomal aberrations with gonadal dysgenesis (gonadal dysgenesis = Turner syndrome, testicular feminization)
- Ovarian pathology (polycystic ovaries = Stein–Leventhal syndrome)
- Physiologically delayed puberty
- Uterine or vaginal abnormalities (absence of vagina and uterus = Mayer–Rokitansky–Küstner syndrome, imperforate hymen with cyclical abdominal pain)
- Endocrine causes (adrenogenital syndrome, androgen-secreting adrenal tumors, Addison disease, hypothyroidism)
- Central disorders (pituitary tumors, craniopharyngioma, internal hydrocephalus)
- Anorexia nervosa

Table 2.**8** Causes of secondary amenorrhea

- Physiological (pregnancy, high-performance athletics, reducing diets, changes in circadian rhythm, stress)
- Hypothalamic–pituitary–ovarian axis (tumors, e. g., prolactinoma, Sheehan syndrome, premature menopause, ovariectomy, gonadotropin-resistant ovary)
- Uterine disorders (destruction of the endometrium by infection or extensive curettage after abortion or delivery)
- Other causes (hyper- and hypothyroidism, diabetes mellitus, exogenous androgens, adrenal tumors, psychotropic or other medications, contraceptive agents, illicit drugs)

Thirst/Polydipsia

Thirst is caused by:

- *intracellular dehydration,* when plasma osmolarity is increased in relation to intracellular osmolarity (hypertonic dehydration), or
- *extracellular dehydration,* when the extracellular volume (plasma volume) is abnormally low and there is a free water deficit (isotonic dehydration).

Both conditions lead to a rise of the antidiuretic hormone (ADH, vasopressin) concentration and stimulate the sensation of thirst.

The most important clinical conditions of which thirst is a leading symptom are the following:

- diabetes mellitus
- diabetes insipidus
- primary polydipsia.

Table 2.**9** Etiological classification of diabetes mellitus (WHO classification, 1998)

I	**Type 1 diabetes** – A autoimmune (β-cell destruction) – B idiopathic (without evidence of an autoimmune process; rare)
II	**Type 2 diabetes**
III	**Specific types** – genetic defect of β-cell function (MODY 1–6) – genetic defect of insulin effect (type A insulin resistance) – disease of the exocrine pancreas (pancreatitis, neoplasia, cystic fibrosis, hemochromatosis) – endocrinopathy (acromegaly, Cushing disease, pheochromocytoma) – drug-induced (steroids, pentamidine, nicotinic acid, thiazides) – infections (congenital rubella, cytomegalovirus) – rare types of immunogenic diabetes (stiff man syndrome) – other genetic syndromes associated with diabetes (Klinefelter syndrome, Turner syndrome)
IV	**Gestational diabetes**

Diabetes Mellitus

Clinical Features. Polydipsia and polyuria due to osmotic diuresis may be accompanied by other, less characteristic manifestations including weight loss, impaired cognitive performance, fatigue, visual disturbances, vulvar pruritus, balanitis, etc.

Prevalence and Etiology. Diabetes is the most common endocrine disorder, with a prevalence of 3–5 %. It is actually a group of metabolic disorders characterized by hyperglycemia. In the great majority of patients, diabetes mellitus is diagnosed in the asymptomatic stage by case finding (see above). Genetically determined deficiencies of insulin effect (insulin resistance) and/or insulin secretion, together with precipitating factors in the environment, lead to disturbances of glucose, lipid, and amino acid metabolism. The different etiologic types of diabetes mellitus include type 1 diabetes, type 2 diabetes, specific types of diabetes, and gestational diabetes (Tab. 2.**9**).

Definition of Diabetes Mellitus

Impaired glucose tolerance is said to be present when the fasting blood sugar is below 7.0 mmol/l (126 mg/dl) and a repeated measurement 2 hours after the oral administration of 75 g of glucose yields a value greater than 7.8 mmol/l (140 mg/dl), but less than 11.1 mmol/l (200 mg/dl).

"Elevated" Fasting Blood Sugar. Currently, there is a trend away from the diagnosis of "impaired glucose tolerance" and toward that of impaired fasting glucose, defined as a fasting plasma glucose (FBS) level between 6.1 and 7.0 mmol/L (110–126 mg/dL).

Epidemiologic studies have shown, however, that not all persons with impaired glucose tolerance, and a consequently higher risk of cardiovascular disease, will

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satisfy this definition. The expert group of the American Diabetes Association thus recommends lowering the range for the diagnosis of abnormal glucose homeostasis (impaired fasting glucose) to 5.6 mmol/L ≤ FBS < 7.0 mmol/L (100 mg/dL ≤ FBS < 126 mg/dL). Lowering the lower threshold, in this way, results in the "capture" of nearly all persons with impaired glucose tolerance.

The oral glucose tolerance test (OGTT) is used today mainly for the diagnosis of gestational diabetes, and otherwise only rarely and for highly specific indications (glycosuria of uncertain cause, peripheral neuropathy of uncertain cause, epidemiologic studies). OGTT should be performed according to a precisely standardized test protocol.

Type 1 Diabetes

Pathogenesis. Type 1 diabetes is caused by the selective autoimmune destruction of pancreatic β cells by cytotoxic T lymphocytes. Its autoimmune origin is manifest in a strong association with certain class II HLA traits (HLA-DR4, -DR3, -DQ8). Among type 1 diabetic patients, 85–90% have one or more autoantibodies against pancreatic islet cells (islet cell antibodies, ICA) or against β-cell-specific antigens (glutamic acid decarboxylase: GAD antibodies, tyrosine phosphatase: IA-2 antibodies). Autoantibody testing is indicated only when the diagnosis is unclear (e.g., in elderly patients whose clinical course resembles that of type 2 diabetes, for family testing, etc.). The autoantibodies are not directly responsible for the destruction of β cells but are merely an expression of the autoimmune process directed against them.

Clinical Features. Type 1 diabetes arises mainly, but not exclusively, in persons under 40 years of age, often after a flulike infection. Patients complain of polyuria and polydipsia, fatigue, weight loss of several kilograms within a few weeks, and visual disturbances (due to osmotic deposition of glucose and water in the lenses, which alters their refractive index); they are thin and dehydrated and tend to develop ketoacidosis. The family history is typically negative.

Type 2 Diabetes

Pathogenesis. Eighty percent of patients with diabetes mellitus suffer from type 2 diabetes. The clinical forms of this disorder are heterogeneous. The primary underlying lesion is insulin resistance, caused by a "postreceptor defect" that has not yet been fully characterized (presumably affecting intracellular glucose transport, insulin signal transduction, etc.). In addition to peripheral insulin resistance, patients with type 2 diabetes also have a diminished or absent first phase of insulin secretion, which can often be detected years before diabetes becomes clinically overt.

Clinical Features. Type 2 diabetes tends to cluster in families. Increasing age, weight gain, and sedentary lifestyle all tend to increase insulin resistance and to promote the onset of disease in predisposed persons. In addition to polyuria and polydipsia, further manifestations may include fatigue, recurrent skin infections, vulvar pruritus, balanitis, furunculosis, etc. The clinical features, however, are unreliable clues, as more than 50% of patients are asymptomatic at the time of diagnosis. The disease is often diagnosed on the basis of diabetic complications such as neuropathy, nephropathy, and coronary heart disease. In most cases, type 2 diabetes is associated with central obesity, arterial hypertension, and dyslipidemia (elevated triglyceride concentrations and low HDL cholesterol). Type 2 diabetes is a *metabolic syndrome* (insulin resistance syndrome) that confers an elevated risk of cardiovascular disease.

Specific Types of Diabetes

All types of diabetes that are due to a known, specific genetic defect (< 5% of all diabetics) or that arise as a complication of pancreatic or endocrine disease or of other well-defined syndromes are grouped together in the current WHO nomenclature as "specific types of diabetes" (WHO 1998).

Genetic Defect of β-Cell Function, MODY (maturity-onset diabetes of the young). Six types of MODY have been identified to date, each of which is due to a precisely characterized defect of glucokinase (MODY 2) or of a transcription factor (hepatic nuclear factor, HNF; insulin promoting factor 1, IPF-1). MODY is inherited in an autosomal dominant pattern and often becomes manifest by age 25. MODY 2 takes a mild course, but the other types can lead to severe complications and generally need to be treated with insulin.

Insulin Receptor Defects. Various point mutations of the insulin receptor have been identified (e.g., type A insulin resistance). This type of diabetes is usually accompanied by acanthosis nigricans, and patients have a very high insulin concentration in the blood.

"Secondary" Types of Diabetes. A diabetic metabolic condition can be induced by various endocrine diseases, by pancreatic disease, or by medications (e.g., protease inhibitors used to combat HIV infection).

Gestational Diabetes

The initial appearance of a diabetic metabolic condition during pregnancy is called gestational diabetes. Risk factors include overweight, a family history of diabetes, age over 30 years, and delivery of a macrosomal baby (i.e., one weighing over 4500 g) after an earlier pregnancy.

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Complications of Diabetes Mellitus

Chronic hyperglycemia produces the typical late complications of diabetes by a number of different mechanisms, including nonenzymatic protein glycosylation, activation of the sorbitol metabolic pathway, generation of hexosamines, production of free radicals, and intracellular activation of protein kinase C. Diabetic complications are classified as:

- *microvascular* complications (retinopathy, nephropathy, neuropathy)
- *macrovascular* complications (atherosclerotic changes in the coronary arteries and in the cerebral and peripheral vasculature)

Tight control of the serum glucose level, in order to achieve a state as close to normoglycemia as possible, has been conclusively shown to prevent microvascular complications and to slow their progression. The prevention of macrovascular complications, however, requires not only optimal glycemic control, but also strict control of the blood pressure (< 130/80 mmHg) and correction of dyslipidemia.

Patients with diabetes must be regularly examined for the presence of diabetic complications. Long-term monitoring of glycemic control is performed by measurement of the glycosylated hemoglobin (HbA_{1c}) concentration, which is an integrated index of the quality of glycemic control over the preceding 2–3 months.

Diabetes Insipidus

There are two types of diabetes insipidus, central (hypothalamic–pituitary) and renal (Tab. 2.**10**).

Table 2.**10** Causes of diabetes insipidus

Central (neurogenic) diabetes insipidus
– tumors (craniopharyngioma), cysts
– traumatic brain injury, pituitary surgery, stroke
– infectious and infiltrative diseases affecting the pituitary gland (histiocytosis X)
– familial
– idiopathic
Nephrogenic diabetes insipidus
– chronic renal disease
– chronic electrolyte disturbances (hypokalemia, hypercalcemia)
– congenital (V2 receptor and aquaporin gene defects)
– drug-induced (lithium, general anesthetics, antibiotics, foscarnet)

Central Diabetes Insipidus

Pathogenesis. Central (hypothalamic–pituitary) diabetes insipidus is caused by deficient or absent secretion of antidiuretic hormone (ADH, vasopressin) by the neurohypophysis. ADH secretion is normally stimulated by afferent impulses from the hypothalamic osmoreceptors and from the volume receptors in the carotid sinus and aortic arch. Depending on whether the ADH deficiency is partial or total, hypotonic urine is produced in a volume of 3–4 liters per day or 15–20 liters per day, with a specific gravity between 1.001 and 1.005 (20–50 mOsm/kg [= mmol/l]). The serum osmolarity is elevated, and the urine osmolarity is low.

Clinical Features. The clinical syndrome typically begins with the sudden onset of polyuria and polydipsia. These symptoms are usually present at night as well. As long as the patient can keep up an adequate water intake, there is no danger of dehydration. If the water intake is no longer adequate, however (e. g., if the patient cannot drink because of unconsciousness, or if he or she is subjected to an excessively prolonged fluid restriction test), life-threatening dehydration may ensue, with hemoconcentration and rapidly progressive confusion, fever, and shock.

Causes. Diabetes insipidus has multiple causes. It is usually due to a tumor (craniopharyngioma, lymphoma, pituitary tumor) or to an infiltrative, inflammatory, or infectious process affecting the hypothalamic–pituitary axis; it can also arise after pituitary surgery or traumatic brain injury. About 1–5 % of cases are familial, with autosomal dominant inheritance; these patients congenitally lack the neurons that synthesize vasopressin. The so-called idiopathic form of diabetes insipidus mainly arises in adolescence and adulthood and is also characterized by a reduction in the number of vasopressin-secreting neurons. Autoantibodies against these neurons can be demonstrated in 30 % of patients with this form of the disease (autoimmune diabetes insipidus).

Diagnosis. Patients with diabetes insipidus, unlike normal individuals or persons with psychogenic polydipsia, will continue to produce hypotonic urine when subjected to a fluid restriction test. Once vasopressin is given by the subcutaneous or nasal route, the urine volume rapidly diminishes, and the urine osmolarity rises.

Renal Diabetes Insipidus

Pathogenesis. Renal (nephrogenic) diabetes insipidus is characterized by inadequate responsiveness of the renal tubules to ADH.

- The rare *congenital type* is due to a defect in the vasopressin receptor gene (V2 receptor) and is found with familial clustering in men. Thus, an X-chromosomal recessive inheritance pattern is suspected, though

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Table 2.**11** Differential diagnosis of polyuria

Laboratory findings	Central diabetes insipidus	Nephrogenic diabetes insipidus	Psychogenic polydipsia
Plasma osmolarity	↑	↑	↓
Urine osmolarity	↓	↓	↓
ADH concentration (plasma)	↓	normal/ ↑	↓
Urine osmolarity in fluid restriction test	↔	↔	↑
Urine osmolarity after ADH injection	↑	↔	↑

girls with the disease have also been described. Congenital diabetes insipidus can also be due to a defective gene for aquaporin-2 (a water channel in renal tubular cells).

➤ The *acquired type* of nephrogenic diabetes insipidus is usually due to chronic renal disease (pyelonephritis, polycystic kidney disease), chronic electrolyte disturbances (hypokalemia, hypercalcemia), or the use of medications such as lithium, amphotericin, colchicine, methoxyfluorane, foscarnet, etc. Rarer causes are sickle cell anemia, Sjögren syndrome, amyloidosis, and multiple myeloma.

Primary Polydipsia

Primary polydipsia is the most common cause of pathologically increased thirst, aside from diabetes mellitus. The thirst is primary, the polyuria secondary. This condition can be distinguished from diabetes with a fluid restriction test (Tab. 2.**11**).

Causes. Compulsive drinking (psychogenic polydipsia or dipsomania) is nearly always due to mental illness (neurosis, incipient psychosis), and only rarely to organic brain disease. Pathological thirst can also be produced by medications such as thioridazine (Melleril), chlorpromazine, and anticholinergic drugs causing dry mouth.

Clinical Features. Patients with primary polydipsia feel a markedly elevated need to drink and often drink more than 5 liters of water per day. Unlike patients with diabetes insipidus, they do not need to drink as much at night, and circadian fluctuations in fluid intake are typical. The serum osmolarity is low (around 270 mOsm/kg [= mmol/l]), and the urine osmolarity is also low.

Vomiting

Vomiting, often combined with nausea, is a common symptom in everyday clinical practice. Its potential causes lie not only in the gastrointestinal system, but in other organ systems as well (Tab. 2.**12**). The term "chronic vomiting" refers to vomiting that persists for 4 weeks or more.

Definition. The term "vomiting" refers, not to the mere regurgitation of swallowed food (nonacidic pH), but to the upward propulsion of gastric, and possibly also duodenal, contents out of the gastrointestinal tract by rapid contractions of the abdominal and diaphragmatic musculature.

The etiology of vomiting can usually be determined from the history and physical examination. Its precise clinical characteristics generally provide the key to the diagnosis (Tab. 2.**13**).

Complications. Vomiting may be complicated by lacerations of the gastroesophageal junction (Mallory–Weiss syndrome), aspiration, hypokalemic metabolic alkalosis, or cardiac arrhythmia.

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Table 2.**12** Causes of vomiting

Abdominal causes
- reflux esophagitis, achalasia
- (alcoholic) gastritis, gastroenteritis (bacterial, viral, parasitic)
- peptic ulcer (rare)
- malignancy (e. g., gastric retention in gastric carcinoma)
- Crohn disease
- diseases of the gall bladder (cholecystitis), liver, and pancreas (acute pancreatitis)
- appendicitis, peritonitis
- food intolerance or allergy
- diabetic gastroparesis, ileus (e. g., adhesions, mesenteric infarct, tumor)
- pyloric stenosis (in neonates), pyloric spasm

Central causes
- intracranial hypertension (in waves, usually without nausea), head trauma, brain tumor
- encephalomalacia
- migraine
- acute rotational vertigo, e. g., in Ménière disease (vertiginous attacks)

Metabolic causes
- early pregnancy (first trimester)
- uremia, electrolyte disorders
- diabetic coma, hepatic coma
- Addison disease, hyperparathyroidism, thyrotoxicosis
- hypertensive encephalopathy

Medications and illicit drugs
- digitalis intoxication
- NSAID
- steroids, estrogens
- cytostatic agents
- iron sulfate, potassium chloride
- aminophylline, antibiotics, levodopa
- opiates, alcohol, many other substances

Other causes
- psychiatric disturbances (bulimia, anorexia nervosa, depression, psychogenic vomiting)
- cardiac causes (biventricular heart failure, myocardial infarction [posterior wall])
- heavy metal poisoning, radiation
- infectious diseases (pneumonia, pyelonephritis, pelvic inflammatory disease, sepsis)
- postoperative vomiting

Table 2.**13** The significance of clinical features of vomiting

Features of vomiting	Possible causes
Early morning hours (vomitus matutinus)	Pregnancy (first trimester), alcohol abuse, depression, uremia
Shortly after eating	Ulcer disease, gastritis, gastric carcinoma, psychogenic
In waves	Intracranial hypertension, gastric outlet obstruction
Only symptom for years	Psychogenic
Acidic mucus, food residue	Gastritis, gastric carcinoma
"Bilious"	Postoperative, gastrectomy
"Putrid"	Gastric outlet obstruction
"Feculent"/"fecal" (miserere)	Ileus

Infertility

A couple is called infertile when conception has not occurred despite regular, unprotected sexual intercourse. Infertility may be caused by a medical problem affecting either partner or both.

Causes. Some factors that commonly impair fertility are: relatively advanced age of the female partner, exposure to sexually transmitted diseases, environmental factors, toxic substances, and medications (e. g., cytostatic agents, spironolactone, cimetidine, sulfasalazine).

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Many infertile men have oligospermia or azoospermia because of primary or secondary hypogonadism. Disturbances of spermatogenesis are usually due to testicular disorders (absence or atrophy, post-infectious after mumps, traumatic), or to Klinefelter syndrome.

The common causes of infertility in women are ovulatory dysfunction, pathological changes in the oviducts, and endometriosis. No cause is found in about 30% of cases. Other, less common causes of female infertility include coital problems and cervical factors.

Hemoptysis

Definition. "Hemoptysis" means "coughing up blood," whether the sputum is merely lightly blood-tinged or large quantities of blood are expectorated. Blood loss in large amounts (100–600 ml in 24 hours) is usually due to tuberculosis, bronchial carcinoma, or bronchiectasis.

Causes. The common causes of hemoptysis nowadays are acute and chronic bronchitis, bronchial carcinoma, and pneumonia (Tab. 2.**14**). The cause cannot be determined in about 30% of cases. Pulmonary metastases rarely cause hemoptysis.

Table 2.**14** Causes of hemoptysis

Infectious/inflammatory causes
- bronchitis, pneumonia
- bronchiectasis
- tuberculosis
- lung abscess

Tumors
- bronchial carcinoma, bronchial adenoma

Other causes
- pulmonary embolism
- left heart failure, mitral stenosis
- traumatic (foreign body aspiration, blunt thoracic trauma)
- rare: vascular malformation, vasculitis, Wegener granulomatosis, Goodpasture syndrome, idiopathic pulmonary hemosiderosis, pulmonary endometriosis, aortic aneurysm eroding into the bronchial system, bleeding diathesis

Cough

Pathogenesis. Cough is a complex physiological reflex induced by chemical or mechanical irritation. It cleans the bronchi and serves as a protective mechanism against injury from toxic inhalable substances.

Clinical Features and Differential Diagnosis. The distinction between acute and chronic cough is important for clinical classification, differential diagnosis, and treatment.

- *Acute cough* (lasting less than 3 weeks) can arise at any age and is usually caused by an upper respiratory infection, usually viral, less commonly bacterial. Pneumonia only rarely causes acute cough. The symptoms are self-limited and usually do not require diagnostic evaluation or treatment.
- *Chronic cough* (lasting more than 3 weeks) is a difficult problem in differential diagnosis (Tab. 2.**15**).

Table 2.**15** Differential diagnosis of chronic cough

Frequency	Adults	Elderly patients
Common	– smoking – chronic bronchitis/ bronchial asthma – gastroesophageal reflux – postnasal drip syndrome	– smoking – chronic bronchitis – postinfectious
Rare	– bronchial carcinoma – tuberculosis – bronchiectasis – pneumonia – interstitial pneumopathy – psychogenic – foreign body aspiration – cystic fibrosis	– bronchial carcinoma – heart failure – asthma – aspiration – tuberculosis – pneumonia
Iatrogenic	– ACE inhibitors – steroid aerosols	– ACE inhibitors

The clinical features of cough provide important diagnostic clues:

- *Productive cough* expels retained secretions and is a useful protective mechanism in acute and chronic inflammatory diseases of the lungs. The most common cause of productive cough is bronchitis. The color, odor, and consistency of the secretions or sputum should be noted (Tab. 2.**16**).
- *Non-productive, irritative cough* is due to irritation of the airway mucosa by a mechanical, chemical, or thermal stimulus.
  - Mechanical causes include dust inhalation, pressure on the airway from within due to a tumor, foreign body, or granuloma or from outside due to a tumor, metastasis or aortic aneurysm, and trac-

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Table 2.**16** Clinical features and etiology of productive cough

Secretion/Sputum	Causes
Yellowish-green, purulent	Chronic bronchitis, pneumonia, pulmonary tuberculosis, tumor, mucoviscidosis
Purulent, large amounts, putrid odor (anaerobes)	Lung abscess, bronchiectasis, decomposing tumor
Frothy, reddish-tinged	Pulmonary edema, pneumococcal pneumonia
Viscous, voluminous, frothy	Alveolar cell carcinoma

tion on the lung parenchyma due to a tissue-contracting process (fibrosis, atelectasis).
  - Chemical causes include various gases (ammonia, tear gas) and tobacco smoke. Irritative cough is a possible side effect of treatment with angiotensin converting enzyme (ACE) inhibitors.
  - Thermal causes include hot and cold air.
- *Pharyngeal cough* (throat-clearing) is usually due to pharyngitis or to an annoying buildup of mucus in the back of the throat. It can also be a nervous phenomenon.
- *Barking or crouplike cough* (hoarse, pitchless) implies involvement of the epiglottis or larynx.
- *Paroxysmal cough* followed by a deep, stridorous inspiration is typical of pertussis (whooping cough).
- *Nocturnal cough* may be due to left heart failure (asthma cardiale).
- *Morning cough* is typical in bronchiectasis and chronic bronchitis.
- *Repetitive coughing during or shortly after meals* may be a sign of hiatus hernia, an esophageal diverticulum, or neurogenic dysphagia.

The additional symptoms that accompany cough may provide further clues to the differential diagnosis:
- *Retrosternal pain on coughing* may be a sign of viral tracheobronchitis (influenza).
- *Weakness and weight loss* are seen in tuberculosis, malignant disease, and recurrent pneumonia due to bronchiectasis.
- *Cough-induced syncope* can occur during paroxysmal coughing attacks. It is due to a transient elevation of the intrathoracic pressure, which, in turn, decreases the venous return to the heart and thus also the left ventricular output.

Fatigue

Fatigue is a subjective feeling of tiredness and lack of energy during or after physical activity, or an aversion to physical activity. It is a nonspecific symptom with many possible causes and is thus difficult to define in general terms. It is important to distinguish fatigue from somnolence, dyspnea, and weakness; all of these symptoms are distinct from fatigue, though they may be accompanied by it. Among patients seen in a general office practice 20–30% complain of fatigue. Chronic fatigue is defined as fatigue lasting longer than 6 months.

Causes. Fatigue affects women more commonly than men. An organic cause is found in only 2–5% of cases (Tab. 2.**17**).

"Chronic fatigue syndrome" (CFS) is diagnosed (after the exclusion of mental or organic illness or drug addiction) when the patient has suffered from clinically confirmed fatigue of undetermined origin for more than 6 months and also has certain other symptoms (see Chapter 4 for details). About 2% of patients complaining of fatigue meet the criteria for CFS.

The most common cause of fatigue is an affective disorder, usually depression or anxiety disorder. Often, no cause can be identified; in such cases, a presumed psychosocial cause should be sought (e. g., at the workplace or in the patient's family life).

Diagnosis. The history (including the social, occupational, and family history) and physical examination yield a diagnosis in about 80% of patients. A reasonable battery of laboratory screening tests includes a complete blood count, sodium, potassium, calcium, glucose, creatinine, alanine aminotransferase (ALAT), TSH, urinalysis, erythrocyte sedimentation rate, and chest radiograph. Further workup may be indicated in special clinical situations (e. g., HIV testing or other serological or imaging studies).

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Table 2.**17** Causes of fatigue

Cause/etiologic category	Particular disorders
Psychiatric causes	Depression, anxiety disorder, somatoform disorder, eating disorder
Psychosocial stress situation (reactive)	Stress, overwork, relationship difficulties, illness in the family, not enough sleep
Hematologic	Anemia, leukemia
Endocrine	Hypothyroidism, Addison disease, Cushing syndrome, hypopituitarism, diabetes mellitus
Electrolyte disturbance	Hypokalemia, hypercalcemia
Infectious	Hepatitis, endocarditis, tuberculosis, mononucleosis, parasites, HIV
Malignant	All malignant tumors
Cardiovascular	Heart failure, hypotension
Pulmonary failure	Chronic obstructive pulmonary disease, chronic lung diseases
Metabolic	Chronic renal failure, chronic hepatic failure
Medications	Sedatives, opiates, antidepressants, antihypertensive drugs
Insomnia	Sleep apnea syndrome, gastroesophageal reflux, allergic rhinitis
Myopathy	
Neurological	Dementia, delirium

Palpitations

The heartbeat is normally not consciously felt. The term "palpitations" refers to an awareness of the heartbeat that the patient finds unpleasant or abnormal. Palpitations are very common and usually cause worry. Nonetheless, this symptom does not in itself imply the presence of an arrhythmia. Its initial differential diagnosis is mainly based on the history, which indeed, often suffices to establish the diagnosis definitively. The basic evaluation includes a history, physical examination, and 12-channel ECG.

Causes. The differential diagnosis of palpitations is broad and depends on the patient's age (Tab. 2.**18**). Current evidence suggests that 7–40% of patients have a potentially dangerous arrhythmia, and the cause is psychiatric in 30%.

Table 2.**18** Causes of palpitations

Cardiac causes
- cardiac arrhythmia (any type)
- valvular heart disease
- cardiomyopathy
- pacemaker
- atrial myxoma
- intracardiac shunt

Psychiatric causes
- anxiety disorder, depression
- functional cardiac complaints (effort syndrome, Da Costa syndrome, soldier heart)

Metabolic causes
- hyperthyroidism
- pheochromocytoma
- hypoglycemia
- mastocytosis

Medications/other substances and illicit drugs
- sympathomimetic agents
- vasodilators
- discontinuation of a β-blocker
- anticholinergic agents, hydralazine
- cocaine, amphetamines, alcohol, caffeine, nicotine

High output states
- anemia
- fever
- pregnancy
- hyperthyroidism
- aortic or mitral valvular insufficiency

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Insomnia

The widespread notion that everyone needs 8 hours of sleep each night is false. The actual sleep requirement varies very widely among individuals.

Sleep History. The general review of systems should include a few specific screening questions about possible disturbances of the sleep–wake cycle. These questions can be divided into two groups:

- Questions about *sleep*:
  - sleep duration and quality (restorative?)
  - difficulty falling asleep or difficulty staying asleep
  - snoring (loud? every night? in every position?), respiratory pauses
  - talking/shouting in one's sleep, sleepwalking
  - enuresis/nocturia
  - grinding of teeth (bruxism), twitching during sleep (usually in the legs), acting out of dreams
  - injuries during sleep
  - hallucinations/nightmares
  - sleep paralysis (= total inability to move despite full awareness)
- Questions about *wakefulness*:
  - daytime fatigue, excessive daytime sleepiness (i. e., tendency to fall asleep)
  - "sleep attacks," loss of muscle tone induced by emotion (cataplexy)
  - abnormal sensations in the legs and compulsive leg movements in resting situations/in the evening (restless legs syndrome).

The distinction between fatigue and excessive daytime sleepiness is important (though not always easy), because the former is usually of mental origin, and the latter is usually organic. The Epworth Sleepiness Score may be helpful in distinguishing these two conditions. Patients who spontaneously complain of problems relating to the sleep–wake cycle or give positive answers to the screening questions above should, of course, be asked about their symptoms in greater detail.

Insomnia. Insomnia (sleep disturbance) is often a complex matter, and the term means different things to different patients. The prevalence of insomnia in the industrialized nations is 30–40%. An attempt should always be made to discover its etiology as this will determine the treatment (Tab. 2.**19**).

Table 2.**19** Differential diagnosis and clinical features of insomnia

Causes	Conditions	Features
Mental illness	Depression (very common), neurosis, affective psychosis, schizophrenia (rare), anxiety disorder	Usually difficulty falling asleep
Reactive insomnia due to stress	Psychosocial stress, shift work, lack of opportunity to sleep comfortably, noise, nightmares (due to stress, β-blockers, or ketamine), pavor nocturnus	Usually transient
Medications and other substances	Caffeine, discontinuation of hypnotics, alcohol abuse (impaired REM sleep), nicotine, stimulants (amphetamines, ecstasy, methylphenidate), steroids	Beware of self-administered medications (take a thorough history!)
Organic illness	Central nervous system diseases Heart failure Pulmonary diseases Prostatic hyperplasia Pain Neurological diseases Obstructive sleep apnea syndrome (less commonly, central sleep apnea syndrome)	Dementia, brainstem and diencephalic disorders Dyspnea, orthopnea, nocturia Coughing, dyspnea Pollakisuria Musculoskeletal, duodenal ulcer, malignancy, reflux esophagitis Carpal tunnel syndrome, restless legs syndrome, headache Loud snoring with nocturnal respiratory pauses, neck circumference usually > 42 cm, daytime fatigue
Primary insomnia	No identifiable cause	Nonrestorative sleep for many years, frequent awakening, shortened REM phases

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Dysphagia

Dysphagia is defined as difficulty swallowing, including the occurrence of unpleasant sensations during swallowing (pain on swallowing is called odynophagia). Dysphagia has may causes (Tab. 2.**20**). The clinical history alone suffices to establish the diagnosis in 80% of patients.

Rule of thumb: dysphagia for solid food is commonly due to organic stenosis of the esophagus, while dysphagia for both solids and liquids is commonly due to impaired esophageal motility (see Chapter 26).

Table 2.**20** Causes of dysphagia

Localization	Causes	Clinical features
Oropharnygeal (swallowed material goes down wrong pathway)	– *Neuromuscular* bulbar palsy, stroke, myasthenia gravis, Parkinson disease, brainstem tumor, amyotrophic lateral sclerosis, multiple sclerosis, post-infectious (poliomyelitis, syphilis), poly- or dermatomyositis – *Mechanical* mediastinal tumor, dysphagia lusoria, goiter, Plummer Vinson syndrome, dry mouth, Zenker diverticulum – *Infectious/inflammatory* glossitis, esophagitis – *Neoplastic* cancer of the tongue	Immediate regurgitation, aspiration
Esophagus	– *Odynophagia* esophagitis, esophageal ulcers – *Mechanical* stenosing tumors or membranes (scleroderma), foreign body, spasm, achalasia	Pain along the esophagus as food passes through; retrosternal pressure
Stomach	– Hiatus hernia, tumor	

Hiccups

Hiccups (singultus) are usually transient and harmless. They consist of audible, very rapid inspirations that are produced by sudden and involuntary contraction of the diaphragm and terminated by abrupt closure of the glottis.

Causes. Usually no specific cause is found. Benign, transient episodes of hiccupping are mostly due to gastric distention after a large meal, swallowing air (aerophagia), or carbonated drinks. Other causes include sudden stress, excessive alcohol consumption and very commonly, gastroesophageal reflux. Persistent, intractable hiccups may be due to a serious illness.

- *Peripheral causes* include, for example, processes affecting the diaphragm (subphrenic abscess, cholecystitis, gastric distention, hiatus hernia). Dysphagia combined with hiccups may be due to a distal esophageal carcinoma. Mediastinal tumors, hilar tumors, mediastinitis, pleuritis, and pericarditis are not uncommon causes of hiccups.
- *Central causes* include uremia, encephalitis, brain tumor, encephalomalacia, tabes dorsalis, and opiate addiction.

Pain

Pain is far and away the most common symptom that brings patients to the physician. Its cause is often obvious, but its correct diagnosis and treatment will sometimes pose a difficult problem, particularly if it is chronic. Pain is inherently subjective; one patient's perception of pain cannot be compared to that of another. Psychological, cultural, and educational influences can all modulate the patient's sensitivity to pain either upward or downward. Painful complaints are very often an essential component of the process of differential diagnosis. They are thus discussed in the remaining chapters in the context of the individual conditions that produce them.

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Superficial and Visceral Pain. Superficial pain (in the skin and superficial anatomical structures) is typically precisely localizable and of sharp, stabbing character. Visceral pain (in the internal organs and musculoskeletal system) is imprecisely localizable and may radiate into neighboring areas and dermatomes. It is typically dull, aching, or cramplike.

Neuropathic Pain is due to damage of the nociceptive nerve pathways. Common types of neuropathic pain are neuralgias, dysesthesias, hyperesthesias, and the often symmetrical pain of peripheral neuropathy. Neuropathic pain tends to respond poorly to conventional analgesic medications (aspirin, nonsteroidal antiinflammatory drugs, opiates).

Sexual Dysfunction

Erectile dysfunction (impotence) becomes more prevalent with advancing age and affects a third of all men over age 65. An organic cause can be found in about 90% of cases (Tab. 2.**21**). Any complaint of erectile dysfunction should, therefore, be evaluated for a treatable cause. Psychological causes account for the remaining 10% of cases, though this, of course, does not mean the patient cannot have problems of both types at once.

Table 2.**21** Causes of erectile dysfunction

Atherosclerosis (80%) and its risk factors
– smoking
– arterial hypertension
– diabetes mellitus
– positive family history of cardiovascular disease
– dyslipidemia
Endocrine (5%)
– hypothalamic–pituitary–gonadal axis
– thyroid diseases (hyper- and hypothyroidism)
– adrenal and other hormone-secreting tumors
– hepatic diseases
Neurogenic
– trauma
– infection/inflammation
– tumor
– paresis
– multiple sclerosis
Medications
– antihypertensive drugs (β-blockers, diuretics)
– psychotropic drugs (antidepressant, neuroleptic, hypnotic, and tranquilizing agents)
– anticonvulsants
– anti-inflammatory drugs
– opiates, drugs of abuse (marijuana, heroin, alcohol)
– hormone preparations, steroids
– anticholinergic drugs
Psychogenic (10%)
– depression
– relationship conflicts
– anxiety
Genital disorders
– phimosis
– induratio penis plastica
– tumors

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3 Skin and External Appearance

S. Lautenschlager, M. Battegay, and G.A. Spinas

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The correct interpretation of changes in the skin, its auxiliary structures, and the neighboring mucous membranes furnishes important clues to the presence of systemic disease. It is not uncommon for the cutaneous manifestations of systemic disease to appear before the disease process causes symptoms in its major target organs. Thus, skin changes often serve as important premonitory markers of disease. Many types of cutaneous abnormality, however, can be caused by a wide variety of systemic conditions and thus pose difficult problems of differential diagnosis (e. g., skin calcifications, purpura).

3.1 Skin

Method of Examination

The specialized clinical examination in dermatology, unlike that in most other medical disciplines, begins right away with inspection of the organ in question, i. e., the skin. First, the site of the primary pathological process is identified (epidermis, dermis, subcutis, vessels). Its extent is then determined by inspection of the entire body. Once the main clinical characteristics of the process have been determined, it can be further classified according to type, shape, pattern, and distribution. A definitive diagnosis is sometimes not possible until a follow-up visit some time later, when the characteristic evolution of the process can be observed. Just as important as the physical examination is a precise history, with a description of how and when the cutaneous process first appeared, and how it evolved thereafter.

Clinical Findings

The following sections deal with specific kinds of skin lesions and the possibly underlying systemic illnesses in the differential diagnosis of each.

Skin Color

Skin color depends not only on skin pigmentation (melanin, carotenoids) but also on the hemoglobin concentration of the blood and the degree of perfusion of the skin.

Pallor

Pale skin (Fig. 3.**1a**) may be due to an inherited light complexion, but is also a characteristic sign of anemia. Normal skin, of course, has a highly variable melanin content (Fitzpatrick skin types I–VI), and therefore the color of the mucous membranes is a more reliable indicator of anemia than skin color. In pernicious anemia, the skin usually has a pale yellowish hue. In renal failure, it is often not only diffusely pale, but also mildly edematous. In diffuse myxedema due to hypothyroidism, the skin is markedly dry, sallow, waxen, and bloated, particularly in the acral regions. In hypopituitarism, the skin is alabaster white.

Redness

A combination of prominent redness of the face (Fig. 3.**1b**) and conjunctival injection suggests the presence of either polycythemia vera or some type of secondary erythrocytosis. Any accompanying cyanosis suggests that the latter is more likely. Facial erythema is often also seen in alcohol abuse, Cushing disease (moon facies), and arterial hypertension. Some typical findings in other conditions include facial redness mainly in the cheeks in diabetic rubeosis, facial flushing in carcinoid syndrome (cf. Chapter 27), and the red cheeks and cyanotic lips of mitral stenosis (so-called mitral facies).

Periorbital livid edema is highly characteristic of dermatomyositis. Rapidly developing skin erythema accompanied by abnormal warmth may be due to erysipelas or to Melkersson–Rosenthal syndrome. Erythema with edema is seen in dermatomyositis and also in trichinosis.

Discoloration

Yellowish skin discoloration (Fig. 3.**1c**) is seen not only in hepatic disease, but also in hemolytic anemias and pernicious anemia. Carotenemia produce a similar picture but without yellowing of the sclerae. A brown-black pigmentation is seen in ochronosis, while yellowish-green discolorations result from biliary cirrhosis or bile duct carcinoma.

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a **b** **c**

Fig. 3.**1** Typical skin color in:
a anemia,
b polycythemia, and
c jaundice.

Disturbances of Pigmentation

Most systemic illnesses that alter skin pigmentation do so by changing the melanin content of the skin.

Depigmentation/Hypopigmentation. Generalized, diffuse, or local diminution of skin pigmentation can be caused by any of the following:

- *Genetic causes.* Vitiligo (focal, segmental, acral, or generalized). Possibly associated illnesses include diabetes mellitus, thyroid diseases, and pernicious anemia. Tuberous sclerosis produces characteristic leaf-shaped amelanotic macules on the trunk and buttocks.

Fig. 3.**2** Café-au-lait spots and neurofibromas in neurofibromatosis (von Recklinghausen disease).

- *Chemical and physical causes, including medications.* Local treatment with corticosteroids or with hydroquinone and its derivatives, burns, radiotherapy, cryotherapy, and local trauma can often cause circumscribed hypopigmentation of the skin.
- *Postinflammatory hypopigmentation.* Transient hypopigmentation is seen in the freshly healed lesions of psoriasis, eczema, and lichen ruber planus, and less commonly in chronic cutaneous lupus erythematosus (scarred stage), sarcoidosis, syphilis (leukoderma specificum), and tuberculoid leprosy. Other causes of localized hypopigmentation include subacute prurigo (shoulder girdle, limbs) and white atrophy (legs).
- *Endocrine causes.* Addison disease and hyperthyroidism are rare causes of localized hypopigmentation.
- *Pityriasis versicolor alba.* Mainly on the trunk.
- *Congenital localized depigmentation.* Nevus anemicus, nevus depigmentosus.

Hyperpigmentation. Melanin, the most important skin pigment, is synthesized in melanocytes and deposited in keratinocytes. Changes in the number of melanocytes and functional disturbances of melanin synthesis and melanin transport make the skin lighter or darker. The main causes of hyperpigmentation are summarized in Tab. 3.**1**. It is important to distinguish diffuse from circumscribed types.

- *Neurofibromatosis (von Recklinghausen disease):* the presence of more than six café-au-lait spots is pathognomonic for this disease (Fig. 3.**2**).

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Table 3.**1** Causes of skin hyperpigmentation

Genetic causes Neurofibromatosis (von Recklinghausen disease), xeroderma pigmentosum, Peutz–Jeghers syndrome, Cronkhite–Canada syndrome, Albright syndrome, freckles, congenital dyskeratosis, Fanconi syndrome
Chemical, medication-induced, and physical causes Antiovulatory drugs (melasma), cytostatic agents (bleomycin can cause hyperpigmented striae), chlorpromazine, arsenic, antimalarial drugs, phenytoin, minocycline, amiodarone, phenothiazides, gold (chrysiasis), silver (argyrosis), clofazimine, UV light, burns, ionizing radiation, chronic trauma, Berloque dermatitis
Endocrine disorders Addison disease, post adrenalectomy status (Nelson syndrome), pituitary tumors, hyperthyroidism (rare), estrogen therapy, adrenocorticotropic hormone (ACTH) therapy, paraneoplastic melanocyte-stimulating hormone (MSH) production
Metabolic diseases Hemochromatosis, porphyria cutanea tarda, Wilson disease, Gaucher disease, Niemann–Pick disease, macular amyloidosis
Infectious and inflammatory diseases/postinflammatory hyperpigmentation Lichen planus, lupus erythematosus, psoriasis, herpes zoster, leg ulcers, malaria, persistent drug exanthem
Tumors Malignant melanoma (metastatic disease can cause generalized hypermelanosis), urticaria pigmentosa (generalized mastocytosis), paraneoplastic (acanthosis nigricans)
Other causes Whipple disease, hepatic cirrhosis, sprue, vitamin B_{12} deficiency, chronic malnutrition, kwashiorkor, chronic interstitial nephritis

Fig. 3.**3** Acanthosis nigricans in insulin resistance.

- *Acanthosis nigricans* is characterized by areas of velvety, grayish-black, partly hyperkeratotic and papillomatous skin change, which are mainly found in skin folds (e. g., the axillae) (Fig. 3.**3**). This condition is sometimes seen in obese adolescents (as a marker for an elevated insulin concentration) and in certain endocrine diseases, but, when it appears in an adult, it is usually due to a malignant tumor, most often an adenocarcinoma of the bowel.
- *Albright syndrome* consists of the classical triad of hyperpigmentation (typically in sharply but irregularly demarcated areas of skin), precocious puberty, and fibrous bone dysplasia. It most often affects young girls. Radiography reveals multiple cystic abnormalities in the long bones, skull, and pelvis.
- *Mastocytoses* are a group of diseases characterized by mast cell proliferation. Purely cutaneous mastocytosis is called urticaria pigmentosa. Systemic mastocytosis can additionally involve bone (osteosclerosis, osteomalacia) as well as the liver, spleen (hypersplenism with thrombocytopenic purpura), and gastrointestinal tract. It does not necessarily involve the skin, though it sometimes produces "pruritus sine materia," i. e., itching without any visible skin lesion.

Urticaria pigmentosa is grossly divided into juvenile and adult types. The *juvenile* type very rarely involves the internal organs and resolves spontaneously within a few years of onset. The *adult* form is characterized by brownish-red, macular, or maculopapular generalized eruptions, occasionally accompanied by telangiectasias (telangiectasia macularis eruptiva perstans) (Fig. 3.**4**); it does not resolve spontaneously. The individual lesions are about 5 mm in diameter and usually round. When they are mechanically stimulated by rubbing, histamine is released from the mast cells and produces severely itching hives (Darier sign) (Fig. 3.**5**). In about one third of adult patients, the internal organs are also infiltrated with mast cells. In these patients, episodes of generalized histamine release produce a so-called histamine flush, i. e., a dark red exanthem in the upper half of the body that may persist for as long as 30 minutes. Histamine flushes are often accompanied by systemic manifestations such as vomiting, diarrhea, abdominal colic, and hypotension ranging to shock, as well as nausea, fever, and shaking chills. An important point for differential diagnosis is that the flushes associated with carcinoid syndrome have a more cyanotic color than histamine flushes and usually last no longer than 10 minutes.

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Fig. 3.**4** Urticaria pigmentosa of the type telangiectasia macularis eruptiva perstans.

Fig. 3.**6** Erythema migrans.

Fig. 3.**5** Urticaria pigmentosa after manual stimulation (positive Darier sign).

The following are all signs of systemic involvement: skeletal changes (foci of osteosclerosis and osteoporosis), hepatosplenomegaly, malabsorption syndrome, bone marrow infiltration, eosinophilia, anemia, leukopenia, and thrombocytopenia.

Disseminated brownish-red papules with a negative Darier sign are most likely due to another condition. The differential diagnosis includes melanocytic nevi, lentiginosis, histiocytosis, xanthomas, papular sarcoidosis, and papular syphilid.

Erythema and Exanthems

Definitions. Erythema is redness of the skin due to hyperemia (increased blood flow); it may or may not be caused by inflammation. An exanthem (rash) consists of multiple inflammatory changes in the skin which take a characteristic course over time.

Localized erythema may be due to erysipelas, cutaneous burns (sunburn), drug reactions (especially to barbiturates, sulfonamides, tetracyclines, and nonsteroidal anti-inflammatory drugs [NSAIDs]), contact dermatitis, erythema chronicum migrans (Fig. 3.**6**), acrodermatitis chronica atrophicans as an early or late manifestation of tick-borne *Borrelia burgdorferi* infection (Figs. 3.**7a, b**; in late manifestations, the skin is livid and atrophic), or dermatomyositis. Livid discoloration is a feature of certain diseases listed in Tab. 3.**2**. Erythema can also be purely functional (e. g., "erythema e pudore," otherwise known as blushing).

Generalized exanthems can be of several different types:

- *A scarlatiniform exanthem* is seen in scarlet fever and as an adverse drug reaction (β-lactam antibiotics, erythrocyte concentrates, heparin, benzodiazepines, barbiturates).
- *A morbilliform exanthem* (small, pale, red spots at first, later becoming dark red, papular, and confluent) is seen in measles and as an adverse drug reaction (Fig. 3.**8**).
- *A rubeoliform exanthem* has smaller and less confluent spots than a morbilliform exanthem.
- *Other viral illnesses,* such as those due to echoviruses and coxsackieviruses, but also including mumps, infections with Epstein–Barr virus and cytomegalovirus, and primary HIV infection, can produce exanthems (Fig. 3.**9**).

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Table 3.**2** Diseases causing livedo

Functional (livedo reticularis)
- cutis marmorata (after exposure to cold)
- congenital livedo reticularis

Organic (livedo racemosa)
- **idiopathic**
  - livedo racemosa with summer/winter ulcerations
  - livedo racemosa generalisata (Sneddon syndrome)
- **symptomatic**
  - polyarteritis nodosa
  - systemic lupus erythematosus
  - dermatomyositis
  - primary chronic polyarthritis (= rheumatoid arthritis)
  - arteriosclerosis
  - hyperparathyroidism
  - cold hemagglutination disease
  - cryoglobulinemia
  - oxalosis
  - embolism (cholesterol)
  - thrombocytosis
  - shock
  - intravascular coagulopathy

- *"Toxic shock syndrome"* is caused by streptococcal and staphylococcal endotoxins and produces an exanthem (see Chapter 4).
- *Other bacterial infections* can also produce exanthems, including typhus, leptospirosis, brucellosis, and, characteristically, secondary syphilis (roseola, Fig. 3.**10**).
- A diffuse, morbilliform or scarlatiniform exanthem with scaling of the skin of the palms and soles is seen in *Kawasaki syndrome* (mucocutaneous lymph node syndrome). This condition mainly affects children. *Staphylococcal scalded skin syndrome* also mainly affects children and is characterized by superficial bullae and conjunctivitis.
- Other causes of *scaly exanthem* include pityriasis rosea, parapsoriasis en plaques, psoriasis, and eczema of various etiologies.
- *Erythroderma* (generalized inflammatory reddening of the skin) is seen in various dermatoses, as an adverse drug reaction, and as a paraneoplastic phenomenon.

Vesicular Skin Diseases

Herpes Simplex Infection. Primary or recurrent infection with a herpes simplex virus (see Chapter 4) produces clusters of painful vesicles that can, in principle, be found anywhere on the body, but are usually found on the lips and genitals. The eyes can also be involved (keratoconjunctivitis). Eczema herpeticum is a rapidly spreading herpes virus infection occurring in the aftermath of a previous skin disease, usually atopic eczema (Fig. 3.**11**).

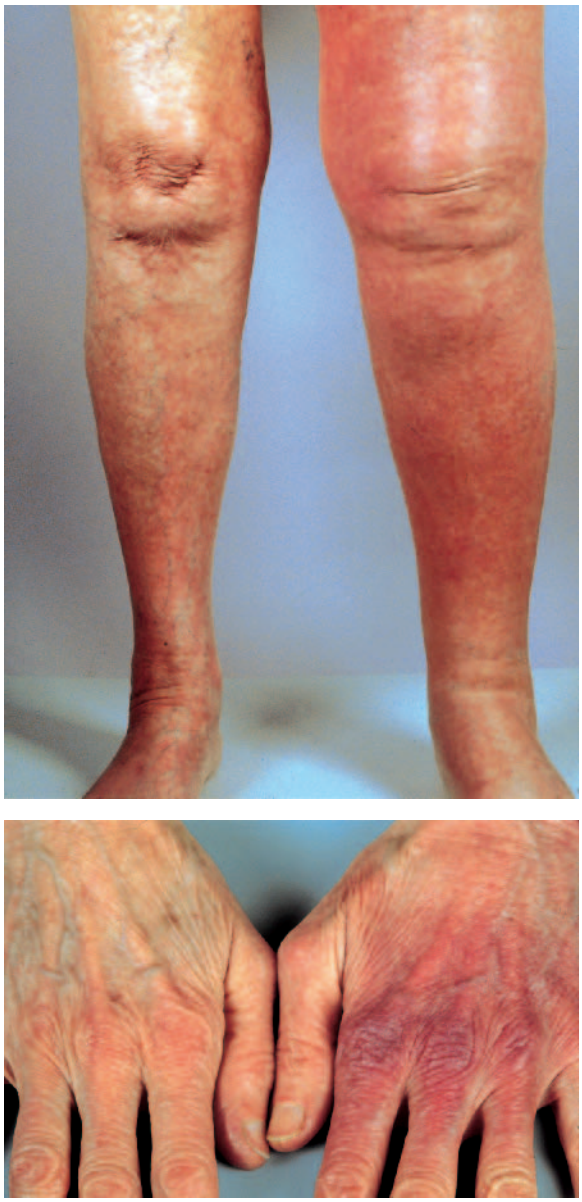

Fig. 3.**7** Acrodermatitis chronica atrophicans.
a Inflammatory early stage.
b Atrophic late stage.

Fig. 3.**8** Morbilliform drug exanthem.

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Fig. 3.**9** Macular exanthem in primary HIV infection.

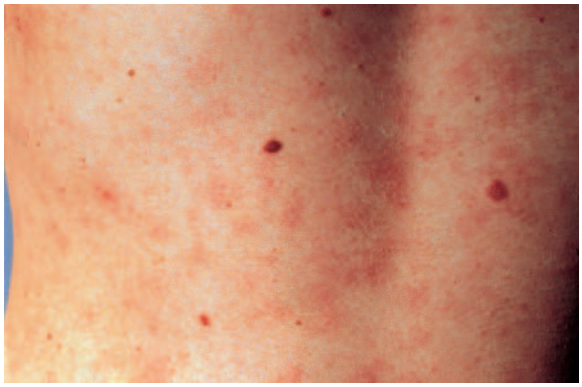

Fig. 3.**10** Roseola syphilitica.

Fig. 3.**11** Eczema herpeticum in atopic dermatitis.

Fig. 3.**12** Herpes zoster.

Herpes zoster (Fig. 3.**12**) is due to the reactivation of an earlier infection with varicella-zoster virus, the same virus that causes chickenpox. It is characterized by focal pain in a particular location on one side of the body. The pain may develop before the exanthem becomes evident. The exanthem consists of partly confluent vesicles in a segmental distribution. It sometimes becomes generalized, particularly in immunocompromised patients. Even in such cases, however, the originally affected dermatome remains visually apparent (a valuable point for the differential diagnosis of herpes zoster versus chickenpox).

Varicella (chickenpox) produces an exanthem in a typical "starry sky" distribution (simultaneous occurrence of lesions in diverse stages of development).

Other Causes. Vesicles accompanied by marked pruritus are found in acute eczema, parasitic skin infections, Grover disease (transient acantholytic dermatosis), and light-induced dermatoses. Duhring herpetiform dermatitis is characterized by a pleomorphic, mainly papulovesicular exanthem. The chronic and markedly pruritic skin changes are usually found in a symmetrical distribution on the elbows, knees, shoulders, and buttocks, as well as on the hairy scalp. Many affected patients also suffer from an enteropathy that responds to a gluten-free diet (though this may be asymptomatic).

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Bullous Skin Diseases

Pemphigus vulgaris is characterized by bullae that arise in previously intact skin. The large, slackly filled bullae burst easily and leave round, wet areas of skin behind. The Nikolski phenomenon (separation of the epidermis on tangential pressure) is usually present. The oral mucosa is typically affected and often the site of the initial manifestation. Sufferers are usually 40–50 years of age.

Bullous pemphigoid is the most common autoimmune blistering disease. Its clinical picture is pleomorphic at first, with disseminated, confluent areas of erythema as well as urticarial and multiform-type lesions and bullae of variable size. As the condition progresses, the typical tense bullae, filled with serous fluid, appear. These cannot be pressed away (negative Nikolski sign) and tend to last longer than the bullae of pemphigus vulgaris because of their thicker covering, which is composed of the entire epidermis. Bullae of all developmental stages are seen simultaneously (small, very large, tense, dried up, scaling off) (Fig. 3.**13**). Sufferers are usually 60–80 years of age. The oral mucosa is only rarely involved. This condition may be a paraneoplastic manifestation.

Fig. 3.**13** Bullous pemphigoid.

Erythema exsudativum multiforme (*minor type*) is an acute, self-limited disease of the skin and mucous membranes with variable clinical manifestations ("multiforme" because of the different types of lesions present, i. e., erythema, papules, and vesicles). Iris- or target-shaped skin lesions up to 3 cm in diameter (Fig. 3.**14a**) usually appear abruptly and are found symmetrically on the extensor surfaces of the forearms and legs and on the hands, feet, and neck. The periphery of the lesion typically remains erythematous while its center becomes livid and may turn into a bulla.

Patients with this condition are usually young and rarely over age 50. Its pathogenetic mechanism is not understood. It tends to recur. It can be precipitated by:

- viral infection (herpes simplex virus is by far the most common cause, followed by adenoviruses and Epstein–Barr virus)
- mycoplasmal infection
- medications (penicillin, sulfonamides, hydantoins, NSAIDs, barbiturates, carbamazepine, allopurinol, and others)
- collagenoses
- neoplasia.

The nosology of this group of illnesses is not entirely settled. In general, one speaks of erythema exsudativum multiforme of *major type* when there are lesions in two different locations, involving the mucous membranes as well, and systemic symptoms are also present (Fig. 3.**14**).

Cases with severe systemic manifestations are usually due to an adverse drug reaction and are known as *Stevens–Johnson syndrome* or, at worst, *toxic epidermal necrolysis,* which can involve the entire integument. Often, a rapidly spreading exanthem appears after a prodromal phase with fever, cough, diarrhea, vomiting,

a

b

Fig. 3.**14** Erythema exsudativum multiforme:
a Minor type.
b Major type.

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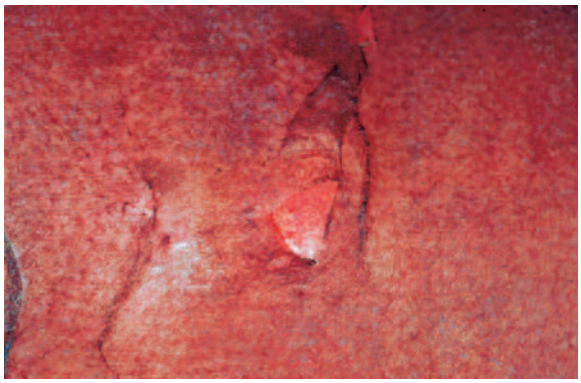

Fig. 3.**15** Toxic epidermal necrolysis (Lyell syndrome).

and arthralgia. The initial erythematous lesions tend to become confluent but lack a typical target pattern. They tend to become necrotic quite soon (Fig. 3.**15**), and flaccid, sometimes hemorrhagic bullae can appear spontaneously. Mucosal involvement (ectodermosis pluriorificialis) and conjunctivitis are typical accompaniments. Toxic epidermal necrolysis (*Lyell syndrome*) is said to be present when more than 20% of the body surface is involved.

Other Causes. Bullae that arise only in skin areas exposed to light may be due to porphyria or to a photodermatosis. Various substances can heighten photosensitivity, including furosemide, nalidixic acid, phenothiazines, psoralen, sulfonamides, and tetracyclines. Individual bullae may represent a localized allergic reaction (fixed drug exanthem). Erysipelas, too, has a rare bullous variant. Bullae are also typically found in acrodermatitis enteropathica with zinc deficiency, in the bullous form of impetigo contagiosa caused by staphylococci, and in diabetes mellitus (bullosis diabeticorum).

Epidermolysis bullosa is actually a spectrum of rare inherited disorders in which the coherence of the skin and mucous membranes is impaired and bullae are therefore likely to form after even mild mechanical trauma. These disorders have diverse pathophysiological mechanisms, modes of inheritance, and clinical features. They are classified according to the location of the bullae. Over time, the bullae leave scars behind, as well as deeper fissures and dystrophic areas.

Papular Skin Diseases

A papule is a solid cutaneous nodule less than 5 mm in diameter. The color of the papules often indicates the underlying illness.

- *Reddish papules* are mainly due to an epizoonosis, polymorphic light dermatosis, prurigo simplex acuta, an acneiform exanthem, a viral exanthem, or secondary syphilis (in which the papules have a copperlike hue).
- *Livid,* flattened, and typically polygonal papules are seen in lichen ruber planus; additional clues to the presence of this condition are fine white lines (Wickham striae) and severe itch. A lichenoid drug exanthem is another possibility.
- *Brown* papules are seen in histiocytosis, micronodular sarcoidosis, urticaria pigmentosa, and bowenoid papulosis.
- *Blue* papules may be angiokeratomas, blue nevi, melanoma metastases, or the lesions of Fabry disease or eruptive angiomatosis.
- *Pigmented* or *black* papules are typical of nevus cell nevi, basal cell carcinoma, malignant melanoma, Kaposi sarcoma, and sometimes histiocytoma.
- *Yellowish* papules are more likely due to xanthomas, histiocytosis, or granulomatous processes.
- Papules of *normal skin color* include those of adenoma sebaceum (Pringle disease), cutaneous amyloidosis, and various types of mucinosis.

Plaque-forming Skin Diseases

Plaques (circumscribed, flat or plateaulike skin changes) often arise by the confluence of papules or nodules (e. g., in psoriasis, lichen ruber planus, or mycosis fungoides).

- *Reddish plaques* are also seen in sarcoidosis, pseudolymphoma, lupus erythematosus profundus, tuberous syphilid, and Sweet syndrome.
- *Yellowish plaques* are seen in necrobiosis lipoidica, xanthomatosis, nevus sebaceus (yellowish-orange), and lepromatous leprosy. They are accompanied by atrophy in discoid lupus erythematosus and necrobiosis lipoidica (Fig. 3.**16**).

Nodular Skin Diseases

Superficial cutaneous nodules are seen in processes that produce epidermal tumors, such as carcinoma (including basal cell carcinoma), keratoacanthoma, malignant melanoma, and nevi and benign epithelial proliferations, e. g., warts. Deeper cutaneous nodules are usually due to a systemic disease.

Erythema nodosum (Fig. 3.**17**) is characterized by a nonspecific prodrome (fever, arthralgias) followed by the development of symmetrically distributed, red, raised nodules, mainly on the shins, sometimes also on the thighs and the extensor surfaces of the forearms. These nodules are painful, never ulcerate, and may reach a size of 5 cm. Over time, they become discolored like a bruise and then heal without scarring. The erythrocyte sedimentation rate is usually markedly elevated. Systemic symptoms are always present, but of variable severity. Most patients are young women.

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Erythema nodosum is produced by an immunological reaction to various factors. The most common cause, formerly tuberculosis, is now upper respiratory infection with β-hemolytic streptococci, which is followed by erythema nodosum at a latency of about 3 weeks. Other possible causes include sarcoidosis (Löfgren syndrome); infection due to *Yersinia*, chlamydia, *Campylobacter*, viruses, or fungi; Behçet syndrome; Crohn disease; ulcerative colitis; and the use of ovulatory inhibitors. Other medications such as penicillin and analgesics are only rarely responsible.

Subcutaneous Nodule Formation. Subcutaneous nodules may be found on the chest, back, and abdomen in polyarteritis nodosa, usually accompanied by skin necrosis, erythema, purpura, and urticaria, most commonly on the legs.

Nodular vasculitides are usually found on the calves and often lead to ulceration. Erythema induratum (Bazin disease) (due to tuberculosis) is now very rare. Another possibility is nodular panniculitis, whose possible causes include acute pancreatitis, pancreatic carcinoma, and others listed in Tab. 3.**3**. In many cases, the cause cannot be identified.

The following diseases can produce subcutaneous nodules: cutaneous tuberculosis (lupus vulgaris), syphilis, xanthomatosis, metastatic tumors (carcinoma of breast or lung, malignant melanoma), lymphoma, deep fungal infections, foreign-body reactions, rheumatoid nodules, benign tumors (lipoma, lymphangioma), and parasitic diseases (e. g., echinococcosis).

Fig. 3.**16** Necrobiosis lipoidica.

Pustular Skin Diseases

Pustules are cutaneous vesicles containing pus (either infected or sterile). They are typically seen in the following conditions:

- rosacea
- pustular psoriasis
- adverse drug reactions (acute, generalized, exanthematous pustulosis), usually due to amoxicillin, hydroxychloroquine, diltiazem, or carbamazepine
- viral infection (herpes simplex, herpes zoster, varicella) with bacterial superinfection
- Reiter disease
- subcorneal pustular dermatosis (Sneddon–Wilkinson disease)
- candidiasis.

Table 3.**3** Causes and classification of panniculitis

	Septal panniculitis	Lobular panniculitis
Without vasculitis	– erythema nodosum – eosinophilic fasciitis – eosinophilia-myalgia syndrome – systemic scleroderma	– idiopathic panniculitis (Pfeiffer–Weber–Christian) – α_1-antitrypsin deficiency – physical panniculitis (cold, traumatic, chemical) – neonatal panniculitis – systemic lupus erythematosus – sarcoidosis – pancreatic disease – lymphoma
With vasculitis	– in thrombophlebitis – in arteritis	– nodular vasculitis

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a

b

Fig. 3.**17** Erythema nodosum.
a Overall view.
b Detail.

◁ Fig. 3.**18** Pyoderma gangrenosum in Crohn disease.

Ulcerations of the Skin

Leg ulcers are caused by:
- chronic venous insufficiency
- arterial hypoperfusion, mainly in smokers and diabetics
- necrobiosis lipoidica
- pyoderma gangrenosum (Fig. 3.**18**) (large ulcers, most commonly in Crohn disease and ulcerative colitis)
- malignant tumors of the skin.

Further causes are listed in Tab. 3.**4**.

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Table 3.4 Causes of leg ulcers

Vascular diseases
- venous
- arterial
  - arteriosclerosis
  - hypertension (Martorell ulcers)
  - thrombangiitis obliterans
  - arteriovenous malformations
  - cholesterol emboli
- small-vessel vasculitis
  - hypersensitivity vasculitis
  - rheumatoid arthritis
  - systemic lupus erythematosus
  - scleroderma
  - Sjögren syndrome
  - Behçet disease
  - white atrophy
- medium-sized and large-vessel vasculitis
  - polyarteritis nodosa
  - nodular vasculitis
  - Wegener disease
- lymphatic vessels
  - lymphedema

Neuropathic
- diabetes mellitus
- tabes dorsalis
- syringomyelia
- poliomyelitis
- peripheral nerve lesions

Metabolic
- diabetes mellitus
- gout
- prolidase deficiency
- Gaucher disease
- calciphylaxis

Hematologic
- sickle cell anemia
- hereditary spherocytosis
- thalassemia
- polycythemia vera
- leukemia
- dysproteinemias
  - cryoglobulinemia
  - cold hemagglutination disease
  - macroglobulinemia

Trauma
- pressure
- cold
- radiation-induced dermatitis
- burns
- factitious injury

Neoplastic
- epithelial tumors
  - spinocellular carcinoma
  - basal cell carcinoma
  - keratoacanthoma
- sarcomas
  - Kaposi sarcoma
- lymphoproliferative disorders
  - lymphoma
  - cutaneous T-cell lymphoma
- metastases

Infectious
- bacterial
  - furuncle
  - ecthyma
  - ecthyma gangrenosum
  - septic emboli
  - Gram-negative infections
  - anaerobic infections
  - mycobacteria
  - spirochetes
- fungal
  - Majocchi granuloma
  - deep fungal infection
- protozoal
  - leishmaniasis
  - sting reactions

Specific dermatoses
- necrobiosis lipoidica
- necrobiotic xanthogranuloma
- pyoderma gangrenosum

Sarcoidosis

Genetic
- Klinefelter syndrome

Topical and systemic medications

Urticarial Skin Diseases

Urticaria consists of well-circumscribed, sharply demarcated, slightly raised, reddened skin lesions (hives) produced by an accumulation of interstitial fluid. It is one of the more common dermatological conditions and can appear at any age.

Causes. Acute urticaria, the most common type, heals in 2–4 weeks. Its cause often cannot be identified. It is rarely due to an IgE-mediated reaction (e. g., to food, medications, or insect toxins), but more commonly to a nonallergic intolerance reaction (e. g., to preservatives, dyes, or medications). It is to be distinguished from the various types of physically induced urticaria, including urticaria induced by light, cold, pressure, heat contact, or vibration, and factitious urticaria.

Angioedema. Urticaria is often combined with analogous swellings of the deep dermis, subcutis, and submucosa (angioedema). Angioedema may be the result of a hereditary or acquired C1 inhibitor deficiency, an adverse drug reaction (ACE inhibitors), a systemic disease (e. g., lymphoma, serum sickness), or a parainfectious process. In many cases, however, the causes of chronic urticaria (i. e., urticaria for more than 6 weeks) and angioedema cannot be identified.

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Fig. 3.**19** Palpable purpura in allergic vasculitis (quinidine sulfate).

Table 3.**5** Causes of skin calcification

Dystrophic calcification
- localized
  - traumatic (foreign body, hematoma, fat necrosis)
  - infectious/inflammatory (acne, varicosis, tuberculosis)
  - degenerative (necrosis, venous stasis, parasitic [e. g., echinococcal cyst])
  - neoplastic (sebaceous cyst, lipoma, angioma, calcifying epithelioma of Malherbe [= pilomatricoma], liposarcoma)
- in systemic disease
  - dermatomyositis (esp. in adolescents)
  - scleroderma
  - systemic lupus erythematosus
  - acrodermatitis chronica atrophicans
  - pseudoxanthoma elasticum
  - Ehlers–Danlos syndrome

Idiopathic calcification
- calcinosis circumscripta, calcinosis universalis
- calcinosis helicis

Metastatic calcification
- hypercalcemic types
  - hyperparathyroidism
  - sarcoidosis
  - vitamin D intoxication
  - milk alkali syndrome
  - tumor hypercalcemia (metastatic carcinoma, lymphoma, multiple myeloma)
  - Paget disease
- normocalcemic types
  - chronic renal failure
  - pseudohypoparathyroidism

Purpura

Definition. Purpura (Fig. 3.**19**) is a general term for bleeding in the skin. The extent of bleeding is more precisely specified by other terms, such as petechiae (punctate bleeding), sugillation (coin-sized hematoma), ecchymosis, and suffusion (large area of hematoma).

Causes. Purpura has many causes, which are best discussed in the context of their etiology and pathogenesis (see Chapter 15).

Telangiectasias

Telangiectasias are clusters of permanently dilated capillaries and very small venules that are usually found in a network and blanch when compressed with a glass spatula.

- *Idiopathic types* include nevus telangiectaticus, essential telangiectasias, facial rubeosis, and others. *Secondary types* are due to exogenous factors such as light exposure, corticosteroids, trauma, and radiation (chronic radiodermatitis).
- *Symptomatic types* can be seen in collagenoses, poikilodermatous parapsoriasis, acrodermatitis chronica atrophicans, rosacea, basal cell carcinoma, and necrobiosis lipoidica.
- *Genetic dermatoses* with telangiectases are rare. They include ataxia telangiectatica, Bloom syndrome, Fabry disease, Osler–Weber–Rendu disease, and xeroderma pigmentosum.
- *Spider nevi* are usually found on the chest, less often on the face and hands. They commonly accompany liver disease but may be idiopathic or arise during pregnancy.

Disturbances of Skin Turgor

Skin turgor is an indirect reflection of tissue hydration. If a fold or crease in the patient's skin is produced by a pinch and does not immediately flatten out when the skin is released, this indicates fluid deficiency, particularly in younger individuals.

Calcifications of the Skin

Various diseases can cause calcification or even ossification of the skin and subcutis. Calcium and phosphate are deposited in the skin under diverse circumstances (Tab. 3.**5**). Disorganized deposition is called calcification, while the formation of actual bone tissue is called ossification. The causes of skin calcification can be broadly classified as dystrophic, idiopathic, and metastatic. (Note that the term "metastatic" is used here in an unusual sense and does not refer to a malignant neoplasm.)

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Skin Changes Due to Systemic Disease

Skin Changes Due to Metabolic Disorders

Disorders of Lipid Metabolism. Xanthomas and xanthelasmas are found in various disorders of lipid metabolism (see Chapter 20).

Lipid Storage Diseases. Fabry disease (angiokeratoma corporis diffusum) is a rare lipidosis of X-chromosomal recessive inheritance characterized by progressively severe cardiovascular and renal dysfunction and characteristic changes of the skin. It presents in males at puberty and usually leads to death between the ages of 30 and 50. Only about 20% of heterozygous females are symptomatic, and then only mildly affected. The underlying genetic defect causes a deficiency of the enzyme α-galactosidase A, leading to an accumulation of trihexosylceramides in the endothelial cells of many different organs.

Even before the skin changes are manifest, patients may present with muscle weakness, fever, and very painful shooting pains and paresthesiae in the palms, soles, and proximal segments of the limbs (Fabry crises). The skin lesions are found in a symmetrical distribution on the trunk, mainly in the inguinal, scrotal, and periumbilical areas. They consist of small, dark red to black, noncompressible vascular ectasias, which are few in number at first, then gradually become very numerous. They often (though not always) have a palpably hyperkeratotic surface. Ocular changes are often found as well (corneal opacification, tortuosity of conjunctival and retinal vessels, cataracts, lid edema). Patients frequently suffer from hypohidrosis or anhidrosis, which predisposes them to exercise-induced hyperthermia. They may have reduced hair growth. Trihexosylceramide deposition causes cardiac (myocardial infarction, cardiomegaly, heart failure) and renal changes (progressive renal failure, hypertension). The disease can be diagnosed before birth.

Disorders of Amino Acid Metabolism. *Tyrosinemia* is a rare disease causing central nervous dysfunction and severe damage to the liver and kidneys. On the skin, there are painful palmar and plantar hyperkeratoses. *Phenylketonuria* is characterized by eczematous foci, generalized hypopigmentation, and fair hair. In *alkaptonuria*, homogentisic acid is deposited in cartilage (ochronosis), causing a typical blue-green discoloration of the tip of the nose and of the ear cartilage (see Chapter 10).

Disorders of Carbohydrate Metabolism. *Diabetes mellitus* causes a number of characteristic skin changes:

- The most common is so-called *diabetic dermopathy,* consisting of atrophic, reddish-brown, painless and irregularly demarcated foci, particularly on the shins. Men are affected about twice as commonly as women.
- *Necrobiosis lipoidica diabeticorum,* on the other hand, is more common in women (3:1) (Fig. 3.**16**). Like diabetic dermopathy, it is found mainly on the shins but can also affect the arms, trunk, and face. It typically begins as a small, reddish nodule that slowly enlarges, flattens, and then transforms into an extensive yellowish-brown patch with marked central atrophy and an erythematous edge. These lesions occasionally ulcerate and are then slow to heal.
- *Other skin changes* commonly found in diabetics include bullous dermatoses, pyoderma, and fungal infections. Less commonly, they may have xanthomas, hypertrichosis, or scleroedema adultorum. The combination of diabetic angiopathy and neuropathy can create deep ulcers in the skin and underlying tissue ("diabetic foot").

Eczemalike, polycyclically demarcated foci with peripheral vesicles and scabs, located mainly on the abdomen, buttocks, and lower limbs, may be the first manifestation of a *glucagonoma* (necrolytic migratory erythema).

Gout. Gouty tophi are hard, painless subcutaneous nodules located on the helices of the ears and over the finger joints and elbows. They are composed of urate crystals and are specific for gout; they are to be distinguished from rheumatoid nodules and, when found on the ear, from neoplasms and the so-called Darwinian tubercle (see Chapter 10).

Porphyria. Porphyrin deposited in the skin is activated by the absorption of light at a wavelength of 400 nm and then combines with oxygen to damage cell membranes and lysosomes. Different types of porphyria are characterized by the formation of bullae, vesicles, or erythematous changes (see Chapter 7).

Congenital Disorders of Connective Tissue. Marked hyperextensibility of the skin with normal elasticity and vulnerability to injury (atrophic scars) is characteristic of *Ehlers–Danlos syndrome,* of which there are 10 known subtypes with different modes of inheritance. The joints, too, are hyperextensible. Affected individuals rarely suffer from arterial ruptures and spontaneous bowel perforations.

Pseudoxanthoma elasticum is characterized by yellowish, xanthomalike plaques and loose, easily lifted skin (cutis laxa) (Fig. 3.**20**). It is called Groenblad–Strandberg syndrome when accompanied by angioid streaks on the retina. Extensive vascular involvement may lead to gastrointestinal hemorrhage, coronary

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Fig. 3.**20** Pseudoxanthoma elasticum (Groenblad–Strandberg syndrome).

artery occlusion, or renovascular hypertension. The disease is usually transmitted in an autosomal recessive inheritance pattern and is due to abnormal synthesis of elastic fibers.

Cutis laxa (generalized elastolysis) is also seen as an independent disorder in which the skin has many folds and appears to be too large for the patient's body. The most important accompanying manifestation is progressive pulmonary emphysema.

In *Marfan syndrome,* "stretch marks" (striae distensae) may be seen on the chest and hips. Disordered development of the subcutaneous fat layer gives these patients an abnormally thin, translucent, and injury-prone skin, as is also seen in osteogenesis imperfecta.

Skin Changes Due to Endocrine Disorders

- *Cushing syndrome* and chronic steroid treatment very often cause skin changes including atrophy, abdominal striae (striae distensae), purpura, hypertrichosis, facial rubeosis, acanthosis nigricans, and redistribution of subcutaneous fat.
- Prolonged use of *local steroids* (ointments, creams) causes skin atrophy and telangiectasias.
- Hyperpigmentation (of the elbows, knees, palmar creases, nipples, and genitalia) is the first sign of *Addison disease* in 20–40% of patients. It is accompanied by diffuse hair loss.
- In *hyperthyroidism*, the skin is moist, warm, and very soft. Other signs may include palmar erythema, onycholysis, pruritus, urticaria, diffuse hair loss, vitiligo, and pretibial myxedema, in which one finds hard, noncompressible, brownish areas of edema symmetrically in both legs.
- Cold, dry, and fair skin with doughy swellings is typical of *hypothyroidism*. The skin condition is often accompanied by hair loss and fragile nails.
- The epidermis is thickened in *acromegaly*, which can also cause hypertrichosis, acanthosis nigricans, and hyperhidrosis.
- Patients with *panhypopituitarism* (e. g., post partum in Sheehan syndrome) have marked skin pallor (usually because of anemia), sunlight intolerance, soft skin, and a prematurely aged facial appearance due to increased wrinkling around the mouth and eyes. Affected women lose their axillary hair first and later their pubic hair. The hair of the head is fine and dry.
- *Hypoparathyroidism* causes xeroderma and a tendency toward eczema, as well as trophic disturbances of the hair and nails (often with horizontal grooving).

Skin Changes Due to Tumors

General types of skin change that can be caused by tumors include the following:

- pallor (anemia)
- jaundice (e. g., in carcinoma of the head of the pancreas)
- purpura, thrombocytopenia (bone marrow infiltration)
- hyperpigmentation (ectopic MSH production, metastatic melanoma)
- lobular panniculitis (carcinoma of the pancreas)
- psoriasislike skin changes (glucagonoma, lung cancer, and malignant tumors of the ear, nose, and throat [acrokeratosis of Bazex])
- Raynaud phenomenon (cryoglobulinemia in multiple myeloma).

The following cutaneous manifestations may be due to an occult tumor:

- dermatomyositis (often due to tumors of the female reproductive tract)
- acanthosis nigricans (mainly due to carcinoma of the stomach)
- thrombophlebitis migrans (often due to pancreatic carcinoma)
- acquired ichthyosis (mainly due to lymphoma) (Fig. 3.**21**)
- pachydermoperiostosis (mainly due to lung cancer)
- pemphigus (paraneoplastic type with hemorrhagic cheilitis and stomatitis, mainly due to myeloproliferative disorders)
- bullous pemphigoid
- hypertrichosis languinosa (mainly due to cancer of the lung and colon)
- "tripe palms" (accentuated palmar crease pattern, mainly in men with lung cancer).

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Fig. 3.**21** Acquired ichthyosis in non-Hodgkin lymphoma.

Fig. 3.**22** Sweet syndrome in acute myeloid leukemia.

Fig. 3.**23** Nail-fold keratosis and Gottron papules in dermatomyositis.

In *carcinoid syndrome,* particularly after stress, alcohol consumption, or compression of the abdominal organs, the patient may develop a characteristic bright red or bluish-red flush, beginning on the face and spreading to the nuchal region and shoulders.

Brownish-red plaques on the face, neck, and arms suggest *Sweet syndrome* (Fig. 3.**22**). The affected patients are usually febrile and have an elevated neutrophil count, and histological examination reveals dense neutrophilic infiltration. The syndrome is usually a postinfectious reaction (after an upper respiratory infection), but some 20% of cases are due to a lymphoproliferative disorder.

Skin Changes Due to Collagenoses

Lupus Erythematosus. Chronic discoid lupus erythematosus is to be distinguished from the systemic form of the disease. In the chronic discoid form, papular and plaque-forming hyperkeratotic lesions are typically found at locations exposed to sunlight (dorsum of hand, nose, scalp, ears). This form rarely undergoes a transition to the systemic form (approximately 5%). In the systemic form of the disease, there are skin changes in 85% of patients (see Chapter 4).

Dermatomyositis and polymyositis (the latter does not involve the skin) are probably two variants of a single underlying disease. In 25% of patients with dermatomyositis cutaneous symptoms are the major complaint. Skin edema with violet-reddish discoloration of the upper eyelids is a practically pathognomonic finding. It may be accompanied by nail–fold keratoses and erythema, as well as by striated livid discolorations on the extensor surface of the fingers, with lichenoid papules (Gottron papules) (Fig. 3.**23**).

Scleroderma can be localized or generalized. The localized forms (morphea, linear scleroderma, scleroderma "en coup de sabre") take a benign course. Generalized scleroderma involves the skin and internal organs (see Chapter 4) in either a diffuse or a restricted fashion.

Rheumatological Diseases. *Primary chronic polyarthritis* (rheumatoid arthritis) often causes skin lesions in severely affected patients. The most common kinds are rheumatoid nodules (mainly on the olecranon, extensor surface of the forearm, and Achilles tendon) and vasculi-

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Fig. 3.**24** Balanitis erosiva circinata in Reiter syndrome.

Fig. 3.**25** Coumarin necrosis.

tis. Other occasional manifestations include acral ulcerations (which may become gangrenous), leg ulcers (in chronic venous insufficiency or pyoderma gangrenosum), palmar erythema, yellowish and atrophic skin, and Sweet syndrome.

Still disease (juvenile polyarthritis) is characterized by a transient, salmon-colored, confluent, maculopapular exanthem.

Rheumatic fever is very rare today. As many as one third of affected patients have pea-sized subcutaneous nodules located at the ankles, elbows, occiput, and (rarely) other sites. Ten percent of affected patients, mainly children, develop mainly truncal polycyclical erythema (erythema marginatum, see Chapter 4).

In *Reiter syndrome* (conjunctivitis, urethritis, and asymmetrical arthritis), there may be psoriasislike skin changes, palmoplantar keratoderma, erosive changes of the glans penis (circinate erosive balanitis, Fig. 3.**24**), lesions of the oral mucosa, and onycholysis.

Skin Changes as Adverse Effects of Medications and Intoxications

An adverse drug reaction is in the differential diagnosis of every type of skin change. The diagnosis is suggested by the clinical history and confirmed by improvement after discontinuation of the causative drug.

Some medications cause allergic reactions by themselves, while others affect the skin by rendering it more sensitive to light. Reactions can be toxic or nonimmunological (pseudoallergies).

Coumarin necrosis (Fig. 3.**25**) occurs in oral anticoagulant therapy with coumarin and is characterized by edema and reddening of the skin in areas of the body with abundant subcutaneous fat. The skin later turns a dark bluish-red color. Skin necrosis is often seen after the unintended paravenous infusion of *cytostatic agents.*

Chronic use of, or *intoxication* (poisoning) with the following substances causes typical skin changes: carbon monoxide (cherry-red skin); agents causing methemoglobin formation, such as nitrobenzol and diaminodiphenylsulfone (cyanosis); arsenic (hyperkeratoses); alcohol (palmar erythema, spider nevi); ACTH, glucocorticoids, anabolic drugs, anticonvulsants, isoniazid (acne); nitrogen mustard, chlorpromazine, thallium (hypohidrosis); lead (black gingival edge); silver (argyrosis, blue-gray discoloration of the skin); mercury (stomatitis). Hydralazine, β-blockers, procainamide, and other substances can induce a lupuslike syndrome.

Eosinophilic fasciitis (Shulman syndrome) is a complex of symptoms including sclerodermalike, painful, reddish, firm swelling of the limbs, marked eosinophilia in the blood (as high as 30% or more), hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate, but without Raynaud phenomenon or involvement of the internal organs. It often appears in the aftermath of trauma or physical exercise. Histological examination reveals eosinophilic infiltration of the cutis, the subcutis, and the thickened muscle fascia. The differential diagnosis of this entity from the *eosinophilia-myalgia syndrome* is mainly based on the history (no intake of tryptophan-containing hypnotic drugs) and on the lack of visceral involvement.

Skin Changes Due to Hematologic Diseases

- Patients with *megaloblastic anemia* have diffusely pale skin combined with mild icterus, giving them a characteristic lemon-yellow skin color. Further findings usually include dry skin, stomatitis and glossitis with atrophy of the tongue papillae, and, particularly in persons with darker skin, localized hyperpigmentation of the face, hands, and feet.
- About 10% of patients with *pernicious anemia* develop vitiligo, premature graying of the hair (cani-

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ties), nonspecific stomatitis, and ulcerations in the oral cavity.

- One quarter of patients with *sickle cell anemia* develop poorly healing leg ulcers with a diameter up to 10 cm, mainly after puberty.
- Both *thalassemia major* and *sickle cell anemia* can cause punched-out leg ulcers and lesions of the oral mucosa.
- *Iron deficiency anemia* causes skin pallor, glossitis (a smooth, reddened tongue), fragile nails, and diffuse alopecia. Koilonychia (concavity of the fingernails, "spooning") is rarely seen today. Plummer–Vinson syndrome (sideropenic dysphagia), which mainly affects elderly women, is the combination of iron deficiency anemia with dysphagia due to mucosal atrophy in the pharynx and esophagus.
- *Polycythemia vera* causes a characteristic livid discoloration of the face. Another typical feature is the sudden development of generalized itching after contact with water. Erythromelalgia, i. e., erythema of the distal limbs triggered by warmth, may be present before the underlying illness is diagnosed.
- *Cutaneous hemorrhages* may be due to a low platelet count or to a disturbance of platelet function, clotting factors, or blood vessels (see Chapter 15).

Skin Changes Due to Gastrointestinal Disorders

Skin changes are often caused by gastrointestinal disorders. The underlying diseases can be classified into four groups: genetic syndromes, chronic inflammatory diseases, infectious diseases, and malignant neoplasia. The main diseases of each type are listed in Tab. 3.**6**.

Skin Changes Due to Hepatic Diseases

Skin changes due to liver disease are usually of a nonspecific character. They are most commonly caused by chronic active hepatitis or alcoholic-induced liver disease. Jaundiced skin and mucous membranes are a frequent finding.

Hepatic cirrhosis produces thin, parchmentlike skin, particularly on the hands, palmar erythema, Dupuytren contractures, spider nevi, and telangiectasias of the face. Hormonally induced changes can also be seen (loss of male-type body hair with hairless abdomen and gynecomastia). Longstanding cirrhosis may also cause a diffuse or local dirty gray hyperpigmentation, pruritus, and white discoloration and flattening (leukonychia) of the nails.

Hepatitis. Chronic active hepatitis is associated with marked striae distensae, while hepatitis B and C can cause leukocytoclastic vasculitis (mostly in combination with cryoglobulinemia), erythema nodosum, urticaria, erythema exsudativum multiforme, polyarteritis nodosa, and porphyria cutanea tarda.

Skin Changes Due to Heart Disease

Congenital Heart Defects. Patients with congenital heart defects often manifest cyanosis (right-to-left shunt), facial reddening (mitral stenosis), and clubbing of the fingers. In patients with cyanosis due to peripheral hemoglobin desaturation (heart failure), the skin is cold, unlike in patients with congenital cyanotic heart defects.

Endocarditis. Patients with endocarditis may have painful Osler nodes (microemboli), mainly on the fingertips and toes, which last for 12–24 hours. In contrast to Osler nodes, Janeway lesions, macular, hemorrhagic lesions up to 1 cm in size, are painless and are usually found on the palms and soles. The most common cutaneous manifestation (50%) is petechiae, usually on the limbs, chest, and mucous membranes (palate, conjunctiva). Subungual "splinter hemorrhages," on the other hand, are not specific for endocarditis, as they can be seen in many other diseases.

Neurocutaneous Diseases

Tuberous Sclerosis (Bourneville–Pringle disease) is an autosomal dominant genetic disorder producing characteristic small, leaf-shaped hypopigmented areas on the back. The hair of the scalp and eyebrows may turn gray in childhood. Most patients already have the pathognomonic, small, centrofacial angiofibromas (adenoma sebaceum) in childhood (Fig. 3.**26a**). Other typical findings include periungual fibromas (Koenen tumors, Fig. 3.**26b**) and, more rarely, oral fibromas. Gingival hyperplasia and defects of the dental enamel may already be apparent in childhood (early sign of the disease).

Neurofibromatosis. Persons with type I neurofibromatosis, also called von Recklinghausen disease, already display the characteristic café-au-lait spots at birth, mainly on the trunk; the spots may become larger and more numerous in the first year of life. More than six spots with a diameter greater than 1.5 cm are pathognomonic for the disease and are present in more than 85% of patients. Other characteristic hyperpigmented lesions arise in the axillary and inguinal areas later on in the course of the disease.

The slowly growing neurofibromas are found not only in the skin (see Fig. 3.**2**), but also in peripheral nerves and nerve roots, and sometimes also in the viscera, causing correspondingly diverse symptoms and signs. Bone changes are common (most often kypho-

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a

b

Fig. 3.**26** Tuberous sclerosis.
a Adenoma sebaceum.
b Koenen tumors.

Table 3.**6** Skin changes in gastrointestinal disease

Genetic cutaneous–intestinal syndromes (polyposis syndromes)	**Cutaneous symptoms and signs**
Gardner syndrome	Intestinal polyps, osteomas, hepatoblastoma, thyroid carcinoma, endocrine adenomas, and skin tumors (dermoid cysts, lipomas, and fibromas)
Peutz–Jeghers syndrome	Intestinal polyps, perioral lentigines, pigmentation of the oral mucosa, acral pigmentation (especially of the fingers), increased frequency of intestinal and gynecological tumors
Cowden syndrome	Intestinal polyps, multiple neoplasias, multiple benign cutaneous tumors (particularly on the face and in the mouth) and acral keratoses, increased frequency of breast cancer and thyroid carcinoma in female patients
Muir–Torre syndrome	Intestinal polyps, sebaceous adenomas and keratoacanthomas, increased frequency of visceral malignancy
Cronkhite–Canada syndrome	Multiple polyps of the stomach and small intestine, alopecia, nail dystrophy, focal hyperpigmentation
Inflammatory diseases	
Crohn disease, ulcerative colitis	Pyoderma gangrenosum, erythema nodosum, cutaneous fistulae, recurrent oral aphthous ulcers, psoriasis
Bowel bypass syndrome	Folliculitis, fever, arthritis
Celiac disease	Psoriasiform exanthems, dermatitis herpetiformis Duhring
Pancreatitis	Panniculitis
Whipple disease	Hyperpigmentation, erythema nodosum, lichenoid exanthems
Infectious diseases	
Enteritis	Erythema nodosum, nonspecific exanthems, erythema exsudativum multiforme
Typhus	Mild roseola (rose spots) on the trunk
Malignancy in the gastrointestinal tract	
Cutaneous metastases, umbilical metastasis	“Sister Mary Joseph nodule”
Carcinoid syndrome	Flush and telangiectases
Glucagonoma syndrome	Necrolytic migratory erythema
Acanthosis nigricans	Velvetlike hyperpigmented thickening of the skin
“Tripe palms”	Exaggeration of the ridge pattern of the palms

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scoliosis). Patients sometimes have macrocephaly; 5–10% have tumors of the central nervous system (optic glioma, astrocytoma, meningioma). Iris hamartomas (Lisch nodules) can be demonstrated in more than 90% of adult patients. About 6% are mentally retarded. Five percent have associated neoplasms (schwannoma, myeloproliferative diseases, rhabdomyosarcoma, pheochromocytoma).

Von Hippel–Lindau syndrome is a rare genetic disorder of autosomal dominant inheritance. Its major manifestation is cerebellar hemangioblastoma, which produces cerebellar neurologic signs and symptoms. Retinal angiomas and nevus flammeus (mainly in the occipital and nuchal region) are rare.

Sturge–Weber syndrome is another rare syndrome in which the affected persons are born with a vascular nevus (nevus flammeus) in the distribution of the first and/or second branch of the trigeminal nerve, usually on one side of the face (Fig. 3.**27**). Sometimes the oral mucosa is affected as well. Twenty percent of patients also have angiomatosis of the ipsilateral eye with glaucoma (buphthalmos). It is also not uncommon for the meninges to be affected.

Spina Bifida Occulta. A circumscribed area of hypertrichosis over the vertebral column may indicate the presence of spina bifida occulta.

Fig. 3.**27** Nevus flammeus in Sturge–Weber syndrome.

Skin Changes Due to Infection

Bacterial infection can affect the skin alone (follicular and nonfollicular types) or involve the skin secondarily in the setting of systemic infection.

- The more common types of localized, nonfollicular bacterial infection are *impetigo contagiosa, ecthyma,* and *erysipelas.*
- Rarer varieties include *erysipeloid* (a warm, erythematous area, usually on the hands) and *cutaneous diphtheria,* which is usually seen in persons with poor hygiene and in travelers returning from the tropics. It manifests as punched-out ulcers covered with a greasy, yellowish-gray pseudomembrane.
- A common finding in *cat-scratch disease* is an inflamed wound in the hand associated with prominent lymphadenopathy.
- *Actinomycosis* is characterized by firm inflammatory nodules, most commonly found at the angle of the jaw, with a tendency to form fistulae.
- *Nocardiosis* is another possible cause of chronic abscesses and fistulae.
- *Bacillary angiomatosis (Bartonella sp.)* is a very rare disease that manifests itself with dark red or bluish papules and nodules. It is seen almost exclusively in HIV-positive individuals.
- The classic cutaneous manifestation of *anthrax* is a painless papule that develops into a hemorrhagic blister on an edematous ground; these are mainly found on the hands.
- *Cutaneous tuberculosis* is currently rare. It is found at the portals of entry, usually the face or lower limbs, and most commonly in children; it consists of a painless papule that develops into an ulcer. *Lupus vulgaris* is a post-primary form of cutaneous tuberculosis that takes a very long course with ulcerating, hyperkeratotic, and sometimes scar-forming lesions.

The following characteristic changes are produced by systemic infections and toxic effects:

- Subacute bacterial *endocarditis* can cause petechiae, subungual splinter hemorrhages, and Osler and Janeway lesions (see section on cutaneous changes in heart diseases, above, and Chapter 4).
- *Streptococcal infections* are sometimes followed by erythema nodosum. In the aftermath of a soft-tissue infection, there may be progressively severe erythema, with the formation of bullae and systemic manifestations of shock (streptococcal toxic shock syndrome).
- *Staphylococcal infections* can produce staphylococcal toxin, with major clinical effects. The staphylococcal scalded skin syndrome usually affects children, while adults usually suffer from toxic shock syndrome,

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which consists of fever, erythrodermia, hypotonia, and desquamation of the skin, particularly on the hands.

- In *meningococcal sepsis,* urticaria may be present transiently before the classic petechial lesions appear (see Chapter 4).
- Hemorrhagic bullae on an indurated base, which ulcerate and form central black areas of necrosis (ecthyma gangrenosum), are seen in *Pseudomonas sepsis.*
- So-called roseola is typical of *salmonellosis* (see Chapter 4).
- In *gonococcal sepsis* (the arthritis–dermatitis syndrome), one finds papules and pustules, mainly on the lower limbs, together with joint swelling and tenosynovitis. A similar picture is seen in chronic meningococcal sepsis (see Chapter 4).
- *Secondary syphilis* can produce a wide variety of exanthems, which often mimic those due to other illnesses (viral exanthems, psoriasis, lichen ruber planus, etc.).
- Other infectious diseases that involve the skin less commonly include brucellosis, leptospirosis, yersiniosis, and listeriosis.

Fungal infections affecting the skin are of various types: superficial fungal infections (dermatophytoses, candidiasis); fungal infections with subcutaneous nodules (sporotrichosis, blastomycosis, coccidioidomycosis); and systemic mycoses with cutaneous manifestations (e. g., histoplasmosis and cryptococcosis).

Viral infections involve the skin either by direct exogenous infection (e. g., herpes simplex virus) or as a cutaneous manifestation of systemic disease. Sometimes a clinical diagnosis can be made from the skin lesions alone, because of their characteristic morphology (e. g., varicella, with the simultaneous appearance of vesicles in different stages of development) or mode of appearance (e. g., exanthem beginning behind the ears in measles).

HIV infection produces a number of characteristic skin changes due to various pathogens, depending on the severity of immune compromise (see Chapter 4).

Hair

Hair growth is mainly under hormonal control, though ethnic and familial differences in hair type are, of course, readily apparent. Important clues to the diagnosis of endocrine diseases can be obtained from the location of the hairline, the type of hair loss, the density of beard and eyebrow growth, and the density and extent of axillary and pubic hair. Hair changes can likewise furnish important evidence of metabolic, inflammatory, or infectious disease.

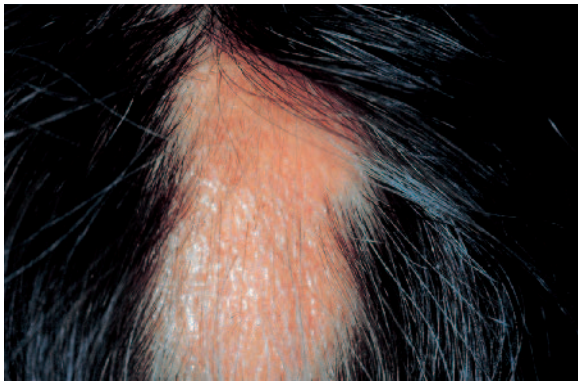

Fig. 3.**28** Alopecia areata.

Hair Loss

Hair loss (effluvium) is a general term for accelerated loss of hair, while alopecia denotes a condition of acquired, visible hair loss on normally hairy skin. Hair loss is physiological from a certain age onward, but its time of onset and rapidity of progression depend on genetic factors (androgenic alopecia). Normal hair loss in women is usually restricted to the parieto-central area and does not cause the hairline to recede.

Severe hair loss (*diffuse telogenic effluvium*) is often seen at a latency of 3–4 months after highly febrile infectious illnesses (e.g., influenza, typhus), childbirth, surgery, acute blood loss, malnutrition (kwashiorkor, marasmus), iron deficiency, thyroid dysfunction (and its medical treatment), adverse drug reactions (mainly to anticoagulants and cytostatic agents), hyperprolactinemia, collagenoses, and systemic amyloidosis.

Alopecia areata (Fig. 3.**28**) is probably an autoimmune disorder; it consists of nonscar-forming hair loss in a circumscribed area. Its course in the individual case is difficult to predict. It may appear together with other autoimmune processes (vitiligo, autoimmune thyroiditis, pernicious anemia) or an atopic diathesis. In severe cases, it can also involve the nails (pitted nails, sandpaper nails, red lunula). It must be distinguished from localized alopecia due to fungal infection, trichotillomania, neoplasia (alopecia neoplastica), and second-

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ary syphilis (alopecia areolaris luetica) (Fig. 3.**29**), as well as from the many types of scar-forming alopecia (e. g., in discoid lupus erythematosus or lichen ruber planus).

Secondary loss of axillary and pubic hair is seen in adult hypopituitarism. Primary axillary and pubic hypertrichosis is typical of Turner syndrome and testicular feminization. A primary or secondary deficiency of testicular function (pituitary dwarfism, pituitary tumors, Klinefelter syndrome, anorchia, cryptorchidism, etc.) manifests itself in an absence or reduced density of pubic, axillary, and facial hair.

Fig. 3.**29** Alopecia areolaris luetica (in secondary syphilis).

Hirsutism and Virilism

Definitions. *Hirsutism* in women is a male-type hair pattern occurring in the typical sites associated with maleness, as well as on the entire body surface. It may be either pathological (endocrine, drug-induced) or physiological (familial). *Virilization* is hirsutism accompanied by other signs of an abnormal differentiation toward maleness (clitoral hypertrophy, deepening of the voice, muscle hypertrophy, breast atrophy, menstrual disturbances, alopecia, acne).

History. Clinical history-taking in a woman with hirsutism should include questions not just about the age at onset and the patient's menstrual cycle, libido, and fertility, but also about her familial and ethnic background. Southern European women often have a heavier growth of hair on the limbs and face than women of Northern European or Asian descent.

Causes. Isolated hirsutism is seen in congenital adrenal cortical hyperplasia, a rare condition, as a result of various enzyme deficiencies. It can also be caused by growth hormone-secreting pituitary tumors, Cushing syndrome, hyperprolactinemia, and adverse reactions to various medications (cortisone, ACTH, gonadotropins, gestagens with androgenic effects, phenytoin, danazol, and minoxidil).

Virilization of sudden onset should always raise suspicion of an androgen-producing adrenal cortical tumor (adenoma or, more commonly, carcinoma of the adrenal cortex), or of an ovarian tumor (arrhenoblastoma, androblastoma, hilus cell tumor, gonadoblastoma).

In polycystic ovary disease (Stein–Leventhal syndrome), virilization and amenorrhea often appear during puberty. The concentration of luteinizing hormone (LH) is high and the concentration of follicle-stimulating hormone (FSH) is low.

Idiopathic hirsutism is diagnosed when hirsutism is not accompanied by virilization and cannot be attributed to any of the other possible causes listed above, and the serum androgen levels are normal. It is caused by abnormalities of end-organ (i. e., hair follicle) metabolism, such as variations in enzymatic activity or in the cellular response to androgenic stimulation.

Pigmentation Disorders

Light blond hair is typically seen in phenylketonuria and homocystinuria.

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Nails

Various systemic illnesses, medications, and locally applied substances can cause typical changes in the appearance of the nails.

Changes in Nail Shape and Structure

Fragile, thin nails are seen in iron deficiency anemia (Fig. 3.**30**), vitamin A overdose, vitamin deficiency states (vitamins A, C, and B_6), chronic infections, arsenic poisoning, and many different genetic syndromes. "Brittle nails," however, are more commonly caused by soaps, detergents, and frequent exposure to moisture (particularly to hot water).

Transverse grooves (Beau–Reil lines) indicate temporary cessation of matrix activity and are easiest to see in the thumbs and great toes. They can be caused by transient, serious illnesses such as acute infections and Stevens–Johnson syndrome, or by the use of cytostatic agents. The maximal variant of this condition, with permanent cessation of nail growth and loss of the nail, is called onychomadesis.

Longitudinal grooves are usually seen in advanced age as a physiological variant but may be due to ischemia or rheumatoid arthritis. Longitudinal grooves combined with fissure formation are seen in hypoparathyroidism, underlying neoplastic disease, or trauma.

Concavity or "spooning" of the nails (*koilonychia*) may be idiopathic, congenital, or acquired. It often accompanies iron deficiency anemia, hemochromatosis, and polycythemia vera, and is occasionally due to endocrine disease (thyroid dysfunction, diabetes mellitus).

Onycholysis (detachment of the nail from its bed) is seen in skin diseases (psoriasis, eczema, bullous diseases), as an adverse drug effect (cytostatic agents), as an effect of photosensitizing medications (photo-onycholysis after the use of tetracyclines, chlorpromazine, allopurinol, or PUVA therapy), in systemic disease (lupus erythematosus, thyroid dysfunction, iron deficiency anemia), as a hereditary condition, and in infectious diseases (fungal infection, syphilis, viral infection). It can also be induced by local factors (trauma, detergents, solvents).

Subungual splinter hemorrhages appear in many different types of disease (collagenoses, vasculitis, diabetes mellitus, hepatitis, HIV infection, sarcoidosis, amyloidosis, and mechanical trauma). They are by no means specific for endocarditis and may also be seen in uncomplicated mitral stenosis.

Crumbly nail dystrophy (subungual hyperkeratosis) is typically seen in fungal infections and psoriasis vulgaris. In addition to crumbly decomposition of the nails, psoriasis produces typical "*oil droplets*" (nail bed psoriasis) and pinhead-sized indentations (pitted nails, Fig. 3.**31**), in combination with distal onycholysis. *Pitted nails* are highly characteristic, but not pathognomonic, of psoriasis vulgaris; similar changes are seen in eczema and severe cases of alopecia areata. Subungual hyperkeratoses can also have a mechanical cause, as it can be induced by continuous pressure on the nail (often seen in the fourth and fifth toes).

The *transverse lines of Mees* (white stripes) are usually the product of a febrile illness, intoxication (usually arsenic or thallium), or traumatic event.

Hourglass nails ("clubbing") are broader than normal nails; drumstick nails are a more advanced form of the same phenomenon. Drumstick nails are occasionally seen as a hereditary phenomenon but are usually caused by one of the following conditions:

- lung diseases (bronchiectasis, empyema, emphysema, bronchial carcinoma, cystic fibrosis, mesothelioma, sarcoidosis with pulmonary fibrosis)
- cyanotic congenital heart defects

Fig. 3.**30** Thin, fragile nails in iron deficiency anemia.

Fig. 3.**31** Pitted fingernails in psoriasis.

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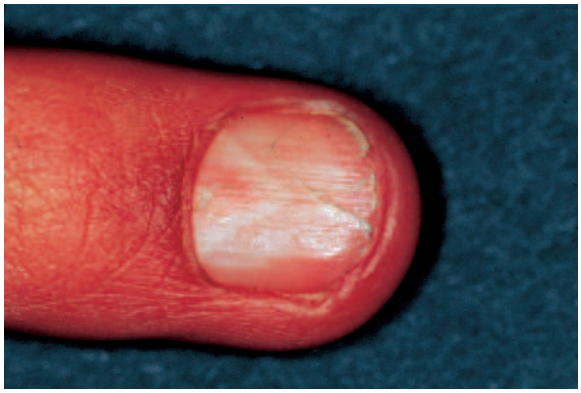

Fig. 3.**32** Triangular lunula in the nail–patella syndrome.

Fig. 3.**33** Nail dystrophy in lichen ruber planus.

- malignant tumors (mainly intrathoracic tumors and metastases)
- less commonly (5% of cases), gastrointestinal disorders (Crohn disease, ulcerative colitis, primary biliary cirrhosis, polyposis, sprue)
- and, rarely, hematologic diseases causing hypoxia, and endocrine diseases (hyperthyroidism).

Drumstick fingers are frequently associated with a hypertrophic osteoarthropathy: for example, hypertrophic pulmonary osteoarthropathy (Bamberger–Marie syndrome) manifests itself with drumstick fingers (and toes) as well as periosteal neo-ossification of the long bones, arthralgias, and symptoms such as flushing and profuse sweating. This syndrome is practically pathognomonic for malignant tumors, particularly bronchial carcinoma and pleural mesothelioma, though bronchiectasis also rarely causes it.

Characteristic nail dystrophies appear in congenital disorders including epidermolysis bullosa, progeria, congenital dyskeratosis, congenital pachyonychia, and the *nail–patella syndrome* (Fig. 3.**32**). The last-named condition is transmitted in an autosomal dominant mode and manifests itself with hypoplastic thumbnails, a typical, triangular lunula, the lack of one or both patellae, other skeletal deformities, and, in just over half of all patients, renal involvement (glomerulonephritis). Heterochromia of the iris is also present and serves as a helpful clue to the diagnosis.

Lichen ruber planus occasionally affects the nails in isolation. It can cause a very wide variety of nail changes, ranging from rough, sandpaperlike nails (trachyonychia) to fragile nails, subungual hyperkeratoses, pterygiumlike changes, and complete nail loss, with atrophy and scarring (Fig. 3.**33**).

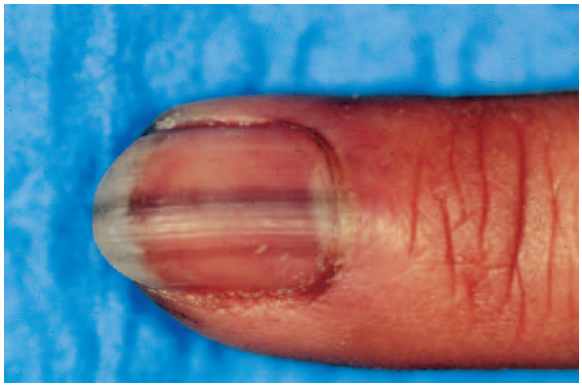

Fig. 3.**34** Melanonychia striata after treatment with zidovudine.

Nail Discoloration

Nail pigmentation (chromonychia) can affect the nail plate diffusely or in striated fashion. It can be caused by excess production of pigment (e. g., melanin) or by the deposition of various substances (e. g., copper, medications, occasionally hemosiderin).

Brown or black discoloration is seen in Addison disease, Peutz–Jeghers syndrome, Laugier–Hunziker syndrome, hyperthyroidism, hemochromatosis, Cushing disease, and vitamin B_{12} deficiency. Local application of, or contact with, silver nitrate, potassium permanganate, iodine, 5-fluorouracil, and nail hardeners, as well as the systemic administration of gold salts, arsenic, cytostatic agents, ACTH, and PUVA therapy can also discolor the nails. If only one nail is affected, or if a striated, brown discoloration (melanonychia striata) is seen, the physician must suspect malignant melanoma. Other causes of striated discoloration include melanocytic nevi, various medications (zidovudine, antimalarial agents) (Fig. 3.**34**), subungual tumors, radiation, and, rarely, carcinoma of the breast.

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Fig. 3.**35** Yellow nail syndrome.

Fig. 3.**37** "Half-and-half nail" in uremia.

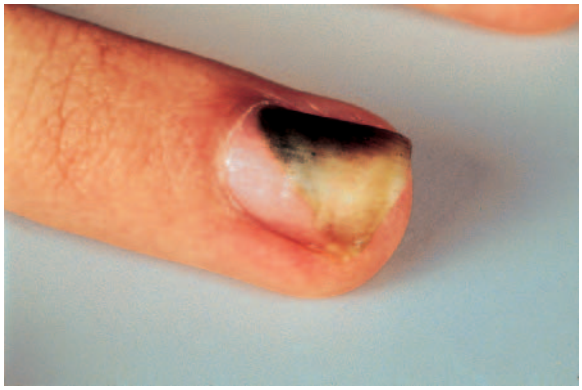

Fig. 3.**36** Green discoloration in subungual *Pseudomonas* infection.

Blue-gray discoloration of the nails is seen after silver or chloroquine intake. Gray discoloration can also result from malaria or visceral leishmaniasis. In Wilson disease, the lunula, in particular, takes on a blue color.

Yellow nails may be due to jaundice, Cronkhite–Canada syndrome, or the use of tetracyclines, D-penicillamine, or lithium. Yellow discoloration of exogenous origin is seen in heavy smokers and after the topical application of picric acid and glutaraldehyde. Yellow nail syndrome consists of yellow fingernails and toenails in combination with lymphedema and pulmonary manifestations (chronic pleural effusion, bronchiectasis, bronchitis) (Fig. 3.**35**).

The nails appear *green* in local *Pseudomonas* infection (Fig. 3.**36**).

White nails (leukonychia) may be familial; total white discoloration is to be distinguished from transverse striate white discoloration or partially whitened nails (e. g., Terry nails, with a normal distal edge, seen in hepatic cirrhosis). White nails can also be a manifestation of chronic infection (leprosy), tumors (Hodgkin disease), hypoalbuminemia, and uremia ("half-and-half nail") (Fig. 3.**37**).

Oral Cavity

Oral changes are usually due to local disease but may be an early manifestation of a systemic disease or dermatosis.

Changes of the Teeth

Impaired embryonic development of the number and shape of the teeth is a feature of the multiple ectodermal dysplasias. Enamel defects (transverse grooves, white spots) may be due to previous illnesses such as rickets, hypoparathyroidism, or celiac disease. Hypoplasia can result from congenital infections such as rubella or cytomegalovirus infection. Discoloration of the teeth has a number of exogenous causes (poor hygiene, smoking, tea, or local medications such as chlorhexidine). Systemic tetracycline use in the latter half of gestation, and up to the age of 8 years, can cause irreversible yellow discoloration of the teeth, as well as enamel defects, through the deposition of tetracycline–calcium phosphate complexes. Radiotherapy or the use of cytostatic agents causes dental hypoplasia, as do malabsorption syndromes, severe childhood illnesses, and immune suppression after organ transplantation. In Down syndrome, the teeth tend to be small and fall out prematurely. The barrel-shaped teeth typical of con-

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genital syphilis (Hutchinson teeth) are, fortunately, very rarely seen today. Premature tooth loss can be caused by vitamin D resistant rickets, hypophosphatasia, Ehlers–Danlos syndrome, and immune deficiencies.

Changes of the Gums

Gingival hemorrhage can be caused either by local factors (acute or chronic gingivitis) or by systemic disease (myeloproliferative disorders, HIV infection, coagulopathies and other diseases causing purpura). Gingival hyperplasia is seen in pregnancy, leukemia (mainly acute monocytic leukemia), sarcoidosis, and Crohn disease, and as an adverse effect of treatment with phenytoin, cyclosporine, or calcium-channel blockers. Kaposi sarcoma of the gums presents with violet-colored tumors (Fig. 3.**38**). Gingivitis has many causes; it is especially common in immune-suppressed individuals. A black gingival edge indicates lead poisoning, while a blue-gray edge indicates silver or bismuth poisoning. A reticulated whitish pattern is typically seen in lichen ruber mucosae.

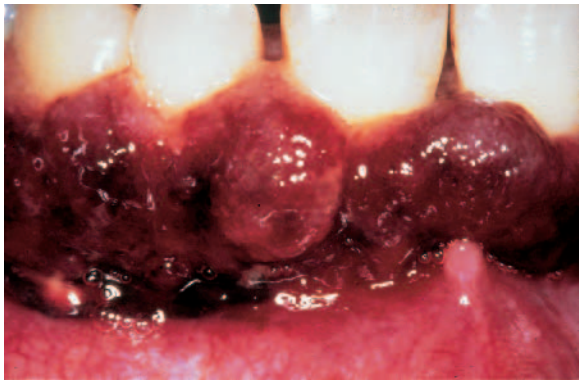

Fig. 3.**38** Kaposi sarcoma of the gingiva.

Changes of the Oral Mucosa

Leukoplakia. Circumscribed whitish lesions of the oral mucosa and lips have multiple causes (Tab. 3.**7**).

Table 3.**7** Causes of leukoplakia

Local factors
- mechanically induced keratosis
- nicotinic keratosis
- precancerous lesions
- squamous cell carcinoma
- burns

Systemic factors
- candidiasis
- lichen ruber mucosae
- systemic lupus erythematosus
- papillomas (viral/nonviral)
- oral hairy leukoplakia (especially in HIV infection)
- syphilitic foci
- chronic renal failure
- hereditary ("white sponge nevus")

Thrush. Oral thrush often indicates an underlying systemic disease. It can be a complication of malignant neoplasia or of pregnancy, or of treatment with steroids, immunosuppressive drugs, cytostatic agents, or antibiotics. *Candida* stomatitis is often seen in HIV disease as early as the primary infection.

Aphthae and Ulcers. Intraoral ulcerations are seen in infectious diseases (gingivostomatitis herpetica, varicella, infectious mononucleosis, hand, foot, and mouth disease, primary HIV infection, secondary syphilis, and occasionally, tuberculosis). They can also be caused by hematologic disease (pernicious anemia, iron deficiency anemia, folic acid deficiency, cyclic neutropenia, leukemia) or gastrointestinal disorders (celiac disease, Crohn disease, or, less commonly, ulcerative colitis). Further causes of intraoral ulcerations include rheumatic diseases (systemic lupus erythematosus, Behçet syndrome, Reiter disease), medications (cytostatic agents, aspirin), and skin diseases (lichen ruber, less commonly bullous pemphigoid, dermatitis herpetiformis Duhring, erythema exsudativum multiforme [Stevens–Johnson syndrome], and epidermolysis bullosa). Chronic ulcers may be due to a tumor of the oral mucosa. Recurrent, painful ulceration is seen in chronic recurrent aphthous stomatitis.

Xerostomia. Dry mouth is not uncommon with advancing age but can also be caused by any of the following: inflammation of the salivary glands in sarcoidosis, Sjögren syndrome, prior radiotherapy, prior graft-versus-host disease, HIV infection, diabetes mellitus (dehydration), botulism, hyperthyroidism, and depression. The following medications, too, can cause dry mouth: atropine, sympathomimetic agents, tricyclic antidepressants, antihistamines, antiemetic agents, β-blockers, lithium, and appetite suppressants.

Hyperpigmentation in the oral cavity is mostly a normal, inherited (racial) characteristic but can also be a sign of disease states, including Addison disease, the Carney complex (myxomas, patchy hypopigmentation, testicular tumor, and pituitary adenoma), Peutz–Jeghers syndrome, hemochromatosis, porphyria, lead poisoning, hemorrhages, and amalgam tattooing. It can also be a side effect of medication (chloroquine, quinine, chlorpromazine).

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Fig. 3.**39** Geographic tongue due to atopy.

Fig. 3.**40** Mucous patches on the tongue in secondary syphilis.

Table 3.**8** Common causes of burning mouth syndrome

Local factors
- candidiasis
- other infections
- geographic tongue
- lichen ruber mucosae
- contact eczema (especially dental filling material)

Systemic factors
- psychogenic (cancer phobia, depression)
- deficiency states
  - pernicious anemia and other vitamin B deficiency states
  - folic acid deficiency
  - iron deficiency
- diabetes mellitus
- medication side effect (especially captopril)

Tongue

A coated or furred tongue has been recognized as a sign of disease for millennia but may also be present in normal individuals (e. g., when not rubbed away after the ingestion of semiliquid food); it may also have local, mechanical causes (insufficient chewing or a motor disturbance). An extreme variant of this finding is the black, hairy tongue that is sometimes seen after antibiotic therapy, e. g., with tetracycline. Geographic tongue (Fig. 3.**39**), which is often asymptomatic, is frequently due to atopy, but psoriasis and Reiter disease also belong in the differential diagnosis. A furrowed (so-called "scrotal") tongue is a normal, innocuous finding but can also be seen in Down syndrome and Melkersson–Rosenthal syndrome. Tongue enlargement (macroglossia) is seen in Down syndrome, amyloidosis, and acromegaly, as well as in the acute setting as a manifestation of Quincke edema. Its differential diagnosis includes angioneurotic edema as an adverse effect of an angiotensin converting enzyme inhibitor. Inflammatory hypertrophy of the tongue papillae causes strawberry tongue, which can be seen in scarlet fever, toxic shock syndrome, or Kawasaki syndrome. A white coating that can easily be scraped off the tongue is typical of thrush. Total atrophy of the tongue (Hunter glossitis) may be due to a deficiency of vitamin B_{12}, iron, or folic acid. Similar changes are caused by pellagra and syphilis; the latter usually produces mucous patches on the tongue, as seen in Fig. 3.**40**. Burning of the tongue, without any objective correlate, is a common symptom and has many causes (Tab. 3.**8**).

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3.2 External Appearance

Stature and Posture

Tall Stature

For most very tall individuals, their stature is simply a normal variant. Children with constitutional tall stature or genetically determined familial tall stature grow more rapidly than others, but their rate of growth lies within the upper limit of normal, and their bone age corresponds to their chronological age. Their final height can be predicted from their family history.

A number of congenital syndromes, however, can cause abnormally tall stature as a pathological phenomenon, and, in rare cases, tallness can be a consequence of endocrine disease (Tab. 3.**9**).

Table 3.**9** Causes of tall stature

Tall stature of nonendocrine origin
- constitutional
- genetic/familial
- as part of a *syndrome*
  - cerebral gigantism (Sotos syndrome)
  - Marfan syndrome
  - homocysteinuria
  - Beckwith–Wiedemann syndrome
  - Klippel–Trénaunay syndrome
  - XYY syndrome
  - Klinefelter syndrome

Tall stature of endocrine origin
- pituitary gigantism
- precocious puberty
- hyperthyroidism

Tall Stature Due to Congenital Syndromes

Cerebral Gigantism (Sotos Syndrome). Patients with this syndrome are abnormally tall and have a prominent forehead, an arched palate, a pointed chin, and hypertelorism.

Marfan syndrome is due to impaired collagen synthesis because of a mutation in the fibrillin-1 gene on chromosome 15q21.1. Its mode of inheritance is autosomal dominant.

Most patients with Marfan syndrome are quite tall. Other typical findings include long, slender limbs (Fig. 3.**41**), so-called spider fingers (arachnodactyly), hyperextensible joints, chest deformities (pectus excavatum or pectus carinatum, scoliosis), a high palate, and, usually, a long face. 80% of patients suffer from dislocation of the lenses (usually upward), tremulousness of the iris, and often severe myopia. In 90% of patients, cystic necrosis of the vascular tunica media leads to aortic dilatation or aneurysm formation, and to mitral valve prolapse.

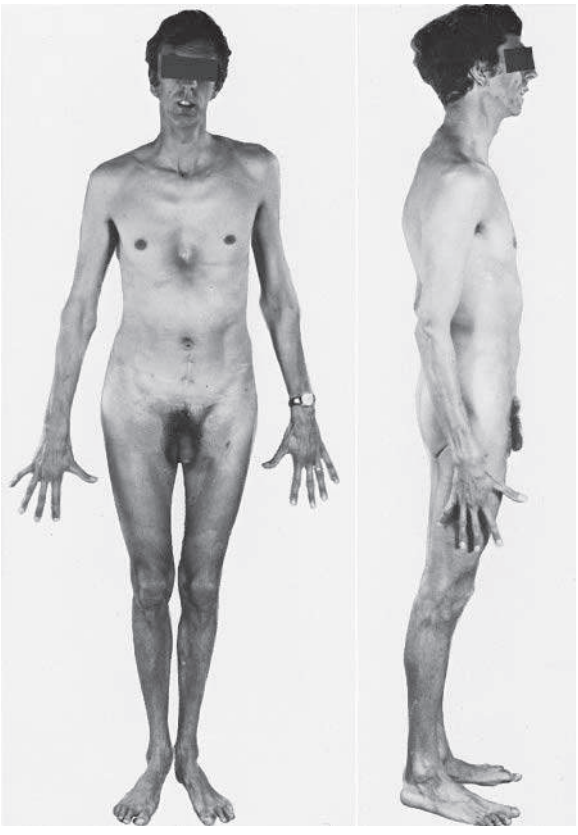

Fig. 3.**41** Marfan syndrome: long limbs, arachnodactyly, pectus excavatum, dolichocephaly.

Homocystinuria is an autosomal recessive disorder due to a mutation of the cystathione-β gene on chromosome 21q22.3. Patients have a similar habitus to that seen in Marfan syndrome but are usually also mentally retarded and tend to develop epilepsy. The lenses are usually dislocated downward. The diagnosis is confirmed by a finding of abnormally high amounts of homocystine in the urine, combined with elevated plasma concentrations of homocystine and methionine and a low plasma concentration of cysteine.

Beckwith–Wiedemann Syndrome. Patients with this syndrome are tall and overweight; in 80% of cases, they have an omphalocele and macroglossia. Hyperplasia of

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Fig. 3.**42** Klippel–Trénaunay syndrome: nevus flammeus and disproportionate gigantism.

the pancreatic islet cells causes hyperinsulinism and therefore a tendency to develop hypoglycemia.

Klippel–Trénaunay syndrome is a variant of hereditary angiodysplasia causing a special type of disproportionate gigantism. Typical features include vascular nevus, unilateral varicosis, and hypertrophy of bone and soft tissue (Figs. 3.**42** and 3.**43**).

XYY Syndrome. Patients with one or more supernumerary Y-chromosomes (47,XYY or 48,XYYY) grow more rapidly than normal and achieve an above average height.

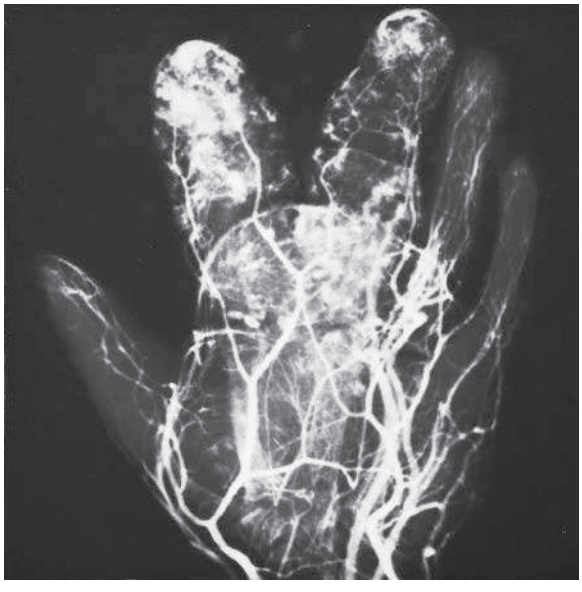
Klinefelter syndrome (47,XXY), found in 1 in 1000 males, is the most common type of primary hypogonadism. Its typical features include bilateral, painless gynecomastia, small, firm, fibrotic testes, and azoospermia. The affected individuals are often overweight (eunuchoid habitus) and taller than average, with long lower limbs (Fig. 3.**44**).

Tall Stature Due to Endocrine Disorders

Pituitary gigantism is due to excessive growth hormone (GH) production by a hormone-secreting pituitary adenoma, or, in rare cases, excessive hypothalamic secretion of growth hormone releasing hormone (GHRH), occurring before the closure of the epiphyses. These patients are very tall and have coarse, cragged facial features, large hands and feet with broad, plump fingers and toes, a prominent skull, and prominent cheek and jaw bones (Fig. 3.**45**). If the excessive hormone secretion occurs only after the epiphyses have closed, then the result is not pituitary gigantism, but acromegaly (see Chapter 23), typified by abnormal growth of the hands (Fig. 3.**46**), feet, chin (prognathism), tongue (Fig. 3.**47**), and internal organs.

Abnormally Tall Stature in Childhood. The most common endocrine cause of abnormally tall stature in childhood is precocious puberty, as a result of unusually early secretion of androgens or estrogens, which accelerates bone growth. The sex steroids cause epiphyseal closure

a



b

Fig. 3.**43** Hereditary angiodysplasia
a of two fingers and part of the left palm,
b arteriogram of the left hand: markedly enlarged blood vessels and arteriovenous shunting.

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Fig. 3.**44** Typical eunuchoid habitus in a 26-year-old man with Klinefelter syndrome: bilateral gynecomastia, testicular atrophy.

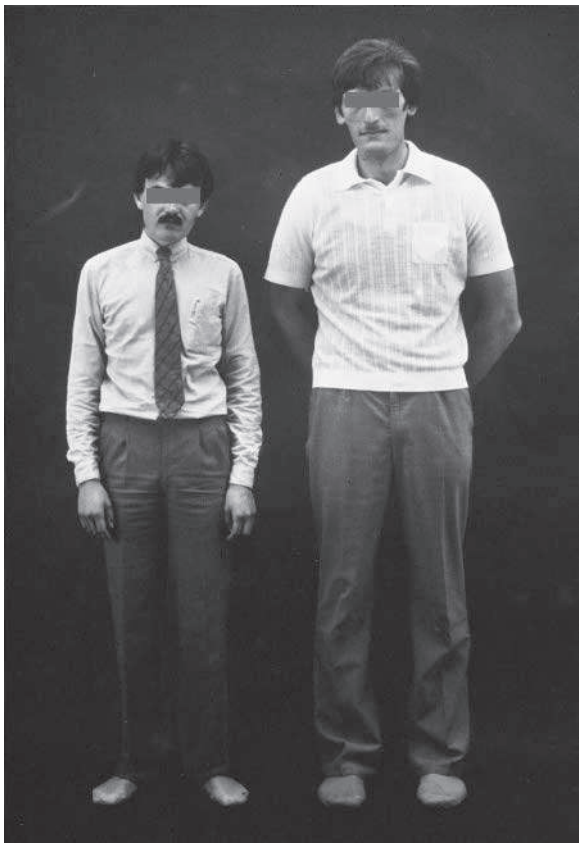

Fig. 3.**45** Patient with pituitary gigantism (205 cm) compared to a person of normal stature (177 cm).

a

b

Fig. 3.**46** Acromegalic hand (**a**) compared to a normal hand (**b**).

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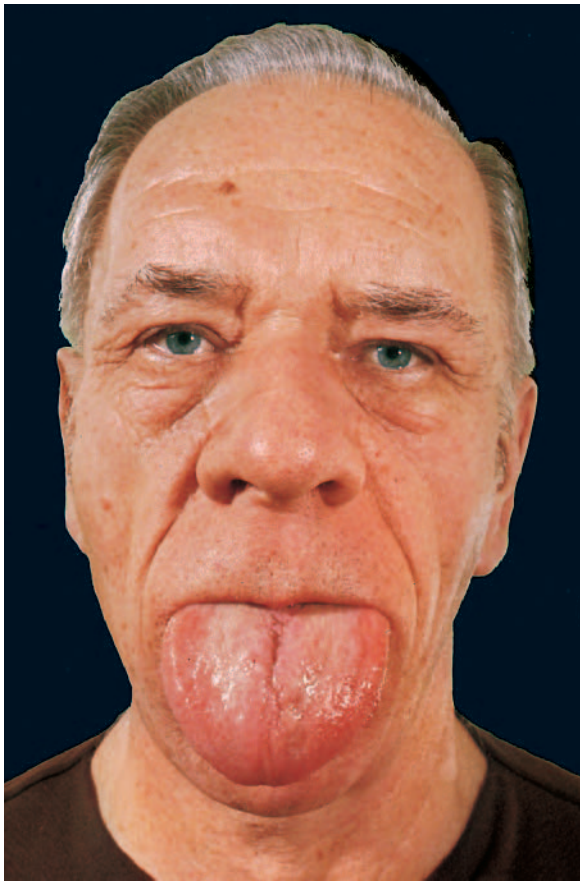

Fig. 3.**47** Acromegaly. Enlarged tongue and nose.

to occur abnormally early. Thus, once they reach adulthood, these patients tend to be short.

Hyperthyroidism in childhood can accelerate bodily growth and bone maturation.

Short Stature

Short stature is defined as height below the third percentile (for 18-year-olds), i. e., 166 cm for men, 152 cm for women. Short stature need not be pathological. In many cases, it is due to constitutionally delayed development, with slow growth of the body and delayed puberty within the normal range. The individual's height is lower than average and his or her bone age is mildly delayed. Short stature can also be genetic/familial: in such cases, the individual's parents and siblings are typically short as well.

The differential diagnosis of short stature should always include endocrine and nonendocrine causes, as well as a number of syndromes and chromosomal anomalies known to be associated with this condition (Tab. 3.**10**).

Table 3.**10** Causes of short stature

Short stature of nonendocrine origin:
- constitutional
- genetic/familial
- premature birth and intrauterine growth delay
- as part of a *syndrome*
  - Turner syndrome
  - Noonan syndrome
  - Prader–Willi–Labhart syndrome
  - Lawrence-Moon/Biedl–Bardet syndrome
  - autosomal chromosome aberrations
- chronic illnesses
- malnutrition
- medications
- psychosocial factors

Short stature of endocrine origin

Growth hormone (GH) deficiency
- congenital GH deficiency
  - hypothalamic growth hormone-releasing hormone (GHRH) deficiency
  - isolated pituitary GH deficiency
  - combined with other pituitary hormone deficiencies
  - pituitary agenesis
- acquired GH deficiency
  - suprasellar/intrasellar tumors
  - CNS birth defects, hydrocephalus
  - radiotherapy of the brain
  - traumatic brain injury
  - infectious disease (meningitis, encephalitis)
  - histiocytosis
- inadequate GH effect (GH resistance) and insulin growth factor (IGF) deficiency
  - Laron dwarfism
  - pygmies
  - undernourishment, liver disease

Hypothyroidism
Glucocorticoid excess (endogenous, exogenous)
Pseudohypoparathyroidism
Vitamin D deficiency
Diabetes mellitus
Diabetes insipidus

Short Stature Due to Congenital Syndromes

Turner Syndrome (gonadal dysgenesis) is a chromosomal anomaly with karyotype 45,X. It is found in 1 in 5000 newborn girls. It manifests itself phenotypically in a shieldlike chest, a wide intermammillary distance (Fig. 3.**48**), a webbed neck (pterygium colli), and a deep hairline in the nuchal region (Fig. 3.**49**). Its major symptoms are primary amenorrhea, absence of pubertal development, and short stature (usually < 150 cm). The external genitalia are female and poorly developed; the gonads consist merely of fibrous strands.

Turner syndrome and its variants are associated with a number of anomalies, including epicanthus, micrognathia, low-lying or deformed ears, hand deformities, stenosis of the aortic isthmus, ventricular septal defect, renal defects, nail changes, and cubitus valgus. Pure chromatin-negative forms (45,X) account for about 60 % of patients, while the remainder are mosaics (45,X/46,XX).

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Fig. 3.**48** Turner syndrome. 18-year-old woman, karyotype 45,X0, shieldlike chest with widened intermammillary distance, and absence of breast tissue.

Noonan syndrome (pseudo-Turner syndrome) is another cause of a markedly webbed neck to be considered in the differential diagnosis of Turner syndrome. Unlike the latter, Noonan syndrome has a normal karyotype, i. e., 46,XX in women or 46,XY in men. It is an autosomal dominant genetic disease due to a mutation on chromosome 12q24.

Prader–Willi–Labhart syndrome, another syndrome causing short stature, is characterized by fetal and infantile hypotonia, acromicria (small hands and feet), developmental delay, almond-shaped eyes, and marked obesity. Further typical findings are glucose intolerance and delayed puberty.

Lawrence–Moon syndrome and Biedl–Bardet syndrome are autosomal recessive inherited diseases that also cause short stature and obesity and should be considered in the differential diagnosis of Prader–Willi–Labhart syndrome.

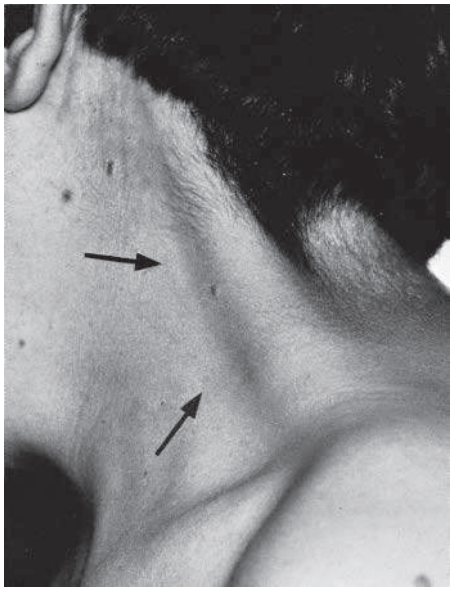

Fig. 3.**49** Pterygium colli (webbed neck) in Turner syndrome.

Short Stature Due to Skeletal Dysplasias

The more than 100 known types of genetically determined skeletal dysplasia (osteochondrodysplasia) are a further important cause of short stature.

Achondroplasia, an autosomal dominant genetic disease, is the most common and most important type of skeletal dysplasia. The underlying mutation in the fibroblast growth factor receptor gene (FGFR3) impairs enchondral ossification, causing impaired growth of the long bones and the base of the skull. The result is a characteristic form of disproportionate dwarfism, with a large head, a prominent forehead (Fig. 3.**50**), and limbs that are too short in relation to the trunk. The affected individuals are not ill in any other way, however, and are of entirely normal intelligence.

Short Stature Due to Chronic Diseases and Malabsorption Syndromes

Short or reduced stature can also be due to chronic illness in childhood or to malabsorption syndromes and malnutrition. The potential causes of developmental delay and short stature include renal disease (birth defects, renal tubular acidosis, chronic glomerulo-

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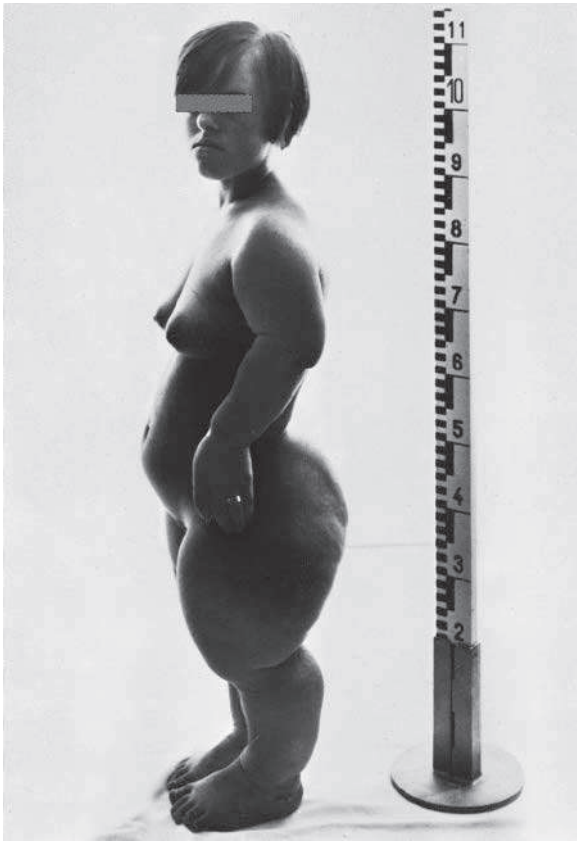

Fig. 3.**50** Dwarfism with disproportionate growth in achondroplasia (chondrodystrophy).

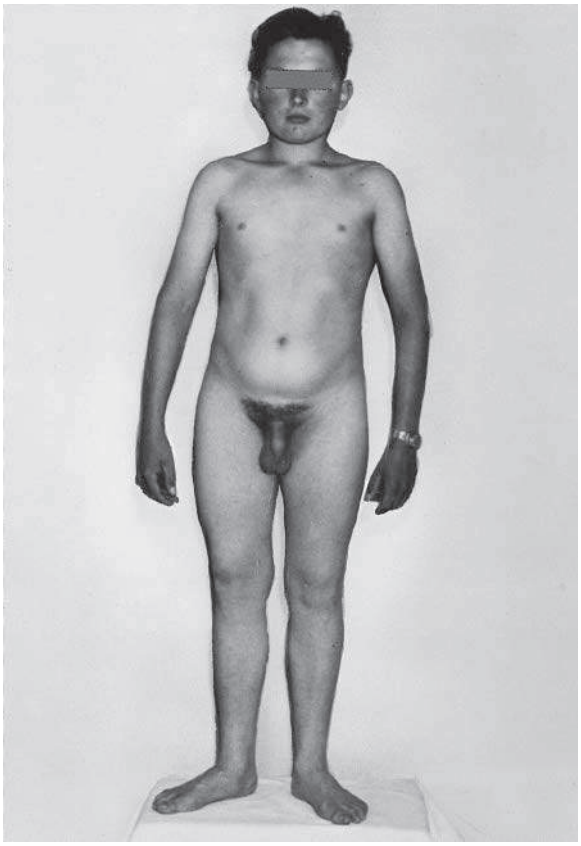

Fig. 3.**51** Pituitary dwarfism with proportionate growth in a 21-year-old man.

nephritis), congenital heart defects, chronic pulmonary disease (cystic fibrosis, asthma), malabsorption syndromes (celiac disease, Crohn disease, ulcerative colitis, zinc or iron deficiency), hematologic disease (thalassemia, sickle cell anemia), and immunological disease (juvenile rheumatoid arthritis, chronic infections).

Short Stature Due to Endocrine Disorders

Growth hormone deficiency is by far the most common hormonal cause of short stature. Its cause may lie anywhere along the hypothalamic–pituitary–end-organ axis and may be either congenital or acquired (Tab. 3.**10**). The resulting clinical picture is known as pituitary dwarfism (Fig. 3.**51**) and is characterized by proportionate short stature due to growth delay that is already manifest in early childhood. The patient's bone age is substantially delayed, there is mild truncal obesity, and the face is doll-like. Intelligence is normal.

Hypothalamic causes of GH deficiency include a congenital deficiency of GHRH (growth hormone releasing hormone), hypothalamic tumors such as craniopharyngioma, dysgerminoma, and neurofibroma, postinfectious states (meningitis), histiocytosis X, hydrocephalus, and prior cranial radiotherapy.

Primary pituitary disorders causing GH deficiency (pituitary hypoplasia or aplasia, isolated GH deficiency) are associated with further congenital defects such as midline defects, optic nerve hypoplasia, cleft lip, jaw, palate, etc. Other causes of pituitary dysfunction include trauma, intrasellar tumors, and local inflammatory processes.

Congenital or acquired *growth hormone resistance* causes inadequate production of insulinlike growth factor (IGF)-1 and therefore results in the clinical picture of growth hormone deficiency. *Laron dwarves* have a genetic defect of the GH receptor, or else a post-receptor defect, with an autosomal recessive inheritance pattern. The plasma GH concentration is elevated and the IGF-1 concentration is low. The affected children are abnormally small at birth and have a tendency to hypoglycemia. *Pygmies* have a congenital IGF-1 deficiency (their GH levels are normal). Severe *liver disease* can impair IGF-1 production and thereby lead to short stature.

Other endocrine causes of short stature include congenital or acquired hypothyroidism in childhood, Cushing syndrome or the exogenous administration of glucocorticoids (including topical application) in childhood (e. g., to treat asthma or eczema), pseudohypoparathyroidism, vitamin D deficiency, rickets, X-linked hy-

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Fig. 3.**52** Typical posture in Parkinson disease.

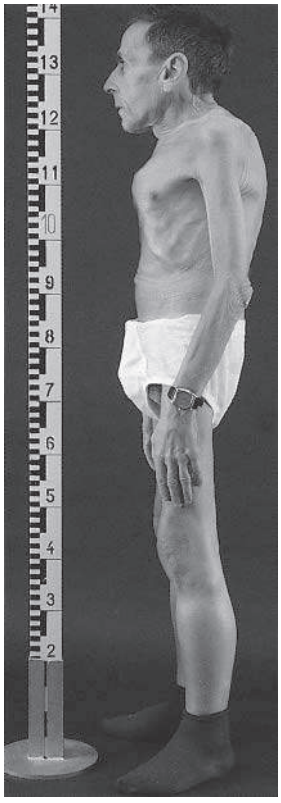

Fig. 3.**53** Marked thoracic kyphosis in a 64-year-old man with multiple myeloma and severe osteoporosis.

pophosphatemia, Fanconi syndrome, and poorly controlled diabetes mellitus (catabolic state with delayed growth).

Standing Posture

Abnormal standing posture is a highly characteristic feature of Parkinson disease. The mildly stooped and stiff stance, hanging shoulders, and slow movements with superimposed tremor are nearly unmistakable (Fig. 3.**52**). Certain diseases of the spine, particularly Bekhterev disease (ankylosing spondylitis), also create the impression of stiffness but leave the limbs essentially unaffected (Fig. 3.**53**). An exaggerated lumbar lordosis is found in muscular dystrophy. Scoliosis was often seen in earlier times as a result of poliomyelitis. Today, it is frequently due to severe osteoporosis.

Lying Posture

Fully developed meningitis can be suspected in patients who press their head back firmly into the pillow. Other, classic manifestations of meningitis may be absent, particularly in the elderly. As long as the patient is conscious, all movements of the head are rigorously avoided. The knees are flexed, but opisthotonus is seen only in the most severe cases. Very marked opisthotonus, so-called "arc en cercle," is hardly ever seen today and must raise the suspicion of hysteria.

Abdominal colic (pain arising from the intraperitoneal organs) causes the patient to toss and turn in bed, and a cringing position is typical. This is to be contrasted with pain caused by inflammation of the parietal peritoneum (peritonitis): here, the affected patients strenuously avoid all movement and try not to touch the abdomen, which is rigid. In colicky pain, pressing affords some degree of relief.

Patients who need to sit up in bed in order not to be short of breath are suffering from orthopnea. Cardiac patients tend to sit up in bed, while patients with pulmonary insufficiency are often no less comfortable when lying. Asthmatics sit up and prop themselves up by the arms during an attack (auxiliary muscles of respiration). A cringing posture is adopted by cyanotic children with the tetralogy of Fallot.

Gait

An abnormal gait with small, shuffling steps (*marche à petits pas*) is typically seen in Parkinson disease. Affected patients have difficulty initiating gait, lack the normally accompanying arm movements, and tend to

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fall forward or backward (propulsion, retropulsion) while walking or standing. Gait ataxia can be due to peripheral neuropathy, spinal cord dysfunction, or cerebellar dysfunction. Patients with tabes dorsalis and multiple sclerosis have a broad-based, dragging gait and watch their feet while walking. Visual control provides no additional help in cerebellar gait disturbances; affected patients tend to fall to the side of the lesion.

Steppage gait is characterized by abnormal raising of the knee with each step in order to keep the toes from dragging along the ground. This type of gait abnormality indicates an inability to dorsiflex the foot (foot drop), which may be due to spinal nerve L5 radicular weakness, a peroneal nerve palsy of traumatic or other origin, or a toxic or diabetic polyneuropathy. In Little disease, i. e., congenital spastic cerebral palsy, the legs cross over each other when the patient walks (scissors gait). A waddling gait is seen in muscular dystrophy. The typical gait of hemiparetic patients, with circumduction of the affected leg, is easy to recognize.

Hysterical gait abnormalities take many forms and are often accompanied by bodily movements that obviously require intact coordination for their performance.

Obesity

Definition. Overweight and obesity are abnormal states characterized by excessive body fat. Both are defined in terms of the BMI (body mass index), which equals the weight in kilograms divided by the height in meters squared. Persons whose BMI exceeds 25 kg/m^2 are overweight, while those whose BMI exceeds 30 kg/m^2 are obese (Tab. 3.**11**).

Epidemiology. Depending on age, sex, and ethnic origin, the prevalence of overweight varies from 1% to 64% and that of obesity from 1% to 31%. The prevalence of both conditions has increased markedly in the industrialized world in the past two decades, and more and more children and adolescents are affected in some countries, as many as 20% of adolescents 12–16 years of age. Primary generalized obesity is to be distinguished from other, secondary types.

Primary Obesity

Pathogenesis. Obesity is of multifactorial origin. In 99% of cases, there is no evident organic or mental disorder underlying it, and it is therefore called *essential* or *primary generalized obesity* (Fig. 3.**54**). Both hereditary and environmental factors play a role in its pathogenesis. Adoption and identical twin studies have shown that genetic factors (multiple genes acting in concert) account for about 70% of the variation in BMI, while the remaining 30% is due to environmental factors; those promoting obesity include dietary habits (fatty food, high caloric intake, alcohol use), low energy consumption (sedentary lifestyle, lack of exercise), and psychosocial factors (stress). Hormones produced in fatty tissue (leptin, adiponectin, resistin, TNF-α, etc.) and neuroendocrine factors (gastrointestinal hormones [GIP, PYY_{3-36}, ghrelin, CCK], insulin, CRF, neurotransmitters [neuropeptide Y, noradrenaline, monoamines, GABA, etc.]) regulate appetite by modulating the production of neuropeptide Y and α-MSH in the hypothalamus. In very rare cases, obesity is caused by a congenital or acquired lesion (tumor, surgery, radiation, encephalitis) of the ventromedial hypothalamic regulatory centers, or else by a mutation in the leptin or melanocortin-4 receptor (MC4R) gene. Obesity due to hypothalamic disease is often accompanied by hypogonadotropic hypogonadism.

Table 3.**11** Standard classification of body weight according to the WHO International Obesity Task Force

Designation	BMI (kg/m^2)
Underweight	< 18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obesity	
– moderate (class I)	30.0–34.9
– severe (class II)	35.0–39.0
– morbid (class III)	> 40.0

Syndromes with Obesity. A number of genetic diseases cause obesity in combination with other manifestations. *Adiposogenital dystrophy* (Fröhlich syndrome) is a very rare disease characterized by hypogonadotropic hypogonadism, obesity, and signs of intracranial hypertension. A typical "flour sack" body shape is seen in *Prader–Willi–Labhart syndrome* along with decreased muscle tone, short stature, and impaired glucose tolerance.

Lawrence–Moon–Biedl syndrome consists of manifestations such as retinitis pigmentosa, an abnormally shaped skull, polydactyly or syndactyly, mental retardation, extrapyramidal motor disturbances, and obesity. Patients with *Alström disease* have atypical retinal degeneration leading to blindness, progressive sensorineural deafness, and often diabetes mellitus.

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Secondary Obesity

Endocrine Causes. About 1% of obese persons suffer from secondary obesity, the usual cause of which is an endocrine disease. Diseases of this type are generally easy to diagnose because of their manner of presentation. Cushing syndrome is characterized by truncal obesity and muscle atrophy, while hypothyroidism (which is often a diagnosis to be ruled out in obese patients) causes typical additional symptoms such as generalized weakness, cold intolerance, fatigue, constipation, myxedema, etc. Other endocrine causes of increased body fat include hypogonadism (gynoid habitus), growth hormone deficiency, and polycystic ovary syndrome (PCOS).

Pharmacological Causes. Weight gain can also be caused by medications. The following medications all promote overweight, by a variety of mechanisms: antidepressants, neuroleptic agents, anxiolytic agents, anticonvulsants, glucocorticoids, estrogens, progestagens, antihistamines, oral antidiabetic agents, insulin, and lithium.

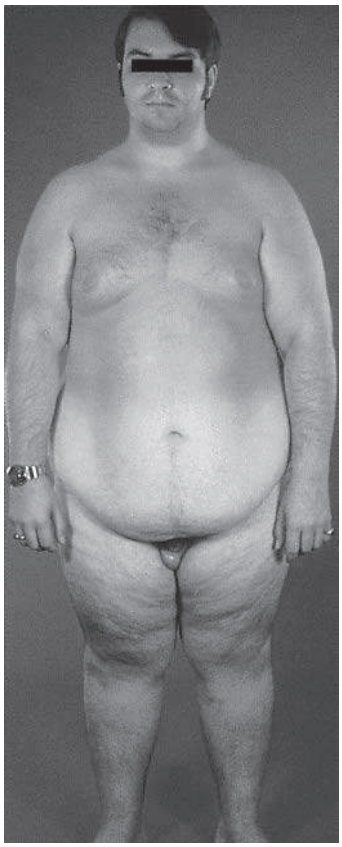

Fig. 3.**54** Essential obesity (adipositas simplex) in a 20-year-old man.

Localized Collections of Fat and Lipodystrophies

While obesity is a generalized excess of body fat, a number of other conditions cause increased fat in a circumscribed area.

Multiple symmetrical lipomatosis can be either inherited or acquired (mainly in alcoholics) and is characterized by symmetrical, lipomalike fat deposits in the region of the shoulder girdle, on the neck, and in the supraclavicular area (so-called Madelung fatty neck disease).

The lipodystrophies are a clinically heterogeneous group of congenital and acquired diseases causing regional or generalized (symmetrical) atrophy of the subcutaneous fatty tissue. The affected patients are often insulin-resistant and tend to have diabetes mellitus, dyslipidemia, fatty liver, and acanthosis nigricans. Women typically have clinical signs such as polycystic ovary syndrome, hirsutism, and oligomenorrhea. The lipodystrophy itself is sometimes very marked; it may symmetrically affect the face as well as the upper and lower limbs.

Acquired lipodystrophies are more common than the inherited forms and are mainly seen in HIV-positive persons treated with nucleoside and protease inhibitors. 10 to 20% of patients treated with these drugs for at least 1 year display more or less severely atrophic areas of the subcutaneous fatty tissue in the cheeks and upper and lower limbs; however, with newer therapies these long term side effects may occur at a lower frequency. At the same time, excessive deposition of fat in the nuchal region or the front of the neck can create a "buffalo hump" or double chin. Lipodystrophy is presumed to be due to mitochondrial toxicity of the inhibitor drugs or to their interference with the expression of important transcription factors for adipocyte differentiation, e. g., sterol regulatory element binding protein 1c (SREBP1c).

Another rare type of acquired lipodystrophy is Barraquer–Simons syndrome, which is sometimes seen in association with membranoproliferative glomerulonephritis or other autoimmune diseases such as systemic lupus erythematosus or dermatomyositis. Weber–Christian syndrome is a type of subcutaneous necrotizing panniculitis that occurs in the setting of various diseases including collagenoses and lymphomas.

Inherited types of lipodystrophy are very rare. Berardinelli–Seip syndrome, an autosomal recessive disease, is a generalized type of lipodystrophy with nearly total absence of subcutaneous fat. It is caused by a defect in an important enzyme for triglyceride synthesis (AGPAT2). Other familiar lipodystrophies affect the limbs and trunk only in part (Dunnigan type) or are associated with skeletal anomalies (mandibuloacral dysplasia).

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Definition of Overweight and of the Pattern of Distribution of Body Fat

Body mass index. Overweight and obesity are currently defined according to established quantitative criteria, by means of the BMI. The BMI is defined as the patient's weight (in kilograms) divided by the square of his or her height (in meters). Thus, a person weighing 90 kg and standing 175 cm tall would have a BMI of $90/(1.75)^2 = 29.4\ kg/m^2$. The BMI values used to define overweight and obesity for men and women are identical and are listed in Tab. 3.**11**.

Determination of Body Fat Distribution. The pathophysiological significance of excess fat depends not just on the amount of weight gained, but on the distribution of the excess fat in the body. The most popular quantitative measure for this is the waist–hip ratio (W/H ratio).

A small absolute amount of weight gain, with additional fat mainly in the *abdomen*, as opposed to a more peripheral fat distribution, is commonly seen as part of a complex of abnormalities including arterial hypertension, dyslipidemia, glucose intolerance, and hyperinsulinemia. This is called the *metabolic syndrome* (insulin resistance syndrome, Tab. 3.**12**) and is associated with markedly increased cardiovascular morbidity and mortality. The currently accepted upper limit of normal for the W/H ratio is 0.80 for women and 0.95 for men. Recent studies have shown, however, that the abdominal circumference alone (measured at the waist) predicts cardiovascular risk just as well as the W/H ratio does. According to the guidelines of the National Cholesterol Education Program (NCEP), Adult Treatment Panel III, an abdominal circumference greater than 88 cm in women and 102 cm in men is one of the defining criteria for the metabolic syndrome (see Tab. 3.**12** for the full list).

Further quantification of the percentage of body fat, e. g., by bioimpedance measurement or other techniques, is of no value in clinical practice as the values obtained do not influence the choice of treatment. Such techniques should not be included in the diagnostic workup of obesity.

Table 3.**12** Definition of metabolic syndromes according to the National Cholesterol Education Program, Adult Treatment Panel III

A metabolic syndrome is said to be present when at least three of the following criteria are met:
- abdominal obesity (abdominal circumference > 102 cm in men, > 88 cm in women)
- elevated triglyceride concentration (> 1.7 mmol/L [> 150 mg/dL])
- low HDL cholesterol concentration (< 1.0 mmol/L [< 40 mg/dL] in men, < 1.3 mmol/dL [< 50 mg/dL] in women)
- high blood pressure (> 130/85 mmHg)
- high fasting blood sugar (> 6.1 mmol/L [> 110 mg/dL])

Gynecomastia

Definition and Distinction from Pseudogynecomastia. True gynecomastia, i. e., true enlargement of breast (mammary glandular) tissue on one or both sides in a man, is to be distinguished from the pseudogynecomastia seen in obese men. The latter consists only of lipomastia, i. e., enlargement of the fatty tissue surrounding the mammary gland itself, which remains of normal size. Gynecomastia arising in puberty or adolescence is physiological and usually reversible (Fig. 3.**55**).

Causes. The new appearance of gynecomastia in a man over age 20 is usually due to an endocrine abnormality or a tumor (Tab. 3.**13**). Its causes include testosterone deficiency, elevated estrogen production, and medication side effects (including increased conversion of androgens to estrogens).

Important points to be addressed in the diagnostic assessment of men with gynecomastia include the medication history, testicular size, liver function tests, and the levels of certain hormones including plasma testosterone, estrogen, LH, β-human chorionic gonadotrophin, and α-fetoprotein, and, depending on the clinical presentation, prolactin, thyroid stimulating hormone, and fT4.

Fig. 3.**55** Medication-induced gynecomastia (spironolactone). ▷

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Table 3.**13** Causes of gynecomastia

Physiologcal Neonatal gynecomastia, pubertal gynecomastia, involutional gynecomastia of old age
Increased estrogen production/increased conversion of androgens to estrogens (*) Testicular tumors, germinoma, Leydig cell tumor, adrenal carcinoma, lung cancer, hermaphroditism, hepatic diseases (*), hyperthyroidism (*), uremia
Decreased testosterone production/decreased testosterone effect (**) Klinefelter syndrome, primary/secondary hypogonadism, anorchia, secondary testicular changes (castration, mumps, tuberculosis, neurological disease), hyperprolactinemia, testicular feminization (**) (= Reifenstein syndrome)
Breast cancer in men
Medications Psychotropic drugs (diazepam, tricyclic antidepressants), cardiovascular drugs (captopril, enalapril, nifedipine, reserpine, verapamil, spironolactone, amiodarone, digoxin), cimetidine, ranitidine, omeprazole, ketoconazole, metronidazole, cisplatin, alkylating agents, isoniazid, phenytoin, estrogen preparations, cyproterone, growth hormone, illicit drugs (heroin, marijuana, methadone), alcohol
Idiopathic gynecomastia (20–50%)

Anorexia

Causes. Anorexia, i.e., lack of appetite, is sometimes constitutional rather than pathological. Undesired weight loss, however, is often a sign of (usually serious) organic disease. Its causes include the following:

- *inadequate nutritional content of food:* undernourishment, protein-calorie malnutrition
- *diminished food intake:* lack of appetite due to wasting diseases (cytokine-induced), depression
- *inadequate resorption:* malabsorption in sprue, organic diseases of the bowel, chronic laxative abuse
- *inadequate digestion:* maldigestion in chronic pancreatitis
- increased energy consumption, e.g., hyperthyroidism

Weight loss despite increased food intake is characteristic of malabsorption syndromes, poorly controlled diabetes mellitus, and hyperthyroidism.

Anorexia Nervosa. Some persons suffering from reactive psychosis refuse to eat and therefore lose weight. A more common psychiatric condition with often quite severe manifestations is anorexia nervosa (Fig. 3.**56**). This disease is 10–20 times more common in girls and young women than it is in males. Its prevalence is estimated at 0.5%. Persons with anorexia are often intelligent, ambitious girls and young women with a heightened awareness of their own body and a strong desire to be, or become, thin. They often retain a high level of physical performance (ballet dancers, athletes), but they commonly have secondary amenorrhea and are at risk of developing osteoporosis.

Fig. 3.**56** Anorexia nervosa.

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Hands

Fig. 3.**57** Clubbed ("drumstick") fingers and hourglass nails in bronchial carcinoma.

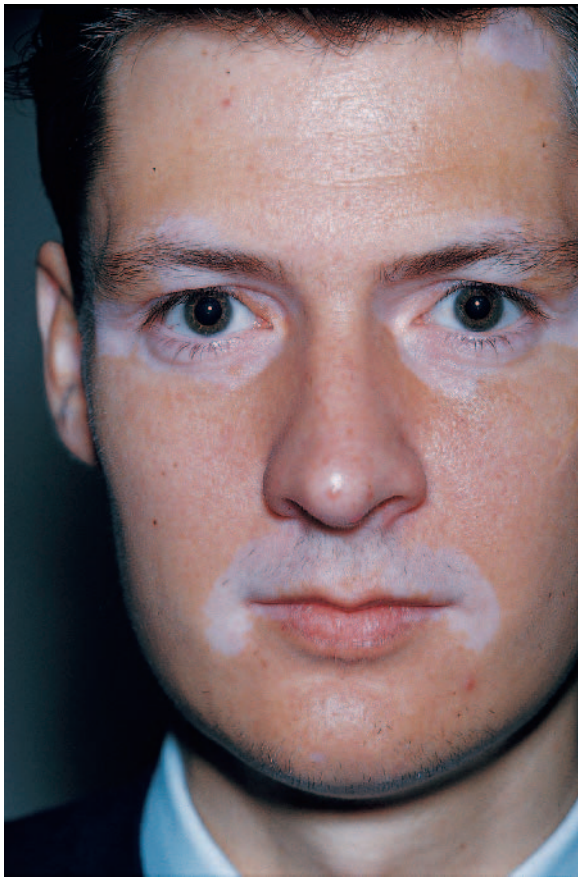

Fig. 3.**58** Vitiligo.

The shape and appearance of the patient's hand and the nature of the patient's handshake can convey important information about his or her personality, occupation, and lifestyle. Typical findings include brown discoloration of the distal phalanges of the second and third fingers in heavy smokers, and Dupuytren contracture in alcoholics and others.

The hand can be affected in many systemic illnesses, sometimes in a way that permits immediate diagnosis:

- The enlarged hands of *acromegaly* (Fig. 3.**46a**) and the slender hand of *Marfan syndrome* (Fig. 3.**41**) are unmistakable.
- In *chronic polyarthritis* (rheumatoid arthritis), the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints are symmetrically swollen and painful. Patients complain at first of pain, swelling, and morning stiffness; later on, the fingers become partially dislocated, ankylotic, and deviate to the ulnar side, and the characteristic buttonhole and swan-neck deformities appear (see Chapter 10).
- *Osteoarthritis* typically produces Heberden nodes at the distal interphalangeal (DIP) joints (see Chapter 10).
- *Clubbing* of the fingers (Fig. 3.**57**) is found in a number of different diseases.
- *Palmar erythema* is seen in hepatic cirrhosis and hyperthyroidism, and can also (rarely) be a normal finding.
- The palmar creases are pigmented in Addison disease, hepatic cirrhosis, and hemochromatosis. Generalized *pigmentation* of the hands is seen in Addison disease, ectopic ACTH secretion, hemochromatosis, uremia, Peutz–Jeghers syndrome, and leprosy. Diminished pigmentation occurs as a post-inflammatory change, or as vitiligo, in pernicious anemia, Addison disease, hyperthyroidism, and diabetes mellitus. In most cases, the cause of vitiligo cannot be determined (Fig. 3.**58**).
- *Palmar hyperkeratoses* can be hereditary and can also be due to chronic arsenic poisoning.
- The skin of the hands is tough and rigid in *scleroderma*. It is markedly tense and partly calcified (Thibierge–Weissenbach syndrome).
- A moderate degree of *atrophy of the hand muscles* is normal in old age. Atrophy of the interosseous muscles, often combined with a claw hand deformity, is typical of amyotrophic lateral sclerosis.
- The *temperature of the skin* is related to its degree of perfusion. The skin is warm in hyperthyroidism and often also in arterial hypotension, dry and cold in myxedema, cold in hypotension and heart failure, and moist and cold in autonomic dystonia.
- The hand is *cyanotic* and cold in severe heart failure (exhaustion cyanosis), but cyanotic and warm in central cyanosis due to a congenital heart defect.
- The hand *trembles* in hyperthyroidism, chronic alcoholism, intoxications, and Parkinson's disease, as

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well as in autonomic instability and in familial or senile tremor. An intention tremor is often seen in multiple sclerosis, and a flapping tremor is typical of decompensated hepatic cirrhosis with hepatic encephalopathy.

- Progressive weakness, often combined with nocturnal paresthesia and numbness of the first three fingers (which improve when the affected upper limb is shaken), is a sign of *carpal tunnel syndrome.* The affected patients (mostly women) complain of difficulty grasping and holding objects.
- Localized conditions affecting the hand are the rare *tuberculous dactylitis* (spina ventosa) and *Jüngling disease,* a form of sarcoidosis.

Face

Facial Expression. Paucity of facial expression, the so-called "mask facies," is often an early sign of *Parkinson disease* and may appear before any abnormality of posture or gait. Movements of the facial musculature are crude and inharmonious. The picture is completed by facial seborrhea and in severe cases by hypersalivation and drooling. The fixed facial expression contrasts markedly with the patient's normal intelligence.

Risus sardonicus, an unmistakable sign of *tetanus*, is produced by tonic rigidity of the muscles involved in smiling. The "sardonic" appearance of the smile in tetanus is due to trismus, i. e., limitation of mouth opening.

Facial redness has a differential diagnosis of its own, based on the nuances indicating which underlying disease is present. The type of facial rubeosis seen in *hypertension* differs only in degree from that seen in *polycythemia*, though, in the latter, the conjunctiva are usually also reddened. Red cheeks are often a sign of *diabetes mellitus* (Fig. 3.**59**). *Mitral stenosis,* too, frequently causes reddening of the cheeks due to vasodilatation, sometimes combined with cyanosis of the lips in what is called "mitral facies" (Fig. 3.**60**). These phenomena are seen to a much greater degree in the "flushes" associated with *metastatic carcinoid of the small intestine.* These are episodes of facial redness that occur at variable frequency and last 1–5 minutes (see Chapter 23). Telangiectasias develop later. *Chronic alcoholism* displays the typical picture of a red face (venous ectasias on the cheeks and nose), chronic conjunctivitis (frequent), and a peculiar "empty stare." The face is intensely reddened in *acute febrile illnesses,* particularly in bacterial pneumonia. Flaring of the nostrils during inspiration completes the characteristic picture of the face in pneumonia.

Other typical abnormalities of facial appearance can be very helpful in diagnosis:

- In fully developed *Graves disease* (or Basedow disease), the face looks so abnormal that even laypersons sometimes make the diagnosis. Exophthalmos, glossy eyes, excessive facial sweating, and hair loss combine to create a characteristic appearance (Fig. 3.**61**).
- *Hypothyroidism* (myxedema) is characterized by a bloated face with dry and wrinkled skin, combined with generalized slowing, a low voice, and hair loss. These changes are almost always completely reversible with treatment (Fig. 3.**62**).
- *Nephrotic edema* is particularly visible in the eyelids and produces a typical, bloated appearance.
- Atrophy and rigidity of the skin of the face and a small, pursed mouth (microstomia) are often seen in *scleroderma*. Systemic lupus erythematosus often produces a typical, butterfly-shaped exanthem centered on the dorsum of the nose (see Chapter 4).
- In *Paget disease* (see Chapter 11), bone is abnormally vulnerable to mechanical stress because of a combination of local osteoclastic bone destruction and local osteoblastic bone generation. Noticeable

Fig. 3.**59** Marked facial rubeosis in a woman with diabetes.

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Fig. 3.**60** Red cheeks and mildly cyanotic lips in a woman with mitral stenosis.

Fig. 3.**61** Bilateral exophthalmos in Graves disease.

a

b

Fig. 3.**62** The face of a patient with hypothyroidism:
a before treatment,
b after treatment.

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Fig. 3.**63** Bowing of the tibiae in Paget disease.

Fig. 3.**64** Saddle nose in Wegener granulomatosis.

enlargement of the skull may result, giving this condition its French nickname, "la maladie du chapeau trop petit" (the too-small hat disease). In severe cases, bony deformities of various types are clinically evident (bowed tibiae, vertebral body fractures, kyphosis) (Fig. 3.**63**).

- A saddle nose is seen in *polychondritis* and *Wegener granulomatosis* (Fig. 3.**64**).

Eyes

Visual disturbances and other problems affecting the eyes are often the first sign of a systemic illness. Careful examination of the eyes often provides the diagnosis, as they are composed of many different kinds of tissue (connective tissue, nerves, vessels, pigmented epithelium) and, among all the body's internal organs, are uniquely accessible to visual inspection.

Exophthalmos

Bilateral exophthalmos and a widened palpebral fissure are typically seen in Graves disease (Fig. 3.**61**). There are other ocular findings as well (see under endocrine orbitopathy, Chapter 16).

Unilateral exophthalmos not due to trauma can be seen in any of the following conditions:

- hyperthyroidism (exophthalmos is unilateral in 50% of cases)
- orbital tumor (Fig. 3.**65**)
- periorbital tumor (paranasal sinuses, epipharynx, palate, mucocele of the paranasal sinuses)
- inflammatory and infectious processes (orbital phlegmon, pseudotumorous myositis of the intraorbital muscles, dacryoadenitis, pseudotumor orbitae)
- various other causes (pseudotumor cerebri, cavernous sinus thrombosis, retrobulbar granuloma in Wegener granulomatosis)
- deformities of the bony orbit (craniofacial dysostosis [Crouzon syndrome], mandibulofacial dysostosis [Apert–Crouzon syndrome], turricephaly, etc.)

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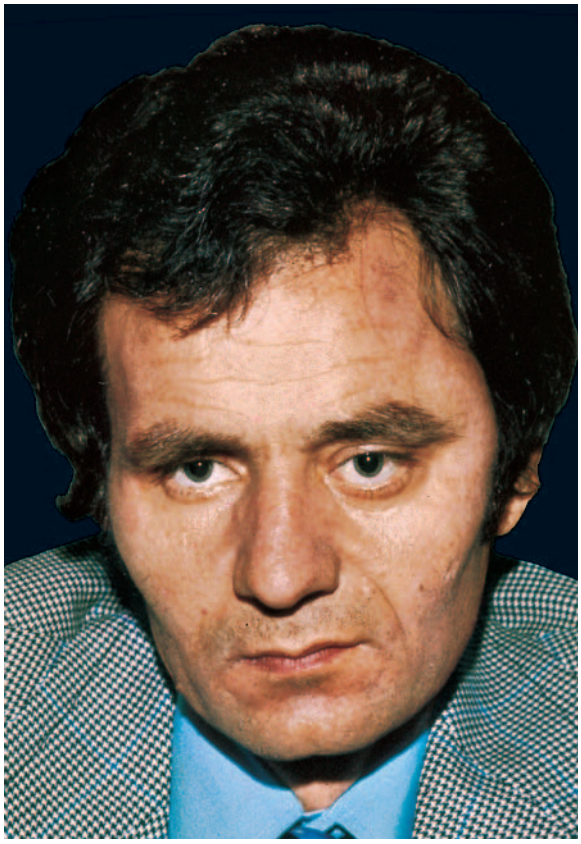

Fig. 3.**65** Left exophthalmos due to retrobulbar malignant tumor (carcinoma).

Pulsating exophthalmos is produced by traumatic arteriovenous shunts between the internal carotid artery and the cavernous sinus (continuous shunting murmur), and also by neurofibromatosis (von Recklinghausen disease).

Horner Syndrome, Enophthalmos

"Enophthalmos" is seen in Horner syndrome (Fig. 3.**66**). Impairment of the sympathetic innervation to the face (whose causes include, but are not limited to, carotid dissection, iatrogenic trauma, goiter, processes at the apex of the lung and in the mediastinum, syringomyelia, cervical rib, trauma and tumors of the cervical spinal cord, and, in rare cases, aortic aneurysm) produces the clinical triad of ptosis, miosis, and anhidrosis. The eye does not really sink inward; the appearance of enophthalmos is produced by ptosis of the upper and lower eyelids.

A narrow palpebral fissure due to ptosis of the upper eyelid is seen in oculomotor nerve palsy and in myasthenia gravis. Ptosis also occurs on a familial basis.

Eyebrows

Absence of the lateral portion of the eyebrows is seen in hypopituitarism and can also be caused by atopy.

Eyelids

Recurrent hordeolum (sty) should raise the suspicion of diabetes mellitus. Inflammatory swelling of the eyelids occurs after insect bites and as an allergic reaction (mainly in contact eczema, also in response to medications and foods). Periorbital edema is seen in many systemic diseases as well, including dermatomyositis, systemic lupus erythematosus, superior vena cava syndrome, thyroid dysfunction, heart failure, glomerulonephritis, and others. Inflammation and swelling of the lacrimal glands (viral infections, Mikulicz syndrome) can be mistaken for lid swelling.

Sclerae

Scleral Icterus. Yellowing of the sclerae is usually due to acute or advanced hepatic disease or to hemolysis (see the relevant discussions elsewhere in this book) (Fig. 3.**67**).

Blue Sclerae. Patients with thin, translucent sclerae that appear light blue should be evaluated for further signs of *osteogenesis imperfecta* (Fig. 3.**68**). A typical finding is multiple long bone fractures, though the frequency of fractures diminishes after puberty. The joints are usually loose, and, in adulthood, there is progressive conductive deafness due to otosclerosis. Further abnormalities include chest deformities, small, misshapen, yellowish-blue teeth, thin skin, and short stature (dwarfism). There is a higher than normal frequency of mitral valve prolapse (as in Ehlers–Danlos syndrome and Marfan syndrome). The condition is most commonly inherited in an autosomal dominant mode, with the typical clinical triad of brittle bones, blue sclerae, and deafness; it also has other, rarer subtypes, some of which are lethal in early childhood. The variable course of the different subtypes is explained by the different locations of the underlying genetic defects.

Abnormal fragility of bone is also a typical finding in osteopetrosis (Albers–Schönberg disease, marble bone disease) and is seen in Paget disease and renal osteodystrophy as well.

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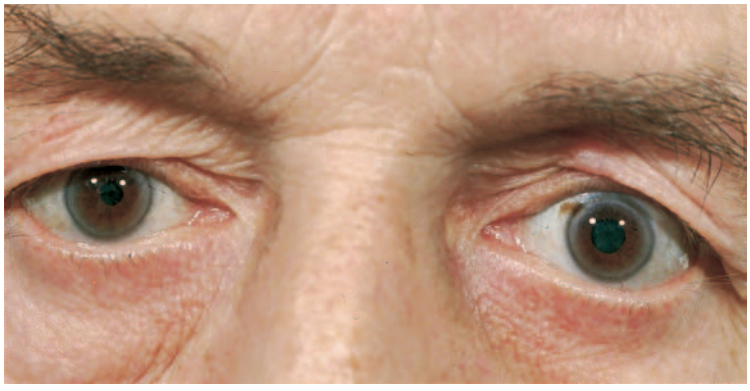
a

Fig. 3.**66** Right Horner syndrome.
a Marked ptosis and narrow palpebral fissure.
b The close-up photograph additionally reveals enophthalmos and a smaller pupil on the right. Incidental finding: bilateral arcus senilis.



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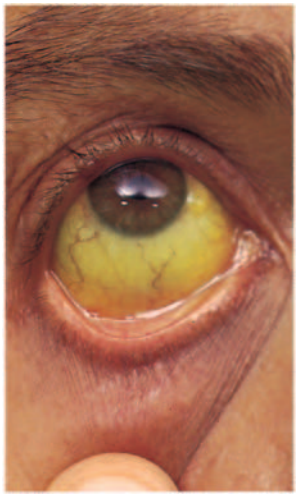

Fig. 3.**67** Yellow sclerae in jaundice.

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Fig. 3.**68** Blue sclerae in osteogenesis imperfecta.

Cornea

Arcus Lipoides. This finding, also known as gerontoxon or more commonly, senile arcus (Fig. 3.**66b**), is due to lipid deposition and is common in the elderly. It can also be seen in younger persons and need not be due to hypercholesterolemia.

Wilson disease (hepatolenticular degeneration) produces a similar picture through the deposition of copper at the edge of the cornea. Kayser–Fleischer rings, unlike arcus senilis, are brownish-green in color.

Band-shaped corneal opacifications are particularly evident in anterior uveitis (e. g., due to juvenile polyarthritis), but are also seen in hypercalcemic states (sarcoidosis, vitamin D intoxication, and hyperparathyroidism). More diffuse opacifications may be due to keratitis (herpes simplex corneae, herpes zoster ophthalmicus, congenital syphilis) or to an adverse drug effect (amiodarone, chloroquine, mepacrine, indomethacin).

Lens

Cataract (opacification of the lens) arises in old age (senile cataract) and at younger ages in the following conditions:

- metabolic diseases (diabetes mellitus, hypoparathyroidism, galactosemia)
- trauma to the lens
- diseases of the eye (chronic iridocyclitis, heterochromic cyclitis)
- intrauterine viral infections (measles, mumps, rubella, chickenpox) and toxoplasmosis (in the second half of gestation)
- myotonia dystrophica (Curschmann–Steinert disease)
- intoxications (dinitrocresol)
- Wilson disease
- medications (glucocorticoids, haloperidol).

Tremulousness of the lens is often found in Marfan syndrome.

Iris

Heterochromia (difference in color between the two irides) occurs after iritis or as a congenital variant.

Iritis or iridocyclitis can be caused by infection (occult infections, leptospirosis, listeriosis, Lyme borreliosis, toxoplasmosis, syphilis, herpes zoster) and by the following diseases: Behçet syndrome, Reiter disease, sarcoidosis (Heerfordt syndrome, see Chapter 19), Graves disease, and Still–Chauffard disease.

Pupil

Sympathetic nerve impulses dilate the pupil, and parasympathetic nerve impulses constrict it.

Abnormalities of pupillary motility can furnish valuable diagnostic clues:

- *Small pupils* are found under general anesthesia and during sleep and can also be caused by illicit drugs (opiates), medications (pilocarpine), organophosphate poisoning (e. g., with Parathion), glaucoma treatment, Horner syndrome, iritis, and pontine lesions.
- *Enlarged pupils* are caused by sympathetic excitation (fear, excitement, pain), medications (atropine, cocaine), attacks of glaucoma, midbrain lesions, and deep coma.
- *Anisocoria* (inequality of the pupils) is usually due to an organic illness or to a locally applied medication.
- When *unilateral pupillary areflexia* is due to blindness, the direct light response is absent, but the pupil of the blind eye will nonetheless constrict promptly upon illumination of the contralateral, seeing eye (consensual light response).
- *Argyll Robertson pupils* lack both the direct and the consensual light responses, but nevertheless constrict promptly on convergence (i. e., the near response is preserved). Other findings may include an irritative miosis, markedly oblong pupils, and a poor response to mydriatic agents; if all of these are pre-

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Fig. 3.**69** Argyll Robertson phenomenon: unequal, mildly oblong, non-reactive pupils in a patient with diabetes mellitus.

sent, the clinical picture is pathognomonic for tabes dorsalis. Argyll Robertson pupils without any of the other features listed can be produced by midbrain lesions (pinealoma, multiple sclerosis) and by diabetic (Fig. 3.**69**) or amyloid polyneuropathy.

- *Absolute pupillary areflexia,* if it is not due to mydriatic agents, indicates a pathological process in the midbrain or at the skull base (encephalitis, tumor, aneurysm, syphilis). Certain diseases of the eye (synechiae, glaucoma) can mimic absolute pupillary areflexia.
- *Adie syndrome* is an innocuous condition of unclear etiology in which the pupillary light response is very slow or absent, and the near response (pupillary constriction on convergence) is tonically slowed.

Vitreous Body

"Floaters," a symptom of vitreous opacifications, are usually harmless as long as the patient's visual acuity is unimpaired and the opacifications are of long standing. Newly arisen and visually disturbing floaters, however, may be a sign of incipient retinal detachment, or of a vitreous hemorrhage due to vascular diseases such as diabetes mellitus or venous thrombosis.

Retina

Retinopathy. In diabetic retinopathy, the patient's visual acuity is often markedly impaired as a result of microaneurysms, hemorrhages, and vascular proliferation in the vitreous body. Retinal hemorrhages can also occur in anticoagulated patients. Degenerative retinal changes are typically seen in retinitis pigmentosa, pseudoxanthoma elasticum, and Lawrence–Moon–Biedl syndrome. Endocarditis, in rare cases, produces small, hemorrhagic retinal lesions (Roth spots).

Senile macular degeneration is a common type of retinopathy. In its more usual form (85%), called "dry" macular degeneration, the loss of centrally located cells on the retina causes a very gradual deterioration of vision. In the rarer "wet" form, fluid collects under the macula and physically distorts the retina, so that patients report, as their first symptom, that straight lines appear to be curved.

Chorioretinitis. The differential diagnosis of chorioretinitis (posterior uveitis) includes infections with *Toxoplasma gondii, Toxocara, Cryptococcus neoformans, Histoplasma capsulatum, Mycobacterium tuberculosis,* and cytomegalovirus (in AIDS patients and others), as well as sarcoidosis.

Candida endophthalmitis is found in about 5% of patients with disseminated candidiasis. Ophthalmoscopy typically reveals white cotton-wool retinal exudates extending into the vitreous body. This condition is seen in immunosuppressed persons, persons receiving prolonged courses of parenteral nutrition, and intravenous drug users.

The Red Eye

A red eye can be due to any of the following:

- *conjunctivitis* (very common, begins slowly, mild burning of the eye, conjunctival injection, e.g., during a flulike illness)
- *uveitis* (common, usually begins slowly, moderately severe eye pain, mildly blurred vision, ciliary injection, small pupil with a sluggish light response)
- *corneal injury/keratitis* (common, keratitis begins slowly, marked superficial pain, ciliary or diffuse injection, corneal ulcerations may be present)
- *acute glaucoma* (rare, sudden onset, pain in the face, ciliary injection, dizziness, vomiting).

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Ocular Motility

Various patterns of abnormality may be encountered in the examination of eye position, rapid eye movements (saccades), and the slow eye movements induced by visual pursuit or vestibular stimuli. Any abnormal findings can provide important clues to the differential diagnosis of diseases of the central nervous system (infratentorial and supratentorial), the peripheral nervous system (nerves, endplates, and muscles), and the labyrinth (see Chapter 31).

Ears

The external ear (pinna) provides diagnostic clues to gout (tophi, see Chapter 10), ochronosis (bluish-gray spots, see Chapter 10), heart failure (cyanosis), and cold agglutination disease (cyanosis in the cold).

Deformities of the pinnae are seen in a wide variety of conditions. Flaccid, hanging ears are pathognomonic for recurrent polychondritis (von Meyenburg–Altherr–Uehlinger syndrome), a rare disorder (Fig. 3.**70**).

Hearing Impairment. The distinction between conductive and sensorineural hearing impairment is essential in the diagnostic evaluation of disturbed hearing. Accompanying symptoms often provide further diagnostic clues.

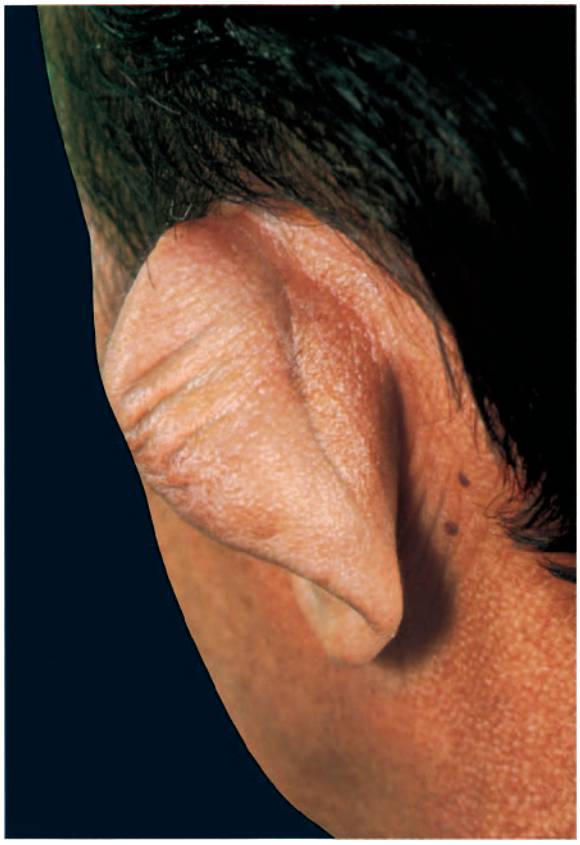

Fig. 3.**70** Limp hanging ear in a patient with recurrent polychondritis.

- *Conductive hearing loss* is due to changes of the external auditory canal or middle ear. The most common causes are obstruction by cerumen, tympanic injury, otitis media, cholesteatoma, tubal or middle ear catarrh, otosclerosis, and congenital anatomical anomalies.
- Lesions of the cochlea, cranial nerve VIII (statoacoustic), and the central auditory pathway cause *sensorineural hearing loss.*
- *Familial* hearing impairment is common; *rubella embryopathy* is another cause.
- *Acute, unilateral hearing disturbance or hearing loss* may be due to a vascular event, acoustic trauma, or (if the history suggests it) a fracture of the petrous bone.
- *Labyrinthitis,* usually a complication of otitis media or a viral infection (infectious mononucleosis), causes unilateral hearing loss.
- Recurrent bouts of unilateral hearing loss, combined with tinnitus, vertigo, and spontaneous nystagmus, typically occur in *Ménière disease.*
- *Ototoxic medications* (aminoglycosides, vancomycin, high-dose salicylates, furosemide, bleomycin) occasionally cause slowly progressive, bilateral sensorineural hearing impairment.
- Chronic, progressive hearing impairment occurs in *presbycusis* (hearing loss of old age) and *noise-induced* hearing impairment.
- *Acoustic neuroma* is a usually slowly growing tumor of cranial nerve VIII which often presents with unilateral, progressive hearing loss as its only symptom. Other potential causes of hearing loss in the central nervous system include brainstem lesions, infarcts, tumors, multiple sclerosis, and other changes in the region of the temporal lobe.
- *Tinnitus* ("ringing in the ears") is a subjective phenomenon in which the patient hears tones and noises of highly variable character, which are usually very disturbing. Knocking and low-frequency noises are often caused by mechanical disturbances of the auditory tube and by tubal and middle ear catarrh. Whistling and musical tones, on the other hand, are heard in cochlear diseases and in processes affecting the cochlear nerve. Tinnitus is almost always accompanied by substantial hearing impairment. Continuous noises are most commonly due to intracranial vascular processes. High doses of salicylates and quinine also sometimes cause tinnitus. Unilateral tinnitus is a typical complaint in Ménière disease.

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Nose

A *saddle nose* (Fig. 3.**64**) is the consequence of an inadequate blood supply to the nasal septum due to vascular processes, congenital syphilis, Wegener granulomatosis, certain types of ectodermal dysplasia, or, rarely, Takayasu syndrome.

Other characteristic abnormalities include *rhinophyma* (cauliflower nose), which is due to hyperplasia of the sebaceous glands of the skin of the nose, and adenoma sebaceum, seen in Bourneville–Pringle syndrome (further findings in the latter are tuberous sclerosis in the brain, intracranial calcifications, periungual fibromas (Fig. 3.**26b**), nodular gingival lesions, retinal tumors, rhabdomyomas of cardiac muscle, angiomas, and renal fibromas). The nose is markedly flattened in recurrent polychondritis.

Odor

Diagnoses are less commonly made by odor nowadays, as modern instrumental techniques usually yield the diagnosis in an earlier stage of the disease, long before characteristic odors can appear. Abnormal odors are often caused by *metabolic diseases* and *intoxications*. They are very difficult to describe precisely and are perceived differently by different people. "Bad breath" can be differentiated into fetor ex ore (a bad smell emanating from a process in the mouth itself) and halitosis (bad breath due to a process in the gastrointestinal or respiratory tract, or elsewhere in the body).

Tab. 3.**14** provides an overview of a few important types of abnormal odor and their potential causes.

Table 3.**14** Typical odors in various diseases

Type of odor	Cause
Breath	
Bad breath	Disturbances of the teeth, nose, tonsils, esophagus, or stomach
Putrid, fecal odor	Intestinal obstruction, esophageal diverticulum, bronchiectases
Sweet, putrid	Lung abscess, empyema (anaerobic), intranasal foreign body
Acetonelike, fruity	Ketoacidosis in diabetes mellitus or starvation; chloroform or salicylate intoxication
Raw liver ("fetor hepaticus")	Liver failure
Sweet	Diphtheria, hepatic precoma and coma
Fresh black bread	Typhus
Sourdough bread	Pellagra
Alcohol	Alcohol or phenol intoxication
Tobacco	Nicotine
Garlic	Phosphorus, malathion, or arsenic intoxication
Shoe polish	Nitrobenzene
Butcher shop	Yellow fever
Urinelike	Uremia
Urine	
Sweet, caramellike	Maple syrup urine disease
Sweet, violetlike	Turpentine intoxication
Fishy, rancid butter	Tyrosinemia
"Mousy"	Phenylketonuria
Ammonia	Urinary tract infection with urea-splitting bacteria (e. g., *Proteus*)

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Table 3.**14** (Continued)

Type of odor	Cause
Skin/Sweat	
Fresh black bread	Typhus
"Mousy," "horselike"	Phenylketonuria
Caramellike	Maple syrup urine disease
Earthy, grapelike, fruity	*Pseudomonas* infection
Putrid	Skin diseases such as pemphigus, anaerobes
Fecal	Intestinal obstruction
Overripe Camembert	Abscesses due to proteolytic bacteria
Sweet, rotten apples	Gas gangrene
Sputum	
Putrid, stinking	Lung abscess, empyema, bronchiectases, purulent bronchitis
Vomit	
Violetlike	Turpentine intoxication
Garlicky	Arsenic or phosphorus intoxication
Fecal	Intestinal obstruction, peritonitis
Stool	
Putrid	Malabsorption (sprue)
Rancid butter	Shigellosis
Garlic	Arsenic intoxication
Vaginal secretions	
Putrid	Vaginitis, malignant tumor, foreign body
Cerebrospinal fluid	
Alcoholic	*Cryptococcus neoformans* meningitis

Language, Speech, and Phonation

Disturbances of Language and Speech

Definitions. An impairment of the communicative use of language is called *aphasia*. Different types of aphasia result from lesions at different sites in the brain (Fig. 3.**71**). The major types of aphasia and their clinical features are listed in Tab. 3.**15**.

Dysarthria, in contrast to aphasia, is an impairment of the mechanical aspect of speech production, rather than of language per se. The underlying lesion causing dysarthria may be located anywhere along the neural and muscular pathways subserving speech. Thus, it may be in the cerebral cortex; in the subcortical white matter (so-called pseudobulbar palsy is due to a lesion in the corticobulbar pathway); in the pontine nuclei of the brainstem; in the cerebellum or basal ganglia (impairing the coordinated movements required for speech); in the peripheral nerves; or in the larynx itself.

Mutism is a general term for absence of speech, including types whose etiology and pathogenesis are not entirely clear. Psychogenic mutism (refusal to speak) is one type, but there are others with a clearly organic basis, e. g., akinetic mutism due to cortical damage in certain areas outside the traditionally identified language areas, or the transient mutism that sometimes follows cerebellar surgery.

Aphasia, an impairment of the intrinsic, communicative functions of language, is caused by damage or dysfunction of the language-related cortical areas, and/or their connections. Lesions at different sites produce characteristic and distinct clinical syndromes. These are seen in their most typical forms in patients who have

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suffered an ischemic stroke (the major language areas all lie in the territory of the middle cerebral artery). When aphasia is due to another cause, such as a tumor, infection, or focal seizure, its clinical features are less likely to correspond perfectly to any of the classic types.

- *Motor aphasia (Broca aphasia)* is caused by lesions affecting Broca's area in the inferior frontal gyrus of the language-dominant hemisphere (usually the left hemisphere). It is characterized by slow, effortful speech with short, truncated sentences (telegraphic style) and agrammatism. The understanding of speech is not impaired (the patient can follow commands).
- *Sensory aphasia (Wernicke aphasia)* is caused by lesions affecting Wernicke's area in the parietal and temporal lobes of the language-dominant hemisphere. Unlike patients with Broca aphasia, those with Wernicke aphasia cannot understand what is said to them or follow commands. They produce speech fluently and effortlessly, indeed in greater amounts than normal, but their speech output is marred by the frequent use of non-words (neologisms) instead of words, and by frequent paraphasic errors of both phonemic and semantic types ("letter salad," "word salad"). The underlying lesion impairs cortical functioning in Wernicke's area itself and also cuts it off from the important neural input that normally reaches it from the visual, auditory, and somatosensory areas.
- *Amnestic aphasia* is characterized by prominent word-finding difficulty, which the patient attempts to circumvent with frequent, occasionally bizarre paraphrases (substitution strategy). The underlying lesion lies in the temporoparietal area and is usually a vascular disturbance or brain tumor. The patient's speech retains near-normal fluency, and language comprehension is only mildly impaired.
- *Global aphasia,* with simultaneous loss of the receptive and expressive functions of speech, is caused by lesions affecting both the anterior and the posterior language areas. The most common cause is massive infarction in the entire territory of the

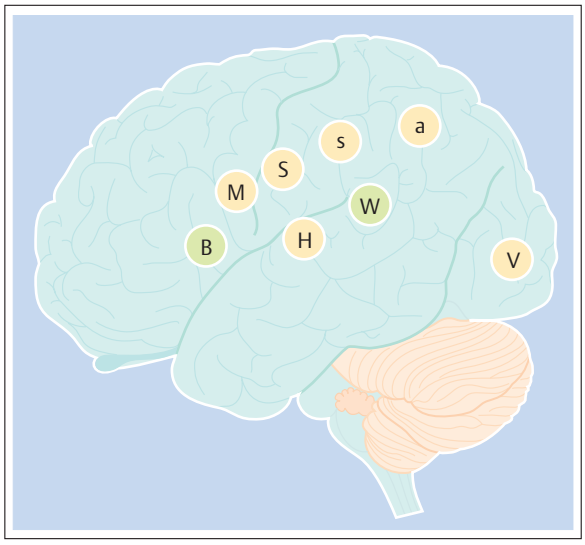

Fig. 3.**71** Possible causes of aphasia due to dysfunction of the language-related area (adapted from Poeck K and Hacke W). Important areas of the language center within the language-dominant hemisphere: **B** Broca's area, **M** motor area, **W** Wernicke's area, **S** somatosensory area, **H** auditory center, **V** visual association area, **s** supramarginal gyrus, **a** angular gyrus.

Tab. 3.**15** Important clinical features of different types of aphasia

	Amnestic aphasia	Wernicke aphasia	Broca aphasia	Global aphasia
Speech output	usually fluent	fluent	markedly slowed	severely restricted, automatisms
Articulation	usually normal	usually unimpaired	often dysarthric	usually dysarthric
Speech melody	usually well preserved	usually well preserved	often flattened, syllabic ("scanning")	often flattened
Sentence construction	minimally impaired	paragrammatism	agrammatism	only individual words, clichés, automatisms
Choice of words	substitutions, semantic paraphasia	many semantic paraphasic errors and neologisms, jargon	markedly reduced vocabulary; hardly any semantic paraphasic errors	markedly reduced vocabulary, frank semantic paraphasic errors
Sound structure	phonemic paraphasia	many semantic paraphasic errors and neologisms, phonemic jargon	many phonemic paraphasic errors	very many phonemic paraphasic errors and neologisms
Comprehension	mildly impaired	severely impaired	mildly impaired	severely impaired

Semantic paraphasic error = wrong word in sentence
Phonemic paraphasic error = wrong letter in a word
Neologism = nonword used in place of word

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middle cerebral artery. Complete global aphasia should not be confused with mutism of other causes (note that comprehension is impaired in global aphasia, but not in mutism per se). Patients who are completely unable to speak should always be carefully examined for any accompanying focal neurologic deficits.

Dysarthria. Central lesions impair the *motor production of speech* in a number of neurological conditions.

- *Cortical dysarthria* is usually due to cortical ischemia and is characterized by slurred, hesitant, and effortful speech.
- *Basal ganglionic dysarthria* in Parkinson disease is characterized by an absence of pitch variation (monotony) and a soft voice that becomes softer as the patient speaks.
- *Bulbar speech* is unclear, slurred ("marble-mouthed"), slow, and soft; the most prominent cause is amyotrophic lateral sclerosis affecting the medullary nuclei. It is frequently accompanied by dysphagia.
- "Staccato" speech, in which individual syllables and words are produced in truncated (scanning) fashion, and absence of the normal modulation of pitch are characteristic of *cerebellar dysarthria,* which is caused by multiple sclerosis or by vascular or neoplastic lesions of the cerebellum. Charcot's triad (scanning dysarthria, nystagmus, and intention tremor) is commonly found in such cases.

Disturbances of Phonation

Peripheral Disturbances of Phonation. Dysphonia and aphonia can be caused by primary or secondary affections of the larynx (laryngitis, tumors), by the normal voice change in pubertal males, and also by hormonal changes preceding menstruation or at the menopause. The voice becomes raw, deep, and hoarse in hypothyroidism. The voice is high-pitched in pituitary dwarfism, deep in acromegaly and virilism. A hoarse, deep voice in an older woman is commonly due to heavy cigarette smoking.

Mechanical, nonneurological disturbances of speech production, e. g., nasal speech due to enlarged adenoids, diseases of the larynx, or myasthenia gravis with progressive fatigue of the muscles of speech, are to be distinguished from neurological disturbances (dysarthria).

Functional dysphonia or aphonia is emotionally induced hoarseness ("I was dumbstruck!"), most commonly affecting girls and young women and characterized by rapid fluctuations in the quality of speech.

Hoarseness, a common complaint in clinical practice, is usually benign and reversible. Laryngitis (viral > bacterial, or induced by cigarette smoke) is the most common laryngeal cause. Posterior laryngitis is frequently due to gastroesophageal reflux. Further causes of hoarseness include foreign bodies, chronic alcoholism, tumors of the vocal apparatus (singer's nodules, papilloma, carcinoma), and trauma, as well as peripheral nerve injury (recurrent branch of laryngeal nerve), tumors of the neck, infection (meningitis), basilar skull fracture, aortic aneurysm, mitral stenosis, mediastinal tumors, and thyroid enlargement (goiter, carcinoma).

> All patients presenting with hoarseness of unknown origin should undergo laryngoscopy within 4 weeks to rule out carcinoma of the larynx.

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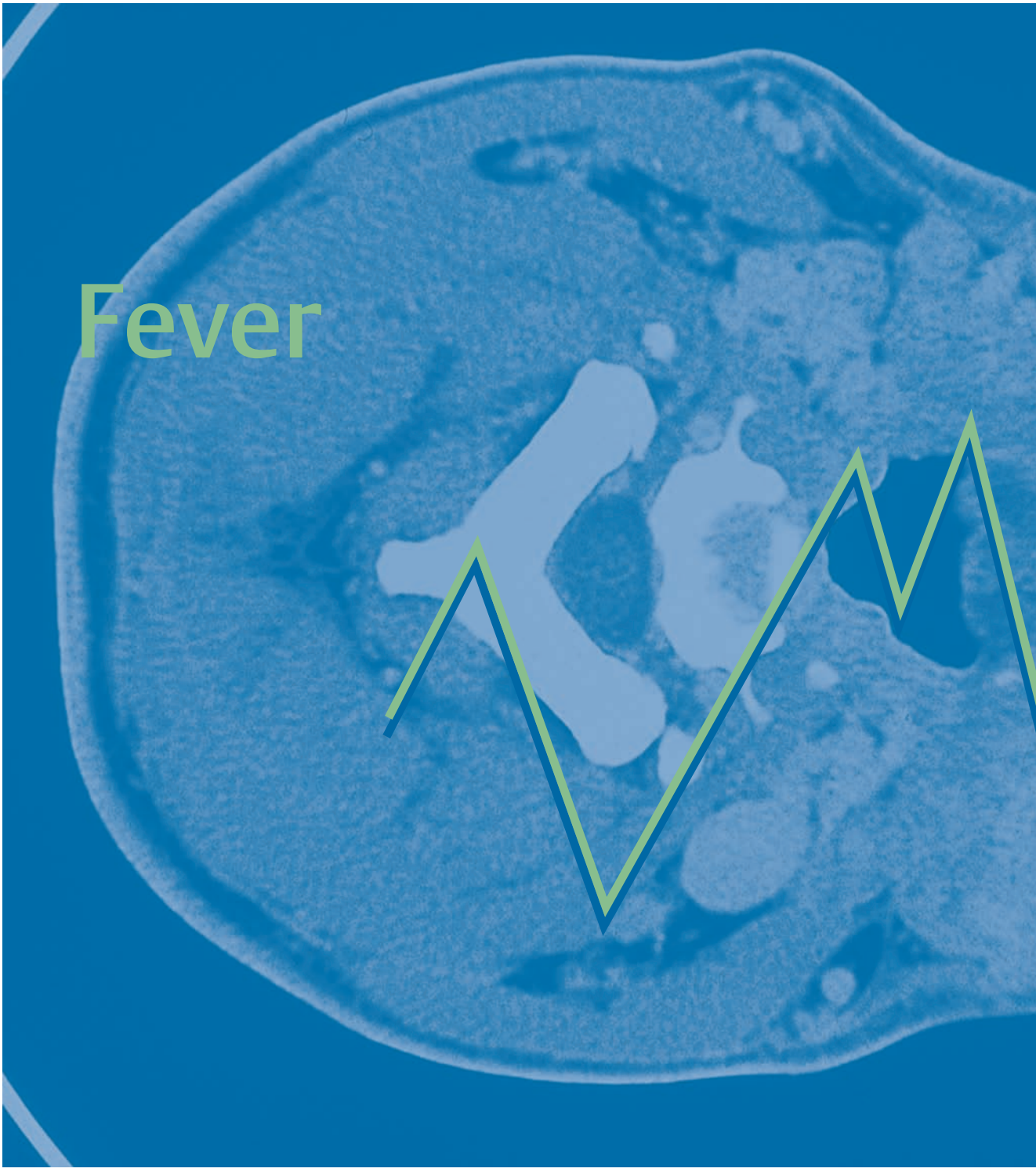
Fever



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4 Fever

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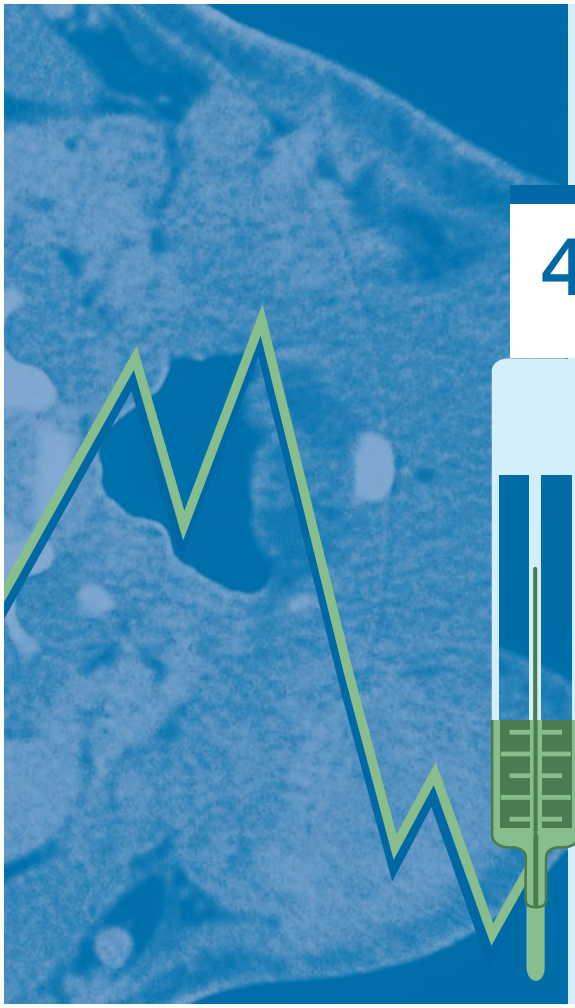

4 Fever

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4.1 General Remarks

Medical History and Clinical Findings

Medical History. The medical history has particular significance. Details about a patient's background, family medical history, occupations, hobbies, participation in sports, international travel (tropical), contacts with animals, insect bites and other injuries, previous illnesses, as well as diagnostic and therapeutic interventions, vaccinations, skin rashes, medications, or illicit (intravenous) drug use can provide important information. A systematic interview concerning the functioning of organ systems and comprehensive information about the present condition are likewise important. The social environment of the patient and his or her sexual preferences should also be discussed.

Clinical Examination. A thorough clinical examination, in combination with the historical information, should lead to a well-founded, tentative diagnosis in most cases. The following parts of the body are occasionally neglected during a physical examination: ocular fundus, temporal arteries, nasal sinuses, thyroid gland, renal beds, spinal column, uterine appendages, and prostate gland. Afflictions of these organs are occasionally clinically asymptomatic, which incorrectly leads to the search for a systemic cause of the fever.

Differential Diagnostic Considerations

Duration of the Fever. The *duration of the fever* is an important differential diagnostic symptom. In outpatients, viral or bacterial infections of the upper and lower respiratory tract or urinary tract infections are the most frequent causes of a brief fever (≤ one week). Fever lasting one to two weeks requires careful evaluation. See Section 4.8, p. 195 for the *fever types*.

Causes of Fever. Aside from *infectious causes*, the physician must consider various diseases with respect to the etiology of febrile conditions (Tab. 4.**1**).

Special Patient Groups. Differential diagnostic considerations also depend on if a fever has occurred *at home* or during the course of *hospitalization* (nosocomial infection). Not only is the spectrum of potential pathogens different in inpatients, but also *iatrogenic* factors must be considered, such as: postoperative infections, pulmonary diseases (atelectasis, pulmonary embolism, pneumonia), urinary tract infections (urinary catheter!), infections of intravasal catheters, as well as phlebitis after parenteral nutrition or therapy.

Patients with *endoprostheses*, *artificial heart valves*, or *intravascular grafts* can experience infections due to these foreign materials perioperatively or thereafter via bacteremia. The clarification of such occurrences can prove to be particularly difficult.

The differential diagnosis of fever in *HIV-infected* or otherwise *immunocompromised* patients (after organ transplants or neutropenia during chemotherapy) also includes opportunistic infections and tumors.

Fever—Definitions and Pathogenesis

Fever. Fever is an elevation of the body temperature > 37.8 °C when measured *orally* or > 38.2 °C when measured *rectally*. Especially in elderly patients, the latter is more reliable than skin or sublingual measurements.
Endogenic and exogenic pyrogens can increase the set point of the body temperature, which is regulated in the hypothalamus. Shivering, trembling, or chills leads to an increased production of heat through muscle work. Simultaneous vasoconstriction reduces the loss of heat through the skin. The most important endogenic pyrogens are interleukin-1, tumor necrosis factor, and interferons. Bacterial endotoxins and exotoxins of Gram-negative or Gram-positive bacteria are typical exogenic pyrogens that stimulate monocytes and macrophages to produce endogenic pyrogens.

Hyperthermia. Hyperthermia (temperature > 41.2 °C) is the consequence of overheating. An adjustment of the set point of the body temperature in the heat-regulating center does not occur, as in the case of fever. The causes of hyperthermia are *exogenic* (e. g., heating pads, sauna, baths) or *endogenic* (muscle work). During this process, the body temperature can rise uncontrollably, whereas the dissipation of heat is disturbed (e. g., as a consequence of unsuitable clothing or high air temperatures with high humidity). Under such conditions *heat stroke* can occur. *Malignant hyperthermia* is a rare complication of general anesthesia in genetically susceptible individuals (autosomal dominant inheritance). It is most frequently caused by succinylcholine and halothane.

Normal Variation in Body Temperature. When evaluating a fever, different normal variations must be considered. Physical exertion or eating an extravagant meal are physiological causes of an elevated temperature. However, body temperature generally does not exceed 37.9 °C. The same holds true for temperatures that can occur in women during the second half of the menstrual

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cycle (ovulation to menstruation). The physiological daily temperature fluctuation is around 1 °C.

Fever in Elderly Individuals. The normal body temperature, as well as the physiological daily temperature fluctuation, can be reduced in frail, elderly individuals, although not necessarily in healthy elderly people. Therefore, a recurrent elevation of the oral (> 37.2 °C) or the rectal temperature (> 37.5 °C) indicates fever in this patient group. Additionally, the fever reaction in a severe infection is absent, or only present in mitigated form, in 20–30 % of elderly individuals.

Table 4.**1** Causes of fever

Infectious diseases	– localized pyogenic infections (e. g., abscesses, pneumonia) – systemic infections (e. g., sepsis, typhoid) – relapsing infections (e. g. due to congenital or acquired immunodeficiency)
Tumors and hematologic malignancies	– lymphoma – leukemia – immunoblastic lymphadenopathy – myeloproliferative disorders – solid tumors – atrial myxoma
Vasculitis and collagen vascular diseases	– (see Tab. 4.**21**)
Rheumatic disorders	– (see Chapter 10)
Granulomatous diseases and organ specific autoimmune disorders	– sarcoidosis – Crohn disease – ulcerative colitis – chronic hepatitis – idiopathic, granulomatous hepatitis – primary biliary cirrhosis – malakoplakia – subacute thyroiditis – postmyocardial infarction syndrome
Endocrine and metabolic diseases	– thyrotoxicosis – Addison disease – pheochromocytoma – acute hyperparathyroidism – porphyria – Fabry disease
Primary neurologic disorders	– hypothalamic dysfunction – cerebrovascular accident, bleeding, stroke, epilepsy – heatstroke, hyperthermia – neuroleptic malignant syndrome – peripheral autonomic dysfunction – trauma of spinal cord
Other causes (in alphabetical order)	– alcoholic hepatitis – allergic reactions – Castleman disease – cholesterol emboli – chronic fatigue syndrome – cyclic neutropenia – drug fever – factitious fever – familial Mediterranean fever – graft versus host disease – hemolysis – hemophagocytic syndrome – histiocytosis X – hyperimmunoglobulinemia D syndrome – hypersensitivity pneumonitis (“metal fume fever”) – inflammatory pseudotumor – Kikuchi disease – pancreatitis – PFAPA syndrome (**p**eriodic **f**ever, **a**denitis, **p**haryngitis, and **a**phthous stomatitis) – pulmonary emboli, thrombophlebitis, thrombosis – retroperitoneal fibrosis – sinus histiocytosis with massive lymphadenopathy – sweet syndrome – tissue infarction/necrosis (hematoma, aortic dissection) – **t**umor necrosis factor **r**eceptor-**a**ssociated **p**eriodic fever **s**yndrome (TRAPS)

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Fever of Unknown Origin

Definition. The diagnosis "fever of unknown origin" (FUO, prolonged FUO) is used for a fever (with temperatures measured several times ≥ 38.3 °C) of at least three weeks' duration in individuals who are not immunocompromised and who have had a comprehensive, but unsuccessful outpatient or inpatient evaluation. While the definition previously required a minimal period of hospitalization, or a certain number of outpatient examinations, currently a minimal evaluation program is proposed before the term FUO can be used (Tab. 4.**2**). The differential diagnostic spectrum of the causes of fever is changed in the presence of an underlying disease (neutropenia, HIV infection, endoprostheses) or a specific epidemiological situation (nosocomial infection, following a stay in, or return from endemic regions, with specific infectious diseases).

Causes. The further development of imaging techniques and detection methods for infectious agents, as well as the possibilities of fine needle punctation or biopsy, has changed the spectrum of the causes for a FUO during the last 50 years (Fig. 4.**1**). Infectious diseases and malignant tumors as causes of a FUO have become rarer. The proportion of noninfectious, inflammatory diseases has increased. In up to one-third of the cases, a cause cannot be found, despite comprehensive examinations. However, the long-term prognosis in these patients is often benign, as long as new symptoms do not occur (e. g., weight loss).

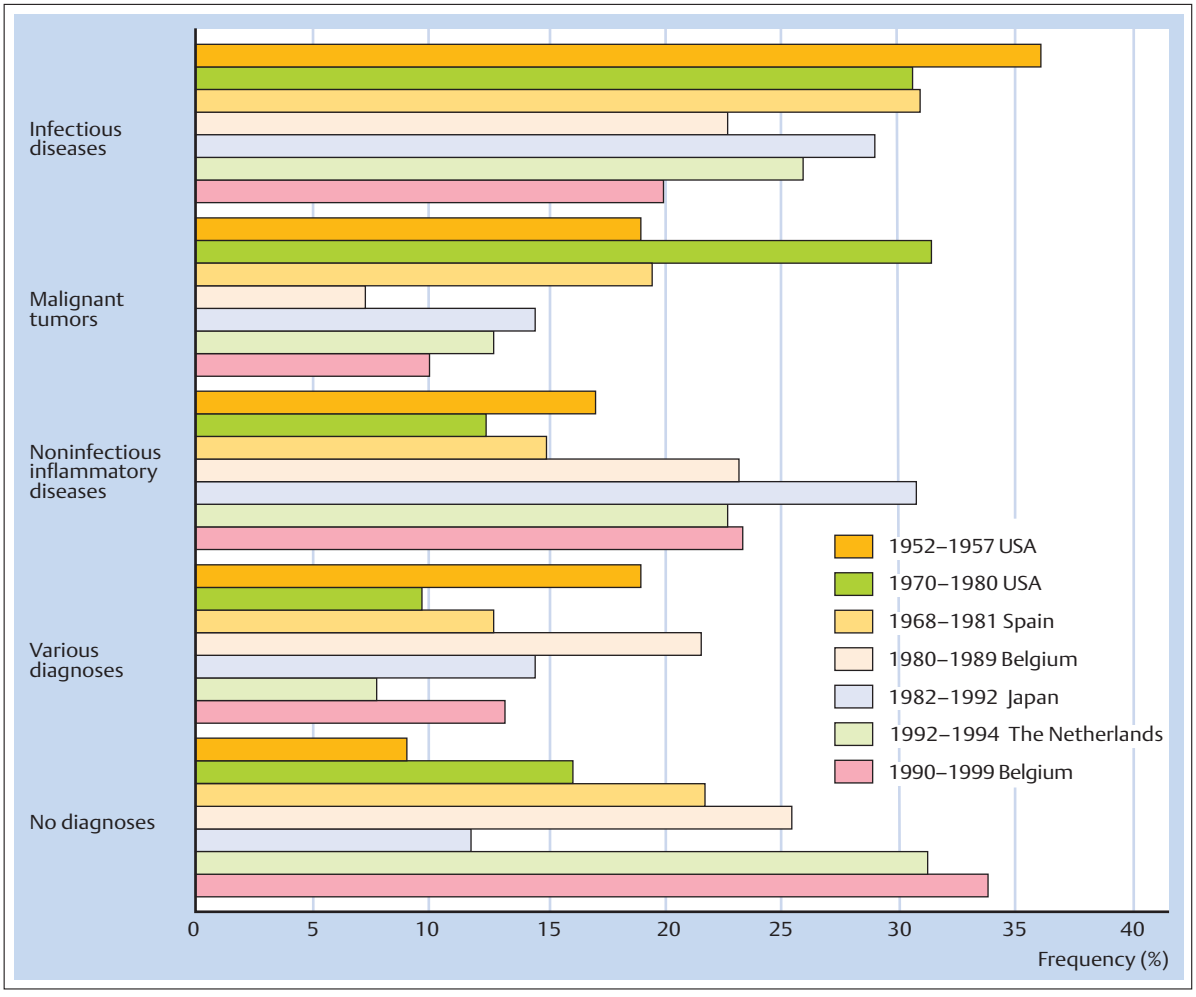

Fig. 4.**1** Final diagnoses in patients with fever of unknown origin (FUO). Time period 1952–1957 (Petersdorf et al., USA); 1970–1980 (Larson et al., USA); 1968–1981 (Barbado et al., Spain); 1980–1989 (Knockaert et al., Belgium); 1982–1992 (Iikuni et al., Japan); 1992–1994 (de Kleijn et al., The Netherlands); 1990–1999 (Vanderschueren et al., Belgium).

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Table 4.**2** Minimal diagnostic work-up to qualify as fever of unknown origin (FUO)

- Comprehensive medical history
- Repeated physical examination
- Complete blood cell count and differential?
- Microscopic examination of blood film
- Routine blood chemistry (including lactic dehydrogenase, bilirubin, and liver enzymes)
- Blood sedimentation rate
- Urinalysis and microscopy
- Chest radiography
- Blood and urine cultures (before initiation of antibiotic treatment)
- Antinuclear antibodies
- Rheumatoid factor
- Serologies for cytomegalovirus and Epstein–Barr virus
- Human immunodeficiency virus antibody and antigen tests
- Hepatitis serology (if abnormal liver enzyme test result)
- Computed Tomography scan of abdomen
- Q fever serology (if exposure risk factors exist)
- Examination for specific endemic infectious diseases in returning travelers or persons living in such geographic areas (e. g., systemic leishmaniasis [India, Mediterranean area], etc.)
- Tuberculin test
- Evaluation of any abnormal symptoms and findings

Modified from Arnow et al., 1997 and Mourad et al., 2003.

4.2 Fever without Localized Symptoms

Infectious Diseases

Causes. In some patients with fever it is not possible to determine if a specific organ is affected. Only nonspecific symptoms, such as shivering, sweating, night sweats, fatigue, or weight loss, are present. The clinical examination also does not yield any disease-specific findings. In this situation, the following diagnoses should especially be considered:

- tuberculosis
- endocarditis
- mycotic aneurysm
- septic thrombophlebitis
- spondylitis
- osteomyelitis
- pneumonia
- intra-abdominal abscesses (liver, bile ducts)
- pyelonephritis.

These diseases occasionally take an asymptomatic course, both clinically and with respect to the medical history. Rarer causes are: cat scratch disease, rickettsiosis (which can occur without the classical exanthema), ehrlichiosis, chronic Q fever with hepatomegaly, brucellosis, leptospirosis, Whipple disease, typhoid fever, and rat-bite fever.

The most important *viral diseases* that are not accompanied by localized symptoms, but occasionally by high fever, are cytomegalovirus infection, mononucleosis, HIV infection, and viral hepatitis in an early stage.

Systemic *mycoses* (cryptococcosis, histoplasmosis) are predominantly found in immunocompromised patients. Of the *parasitic diseases*, toxoplasmosis should be considered, as it can occasionally occur without enlarged lymph nodes. Psittacosis or malaria should also be considered, if appropriate exposure has occurred.

Diagnosis. A series of very specific examination methods is available for diagnosis of each of these infectious diseases. In addition to cultures and serological examinations, echocardiography (endocarditis and atrial myxoma), ultrasound, and computed tomography (CT) examinations of the abdomen (intra-abdominal abscesses, lymphomas) play an important role. Computed tomography and magnetic resonance imaging (MRI) are more sensitive than conventional radiographs for the early diagnosis of spondylitis and osteomyelitis. In FUO or fever without localized symptoms, [^{18}F]-fluorodeoxyglucose (FDG)–positron emission tomography (PET) can deliver important additional information and can visualize occult infectious foci and tumors, as well as noninfectious inflammatory diseases (especially vasculitis) (Fig. 4.**2**).

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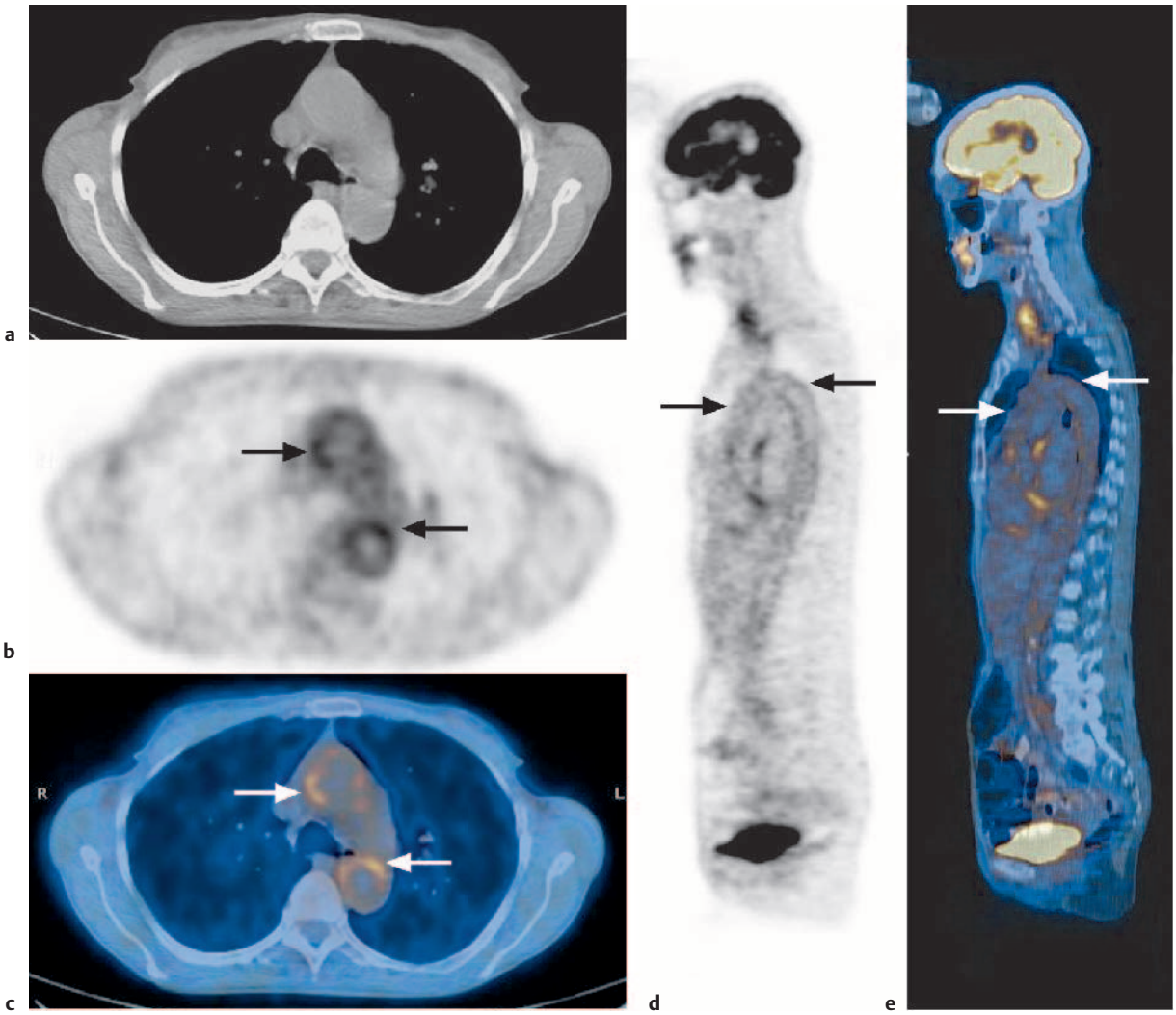

Fig. 4.**2** Vasculitis of large vessels in a 78-year-old woman. [^{18}F]-fluorodeoxyglucose (FDG)–positron emission tomography with integrated CT scan (PET/CT).

a–c Left panel (top to bottom): CT, PET, and PET/CT slice through the aorto-pulmonary region. Increased FDG uptake in the ascending and descending aorta (arrows).

d Middle panel: lateral view of PET scan.

e Right panel: lateral view of PET/CT scans showing increased FDG uptake in the ascending, descending, and abdominal aorta (arrows). The increased FDG uptake indicates the inflammatory process in the aorta (Scans kindly provided by K. Stumpe, Department of Nuclear Medicine, University Hospital Zürich, Switzerland).

Noninfectious Causes

Malignant Diseases. The main noninfectious causes (Tab. 4.**1**) are *malignant lymphomas* and *leukemias*. If peripheral lymph nodes are not accessible to cytological or histological examination, it is frequently possible to make a diagnosis by means of ultrasound-guided fine needle puncture of retroperitoneal lymphomas. The diagnosis of leukemias is primarily based on the peripheral blood count and bone marrow puncture. *Solid tumors* that can be associated with fever include hepatocellular carcinoma, renal carcinoma, hepatic metastases, bronchial carcinoma, pancreatic carcinoma, and atrial myxoma. These tumors generally can be detected with great certainty using imaging techniques.

Vasculitis Syndromes and Connective Tissue Disorders. Among the *vasculitis syndromes* and *connective tissue disorders* (see Tab. 4.**22** p. 177) Polymyalgia rheumatica, nonclassifiable collagen vascular diseases (early form of various collagen vascular diseases), and systemic lupus erythematosus (SLE) must be considered, which at least at the onset of the disease can become manifest without localized symptoms. The adult form of Still disease can also have fever as its only symptom. Whilst antinuclear antibodies are positive in most cases of lupus erythematosus, pathognomonic findings are not available for polymyalgia rheumatica or Still disease.

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Other Causes. *Drug fever* is of great practical significance. Concomitant exanthema can occasionally be present transiently. Especially in elderly patients, *recurrent pulmonary embolisms* can occur with a fever, but without notable pulmonary symptoms or radiological changes. Combined perfusion and ventilation scintigrams or CT analyses are diagnostically valuable. Diffuse abdominal pains and fever can also indicate a *mesenteric infarction* in elderly patients. In younger patients, *Crohn disease* can occur without gastrointestinal symptoms. Colonoscopy with intubation of the ileocecal valve confirms the diagnosis. *Cirrhosis of the liver* and *granulomatous hepatitis* are additional causes of a persistent fever. If the abdominal symptoms in *Mediterranean fever* are initially absent, this diagnosis can be suspected but not confirmed based on a positive family history and appropriate origin.

The suspicion that a *fever* is merely being *feigned* is based primarily on discrepancy between the fever and the pulse curves. This is by no means a complete list of diseases associated with fever that primarily can become manifest without localized symptoms.

Possible causes of fever can usually be determined by means of *follow-up observations* and the *associated signs and symptoms*. In this case repeated clinical examinations are of inestimable value.

Hospitalized Patients

If hospitalized patients develop a fever, infectious causes and drug allergies must first be excluded. Intravasal catheters, implanted prostheses, drains, and intubation facilitate access for nosocomial pathogens. Postoperative cholecystitis or sinusitis after intubation can occur initially without localized symptoms.

4.3 Fever with Associated Cardinal Symptoms

Additional *cardinal symptoms* occur together with a fever in many individuals, which makes the differential diagnosis significantly easier. Although, during the development of a febrile illness, various symptoms can overlap and alternate (e. g., arthralgia and skin rash in arthritis–dermatitis syndrome), classification according to different cardinal symptoms has proven to be clinically effective (Tab. 4.**3**).

The following sections will summarize the differential diagnostic possibilities that can occur in the context of one of these cardinal symptoms.

Table 4.**3** Frequent leading symptoms associated with fever

- Rash
- Joint or bone pain
- Lymphadenopathy
- Swelling of face or neck
- Headache and neck stiffness
- Neurological disorder
- Cold or influenza-like symptoms
- Cough and chest pain
- Jaundice
- Splenomegaly
- Diarrhea
- Abdominal pain
- Dysuria
- Sepsis
- Heart disorder

Fever and Skin Rashes

Petechiae and Purpura

Infectious Diseases. Petechiae and purpura can be caused by various bacteria, rickettsia, and viruses (Tab. 4.**4**). Independently of if disseminated, intravascular coagulation is present, a sepsis with Gram-negative pathogens (rarely a sepsis with Gram-positive pathogens) can lead to petechiae. In endocarditis these lesions are generally very discrete. In meningococcemia, lesions are more noticeable due to confluence. In an early stage of bacteremia, gonococci, streptococci, staphylococci, *Pseudomonas aeruginosa*, *Capnocytophaga canimorsus* (after a dog bite), and *Streptobacillus moniliformis* (rat-bite fever) can cause petechiae. However, vesicles and pustules are more frequently present in these infections. Among the rickettsial diseases, typhus and Rocky Mountain spotted fever should be mentioned as rare causes. A petechial skin rash is more frequently observed in viral diseases, including measles, rubella, mononucleosis, hepatitis, dengue fever, and other hemorrhagic types of fever.

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Table 4.4 Infectious diseases presenting with rash

Disease	Maculo-papular eruptions	Vesiculo-bullous eruptions	Purpuric eruptions	Nodular eruptions	Erythema-tous erup-tions	Urticarial eruptions	Ulcers
Viruses							
– Adenoviruses	×		×				
– Coxsackie viruses	×	×	×		×	×	
– Dengue virus	×		×				
– Echovirus	×	×	×				
– Epstein–Barr virus	×		×			×	
– Yellow fever virus			×				
– Hemorrhagic fever viruses			×				
– Hepatitis B virus	×					×	
– Herpes simplex virus		×					x
– HIV	×					×	
– Human herpes virus 6	×						
– Measles virus	×		×				
– Parvovirus B19	×				×		
– Rubella virus	×						
– Vaccinia virus		×					
– Varicella-zoster virus		×					
– Cytomegalovirus	×						
– Zoonotic pox viruses		×					
Bacteria							
– *Bacillus anthracis*							x
– *Bartonella* species	×			×			x
– *Borrelia burgdorferi*	× *						
– *Borrelia* species (relapsing fever)	×		×				
– *Capnocytophaga* species			×				
– *Chlamydia psittaci*	×						
– *Corynebacterium diphtheriae*							x
– *Ehrlichia* species	×		×				
– *Francisella tularensis*	×						x
– *Leptospira* species	×						
– *Listeria monocytogenes*		×					
– *Mycobacterium leprae*				x	x		x
– *Mycoplasma pneumoniae*	×	×				×	
– *Neisseria gonorrhoeae*			×				
– *Neisseria meningitidis*			×				
– Nontuberculous myobacteria	×			×			x
– *Nocardia* species				×			x
– *Pseudomonas aeruginosa*	×						x
– Rat-bite fever	×		×				
– Rickettsioses	×	×	×				
– *Salmonella typhi*	×						
– *Staphylococcus aureus*	×	×	×		×		x
– Streptococci	×	×	×		×		
– *Treponema pallidum*	×						x
– *Vibrio vulnificus*		×					
– *Yersinia pestis*							x
Fungi							
– *Blastomyces dermatitidis*	×			×			
– *Candida* species	×			×			
– *Coccidioides immitis*	×			×			
– *Histoplasma* species	×			×			x
– Cryptococci	×						
– *Sporotrix* species				×			
Protozoa							
– *Leishmania* species							x
– Malaria			×				

* Ringlike (erythema migrans).

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Noninfectious Causes. The most important *noninfectious* causes include drug reactions, rheumatic fever, Schönlein–Henoch purpura, lupus erythematosus, and other vasculitis syndromes that are associated with antibodies against neutrophilic cytoplasmic antigen (ANCA) (polyarteritis nodosa, Churg–Strauss syndrome, Wegener disease). In chronic hepatitis C infection the vasculitis associated with cryoglobulins, purpura arthralgia nephritis syndrome, should be mentioned. The histology of the purpura in vasculitis syndromes mentioned usually shows an underlying leukocytoclastic vasculitis.

Maculopapular Exanthema

It is usually possible to distinguish maculopapular and vesicopustular rashes, even if morphological transitions from one efflorescence to another are frequently observed (Tab. 4.**4**).

Viral Diseases. A *maculopapular exanthema* usually occurs in measles, rubella, and roseola (exanthema subitum, roseola infantum [human herpesvirus 6]). In infections with coxsackie viruses and echoviruses the rash lasts very briefly. In mononucleosis, the rash is rare and discrete, when present.

> If patients with Epstein–Barr virus infection are given aminopenicillin, they regularly exhibit a very clear maculopapular drug eruption.

In the acute phase of infectious erythema (fifth disease [parvovirus B19]) one observes an erythema of the cheeks that is often associated with an exanthema of the trunk and the extremities. This erythema can reoccur during a one to three week period. In adults, the skin rash often presents atypically or is absent.

Bacterial Diseases. Streptococci and staphylococci have a special affinity for the skin. Erysipelas, scarlet fever, and erythema marginatum (in rheumatic fever) are caused by streptococci. Toxic shock syndrome is caused by an exotoxin produced by staphylococci. The syndrome appears on the skin as an erythema. Later on, scaling develops on the hands and soles of the feet. Group A streptococci can cause a similar clinical picture. A maculopapular exanthema, which occurs on the entire body, but more often on the hands and soles of the feet, is found in secondary syphilis. In typhoid fever, roseolas can develop at the end of the first week of the disease (see Fig. 4.**14**).

Rare Pathogens. Rare causes of maculopapular exanthema are acute HIV infection, infections with adenoviruses, dengue virus, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Bartonella henselae* (cat scratch disease), leptospires, rickettsiae, *Streptobacillus moniliformis*, or *Spirillum minus* (rat-bite fever), systemic mycoses (*Candida, Histoplasma,* cryptococci), *Toxoplasma gondii*, as well as Kawasaki disease.

Noninfectious Causes. *Noninfectious* causes of a maculopapular exanthema are drug reactions, serum disease, lupus erythematosus, Stevens–Johnson syndrome, Sweet syndrome, graft-versus-host disease, and, rarely, dermatomyositis.

Sweet Syndrome. This is an acute febrile disease of unclear etiology with leukocytosis and painful red or crimson papules or nodules on the skin. The lesions also can have a vesicular or pustular appearance. In addition, general symptoms, such as arthralgia, malaise, headaches, and myalgia, are also present. Therapy with systemic steroids results in improvement. The fever can precede the skin lesions by days or weeks. A skin biopsy reveals dense neutrophilic infiltrates. Sweet syndrome can be associated with infections (upper respiratory tract, intestinal tract), inflammatory bowel diseases, pregnancy, malignancies, or medications (especially granulocyte colony stimulation factor [G-CSF]).

Vesicles and Pustules

Bacterial and Viral Infections. Vesicles and pustules are typical skin lesions that occur as a result of an infection with herpes simplex and varicella-zoster viruses. Coxsackievirus A16 is most often responsible for *hand-foot-and-mouth disease* (occasionally, coxsackieviruses A4, A5, A7, A9, or A10). Typically the vesicles develop at the named locations on a clearly red background. The skin lesions that occur in *arthritis–dermatitis syndrome* (Fig. 4.**3**) are so characteristic that it is possible to make a diagnosis at a glance in most cases. A vesicopustular rash can also occur in staphylococcal sepsis. The distribution of the skin lesions, over the entire body, usually permits a distinction to be made with respect to disseminated gonococcal infection, in which the vesicles are particularly located on the distal extremities. Rare causes of vesicular skin lesions are rickettsial pox (*Rickettsia akari*), infection with *Vibrio vulnificus*, and diseases caused by *Monkeypox virus* (see Fig. 4.**7**) or *Cowpox virus* (see Fig. 4.**6**).

Noninfectious Causes. Noninfectious causes of vesicles and pustules are drug eruptions, allergic dermatitis, Stevens–Johnson syndrome, and Sweet syndrome.

Nodular Skin Lesions

Nonerythematous nodular lesions can be a sign of candidal sepsis or other fungal infections (blastomycosis, histoplasmosis, coccidioidomycosis, sporotrichosis).

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Nocardia species or other nontuberculous mycobacteria (*Mycobacterium marinum*) can cause papular or red nodular skin lesions. Individuals infected with HIV occasionally exhibit papular or nodular skin lesions, which are likewise caused by nontuberculous mycobacteria (*M. fortuitum, M. chelonae, M. marinum*) or by *Bartonella henselae* (bacillary angiomatosis). Bacillary angiomatosis can exhibit a comparable morphology to that of Kaposi sarcoma. Erythema nodosum is described in Chapter 3.

Erythema

A diffuse erythema, with susequent desquamation of the skin possible, can be the main manifestation of acute and foudroyant systemic infections with a high mortality rate, such as streptococci or *toxic shock syndrome* caused by staphylococci. Additionally, a generalized erythema can be the predominant symptom in scarlet fever, enterovirus infections, Kawasaki disease, and noninfectious diseases (allergic reactions, lymphoma, and Sézary syndrome).

Urticaria

Urticarial skin lesions occur frequently and can be associated with infections caused by mycoplasma, enteroviruses, adenoviruses, Epstein–Barr virus, HIV, and hepatitis viruses, as well as febrile, noninfectious systemic diseases (allergy, vasculitis, malignancy).

Ulcers

Infectious Causes. Ulcerous skin lesions can be the primary manifestations of cutaneous leishmaniosis, various sexually transmitted infections, and, in addition, of rare infectious diseases such as anthrax, cutaneous diphtheria, ulceroglandular tularemia, bubonic plague, leprosy, Buruli ulcers (*Mycobacterium ulcerans*), ecthyma gangrenosum (*Pseudomonas aeruginosa*), or tropical ulcers. The primary lesion after a bite by a hard tick (which can carry various types of rickettsiae) is manifested as a small, ulcerous, nonpurulent lesion with a dark base (called eschar or tâche noir, see Fig. 4.**5**).

Noninfectious Causes. Ulcers of *noninfectious* origin are caused by: skin ulcers in peripheral vascular diseases, Behçet disease, vasculitis, cholesterol embolisms, inflammatory bowel diseases, lymphomas, erythema multiforme, primary dermatological diseases, tumors, or toxic skin injuries. The occasionally large ulcers in pyoderma gangrenosum can be associated with various underlying interna diseases.

Fig. 4.**3** Skin lesion in arthritis–dermatitis syndrome.

Bacterial Skin Infections

Staphylococcal Infections. Most staphylococcal infections occur on the skin or the soft-tissues and are characterized by pus formation. For example:

- folliculitis
- impetigo
- pyoderma
- sweat gland abscesses
- furuncles
- carbuncles
- paronychia
- wound infections

are characterized by the local findings. Bacteremia occurs in 20–30% of cases of deep, localized infections. Staphylococcal infections of the mucous membranes can also lead to purulent inflammations.

In *toxic shock syndrome* a skin erythema develops, with a characteristic scaling of the palms and soles of the feet occuring approximately one week after infection.

In *pyomyositis* (an acute, localized staphylococcal infection of the skeletal muscles) the collection of pus is initially always intramuscular, such that there is no redness or other visible signs of skin inflammation. The cardinal symptom is localized muscle pain. The disease is mainly observed in tropical regions or in immunosuppressed patients.

Streptococcal Infections. Skin and soft-tissue infections caused by streptococci are:

- *erysipelas* and cellulitis (Fig. 4.**4**)
- contagious impetigo
- necrotizing fasciitis
- surgical wound infections.

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Fig. 4.4 Erysipelas

A complication of a streptococcal skin infection that can occur two weeks later is *acute glomerulonephritis.*

Toxic shock syndrome, caused by streptococci, starts (usually after a minor trauma) with a soft-tissue infection, whose inflammatory margin, unlike that of the erysipelas, is poorly defined. Locally, the soft-tissues can necrotize rapidly. The general health of the patient is poor and a fulminant shock with multiorgan failure develops.

Arthritis–Dermatitis Syndrome (Gonococci). The skin lesions that occur in arthritis–dermatitis syndrome (1–3% of gonococcal infections) are so characteristic that it is possible to make an instant diagnosis in most cases (Fig. 4.**3**). The exanthema is in its evolution like that of varicella but the number of skin lesions is lower (5–20). For gonococcis, vesicles are mainly located on the distal extremities. A second facultative phase of the disease becomes manifest as tendosynovitis and septic arthritis of the large and medium joints.

Anthrax (*Bacillus anthracis*). Anthrax is a rare, usually occupationally related, zoonosis (e.g., stock farming, processing of pelts, animal hair, and wool). Additionally, anthrax spores have been used in bioterrorism attacks in powder form (skin contact) or as an aerosol (inhalation). In humans, dermatoid anthrax is the most common form (95%); pulmonary anthrax (5%) and intestinal anthrax (< 1%) are very rare. These pathogens can enter through the smallest skin injuries (or by inhalation or ingestion of the spores) and can cause purulent hemorrhagic inflammation with severe edema formation. The typical anthrax carbuncle (covered with a black scab) develops two to three days after infection and is relatively painless. These pathogens can be cultured from the carbuncle (particularly the margins) and from the blood.

Mycobacterial Skin Infections

Nontuberculous Mycobacteria Infection. In immunologically healthy persons *Mycobacterium marinum* can lead to granulomatous skin lesions, especially after exposure to contaminated water (e.g., from an aquarium). In Africa *M. ulcerans* causes ulcerous skin and soft-tissue infections (Buruli ulcers). Soft-tissue infections with *M. chelonae* and *M. fortuitum* are rare.

In *immunocompromised patients* skin lesions can also occur during systemic infections with *M. avium complex*, *M. kansasii*, *M. haemophilum*, *M. scrofulaceum*, *M. xenopi*, and *M. chelonae*.

Leprosy (*Mycobacterium leprae*). Leprosy is a chronic, systemic, infectious disease. Airborne transmission probably occurs between humans. The incubation time is extremely variable (one to 20 years). There are two main forms of leprosy, tuberculoid leprosy and lepromatous leprosy. Transitional forms are common:

- *Tuberculoid leprosy* exhibits a relatively benign course. The skin lesions are limited, depigmented, and manifest as erythematous maculae with a mainly unilateral and asymmetric arrangement. In the immediate surroundings, affected nerves can be palpated as painful cords. Superficial skin sensibility is frequently reduced. In contrast, internal organs are not affected.
- In *lepromatous leprosy,* the course is usually progressive. In addition to the infection of sensory nerves, a significant bacterial multiplication occurs in the skin, mucosa, reticuloendothelial system, liver, spleen, or testes. The facial skin, nose, and ears are significantly infiltrated (lion face) and chronic rhinitis and epistaxis develop. Tissue destruction mainly affects the skin and mucous membranes. Spreading along the trunk and the extremities is usually symmetrical.

The detection of acid–fast rods from cutaneous lesions is straightforward in the lepromatous form. These bacteria are rarely detected in the tuberculoid form.

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Rickettsial Diseases

Rickettsiae are transmitted by a variety of vectors (Tab. 4.**5**). These diseases are classified in the spotted *fever group*, *typhus group*, and the *scrub typhus group*, and are manifested through fever and exanthema. Pathogens and vectors are found in specific endemic regions. Additional pathogens belonging to the family *Rickettsiacea* will be discussed under the corresponding primary symptoms: *Ehrlichia* (fever after tick bite), *Bartonella* (cat scratch disease with lymphadenopathy, endocarditis), and *Coxiella burnetii* (Q fever, pneumonia). The diagnosis of rickettsiosis can be confirmed *serologically*.

Spotted Fever. Rocky Mountain spotted fever (*Rickettsia rickettsii*), fièvre boutonneuse (*Rickettsia conorii)* endemic to the Mediterranean area, and the African tick-bite fever *(Rickettsia africae)* are transmitted by *hard ticks*. The clinical picture consists of a maculopapular rash and fever. Rocky Mountain spotted fever frequently presents with petechiae and hemorrhaging. In fièvre boutonneuse and African tick-bite fever, a primary lesion can be frequently found at the location of the tick bite (eschar, tâche noire, Fig. 4.**5**).

Fig. 4.**5** Eschar on abdominal skin after a tick bite in South Africa. Fever and right inguinal lymphadenopathy due to *Rickettsia africae* infection.

Epidemic Typhus. *Rickettsia prowazekii* is transmitted by lice and has caused epidemics, especially during wars and famines. Humans are the sole pathogen reservoir. The clinical picture (*typhus exanthematicus*) is characterized by a suddenly occurring, high fever, severe head and limb pain, and, beginning on the fourth day, a polymorphous, macular, partially hemorrhagic exanthema, which spreads from the lateral thorax. Typically present are conjunctivitis, a reddened face, and hepatosplenomegaly (approximately 50% of the cases). Simultaneously, the central nervous system can be affected, along with the exanthema. Somnolence, apathy, cranial nerve paralysis (deafness, visual, and speech disorders), tremor, central circulation disorders with hypotension, and tachycardia are observed. In severe courses of the disease, the kidneys are also frequently affected.

Endemic Typhus. The course of endemic typhus (*Rickettsia typhi*) is, in general, more benign and shorter. Rats, mice, and other small mammals are the pathogen reservoir and transmission in rats occurs via *rat fleas*.

Table 4.**5** Rickettsial diseases

Pathogen	Vector	Disease	Epidemiology
Spotted fever group			
R. conorii	hard tick	Mediterranean (fièvre boutonneuse), African and Indian tick-bite fever	Mediterranean, Africa, India
R. africae	hard tick	African tick-bite fever	Africa
R. rickettsii	hard tick	Rocky Mountain spotted fever	North and South America
R. sibirica	hard tick	North Asian tick fever	Asia, Russia, China, Mongolia
R. mongolotimonae	hard tick	Chinese tick-bite fever	East Asia
R. australis	soft tick	Queensland tick typhus	Australia
R. japonica	soft tick	Japanese tick-bite fever	Japan
R. akari	mite, rodents	rickettsial pox	USA, Europe, Korea
R. felis	flea	flea typhus	Mexico, Southern USA
R. helvetica	soft tick	febrile illness	Switzerland, France, Sweden
R. slovacae	hard tick	febrile illness, meningoencephalitis	Slovakia, Switzerland, France, Portugal
Typhus group			
R. prowazekii	body louse	epidemic louseborne typhus fever	worldwide, particularly Africa, South and Central America, Mexico, Asia
R. typhi	rat flea	endemic fleaborne typhus fever	worldwide
Tsutsugamushi fever			
Orientia tsutsugamushi	larval mite	scrub typhus (Tsutsugamushi disease)	East, South, Southeast Asia, Japan, Western Pacific, Australia

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Scrub Typhus. Japanese typhus occurs in Central and East Asia. The pathogen, *Orientia tsutsugamushi*, is transmitted by *mite larvae* from rodents to humans. Sometimes a necrotic lesion is visible at the location of the bite. The maculopapular exanthema which occurs after about one week is often visible only for a few days.

Viral Diseases with Skin Rashes

Measles (*Paramyxovirus*). Because of the highly contagious nature of the measles virus, approximately 90% of humans suffer from the disease within the first 10 years of life. The prodromal phase (three to five days) begins with general disease symptoms: fever, conjunctivitis, rhinitis, and dry cough. Typical are Koplik spots (second to third day) on the mucosa of the cheeks in the region of the lower premolars. The measles exanthema usually develops after a brief afebrile interval and starts on the neck, behind the ears, or on the face. The exanthema spreads to the trunk and finally to the extremities.

Rubella (*Togavirus*). Rubella infection also usually occurs before adulthood. The exanthema exhibits a distribution comparable to that of measles. The individual skin lesions are somewhat smaller than for measles (however, larger than in scarlet fever), nonconfluent, light pink, and fade quickly. Usually the nuchal, occipital, and retroauricular lymph nodes are notably enlarged. Splenomegaly is also occasionally present.

Erythema Infectiosum (*Parvovirus B19*). Erythema infectiosum (fifth disease) is a mild, often afebrile, disease with erythematous skin lesions on the cheeks and maculopapular rashes on the trunk and extremities. It mainly affects children. In adults, in whom the exanthema often is absent, persistent arthralgia or arthritis can develop. In individuals with elevated erythrocyte production (e. g., in sickle cell anemia) an aplastic crisis can occur as a consequence of a parvovirus infection, and in immunodeficient patients a severe chronic anemia can develop.

Infections by Herpesviruses. The eight viruses of the herpes group (Tab. 4.**6**) cause a primary infection (often clinically asymptomatic) and persist for life in the body (latent infection). Diseases that are associated with an alteration of immunocompetence can lead to reactivation of these viruses in the form of opportunistic infections. Reactivation can occur without the presence of IgM antibodies. In those individuals infected with HIV, the absence of IgM antibodies is the norm.

Herpes Simplex (Herpes Simplex Virus Type 1 and 2). More than 99% of primary infections with herpes simplex virus 1 occur during the first years of life and take a clinically asymptomatic course. Clinically manifested herpes diseases (especially primary infections) are gingivostomatitis (usually in children) and eczema herpeticatum, which is caused mainly by herpes simplex virus 1. Herpes simplex virus 2 is sexually transmitted and is responsible for herpetic sepsis of the newborn, genital herpes, and herpetic proctitis. *Reactivations* can be provoked by various means: febrile diseases such as an HIV infection, pneumonia, meningitis, malaria, intensive tanning, gastrointestinal disorders, and various types of trauma. The individual skin lesions are similar to those of varicella-zoster virus infections (see below). One to two days after the onset of the lesions, characteristic paresthesia, a feeling of tension, and burning pain develop. Concomitant symptoms such as fever, lymphadenopathy, dysuria, and perianal paresthesia (in genital infections) occur especially in primary infections, but rarely in recurrent diseases.

Varicella. *Chickenpox* (varicella-zoster virus) is a highly contagious childhood disease. After an incubation period of two to three weeks, a prodromal phase (transient exanthema, limb pain) can occasionally occur. The skin lesions of the varicella exanthema are initially pale pink and transform themselves within a few hours into papules, and later into vesicles which dry after one to two days. The exanthema occurs in several consecutive episodes which are accompanied in each case by a rise in temperature. Therefore, various developmental stages of the skin lesions exist simultaneously. A cervical lymphadenopathy is frequently observed. Complications (bacterial secondary infections, or bullous or necrotizing courses of the disease) are rare.

Herpes Zoster. *Shingles* and *chickenpox* are caused by the same virus, varicella-zoster virus. Varicellas are an expression of a primary infection, which frequently can occur asymptomatically, whereas herpes zoster is the reactivation of a latent infection. Malignant diseases (especially lymphomas), HIV infection, trauma, surgical interventions, or irradiation of the spinal cord can reactivate the virus.

Before the exanthema erupts, it is characteristic for unilateral, intense neuralgiform pain to occur within a dermatome. A few days later, skin lesions, which initially are maculopapular, and subsequently vesicular, occur within a dermatome. Occasionally the vesicles become hemorrhagic. In severe cases, necroses and ulcerations occur. Even after the lesions have healed (two to four weeks), it is possible for the intense neuralgiform pain to persist, ever for weeks to months, especially in elderly patients.

Ophthalmic zoster and *herpes zoster oticus* can cause severe local pathologies with pain and functional impairment. Additional complications are meningitis, encephalitis, myelitis, and pneumonia. Especially in severe underlying illnesses with reduced resistance to infection, herpes zoster can generalize secondarily and cause a varicella-like clinical picture.

Exanthema Subitum (Human herpesvirus 6). The acute disease caused by human herpesvirus 6 (exanthema

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Table 4.**6** Clinical manifestations of human herpes viruses

Virus		Primary infection	Reactivation	Chronic infection in immunocompetent persons	Immunodeficiency
Herpes simplex virus 1	HSV-1	Frequently subclinical (80–90 %) Oral lesions (10–20 %) congenital infection	Oral lesions encephalitis	None	Large mucocutaneous lesions
Herpes simplex virus 2	HSV-2	Frequently subclinical (80–90 %) genital lesions (10–20 %)	Genital ulcers encephalitis	None	Large mucocutaneous lesions
Varicella-zoster virus	VZV	Chickenpox	Shingles	None	Multisegmental shingles or severe disseminated infection
Cytomegalovirus	CMV	Mononucleosis-like disease	?	Cofactor in atherosclerosis (?)*	Retinitis colitis pneumonitis encephalitis
Epstein–Barr virus	EBV	Mononuclosis	?	Nasopharyngeal carcinoma Burkitt lymphoma	B-cell lymphoma oral hairy leukoplakia
Human herpes virus 6	HHV-6	Exanthema subitum	?	Multiple sclerosis (?)*	Pneumonia disseminated infection
Human herpes virus 7	HHV-7	Fever exanthema-subitum-like illness	?	None	?
Human herpes virus 8	HHV-8	Febrile illness	?	?	Multicentric Castleman disease Kaposi sarcoma primary body cavity lymphoma

(?)* = not proven

subitum, roseola infantum, three-day fever) affects infants in particular. A sudden high fever (≤ 41 °C) of three to five days duration is followed by a maculopapular exanthema, which usually only lasts for a short time. Additional illnesses associated with herpesvirus 6 are high fever without an exanthema, inflamed eardrums, encephalitis, epileptic seizures, or a fulminant hepatitis. In addition, in immunocompetent adults a mononucleosis-like disease may occur and in immunocompromised individuals pneumonitis has been described.

Viral Hemorrhagic Fevers. These fevers are endemic to Central Africa (Lassa, Ebola, and Rift Valley viruses), South and Central America (Junin, Machupo, and Guanarito viruses), Russia and Korea (Hantaviruses) (Tab. 4.**7**). The endemic regions of dengue fever have very rapidly expanded within the tropical climatic zones of all continents during recent years. As a consequence of global travel, it is possible that infected individuals will seek medical care outside of endemic regions.

During recent years, special attention has been paid to the *Lassa, Marburg* and *Ebola viruses*, as the mortality in nosocomial illnesses is extremely high. In contrast to instances of *Argentine* (Junin virus), *Bolivian* (Machupo virus), and *Venezuelan* (Guanarito virus) hemorrhagic fevers, which appear restricted to certain geographical locations, individual cases of Lassa, Marburg, and Ebola virus infections have been introduced from Africa to Europe and the USA. However, transmission between humans occurs only as a result of close contact or during the processing of blood or secretions (e. g., laboratory personnel) from infected individuals. Therefore, infection chains break down rapidly outside of endemic regions. The pathogen reservoir for the African hemorrhagic fevers is only partially known; certain rat and monkey species have been confirmed as carriers. The detection of these viruses may only be undertaken in specialized laboratories (maximum protection).

The clinical manifestations of the various hemorrhagic fever viruses are almost indistinguishable. With Lassa fever ulcers of the oral mucosa are typical. After an incubation period of three to 16 days, nonspecific, influenza-like, prodromal symptoms occur, which develop to a febrile condition with exanthema, diarrhea, vomiting, thoracic pain, with injuries to the liver, kidneys, heart, and central nervous system, as well as

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Table 4.7 Viral hemorrhagic fevers

Family	Genus	Virus	Disease	Vectors	Endemic region
Filoviridae	*Filovirus*	**Ebola virus***	Ebola hemorrhagic fever	Unknown	Africa
		Marburg virus	Marburg hemorrhagic fever	Unknown	Africa
Arenaviridae	*Arenavirus*	**Lassa virus**	Lassa fever	Rodents	West Africa
		New World Arenaviruses**	Arenavirus hemorrhagic fever	Rodents	Americas
Bunyaviridae	*Nairovirus*	**Crimean Congo hemorrhagic fever virus**	Crimean Congo hemorrhagic fever	Ticks	Africa, Central Asia, Eastern Europe, Middle East
	Phlebovirus	**Rift Valley fever virus**	Rift Valley fever	Mosquitos	Africa, Saudi Arabia, Yemen
	Hantavirus	**Puumala virus**	Nephropathia epidemica	Mice	Central and Northern Europe
		Dobrava virus	Hemorrhagic fever with renal syndrome	Mice	Central and Northern Europe, Balkan region
		Seoul virus	Mild hemorrhagic fever with renal syndrome	Rats	Worldwide
		Hantaan virus	Hemorrhagic fever with renal syndrome	Mice	Southern Europe, Southeast Asia
		Sin Nombre virus and other viruses	Hanta pulmonary syndrome	Mice	North and South America
Flaviviridae	*Flavivirus*	**Dengue virus**	Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome	*Aedes* Mosquitos	Asia, Africa, Pacific region, Central and South America
		Yellow fever virus	Yellow fever	Mosquitos	Africa, tropical America
		Omsk hemorrhagic fever virus	Omsk hemorrhagic fever	Ticks	Central Asia
		Kyasanur Forest virus	Kyasanur Forest disease	Ticks	India

Table adapted from Borio et al., 2002.

* Four subtypes of Ebola viruses: Zaire, Sudan, Ivory Coast, and Reston virus.

** The New World arenaviruses include: Machupo (Bolivian hemorrhagic fever); Junin (Argentinian hemorrhagic fever); Guanarito (Venezuelan hemorrhagic fever); Sabia virus (Brasilian hemorrhagic fever). Novel arenaviruses were also described in California.

hemorrhagic diathesis. The latter is responsible for the especially high mortality rate, which in Ebola fever reaches 50–90%. Laboratory findings reveal a leukopenia in 80% of cases.

> The justified suspicion of a hemorrhagic fever requires that all available safeguards regarding isolation of the sick person and diagnosis be exploited.

Hemorrhagic Fever with Renal Syndrome. Various hantaviruses of the European and Asian continents are the cause of a hemorrhagic fever with a *renal* syndrome (Tab. 4.**7**). The pathogen reservoir of the viruses is small rodents. Severe cases of the disease are observed during the late fall and winter months in the Balkan states (Hantaan and Dobrava viruses). Epidemic nephropathy (Puumala virus) occurs especially in Finland, Russia, and the Balkan states, but also in Germany, Belgium, France, and other European countries.

Hanta Pulmonary Syndrome. In contrast, there have been cases of a *pulmonary* syndrome with frequently fatal, respiratory insufficiency associated with hantaviruses (Sin Nombre virus) in the USA and South America.

Poxviruses. Smallpox (*Variola virus*) was declared by the World Health Organization (WHO) in 1980 to be eradicated. A recurrence of the disease as a consequence of a laboratory accident or activities of bioterrorism cannot be completely ruled out. In Africa, epidemics have occurred in humans due to *Monkeypox virus* infection. *Monkeypox virus* has been transmitted to humans out of Africa through exported rats. The infection leads to a systemic febrile illness with disseminated skin lesions that are virtually identical to those of smallpox. Rare zoonotic infections with orthopoxviruses—*Cowpox virus* (Fig. 4.**6**), *Monkeypox virus* (Fig. 4.**7**)—yatapoxviruses (*Tanapox virus*), or parapoxviruses (milker nodule virus [*Pseudocowpox virus*], Orf virus, sealpox virus) can frequently lead to localized vesicular skin lesions and febrile illness in humans. The single member of the genus *Molluscipoxvirus* (*Molluscum contagiosum virus*) is the cause of molluscum contagiosum.

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Fig. 4.**6** *Cowpox virus* infection. Fever and skin lesions developed after contact with a sick pet rat. *Cowpox virus* was detected in skin lesions (Wolfs et al., 2002).

Fig. 4.**7** *Monkeypox virus* infection following contact with a pet prairie dog. Clinical manifestations included fever, malaise, and disseminated skin lesions similar to pox lesions. *Monkeypox virus* was detected in skin lesions. [Photograph was kindly provided by Marshfield Clinic, USA.]

Fever and Joint or Bone Pain

In Chapters 10, "Pain in Joint Diseases" and 11, "Localized Bone Lesions" those diseases are discussed that are probably *not* associated with an infection.

Arthritis

An *infectious cause* can be determined in approximately 15–20% of inflammatory joint diseases. However, if one counts the reactive cases of arthritis (which can occur following an extra-articular infection) as infectious forms, this increases the proportion to 30–50% depending on the age group. In about one-quarter of the patients with bacterial arthritis a prior or simultaneous infectious disease can be determined. In the affected joint it is often possible to recognize predisposing factors (inflammations, chronic polyarthritis, trauma, intra-articular injections).

Bacterial Arthritis. With the exception of disseminated gonococcal disease, bacterial arthritis is generally monoarticular. Typical polyarticular infections include rubella, hepatitis, and mumps. Also, reactive arthritis, following infections with *Chlamydia*, *Shigella*, *Campylobacter*, *Salmonella*, or *Yersinia*, usually affects several joints.

The *clinical manifestations* of bacterial arthritis are characterized by severe joint pain, swelling, hyperthermia, and a significant functional limitation. A joint effusion is almost always present. The acute forms also usually exhibit a fever. Chronic joint infections, caused by mycobacteria or fungi, are usually afebrile. Bacterial arthritis in adults becomes manifest most frequently in the knee (50%), followed by the hip (25%), shoulder (15%), and elbow (11%). The ankle, wrist, and sternoclavicular joints are each affected in 7% of cases. The iliosacral joint is affected in 2% of the cases.

Diagnostically essential is the examination of the joint aspirate. In addition to the mandatory examination of a Gram-stained smear, synovial fluid should be examined microscopically under polarized light to exclude gout or chondrocalcinosis. The necessity of culture and, if the result is positive, a susceptibility test of the pathogen also goes without saying. The Gram stain is positive in 30–50% of cases, depending on the pathogen: staphylococci are directly diagnosed more frequently than Gram-negative rods. Finding gonococci in a direct smear is rare. In the joint aspirate leukocyte counts $> 50\,000/mm^3$ ($> 50 \times 10^9/L$) with more than

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Table 4.**8** Age-related spectrum of pathogens causing bacterial arthritis

Pathogens	Age* < 1 month	1 month to 2 years	2–15 years	16–50 years	> 50 years
Staphylococcus aureus	20	25	50	15	75
Streptococci	20	20	35	5	5
Haemophilus influenzae	–	50	2	–	–
Neisseria gonorrhoeae	–	–	5	75	–
Enterobacteriaceae and *Pseudomonas aeruginosa*	50	3	5	5	15

* Prevalence in %, summarized from various sources.

90% granulocytes are the rule. The glucose concentration is usually depressed (< 50% of the normal serum concentration) and the lactate concentration, with the exception of gonorrheal arthritis, is elevated. The protein concentration fluctuates between 3–6 g/dL (30–60 g/L). However, with a negative Gram stain these findings are not specific, because they also occur in chronic polyarthritis and gout. After excluding these conditions, the etiology of bacterial arthritis can be predicted with some degree of probability based on the age-related pathogen spectrum (Tab. 4.**8**).

Joint Tuberculosis. Joint tuberculosis usually occurs without fever. It is characterized by a chronic course of infection with joint hyperthermia, swelling, and characteristic capsular thickening. The aspirate or the synovial biopsy detects mycobacteria. The early phase radiograph examination shows capsular swelling and osteoporosis near the joint. Subsequent erosions, both subchondral and at the joint margins, occur.

Viral Arthritis. A viral arthritis is most frequently observed in *rubella* and *hepatitis B* infections. The arthritis in *rubella* affects particularly the wrist and finger joints of adult women. Also up to 30% of girls and 15% of boys who suffered from rubella, or who received a vaccination with a live-attenuated vaccine, experience a one to two week arthritic phase. Usually the joint symptoms occur after the exanthema.

In addition, transient episodes of arthritis occur in all kinds of viral afflictions, such as the prodromal phase of hepatitis B, mumps, smallpox, varicella, vaccinia, mononucleosis, measles, parvovirus B19 infection, as well as infections with HIV, arbovirus, echovirus, coxsackie virus, and influenza viruses.

Fungal Arthritis. Fungal arthritis is extremely rare in Europe. In the United States the following infections have been identified, in order of decreasing frequency: coccidiomycosis, histoplasmosis, blastomycosis, cryptococcosis, and sporotrichosis. The clinical course of fungal arthritis is comparable to that of tubercular arthritis. Usually the primary focus of fungal arthritis lies in the lungs, rarely in the skin.

Reactive Arthritis and Arthralgia. Reactive arthritis, which also includes the Reiter syndrome, occurs frequently after infections with *Chlamydia*, *Shigella*, *Campylobacter*, *Salmonella*, *Yersinia*, and possibly gonococci. A reactive arthritis also occurs occasionally in Lyme borreliosis, ehrlichiosis, Whipple disease, cat scratch disease, parasitic and viral diseases, Crohn disease, ulcerative colitis, and Behçet syndrome.

Arthralgias, which can affect one or more joints without clinically objective findings, must be differentiated from the joint swelling associated with bacterial arthritis.

Arthralgia or arthritis is frequently observed in influenza-like infections, hepatitis B in the prodromal phase, Whipple disease, brucellosis, in all forms of vasculitis, polymyalgia rheumatica, familial Mediterranean fever, hyper-IgD syndrome, and tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS).

Osteomyelitis, Spondylodiscitis, and Joint Prostheses Infections

Pathogenesis. Bone infections are caused by a *hematogenic* dissemination of bacteria or a *per continuitatem* involvement of the bone after skin and soft-tissue infections. An infection *per continuitatem* is facilitated by a *vascular* insufficiency (e. g., diabetic foot) or is the consequence of a trauma or surgical intervention.

The spectrum of pathogens varies according to pathogenetic cause and according to age. The most frequently identified pathogens are *Staphylococcus aureus*, coagulase-negative staphylococci, group B streptococci (mainly in the newborn), *Haemophilus influenzae* (more frequently in children), *Enterobacteriaceae* (rare, mainly in the elderly), *Pseudomonas*, and anaerobes. Rare pathogens identified are enterococci, *Salmonella*, *Tropheryma whippelii*, *Brucella*, *Mycobacteria*, and *Candida* (in intravenous drug users or after catheter infection).

In *infections of joint prostheses* a distinction is made between early infections (within three months after surgery), delayed infections (three to 24 months), and

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late infections (> 24 months), according to when the infection occurs after implantation of the prosthesis. Early infections are usually the consequence of an exogenic, perioperative inoculation with the patient's skin microbes. Delayed infections also occur perioperatively, but do not become clinically manifest until later, because of the minimal virulence of the microbes (*Staphylococcus epidermis, Propionibacterium, Corynebacterium* species). A hematogenic contamination of the prosthesis is assumed in late infections.

Clinical Features. The onset of *acute hematogenic* osteomyelitis is usually abrupt, but can also be slow and nonspecific. Typically localized pain, fever, and local signs of inflammation are present during the course of the disease. Leukocytosis and elevated inflammatory parameters are found. After a hematogenic dissemination of bacteria, several bones can be affected. A *per continuitatem* involvement of the bone is usually indicated by local signs of wound infection or an abscess of the skin and soft tissues. Depending on the proximity to neighboring joints, signs of septic arthritis may additionally be present.

In *spondylodiscitis*, which usually develops by hematogenic infection, the local pain, often mild in nature, predominates. In about 50% of patients, fever and leukocytosis are absent. The erythrocyte sedimentation rate is usually elevated.

The bacteria mentioned previously may also cause bone lesions associated with few symptoms, and in which the local or systemic signs of inflammation (including inflammatory parameters in the blood) can be absent. In such clinical situations other pathogens must also be considered in the differential diagnosis. These pathogens can include tuberculosis, systemic mycoses, depending on the endemic region, or rarely the noninfectious causes (malignancies, leukemia) discussed in Chapter 11.

In *chronic* osteomyelitis, which is often maintained by a sequestrum or foreign body, systemic signs of inflammation can be absent. The differentiation between a chronic infection of the joint prosthesis and its mechanical loosening can cause significant, differential diagnostic problems, because the inflammation parameters in the blood can be practically normal, even in a chronic infection.

Diagnosis. The diagnosis of osteomyelitis is based on the detection of pathogen in blood cultures, cultures of bone biopsies, and imaging techniques. Magnetic resonance tomography can show osteomyelitic foci or sequestra which cannot be seen with conventional radiograph techniques.

> Results from smears taken from the skin or soft tissues can be confusing and may not identify the pathogens responsible for the osteomyelitis.

Fever and Lymph Node Enlargement

Fever and Generalized Lymph Node Enlargement

Infectious Causes. Infectious diseases that can cause a *generalized* enlargement of the lymph nodes include primarily mononucleosis, rubella, cytomegalovirus infection, toxoplasmosis, and HIV infection. It is generally possible to rapidly determine a definitive diagnosis, by means of blood count, serological tests, and fine needle aspiration. If contact with animals or milk products has occurred, brucellosis must be considered. In cat-scratch disease, the lymphadenopathy can be generalized and also affect visceral lymph nodes. In secondary syphilis, the lymph nodes are regularly enlarged in addition to the mentioned maculopapular exanthema.

Noninfectious Causes. Malignant lymphomas, leukemias, metastatic tumors, and paraproteinemias can involve all lymph node stations. A micropolyadenopathy can be caused by circulating immune complexes, initiated by drugs, or other allergies. The rare causes of a generalized lymphadenopathy include sarcoidosis, storage diseases, Sjögren syndrome, Kawasaki disease, Castleman disease, Kikuchi disease, sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease), amyloidosis, autoimmune hemolytic anemia, inflammatory pseudotumor, hyperthyroidism, and histiocytosis X.

Fever and Localized Lymph Node Enlargement

The *localized* enlargement of lymph nodes is of great significance, both topographically and from the perspective of differential diagnosis.

- An acute, painful enlargement of the *cervical* lymph nodes usually occurs in infections of the upper respiratory tract. In addition to various viruses, group A streptococci and Epstein–Barr virus play an important role. Because of inadequate discipline in vaccinations, diphtheria must also be considered in the differential diagnosis. Occasionally, lymph node involvement is limited to the cervical region in toxoplasmosis. Cervical lymph node tuberculosis usually takes a unilateral, chronic, and painless course. Nontubercular mycobacteria are also found in this location.

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If an asymmetric, painless swelling is present, a malignant lymphoma must be excluded.

- Rubella, measles, and nonspecific infections of the scalp lead to *occipital* lymph node enlargement.
- Depending on the location of the primary infection, group A streptococci lead to a painful enlargement of the *inguinal*, *ulnar*, or *axillary* lymph nodes. The concomitant lymphangitis and the local finding on the affected extremity facilitate the diagnosis. An axillary or inguinal micropolyadenopathy can be very often palpated, especially in slender adolescents. These changes are the result of chronic microtraumatization of the extremities and are irrelevant for the clarification of a fever. The diagnosis of cat-scratch disease is usually not considered until a localized lymph node enlargement occurs.
- After a genital chancre due to primary syphilis, an indolent enlargement of the *inguinal* lymph nodes occurs. In contrast, the inguinal lymph nodes are painfully enlarged and partially fluctuant in herpes simplex, lymphogranuloma venereum (*Chlamydia trachomatis*), chancroid (*Haemophilus ducreyi*), and granuloma inguinale or donovanosis (*Calymmatobacterium granulomatis*). Gonorrhea virtually never causes lymph node enlargement.
- In *herpes zoster* the regional lymph nodes are regularly enlarged. The characteristic arrangement of the skin lesions usually permits the diagnosis to be made at a glance in most cases.
- In tropical endemic regions filariasis should be considered in the differential diagnosis. African tick-bite fever also leads to an enlargement of the regional lymph nodes, depending on the location of the tick bite.

Infections of the Lymph Nodes

Toxoplasmosis (*Toxoplasma gondii*). The morbidity of toxoplasmosis is low in immunocompetent persons (with the exception of the ocular infection). Both the congenital and the acquired form usually take an asymptomatic clinical course. Severe disease occurs in the fetus following exposure *during early pregnancy* and in the immunodeficient, especially HIV-infected patients (cerebral abscesses). Lymph node toxoplasmosis occurs most frequently in immunocompetent individuals. General symptoms such as subfebrile temperatures, a reduced state of general health, headache, and limb pain are usually present in clinically manifest toxoplasmosis. Fundamentally, the *Toxoplasma* cysts can settle in all organs. However, the brain, choroid/retina, and the musculature are preferred sites. Diagnosis is based on serology. Although the results of a fine needle aspiration or biopsy of a lymph node are nonspecific in toxoplasmosis, they can prove helpful in excluding a lymphoma in the differential diagnosis.

Cat-scratch Disease (*Bartonella henselae*). Cat-scratch disease is a subacute, usually self-limiting, granulomatous lymphadenitis that follows an infection with *Bartonella henselae* (previously named *Rochalimaea henselae*). The pathogen reservoir consists of healthy cats. The course of the fever is extremely variable. General symptoms can be present. The primary lesion (red papule) after injury by a cat is not always visible or discernible from the medical history. The lymphadenitis of a regional lymph node usually occurs approximately two weeks after infection and an extensive, purulent inflammation can result.

Rare, clinical manifestations are a generalized lymphadenitis, which can persist for weeks to months, oculoglandular syndrome (Parinaud) after inoculation of the pathogen into the eyes, encephalitis, optic neuritis, osteolytic lesions, or granulomas in the liver and spleen.

In immunocompromised individuals (especially HIV-infected persons) the infection with *Bartonella* can lead to bacteremia, hepatic peliosis, or bacillary angiomatosis (Fig. 4.**8**).

Diagnosis is based on the *serological detection of antibodies*. Routine cultures always remain sterile and the pathogen can only be cultivated using specialized methodology. The histological confirmation of *Bartonella* with a silver stain is partially successful. The histology of lymphadenitis can indicate cat-scratch disease, but it is nonspecific.

Tularemia (*Francisella tularensis*). Tularemia is a highly febrile, infectious disease, which is transmitted by a multitude of animal species (especially rodents) and ticks. It occurs throughout North America, in parts of Europe, the former Soviet Union, China, and Japan. In Europe, endemic foci can be found in Sweden, Czechoslovakia, Austria, Germany, and the Balkan states. The most frequent points of entry are the skin or mucous membranes of the gastrointestinal tract or the respiratory tract. Initially a reddish papule forms on the skin. Subsequently, a sharply defined ulcer may form. *Regional lymphadenitis* is typical.

After inhalation of the pathogens, or as a consequence of bacteremia, the clinical picture of an "atypical" *pneumonia* results. Diagnosis is made by the detection of antibodies or bacteriologically (report the tentative diagnosis to the laboratory).

Plague (*Yersinia pestis*). Today, plague is still endemic on all continents and is transmitted to humans by the fleas of various rodents. The *bubonic plague* is characterized by a painful, regional, possibly abscess-forming lymphadenitis. The most frequent location of the primary lesion is, corresponding to the location of the flea bite, the groin (> 80 %), followed by the axilla, and the back of the neck. Symptoms of the general infection are high fever, delirium, endotoxin shock, and rarely, hemorrhagic

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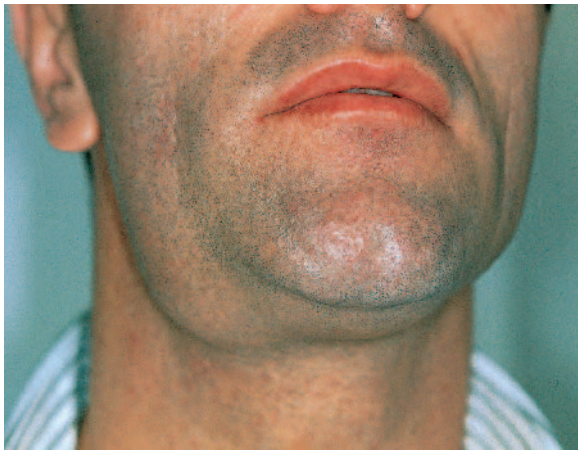

a

b

Fig. 4.**8** Bacillary angiomatosis in an HIV-infected person.
a Right side submandibular lymphadenopathy.
b CT scan of neck: Enlarged lymph node, 4 × 3 × 3 cm, strong, inhomogeneous enhancement of contrast medium. (Histology: Lymph node with lymphoid infiltration, proliferation of capillaries, Warthin–Starry silver stained bacilli.)

pneumonia. A fulminant course is exhibited by *pneumonic plague*, which develops as a result of droplet infection. The detection of the pathogen occurs via culture of the organism from the blood, lymph nodes, or bubonic puncture and sputum.

Mycobacterial Infection. In young adults from endemic regions, cervical lymph node tuberculosis is one of the most frequent causes of a localized lymph node enlargement. Its course is usually unilateral, chronic, and painless.

In children it is possible for nontubercular mycobacteria (*M. avium complex*, *M. scrofulaceum*, *M. kansasii*, *M. malmoense*, *M. chelonae*, *M. fortuitum*, *M. hemophilum*) to cause cervical lymphadenitis or lymphadenitis at another location. In addition to an appropriate clinical presentation, the diagnosis of mycobacteriosis requires the detection of an isolate from sterile tissue samples (biopsy).

Lymphadenopathy of Unknown Origin

Kawasaki Disease. Kawasaki disease is an acute, systemic vasculitis that occurs particularly in infants and has only rarely been observed in adults. Epidemiological data indicate an infectious cause, which so far could not be identified. Possibly bacterial toxins cause the disease, acting as superantigens to massively stimulate macrophages and T cells as seen in toxic shock syndrome.

During the acute disease, the following cardinal symptoms predominate:

- fever (≥ 5 days)
- cervical lymphadenopathy
- bilateral conjunctivitis
- alteration to the lips and tongue (red lips with fissures, strawberry tongue, oropharyngeal erythema)
- erythema and swelling of the palms and soles of the feet, followed by an initial periungual desquamation of these skin locations
- erythematous or maculopapular exanthema.

Approximately 50% of patients develop myocarditis, or less frequently pericarditis, or valvular insufficiency. The most serious complications found are aneurysmatic dilatations of the coronary arteries. During the acute phase, it is also possible to observe aseptic meningitis, hepatic involvement, and arthritic symptoms.

Castleman Disease (Angiofollicular Lymph Node Hyperplasia). *The main finding* of this rare disease of unknown origin is a local or generalized lymphadenopathy. The diagnosis is based on histological findings, in which a "hyaline–vascular type" (90% of the cases) and a "plasma-cell type" are distinguished. While the hyaline–vascular type is a localized, clinically asymptomatic lymphadenopathy, the plasma-cell type is multicentric (involvement of hilar lymph nodes and abdominal

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lymph nodes) and is accompanied by fever, night sweats, weight loss, and arthralgia. In HIV-infected individuals a severe and often fatal course with fever, lymphadenopathy, hepatosplenomegaly, weight loss, respiratory symptoms, edemas, and pancytopenia has been described. In the affected lymph nodes of those infected with HIV and in immunocompetent patients the genome of the human herpesvirus 8 has been detected. In patients afflicted with the likewise etiologically unexplained *POEMS syndrome* (**p**eripheral neuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal paraprotein, and **s**kin lesions) the histological findings are comparable to those of Castleman disease.

Kikuchi–Fujimoto Disease. The histological finding of this etiologically unclear and self-limiting disease of the lymph nodes, which normally takes a benign course, is a necrotizing lymphadenitis which cannot be easily distinguished from a malignant lymphoma or systemic lupus erythematosus. All lymph node locations can be affected, but a cervical lymphadenopathy occurs most frequently. In 30–50% of the patients fever occurs. Other constitutional symptoms are rarer. Often leukopenia with lymphocytosis and an elevated erythrocyte sedimentation rate are present. Elevated transaminase levels occur rarely. The disease was initially described in Japan, but has meanwhile been observed throughout the world.

Sinus Histiocytosis with Massive Lymphadenopathy (Rosai–Dorfman Disease). This is a rare benign disease of unclear etiology. The clinical manifestations include fever, lymphadenopathy, neutrophilia, high erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and in 40% of the cases, extranodal pathology, including the skin, upper respiratory tract, bone, or the retrobulbar tissue. The histological findings are a massive sinus infiltration by histiocytic cells with typical histochemical characteristics.

Inflammatory Pseudotumor. In biopsies of a few patients with peripheral or retroperitoneal lymphadenopathy and with a fever lasting for months to years, as well as weight loss, histological findings were described which differed from a reactive process or malignant lymphomas and which resembled the so-called "plasma cell granuloma." Comparable histological findings also were described in other organs (lung, liver, spleen, pancreas, gastrointestinal tract, meninges). This is an inflammatory process of unclear etiology (*inflammatory pseudotumor*) in the connective tissues of the lymph nodes with spindle cell and/or vascular proliferation.

Fever and Swelling of the Face or Neck

Parotid Swelling

Mumps (*Paramyxovirus*). In *mumps* (infectious parotitis) the swelling of the glands is initially unilateral; after 1–2 days it is bilateral. Characteristic are protruding earlobes and the swollen and inflamed orifice of the parotid duct. Subjectively, significant pain during chewing is present. With increasing age, the frequency of concomitant diseases of other incretory and excretory glands (orchitis, pancreatitis) and of the central nervous system (encephalitis, meningitis) increases. These can also occur as the sole manifestation of mumps. The blood count shows a lymphomonocytosis, whereby it is possible to distinguish mumps from *purulent parotitis*, which is accompanied by relative lymphopenia.

Purulent Parotitis. The so-called marantic parotitis is often unilateral, painful, not reddened, and normally occurs as a secondary infection due to reduced salivation in severe and consumptive diseases.

Noninfectious Parotid Swelling. The differential diagnosis of parotitis must exclude parotid hypertrophy, Sjögren syndrome, mixed parotis tumors, and lymphoepithelial cysts:

- *Parotid hypertrophy* is always bilateral and progresses very slowly. It is usually combined with alcoholism, obesity, undernourishment, or an HIV infection.
- In HIV-infected patients *lymphoepithelial cysts* should also be considered.
- The localized lymphomatosis of the parotid gland, the submaxillary gland, and the lateral tear ducts occurs particularly in *Sjögren syndrome*. A sialogram often shows duct deformations.
- A sialogram is also a good method to identify *salivary calculi* (mainly unilateral, recurrent pain).
- *Mixed parotis tumors* can be easily differentiated from acute parotitis, because of their slow growth and the absence of inflammatory manifestations.

Neck Swelling

Infectious diseases that do not primarily exhibit cervical lymphadenopathy, but show a diffuse neck swelling will be discussed here.

Lemierre Syndrome. Lemierre syndrome (or postanginal septicemia) is a purulent infection of the lateral pharyngeal space that is caused mainly by *Fusobacterium necrophorum* and can occur as a complication of angina. The infection can lead to a septic jugular vein thrombo-

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sis, bacteremia, and septic embolisms in the lungs or rarely other organs (e. g., bones). Sometimes there is no history of a prior pharyngitis. The diagnosis is based on the clinical picture and the detection of the pathogen in the blood culture.

Actinomycosis. Actinomycosis (*Actinomyces israelii*, *A. naeslundii*, and other species) is a rare, subacute, bacterial infectious disease. Typically, granulomas develop which have an explicit tendency to form fistulas. The cervicofacial region is affected in more than 90 % of the cases. The lungs, gastrointestinal tract (ileocecal region), and female adnexa (intrauterine pessaries) are affected rarely. As a consequence of spreading *per continuitatem* osteomyelitis of the mandible, pericarditis, empyema, or spondylitis corresponding to the primary location can occur. Hematogenic dissemination is rare, but can cause abscesses in the brain, liver, or kidneys. An extensive disease results in fever and night sweats. The differential diagnosis resembles most closely that of tuberculosis or a malignancy (hard infiltration into the cervicofacial region).

The existence of a purulent fistula makes the diagnosis much easier. The detection of granules or actinomycetes in the Gram stain or in an anaerobic culture is confirmatory. Actinomycosis is an obligatory mixed infection, which has both aerobic and anaerobic microbial forms.

Fever, Headaches, and Neck Stiffness

Neck stiffness and headaches are cardinal symptoms of *meningeal inflammation*.

Aside from the limited and painful, passive (and active) flexion of the head (which is impossible in extreme cases), the Kernig or Brudzinski sign is frequently positive. The patient often spontaneously assumes a tripod position when asked to sit down.

Causes of Neck Stiffness. Most causes of neck stiffness are of an infectious nature. Rarer causes include adverse drug reactions (e. g., cotrimoxazole, antirheumatic agents), allergic reactions, diffuse involvement of the central nervous system within the scope of leukemias or metastatic tumors, subarachnoid hemorrhaging, and cerebrovascular strokes as a result of thrombosis or embolism.

Symptoms of Meningitis. The following symptoms and findings indicate the presence of *meningitis*:

- neck stiffness
- headaches
- fever
- nausea
- vomiting
- photophobia
- diplopia
- hyperesthesia with respect to other influences
- generalized seizures (especially in infants).

The neurological examination frequently detects a clouding of consciousness which in later stages can progress to coma, congestion of the fundus veins, possibly a papilledema, anisocoria with delayed light reflex, ophthalmoplegia (most frequently cranial nerve VI, abducens), mild coordination disorders, tremor, muscular hypertonus, hyperreflexia, and possibly a positive Babinski sign. The individual symptoms can be developed to varying degrees and in general increase as the disease progresses.

Examination of the Cerebrospinal Fluid (CSF)

Chemical and *microscopic* examination of the cerebrospinal fluid allows a diagnosis to be made as to the infectious agent in most cases, whereby the cell count and the cell differentiation have the greatest significance (Tab. 4.**9**). The protein and glucose concentrations (in comparison with a simultaneously determined blood glucose value) provide additional, valuable information for the differential diagnosis. In this way, several *characteristic constellations* of CSF findings can be described:

Characteristic Constellations of Findings in CSF Diagnostics

- A *high cell count* ($> 1000/mm^3$, $> 10^9/L$), predominantly granulocytes, a *low glucose concentration* (< 40 % of the simultaneously determined blood sample), and a *high protein concentration* (100–700 mg/dL, 1–7 g/L) indicate bacterial meningitis or a burst cerebral abscess.
- A *moderate elevation of the cell count* ($25–500/mm^3$, $25 \times 10^6–500 \times 10^6/L$) with predominantly mononuclear cells, *low* or possibly *normal glucose concentration*, and *elevated protein concentration* (50–500 mg/dL, 0.5–5.0 g/L) occurs in granulomatous and neoplastic meningitis. Mycobacteria and cryptococci are the most important causes of infection in this group. On the one hand, the carcinomatous or leukemic involvement of the meninges can be detected cytologically and on the other hand, knowledge of the underlying disease is suggestive.

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Table 4.**9** Findings in cerebrospinal fluid in different causes of meningitis

Diagnosis	Appearance	Predominant cells and cell count	Protein concentration	Glucose concentration*	Culture	Remarks
Normal findings	Clear, colorless	Lymphocytes only maximally 5/mm³ (5 × 10⁶/L)	15–45 mg/dL (150–450 mg/L)	50–80 mg/dL (2.8–4.4 mmol/L) or > 60 % of plasma glucose level	Negative	Opening pressure 7–20 cm water (5.2–14.7 mmHg)
Bacterial infection	Turbid	> 90 % granulocytes, 500–20 000/mm³ (0.5–20 × 10⁹/L)	50–1500 mg/dL (0.5–15 g/L)	< 35 mg/dL (< 1.95 mmol/L)	Positive	Bacteria often detected by microscopic examination of Gram-stained smears, opening pressure 20–75 cm water (14.7–55 mmHg)
Tuberculosis	Clear, rarely xanthochromia or turbid	Lymphocytes, rarely > 300/mm³ (0.3 × 10⁹/L)	45–500 mg/dL (0.45–5.0 g/L)	0–45 mg/dL (0–2.5 mmol/L)	Mostly positive	Molecular detection of mycobacteria possible; rarely detection of acid-fast bacilli by microscopic examination of auramine- or Ziehl–Neelsen-stained smears; chloride frequently decreased*
Leptospirosis	Clear or xanthochromia	Lymphocytes, mostly > 500/mm³ (0.5 × 10⁹/L)	Increased (mostly at the end of the first week) 50–110 mg/dL (0.5–1.1 g/L)	Mostly normal, rarely decreased	Possibly positive (using special methods)	
Neuroborreliosis	Clear	Lymphocytes	Increased	Normal	Negative	Intrathecal production of specific antibodies; molecular detection of pathogen mostly negative
Viral infection	Clear, rarely slightly opalescent	Initially granulocytes, after 48 h lymphocytes, rarely > 500/mm³ (0.5 × 10⁹/L), after 2 weeks often normal	Increasing up to 120 mg/dL, in parallel to decreasing cell count	Mostly normal (except in case of parotitis)	Echoviruses often positive, other viruses mostly negative	
Cryptococcosis	Clear or opalescent	Lymphocytes, 40–400/mm³ (0.04–0.4 × 10⁹/L)	Mostly increased	Decreased in approximately 50 % of the cases	Mostly positive	Microscopic detection of pathogen in India ink-stained smears in 50 % of the cases
Toxoplasmosis	Clear or opalescent, rarely xanthochromia	Lymphocytes	Increased	Normal or slightly decreased	Negative	Rarely direct detection of pathogen using immunofluorescence staining
Lupus erythematodes	Clear	Lymphocytes, rarely granulocytes	Slightly increased	Slightly decreased	Negative	Often plasma anti-DNA antibody positive

* Compared with blood taken at the same time.

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- A *moderate pleocytosis* (5–1000/mm^3, 5 × 10^6–1 × 10^9/L) with predominantly mononuclear cells, a *normal to slightly elevated protein concentration* (< 100 mg/dL, 1 g/L), and a *normal, possibly low glucose concentration* is designated as "serous" meningitis. Various viruses (e. g., enteroviruses, mumps viruses and herpesviruses), bacteria (e. g., *Treponema pallidum*, *Borrelia burgdorferi*, *Leptospira*, *Listeria*), and protozoa (e. g., *Toxoplasma*, *Trichinella*, *Plasmodium*) can cause these changes. However, in most cases the etiology remains unclear.
- Postinfectious meningoencephalitis (e. g., measles, rubella, varicella), parameningeal infections (cerebral abscess, subdural or epidural empyema, septic thrombophlebitis of the dural sinus, cervical spondylitis, osteomyelitis near the dura, epidural spinal abscess), and bacterial meningitis treated with antibiotics are additional causes of a mild pleocytosis.
- Focal parameningeal infections can be localized with the assistance of computed tomography. The fact that polynuclear cells dominate in the early phase of "serous" meningitis and the change to the predominance of mononuclear cells occurs during the first three days is of practical significance.
- Suddenly occurring headaches, neck stiffness, and fever are typical for a *subarachnoid hemorrhage*. The cerebrospinal fluid is *bloody* or *xanthochromic*.

Bacterial Meningitis

Pathogens that cause meningitis in adults are pneumococci, rarely meningococci, and *Haemophilus influenzae*. After trauma and neurosurgical interventions staphylococci are present in greater quantities. Other pathogens (*Enterobacteriaceae*, *Listeria*) can only be suspected based on the Gram stain. However, the concomitant circumstances occasionally provide additional information.

Meningococcal Meningitis. The reservoir of *Neisseria meningitidis* is found in the nasopharynx of asymptomatic carriers. Mainly children and adolescents, less frequently adults, are afflicted with meningococcal meningitis after a catarrhal infection. After a meningococcal bacteremia, it is possible for the clinical picture of meningitis to occur. However, meningococcal septicemia also occurs without meningitis and meningococcal meningitis can also occur without a clinically evident bacteremia. In meningococcal septicemia a combination of purpura and maculopapular exanthema occurs in approximately 75 % of cases (Fig. 4.**9**).

A fulminant course (*Waterhouse–Friderichsen syndrome*) is observed particularly in children and is characterized by progressive shock, adrenal hemorrhaging, and confluent cutaneous hemorrhaging.

Furthermore, chronic cases of meningococcal septicemia with fever, arthralgia, and skin lesions also exist, as can also occur in arthritis–dermatitis syndrome (Fig. 4.**3**).

Pneumococcal Meningitis. Pneumococcal meningitis affects mainly infants and adults over 40 years of age. Pneumococcal meningitis frequently occurs concomitant with or after pneumonia, otitis, mastoiditis, or sinusitis. Otoneurological complications occur in up to 25 % of cases.

Patients who are asplenic suffer more frequently from pneumococcal infections and septicemia.

Fig. 4.**9** Petechial skin lesions in meningococcal meningitis.

***Haemophilus Influenzae* Meningitis.** *Haemophilus influenzae* meningitis affects mainly children two to 24 months of age, who have not been vaccinated with a *Haemophilus influenzae* B conjugate vaccine. The disease is rare in adults, and like pneumococcal meningitis, typically occurs after an infection of the respiratory tract or the ear.

***Listeria* Meningitis.** About 75 % of the listeriosis cases (*Listeria monocytogenes*) become manifest as meningitis, rarely as encephalitis. In contrast to the acute septic course in the newborn, adults typically experience chronic septicemia with cerebral abscesses.

An initial peak of those afflicted is found during the first weeks of life. This infection mainly occurs transplacentally or after vaginal colonization of the mother during childbirth.

A second peak is found in old age and in patients with underlying immunocompromising diseases (cirrhosis of the liver, diabetes mellitus, Hodgkin disease,

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lymphosarcoma, chronic myeloid leukemia, or immunosuppression after organ transplantation). This infection usually manifests as *meningitis* or *sepsis*. The onset is acute with chills and fever. Pneumonia frequently develops and rarely a maculopapular rash. The *detection of pathogens* occurs in the cerebrospinal fluid, blood, or organ punctures.

Other Types of Bacterial Meningitis. Meningitis caused by staphylococci, group A streptococci, anaerobic streptococci, *Bacteroides*, *Actinomyces*, and mixed infections are mainly observed in cerebral and epidural abscess, cranial trauma, after neurosurgical interventions, or as a consequence of cerebral vein thromboses.

Meningitis in the Neonates. The main responsible pathogens isolated in the newborn include *E. coli*, group B streptococci, *Listeria monocytogenes*, *Klebsiella*, and *Proteus*. These bacteria usually originate in the birth canal. The infection can occur during or directly after childbirth.

Serous Meningitis

Serous meningitis can be caused by *viruses* (enteroviruses, arboviruses, HIV, herpes simplex, mumps, rubella, paramyxoviruses), *bacteria* (*Borrelia*, mycobacteria, *Leptospira*), *fungi*, or *protozoa*. It also occasionally occurs after mumps, rubella, or polio vaccination.

Meningitis or brain abscesses, which usually take a purulent course but which have been *treated with antibiotics*, can be accompanied by CSF findings that are typical for serous meningitis (Tab. 4.**9**).

Noninfectious, serous meningitis is observed in brain tumors, metastatic carcinomas, lupus erythematosus, or after antibody therapy with the immunosuppressant OKT3. Rarely will treatment with cotrimoxazole cause serous meningitis.

Clinical Features. The *clinical symptoms* are fever, severe headaches (especially intense behind the eyes), photophobia in children, loss of appetite, vomiting, and rarely seizures and restlessness. Also in the serous form, neck stiffness remains the primary symptom (may be absent in the newborn or young infants). The following points often permit a *differential diagnosis to be made between serous and purulent meningitis*:

- Neck stiffness generally develops slowly, within two to three days in serous meningitis.
- The patient's general state of health is less severely impaired in serous meningitis, with the exception of meningitis caused by herpes simplex viruses and arboviruses.
- Maculopapular exanthemas occur more frequently.
- Petechiae, as in meningococcal meningitis/septicemia, are occasionally observed in echovirus type 9.
- A papilledema virtually never occurs in serous meningitis.

Etiological clarification of serous meningitis only succeeds in rare cases.

Meningitis Caused by Enteroviruses (Echoviruses, Coxsackie viruses, Polioviruses). The enteroviruses exhibit a distinct frequency peak in the summer months. Two-thirds of the patients are younger than 15 years of age. In this age group, boys are affected more frequently than girls. Enteroviruses not only cause meningitis, but also encephalitis and myelitis.

Enteroviruses can be directly detected in the stool, throat swabs, and the CSF (with the exception of polioviruses). Serological examination can detect a >4-fold, type-specific increase of neutralizing IgG antibodies.

The simultaneous occurrence of pleurodynia or myocarditis during a case of meningitis is typical of infections with *coxsackie viruses*, which can also cause paresis.

Poliomyelitis (polioviruses). Since the introduction of the polio vaccination in 1955, the frequency of poliomyelitis has significantly declined. During recent years only sporadic cases have occurred (vaccination refusal).

After a brief, febrile, catarrhal, prodromal phase, meningitic symptoms develop after an afebrile interval of two to three days with, or more frequently without, subsequent *pareses*. The asymmetrically affected muscle groups are initially painful. The tendon reflexes are frequently intensified. Paralysis normally occurs two to four days after the second rise in temperature and is general, rapidly progressive. After maximally two days, the paralysis is fully developed. Only rarely will additional muscles be affected after this time period. In this stage the associated tendon reflexes are extinguished. The diagnosis of poliomyelitis is unlikely when sensitivity disorders or an involvement of the extrapyramidal motor system are present. Guillain–Barré syndrome (polyradiculitis) must be excluded in the differential diagnosis.

Meningitis in Mumps. Up to 50% of patients with mumps exhibit an increased cell count in the CSF. However, a clinically manifest meningitis or meningoencephalitis is significantly rarer (approximately 10%). The expected CSF findings include a high cell count, slightly increased protein levels, and, in rare cases, a low glucose value. The diagnosis can usually be made from the clinical picture, and insofar as meningitis is the sole clinical symptom, from an elevated antibody titer.

Lymphocytic Choriomeningitis. Lymphocytic choriomeningitis is rarely diagnosed in Europe. It is transmitted by Syrian hamsters (*Mesocricetus auratus*) or from mice to humans. The disease occurs more frequently in the winter months. It usually becomes manifest as a catarrhal infection; bronchitis or pneumonia is less frequent. After a latency period of about one week, the clinical picture of serous meningitis can develop, which in rare cases is accompanied by a

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maculopapular exanthema. The diagnosis can be confirmed by detecting the virus in the blood or CSF or by means of serological antibody detection.

Tubercular Meningitis. The diagnosis is made more difficult by the insidious course of the disease over a period of days to weeks, with uncharacteristic symptoms such as a reduced state of general health, night sweats, weight loss, and subfebrile temperatures. Cardinal symptoms such as headaches, neck stiffness, eye–muscle paralysis (in particular cranial nerve VI, abducens, basal meningitis!), reflex anomalies, and disturbed consciousness necessitate lumbar puncture for CSF analysis. In typical cases one finds a pleocytosis with predominantly mononuclear cells, a distinctly elevated protein concentration, and low sugar and chloride concentrations (Tab. 4.**9**).

Rarely is it possible to directly detect the tubercle bacilli in the CSF sediment by means of a Ziehl–Neelsen or auramine stain. The detection of the pathogen occurs in culture or with molecular genetic methods.

Meningitis in Leptospirosis. Neck stiffness that occurs during the bacteremic phase of *leptospirosis* must be distinguished from *serous meningitis* during the stage of organ manifestation (second phase). Especially the Pomona serotype, which causes the so-called *swineherd disease*, but also the Icterohemorrhagic and Canicola serotypes can be accompanied by serous meningitis. Characteristic is conjunctivitis with suffusions; herpes labialis is rarer. Headaches are usually extensive in leptospirosis. Relative bradycardia is found frequently. The simultaneous occurrence of jaundice, splenomegaly, or pathological urine sediment findings can facilitate the differential diagnosis. After 5–7 days, the CSF exhibits lymphocytosis and a moderately elevated protein concentration with normal glucose values (rarely depressed) (Tab. 4.**9**).

Syphilitic Meningitis. Neurosyphilis occurs in less than 10% of the untreated cases (5–35 years after infection) and is characterized by a low cell count and elevated protein concentration, as well as positive syphilis serology in the CSF. However, false-negative, nonspecific, and persistently positive specific syphilis reactions in the CSF necessarily require the inclusion of the medical history and clinical findings for the diagnosis of neurosyphilis. In HIV-positive patients neurosyphilis can develop early and exhibit an atypical course.

Neuroborreliosis. Neurological *early symptoms* can be observed together with, or directly after, the erythema chronicum migrans. Meningoencephalitis, polyneuritis, or polyneuropathy does not occur for *months to years* after tick exposure, and affects about 15% of the untreated patients. The CSF typically shows a lymphocytic pleocytosis. Confirmation of the diagnosis requires the detection of intrathecal formation of specific antibodies as well as specific serum IgG antibodies.

Fungal Meningitis

The meningeal infection with *Cryptococcus neoformans* causes a subacute to chronic serous meningitis. Underlying illnesses such as lymphomas, leukemias, diabetes, HIV infection, or tuberculosis are significantly more common than in the case of pulmonary infections due to cryptococci. The clinical symptoms are comparable to meningitis cases with various etiology, with the exception of frequently afebrile cases. The CSF examination yields a lymphocytosis with elevated protein and depressed glucose levels (Tab. 4.**9**).

In about one-half of the cases the cryptococci can be detected directly in the CSF sediment by means of India ink stain. Culture or serological confirmation of antigens in the serum or CSF is more reliable.

Meningitis Caused by Protozoa or Helminths

Among the free–living amebas found throughout the world is *Naegleria fowleri,* which lives in fresh water. It can cause an acute, and usually within one week, fatal case of meningoencephalitis. Various *Acanthamoeba* species, which have been isolated from the earth, dirt, and water, as well as *Balamuthia mandrillaris* (unknown reservoir), are the cause of a subacute or chronic, granulomatous encephalitis, which can last for several weeks or months and may be fatal.

The tropical helminths, *Angiostrongylus cantonensis* (Pacific, Asia, Cuba) and *Gnathostoma spinigerum*, are the cause of an eosinophilic meningitis.

Concomitant Cases of Meningitis

Purulent processes in the direct proximity of the meninges (cerebral abscesses, otitis, mastoiditis, sinusitis, and osteomyelitis) can cause extensive meningeal irritation, and thereby pose significant difficulties during the differential diagnosis. The typical CSF findings are a moderate pleocytosis (lymphocytes or granulocytes) and a moderate protein elevation with normal glucose levels. The CSF pressure is usually elevated. The cultures are usually negative.

Meningitic symptoms with a rise in temperature are also observed in intracranial hemorrhaging. The diagnosis of encephalorrhagia is usually indicated in the medical history with sudden onset, headaches, and rapid progression of the neurological symptoms.

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Fever and Neurological Deficits

Primary, noninfectious, neurological conditions are discussed in other chapters.

Encephalitis

Clinical Features, Differentiation from Meningitis. In general, neurological symptoms with changes in *consciousness* stand in the foreground in encephalitis. However, in isolated cases the differentiation of aseptic meningitis from encephalitis can be difficult. The former can be accompanied by functional cerebral impairment and the latter by mild focal symptoms, but extensive meningeal irritation.

Causes. Encephalitis and aseptic meningitis not only overlap with respect to their symptoms, but also in their etiology: most pathogens which cause serous meningitis can also cause encephalitis. Statistically, *viruses* play the largest role. Herpes simplex viruses, which cause acute encephalitis with a high mortality rate, can be detected in skin lesions, in the CSF by means of molecular genetics, or in a brain biopsy. The detection of additional viruses, in general, occurs by means of serology or molecular genetics. These include: other herpesviruses (varicella-zoster, Epstein–Barr, cytomegalovirus), HIV virus, influenza virus, echovirus, poliovirus, mumps virus, measles virus, adenovirus, and enteroviruses.

Various arboviruses (**ar**thropod-**bo**rne viruses, transmitted by mosquitoes and ticks) are endemic in specific geographical regions. These also include rare arboviruses in Europe (Tab. 4.**10**).

Table 4.**10** Arboviruses causing encephalitis

Virus	Vector	Endemic region
Togaviridae		
Alphavirus		
– Eastern equine	Mosquitos (*Culiseta*, *Aedes*)	East and Gulf Coast of USA, Caribbean, and South America
– Western equine	Mosquitos (*Culiseta*, *Culex*)	Western USA and Western Canada
– Venezuelan equine	Mosquitos (*Aedes*, *Culex*, and other)	South and Central America, Florida, and Southwest USA
Flaviviridae		
West Nile complex		
– St. Louis	Mosquitos (*Culex*)	USA
– Japanese	Mosquitos (*Culex*)	Japan, China, Southeast Asia, and India
– Murray Valley	Mosquitos (*Culex*)	Australia and New Guinea
– West Nile	Mosquitos (*Culex*)	USA, Africa, Europe, Middle East, and Asia
– Illeus	Mosquitos (*Psorophora*)	South and Central America
– Rocio	Mosquitos (?)	Brazil
Tick-borne encephalitis viruses		
– Russian	Ticks (*Ixodes*)	East Russia
– Central European*	Ticks (*Ixodes*)	Central Europe
– Kyasanur Forest	Ticks (*Haemophysalis*)	India
– Louping-Ill	Ticks (*Ixodes*)	England, Scotland, and Northern Ireland
– Powassan	Ticks (*Ixodes*)	Canada and Northern USA
– Negishi	Ticks (?)	Japan
Bunyaviridae		
Bunyavirus		
– California	Mosquitos (*Aedes*)	Western USA
– La Crosse	Mosquitos (*Aedes*)	Central and East USA
– Jamestown Canyon	Mosquitos (*Culiseta*)	USA and Alaska
– Snowshoe Hare	Mosquitos (*Culiseta*)	Canada, Alaska, and Northern USA
– Tahyna	Mosquitos (*Aedes*, *Culiseta*)	Czechoslovakia, Balkans, Italy, and Southern France
– Inkoo	Mosquitos (?)	Finland
Phlebovirus		
– Rift Valley	Mosquitos (*Culex*, *Aedes*)	East Africa
– Toscana	Mosquitos (*Phlebotoma*)	Northern Italy
Reoviridae		
Orbivirus		
– Colorado tick fever	Ticks (*Dermacentor*)	Rocky Mountains, USA

Modified from Whitley et al., 2002.

* Synonym: spring–summer meningoencephalitis.

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Among the arboviruses, tickborne encephalitis which causes spring–summer meningoencephalitis is endemic to Western Europe.

The *West Nile virus* has been noted more frequently during recent years after the pathogen has re-established itself in the USA. The pathogen reservoir is found in birds. Transmission to humans and animals occurs via mosquitoes. Epidemics also have been observed in Europe and the Middle East. Previously, the disease was known as a nonspecific, usually mild febrile disease with myalgia, headaches, lymphadenopathy, and rarely a maculopapular exanthema. Currently, encephalitis with fatalities is observed more frequently. This may indicate the presence of a new neurovirulent viral strain.

New zoonotic encephalitis viruses in Asia, in addition to the known *Japanese encephalitis virus,* are the Nipah and Hendra viruses.

The most important, nonviral infectious causes of encephalitis are: syphilis, Lyme borreliosis, bartonellosis, tuberculosis, rickettsiosis, Q fever, Whipple disease, brucellosis, listeriosis, mycoplasma infection, African trypanosomiasis, toxoplasmosis, malaria, trichinosis, schistosomiasis, cysticercosis, and infections by so-called, free-living amebas.

In addition, in immunocompromised individuals, especially HIV-infected individuals, it is possible for opportunistic infections caused by cytomegalovirus, varicella-zoster virus, JC virus (progressive multifocal leukencephalopathy), and fungi (especially cryptococci) to lead to acute, subacute, or chronic infections of the brain or spinal cord. HIV can cause an acute meningoencephalitis or a chronic progressive infection of the central nervous system (myelopathy, "AIDS dementia").

The CSF findings in encephalitis differ little from those in viral meningitis.

Postinfectious Encephalitis. This is an acute demyelinating process (or ADEM, **a**cute **d**isseminated **e**ncephalo**m**yelitis), which is the result of one in 1000 measles virus infections and can also occur after influenza, other viral respiratory infections, and varicella.

Cerebral Abscess

Clinical Features. In a cerebral abscess, *focal* neurological deficits or seizures are most prominent. Depending on the location of the abscess, initially no, or only discrete, clinical manifestations can be determined. About 70% of the patients suffer from headaches and approximately one-half have a fever.

Causes. The following causes can be responsible for a cerebral abscess:

- *Hematogenic dissemination* of bacteria (*Staphylococcus aureus*, *Enterobacteriaceae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus milleri*, anaerobes) or fungi from a distant source with predisposing factors (pulmonary abscess, pulmonary empyema, bronchiectasia, congenital heart defect, endocarditis).
- *Per continuitatem transmission* of an organ infection which is located near the brain (complication of otitis media, mastoiditis, sinusitis, dental abscess).
- *Trauma* or neurosurgical intervention.
- *Hematogenic dissemination* of pathogens in neutropenia (*Aspergillus*, Zygomycetes, *Candida*, Gram-negative bacteria).
- *Opportunistic infections* in those infected with HIV (cerebral toxoplasmosis, cryptococcosis, infections with other fungi, mycobacteria, *Nocardia*, *Listeria*, *Rhodococcus equi*, microsporidia, *Acanthamoeba*).
- Rare *complications of systemic infections* (tuberculoma, ameboma, *Echinococcus* infection, foci in systemic mycoses in corresponding endemic regions, trichinosis, cysticercosis, infections by *Strongyloides stercoralis*, *Schistosoma*, *Paragonimus*, *Acanthamoeba*).
- *Invasion by helminthic larvae* (*Baylisascaris procyonis*, *Toxocara canis*).

Cerebral Toxoplasmosis. While the morbidity of toxoplasmosis in immunocompetent individuals is low, the endogenic reactivation of a previously acquired infection in the severely immunodeficient (especially HIV-infected patients) can lead to cerebral abscesses, rarely encephalitis, chorioretinitis, or a disseminated toxoplasmosis. In those patients infected with HIV, cerebral toxoplasmosis is the most frequent cause of a lesion occupying the cerebral cavity. The cerebral abscesses (usually multiple) frequently manifest clinically through headaches, as well as irritation and/or deficit symptoms, which are caused by the space-occupying lesion. The diagnosis is based on findings provided by imaging techniques or prior to surgery through a response to a specific therapy within two to three weeks. Serological findings are unreliable in immunodeficient persons. Even in clinically manifest toxoplasmosis IgM antibodies characteristically cannot be found. The primary, cerebral lymphoma can lead to similar radiological findings.

Cysticercosis. Cysticercosis is the most frequent cause of seizures in developing countries. This is a tissue infection caused by *larvae* of *Taenia solium* (pork tapeworm). Infection occurs through swallowing the worm eggs (contaminated food, water, fecal–oral transmission from humans infected with *T. solium*). The dissemination of the larvae occurs primarily into the central nervous system, eyes, muscles, and the heart, where cysts are formed. The inflammatory response in the central nervous system can result in epileptic seizures, signs of intracranial pressure, other focal deficits or neuropsychiatric symptoms. The diagnosis is made by means of serology and a CT examination of the brain. During the larval infection, there are no worm eggs in the stool.

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Subdural Empyema, Epidural Abscess

In a subdural empyema pus collects between the dura mater and the arachnoid mater, frequently originating from the paranasal sinus. The symptoms include headaches, fever, neck stiffness, and focal neurological deficits. The disease can quickly progress to a life-threatening condition.

A collection of pus in the epidural space often initially manifests itself discretely through headaches and fever. Dominant are the symptoms of the original focus (sinusitis, otitis). If the process develops into a subdural empyema, or involves more deeply lying cerebral structures, focal neurological disorders can occur.

Fever with Common Cold Symptoms

The symptoms of the common cold ("influenza-like infection") are diverse and extend from conjunctivitis, rhinitis, pharyngitis, otitis, to tracheobronchitis. It is mostly *viruses* which cause these frequent diseases. Fever is not usually present, and when, then generally only for one to two days.

Bacterial Tonsillitis and Pharyngitis

In contrast to the viral common cold, cases of *bacterial tonsillopharyngitis* lead to a significantly more severe clinical picture:

- Typical findings in *streptococcal angina* (especially group A) include sore throat, odynophagia, high fever, cervical lymphomas, a notable leukocytosis, and a local finding of extremely red, swollen tonsils, which can be partially covered with a white membrane, as well as petechiae on the soft palate.
- *Diphtheria* also exhibits a comparable local finding. However, the membranes are more distinct and the wound surface can bleed after their removal.
- *Plaut–Vincent angina* is mostly unilateral. A smear taken from the base of the ulcer shows fusiform rods (*Fusobacterium nucleatum*) and *Borrelia* (*Borrelia vincenti*) upon Gram-staining.
- Rare bacterial pathogens of pharyngitis are *Treponema pallidum*, gonococci, staphylococci, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Listeria monocytogenes*.

Scarlet Fever. These infections, caused by streptococci of group A, have a short incubation time. Acute onset with high fever is typical. Tonsillitis, regional lymphadenitis, and enanthem of the palate are obligatory symptoms of scarlet fever. Scarlet fever exanthema typically occurs two to five days after onset of the disease. Preferred locations are skin folds (axilla, groin), trunk, inner side of the arms and thighs. Scaling of the skin begins after two to four weeks.

A case of *acute glomerulonephritis* can occur six to 10 days after streptococcal angina. *Rheumatic fever* is observed exclusively after streptococcal pharyngitis. The latency period is several days to weeks.

Diphtheria. *Corynebacterium diphtheriae* causes an acute inflammation of the tonsils, pharynx, larynx, and the nose. Other mucous membranes or the skin are affected less frequently. Grayish-white membranes develop, as a result of a cytotoxin, which cannot be wiped off. In severe cases, myocarditis, with significant arrhythmia, can develop. Peripheral and central neuroparalysis, both motor and sensory, can occur as a late consequence of the disease.

Nonbacterial Pharyngitis

Mycoplasma, as well as Epstein–Barr virus, adenoviruses, coxsackie viruses, cytomegaloviruses, herpesviruses, and echoviruses can cause severe angina. In addition to the pharyngeal involvement in viral infections, there are often vesicles and/or small ulcers on the palate, cheek mucosa, and the tongue. A mononucleosis-like clinical picture also can occur as the initial manifestation of a HIV infection.

Infectious Mononucleosis (Pfeiffer Disease, Epstein–Barr Virus). Virtually every case of *mononucleosis* exhibits the symptoms of fever, sore throat, and cervical lymphadenopathy. In about 50% of the cases an exudative to ulcerous angina with grayish-white membranes is present. Usually petechiae are also observed at the transition of the soft to the hard palate. The cervical lymph nodes are involved most frequently (enlarged, slightly sensitive to pressure, readily delimited). However, all of the remaining lymph node locations, including the mediastinum, can be affected. Splenomegaly exists in about one-half of the cases. Hepatomegaly occurs in only approximately 10% of the cases. Jaundice is unusual and elevated transaminase levels are virtually always observed. Often a rubeola-like exanthema develops on the trunk and the proximal extremities. In less than 1% of the cases, symptoms involving the nervous system (meningitis, encephalitis, polyradiculitis, Guillain–Barré syndrome with ascendant paralysis, acute cerebellar ataxia), the heart (myocarditis), or the urogenital system (hematuria with transient hypertension, orchitis) occur. The differential diagnosis should consider a primary infection with HIV or cytomegalovirus.

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Blood smears contain lymphomonocytosis in over 50% of the cases with approximately 10% atypical forms and mainly T lymphocytes (Fig. 4.**10**). In the second to the third week of the disease a leukocytosis often occurs. The diagnosis is confirmed by the presence of antibodies against various viral antigens.

> Antibodies against aminopenicillins can develop in mononucleosis. This finding explains the high frequency of exanthema during such a therapy.

Cytomegalovirus infection (CMV). CMV infection can become manifest as a mononucleosis-like clinical picture. However, lymph node enlargement and angina are unusual and the Paul–Bunnell test is negative. Additional symptoms are fever episodes, hepatosplenomegaly, pathological hepatic functions, and a lymphomonocytosis in the blood count. The diagnosis is confirmed serologically.

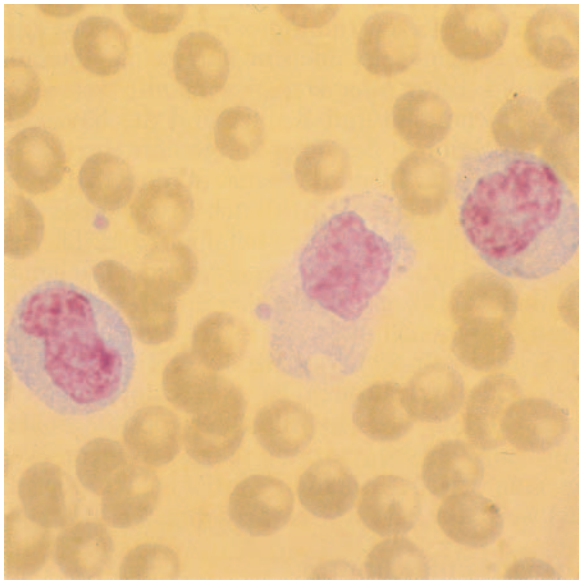

Fig. 4.**10** Blood smear of a patient with mononucleosis showing characteristic atypical, large lymphocytes.

Common Cold

The acute, respiratory diseases are, without a doubt, of great practical and economic significance. In 90% of the cases colds are caused by viruses, rarely by *Mycoplasma* and *Chlamydia*. Numerically, bacteria play a subordinate role.

Clinical Features. The typical, clinical manifestations of the so-called *common cold ("influenza-like" infection)* are: coryza, tonsillopharyngitis, laryngotracheitis, tracheobronchitis, bronchopneumonia, or pneumonia. Infections of the upper respiratory tract predominate by far, according to their frequency. In addition to the leading symptom of rhinitis, there frequently exists pharyngitis, cough, or conjunctivitis.

The differential diagnosis must distinguish *allergic* and *vasomotor* rhinitis as well as local processes (e. g., sinusitis).

Secondary bacterial superinfections throughout the entire respiratory tract occur mostly in infants, the elderly, and in patients with underlying diseases that reduce resistance.

Pathogens. The common cold is most frequently caused by rhinoviruses. Rarer causes are: other picornaviruses (coxsackie A virus, echovirus), reoviruses, paramyxoviruses (influenza A, B, C, parainfluenza), adenoviruses, and especially in infants, *respiratory syncytial virus* (RSV). Occasionally, it is possible for the following to exhibit a course consistent with the clinical picture of an "influenza-like infection": mumps, measles, rubella, varicella, variola, poliomyelitis, hepatitis, mononucleosis, acute HIV infection, lymphocytic choriomeningitis, as well as herpes simplex and coxsackie B virus infections.

***Rhinovirus* Infections.** *Rhinovirus* infections are primarily responsible for rhinitis. However, frequently the mucous membranes of the tracheobronchial tree are also affected. Headaches and subfebrile temperatures complete the clinical picture.

***Coxsackievirus* Infections.** Coxsackieviruses and echoviruses belong to the enteroviruses and mainly appear in the summer and fall. Out of the broad spectrum of clinical manifestations some typical clinical pictures will be mentioned:

- *Herpangina:* herpangina (mainly coxsackieviruses A2, A4, A5, A6, A8, A10) mostly occurs in the summer and especially in children and adolescents. The clinic picture is characterized by an acute onset of high fever, sore throat, and odynophagia, as well as a clearly reduced state of general health. Characteristic are approximately 10–20 early occurring papulovesicular lesions (1–2 mm in diameter) with a narrow, hyperemic marginal seam at the palatoglossal arches, the soft palate, and the uvula. The differential diagnosis must distinguish between Plaut–Vincent angina, streptococcal angina, aphthous stomatitis, or ulcerative stomatitis.
- *Hand-foot-and-mouth disease* is a harmless febrile disease caused by coxsackie A16 virus (also A4, A5, A7, A9, and A10) which also primarily affects adolescents. In the oropharynx, on the hands, and feet vesicles (later ulcers) develop. Although similar to those of herpangina, these lesions are somewhat larger.
- *Bornholm disease* (mainly coxsackie B3 and B4 viruses, epidemic pleurodynia, or epidemic myositis) often begins suddenly with intense muscle pain which is frequently localized in the region of the distal, lateral thorax or in the epigastrium, rarely in the

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proximal muscles of the extremities. The pain is sharp and respiration-dependent. Intense attacks alternate with pain-free intervals. Frequent concomitant symptoms are fever and headaches. Catarrhal manifestations do not belong to the typical clinical picture. Complications are serous meningitis, dry and serous pleuritis, orchitis, epididymitis, pericarditis, and myocarditis.

Echovirus Infections. Echoviruses essentially cause the same clinical pictures as coxsackie viruses. Furthermore, gastroenteritis and febrile exanthemas (Boston exanthema) occur in children and rarely in adults.

Adenovirus Infections. Adenovirus infections usually exhibit the course of a banal common cold. Of the 30 known types, most cause fever, pharyngitis, or conjunctivitis. Frequent concomitant symptoms are headaches, myalgia, as well as a painful regional lymphadenitis. The pharyngoconjunctivitis is occasionally accompanied by vomiting, diarrhea, and hepatosplenomegaly. Pulmonary infiltrates are observed in 10–15 % of the cases.

***Metapneumovirus*.** This virus, which was newly described in 2001, is an increasingly recognized cause of tracheobronchitis, bronchiolitis, otitis, and pneumonia in children and the elderly. The clinical manifestations include fever in most cases, cough in about 70 %, as well as rhinitis, sore throat, and influenza-like symptoms in 40–50 % of the patients. Methods of virus isolation and serology are being developed for diagnostic purposes.

Influenza

The actual *flu* (influenza) is an acute respiratory disease which tends to develop bacterial, secondary infections (staphylococci, pneumococci, *Haemophilus influenzae*) and occurs as an epidemic or pandemic. The influenza virus is highly contagious (droplet infection). Up to 80 % of cases follow a subclinical course or take the form of a mild common cold. Severe cases start after an incubation period of one to two days with a general feeling of malaise, shivering, and a rise in temperature, whereby the fever usually subsides after three days. Characteristic concomitant symptoms are myalgias, headaches (in and behind the eyes), sore throat, cough, lacrimal flow, and substernal pain. The sputum is sparse, viscous, and occasionally slightly bloody.

The most frequent complications are *bronchiolitis* and *bronchopneumonia* with a prognosis that still remains serious, even today. Rare complications are myocarditis, pericarditis, otitis, mastoiditis, sinusitis, meningitis, or encephalitis.

Avian Influenza: During the last few years, isolated incidents of directly transmitting influenza viruses from poultry or waterfowl to humans have occurred. These have included infections with influenza type A virus, subtype H5N1 (hemagglutinin antigen structure 5, neuraminidase antigen structure 1), subtype H9N2, or H7N7 which have resulted in severe systemic cases of influenza and isolated fatalities in humans.

Sinusitis

Acute sinusitis becomes manifest with acute, mandibular pain or headaches and fever. A purulent rhinitis and tenderness to pressure or palpation above the paranasal sinuses is present. The diagnosis can normally be made based on the clinical manifestations without the use of imaging techniques. The most frequent pathogens are pneumococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, rhinoviruses, and rarely *Enterobacteriaceae* and influenza viruses.

In *chronic sinusitis* chronic headaches predominate. Aerobic and anaerobic mixed floras are frequently present.

Otitis

Acute otitis media begins with an earache, hearing loss, and fever. It is most frequently caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, staphylococci, or viruses. The medical history often reveals a prior viral infection of the upper respiratory tract. The diagnosis is based on the otoscopic finding of an inflamed and differentiated eardrum.

In earaches the differential diagnosis must distinguish between *external otitis* and *necrotizing external otitis* caused by *Pseudomonas aeruginosa*.

Epiglottitis

This clinical picture, which predominantly affects infants and preschool-aged children, has become rare through the introduction of *Haemophilus influenzae* (Hib) vaccine (mainly caused by *Haemophilus influenzae* type B). Acute epiglottitis is characterized by a severe infection of the upper respiratory tract with fever, odonophagia, hoarseness, and dysphagia.

A life-threatening obstruction of the respiratory tract can develop with rapid progression.

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Bronchitis

The cardinal symptom in *acute tracheobronchitis* is an initially unproductive, later followed by a productive, cough. Viruses are the cause in more than 90% of the cases. The color of the sputum does not permit a distinction to be made between viral and bacterial causes. Fever is frequently present in patients with influenza, parainfluenza, adenovirus, *Mycoplasma pneumonia*, or *Chlamydia pneumoniae* infections. In other viral infections (rhinovirus, coronavirus) fever is rare. Dyspnea only occurs in patients with a previously injured respiratory tract.

The *exacerbation of chronic bronchitis* in pre-existing *chronic obstructive pulmonary disease* (COPD), in which the clinical picture is characterized by a productive cough, is caused in 60% of the patients by bacteria (pneumococci, *Haemophilus*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*) and in the rest by viruses or *Mycoplasma pneumoniae*.

Whooping Cough (*Bordetella pertussis*, rarely *Bordetella parapertussis*). Whooping cough is an epidemically occurring, childhood disease that typically exhibits three stages:

- In the *catarrhal stage* (one to two weeks) uncharacteristic symptoms such as rhinitis, subfebrile temperatures, as well as a dry, predominantly nightly cough are the rule. Leukocytosis and lymphocytosis develop. In this stage the disease is most contagious (droplet infection).
- The *paroxysmal stage* lasts two to four weeks and is characterized by a paroxysmal cough followed by forced inspiration. After the attacks, vomiting frequently occurs.
- In the *convalescent stage* (one to two weeks) the periods of coughing decrease in frequency and intensity. The children are only rarely still contagious. As a result of decreasing vaccination rates in some populations of Europe, an increasing number of pertussis cases have occurred in adults during recent years.

In adults, *Bordetella pertussis* can assume an atypical manifestation and lead to a protracted cough of three weeks duration and longer (similar to tracheobronchitis).

Fever, Cough, and Thoracic Pain

Pneumonia

The most significant disease that is accompanied by these three symptoms is pneumonia.

Pathogens. In *elderly* patients with pneumonia acquired *outside of the hospital* (*community-acquired*) the pathogens are usually pneumococci, less frequently Gram-negative bacteria. If the infection develops during *hospitalization*, staphylococci and *Enterobacteriaceae* are the most likely causes. *Bacterial* pneumonia generally takes an acute course with high fever, dyspnea, cough, and sputum. Insofar as the pleura are affected, there is associated pain. Pneumococcal infections more frequently occur in alcoholics and after splenectomy.

In addition to pneumococci and *Haemophilus influenzae*, *younger* adults are more frequently afflicted with *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, and *Legionella*, which cause a so-called *atypical pneumonia* with unproductive cough, often normal lung auscultation, and nonsegmental pulmonary infiltrates.

Additional pathogens which cause pneumonia are viruses (influenza, parainfluenza, adenoviruses, *respiratory syncytial virus*, metapneumovirus, Sin Nombre virus, other hantaviruses (*hantavirus pulmonary syndrome*), SARS coronavirus), *Coxiella burnetii*, *Mycobacterium tuberculosis*, nontubercular mycobacteria, and in specific endemic regions infections with fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*), or parasites (*Paragonimus*, *Dirofilaria*).

In addition to frequently occurring bacterial pneumonias, *immunocompromised* patients can also suffer from opportunistic infections caused by *Pneumocystis carinii*, *Pseudomonas aeruginosa* (Fig. 4.**11**), cryptococci, *Nocardia*, *herpes simplex viruses*, *varicella-zoster virus*, and *Cytomegaloviruses*, *Toxoplasma*, and *Strongyloides*.

Clinical manifestations associated with specific pathogens.

- Intense pleuritic pain is typical of *pleurodynia* caused by coxsackie viruses or echoviruses. A pulmonary infiltrate is not present.
- Abscess-forming pneumonias and empyemas caused by staphylococci are a typical complication after influenzal or measles pneumonias.
- In *aspiration pneumonia*, anaerobic microbes of the oral flora predominate.
- A *pulmonary abscess* as a result of aspiration or a stenotic bronchial carcinoma can, like a *pleural empyema*, cause long-lasting fever, cough, and pleural pain.
- The most frequent chronic pleuropulmonary infection is tuberculosis.

Chlamydial Pneumonia. *Chlamydia pneumoniae* (previously TWAR strain of *Chlamydia*) is, apart from

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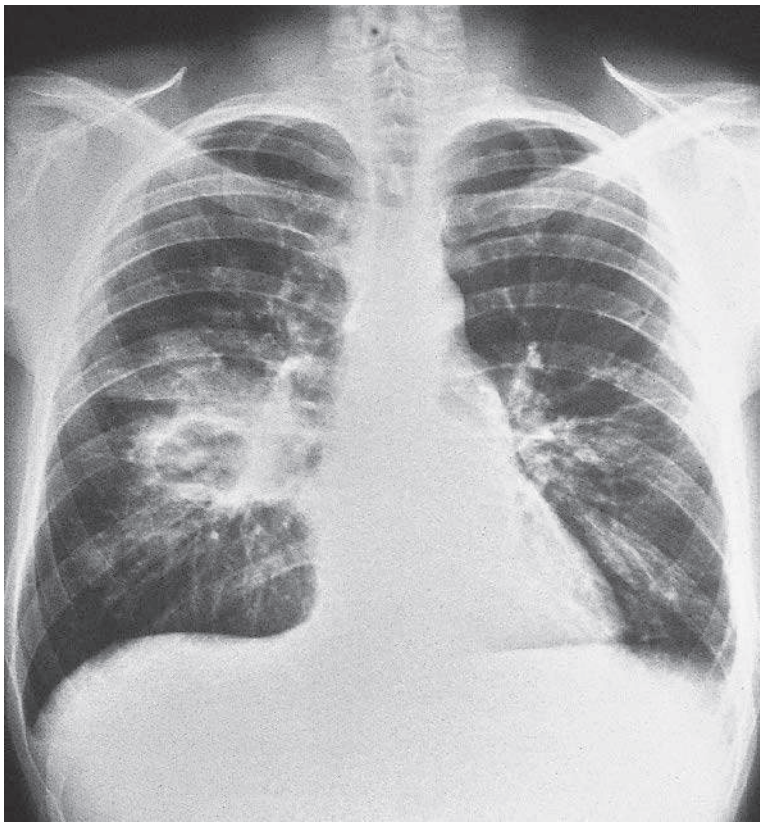

Fig. 4.**11** Lung abscess due to *Pseudomonas aeruginosa* in an HIV-infected person.

viruses, one of the most frequent pathogens that cause pharyngitis, laryngitis, and bronchitis. Pneumonias are comparably rare.

In about one-half of patients with pneumonia the course of the disease is biphasic. Namely, the pneumonia occurs after the bronchitis and pharyngitis symptoms have abated (frequently under antibiotic therapy) and a symptom-free interval of one to two weeks has elapsed. In the remaining patients the symptoms are present simultaneously. Clinically and radiologically the clinical picture cannot be distinguished from other so-called, "atypical" pneumonias. The diagnosis can be confirmed serologically. Not all commercially available serological methods can differentiate between *C. pneumoniae*, *C. trachomatis*, or *C. psittaci.* Cultures or gene probes are not available for the routine diagnosis.

Psittacosis (*Chlamydia psittaci*) is an acute, infectious disease which is transmitted by parrots, but also other birds. The clinical picture corresponds to that of a *highly febrile, atypical pneumonia*. Occasionally splenomegaly, central nervous system disorders, or epistaxis are observed.

Mycoplasma Pneumoniae. *Mycoplasma pneumoniae* causes a so-called, "atypical" pneumonia, tracheobronchitis, pharyngitis, or hemorrhagic myringitis.

Q Fever. *Q fever (Coxiella burnetii)* generally occurs as a highly febrile pneumonia with headaches and a notably reduced state of general health. The typical exanthema of rickettsiosis is absent. Rare complications are hepatitis and endocarditis. The diagnosis is based on the serological detection of antibodies.

Legionnaire Disease (*Legionella pneumophila*, Various Serotypes). This is a systemic, bacterial disease which predominantly affects the lungs. After an incubation period of two to 10 days, the disease begins with influenza-like symptoms. Thereafter, high fever with cough, thoracic pain, and gastrointestinal symptoms occur in addition. Finally, confusion and acute respiratory insufficiency can occur. Mortality is $< 15\,\%$. Apart from the poor state of general health, the objective symptoms are tachypnea and moist rales.

Laboratory test results include an elevated erythrocyte sedimentation rate, leukocytosis with left shift, as well as occasional signs of hepatic and renal involvement (proteinuria, microhematuria). Radiograph examination shows multiple, spotty infiltrates with a tendency towards consolidation. Demonstration of pathogenic organisms occurs by means of antigen detection in the urine, serology, gene probe, or culture. However, the antibody titer does not increase until three to six weeks after disease onset. This means that the serological diagnosis has only epidemiological significance. Infection is airborne (e. g., from air conditioning systems, whirlpools).

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Anthrax. Pulmonary anthrax has a high mortality rate. The early phase of the infection often occurs as a mild, nonspecific, febrile, influenza-like disease and poses great differential diagnostic problems. Prominent symptoms which can help distinguish pulmonary anthrax from other influenza-like infections include dyspnea, pleuritic pain, severe sweating, abdominal pain, as well as nausea, and vomiting. In contrast, nasopharyngeal symptoms like those of the common cold are rare. A severe clinical picture with shock results within three to five days. The chest radiograph frequently shows a widened mediastinal shadow initially, and later in the disease contains pulmonary consolidations and pleural effusions. Pleural puncture often yields hemorrhagic effusions. Blood cultures yield Gram-positive rods within 24 hours, insofar as they were drawn before the application of antibiotics.

SARS (Severe Acute Respiratory Syndrome). A new, probably zoonotic, coronavirus, the SARS coronavirus, led in 2003 to an epidemic of severe, "atypical" pneumonias with a high mortality rate in Southern China, areas of Southeast Asia, Canada, and other countries. Infection occurs by means of direct or indirect contact with the mucous membranes of the eyes, mouth, or nose through infectious droplets or contaminated surfaces. The virus is highly contagious and has in particular led to epidemics among medical personnel in hospitals. These outbreaks could only be stopped by uncompromising isolation and hygiene measures.

The transmission of the virus occurs in the symptomatic phase. The highest viral titer in the blood or respiratory secretions is measured on day 10 of the disease. The incubation period is two to 10 days. A few asymptomatic infections or mild illnesses have been documented. However, the course of the disease is usually severe. The initial symptoms are nonspecific and include fever, myalgia, malaise, and cough. Symptoms of the upper respiratory tract are rare, but do occur. Often diarrhea is present. During the course of the disease, dyspnea and respiratory insufficiency can develop.

The laboratory test results are nonspecific. The chest radiograph in the early phase can still be inconclusive. Later on mainly bilateral, multifocal consolidations are seen. The diagnosis is made by detection of the virus using molecular genetic methods or by serology.

Tuberculosis

Pathogen and Transmission. The most frequent pathogen responsible for causing tuberculosis, since the sanitization of cattle stocks (*Mycobacterium bovis*), has been *Mycobacterium tuberculosis*. Transmission occurs mainly through droplet infection. Enteral transmissions (*Mycobacterium bovis*) have become rare. The transmission rate to immunocompetent household contacts is about 50% in open tuberculosis. In pulmonary tuberculosis, which is microscopically negative, this is about 5%. Only 10% of those infected will develop manifest tuberculosis during the course of their lives. One-half of these individuals will do so within 18 months after the primary infection, the remainder during their remaining lifespan.

Primary Pulmonary Tuberculosis, Postprimary Tuberculosis. The mostly acute pulmonary disease which occurs directly after a primary infection is called *primary pulmonary tuberculosis*. The disease which occurs after hematogenic metastasis, often years later through reactivation of disseminated foci, is the so-called *postprimary pulmonary*, *organ*, or *extrapulmonary tuberculosis*.

The main *risk factors* for the reactivation of tuberculosis are HIV infection, followed by silicosis, carcinomas of the head and neck region, hemodialysis, and immunosuppressive therapy.

Clinical Features. The *primary infection* is usually not noticed. A primary and postprimary pulmonary (as well as an extrapulmonary) tuberculosis can be responsible for a fever. General symptoms such as fatigue, night sweats, weight loss, indication of hemoptysis, therapy-resistant cough, or a nodal fever experience (Fig. 4.**12**), and the presence of risk factors, concomitant with fever must arouse suspicion of tuberculosis. The clinical picture of tuberculosis is extremely diverse. With the exception of

Fig. 4.**12** Erythema nodosum in a 26-year-old woman.

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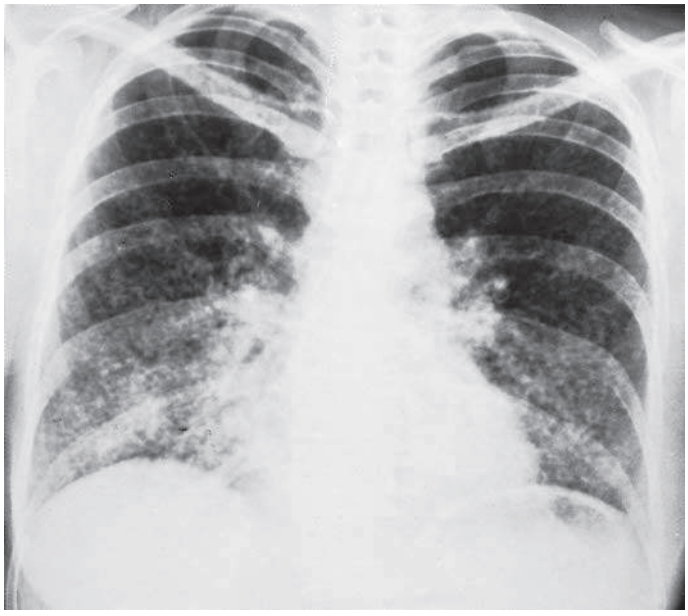

Fig. 4.**13** Miliary tuberculosis showing mottled shadowing throughout both lung fields in a 43-year-old woman.

HIV-infected patients, extrapulmonary tuberculosis is rare. Therefore, the initial examinations (physical, radiological, sputum, both microscopically and bacteriologically) should focus on the lungs. The blood count and the ESR are not characteristically changed. A tuberculin test (even in HIV-infected patients insofar as an advanced immunodeficiency is not present) can possibly provide assistance, especially if a conversion from a negative to positive result is observed. In patients with an HIV infection a diameter of ≥ 5 mm, in other patients of ≥ 10 mm, is deemed positive.

Acute Miliary Tuberculosis. A massive hematogenic distribution (*Landouzy sepsis*) leads to the clinical picture of disseminated tuberculosis (acute miliary tuberculosis) with septic metastases in the liver, spleen, meninges, pleura, and peritoneum. The general state of health is significantly impaired. High intermittent fever, sweats, headaches, dry cough, and increasing dyspnea are frequent and characteristic symptoms. Pulmonary invasion yields the classic miliary image (Fig. 4.**13**). The multiple miliary foci are typically distributed throughout all pulmonary fields. A preponderant localization in the upper lobe can occur and must be distinguished from pulmonary carcinomatosis in the differential diagnosis.

In patients not infected with HIV, anemia is usually present, rarely pancytopenia, or thrombopenia. A normal leukocyte count is frequently found in the blood count. Leukopenia occurs in 20–30 % of the cases. Typical are monocytosis, lymphopenia, and eosinopenia. Toxic changes of the leukocytes are absent. In HIV-infected patients the blood count is usually altered by the underlying illness. Pathological liver function tests are frequent and indicate cholestasis. The erythrocyte sedimentation rate is elevated. Occasionally an ADH syndrome with hypernatremia occurs. The tuberculin test in miliary tuberculosis is usually negative. Diagnostically crucial is the histological detection of epithelioid granulomas or acid-fast rods in the liver and the bone marrow (biopsies). Splenomegaly and granulomas in the choroid each occur in 10 % of the cases.

In patients not infected with HIV, who are afflicted with acute miliary tuberculosis the sputum and urine cultures are each positive in one-third of the cases. Blood cultures from HIV-infected patients with disseminated tuberculosis are frequently positive.

Chronic Miliary Tuberculosis. In immunocompetent patients *chronic miliary tuberculosis* can also occur. This is characterized by fever episodes that often last for weeks and exhibit the general symptoms described above, albeit in milder form. In one-half of cases the chest radiograph exhibits nonspecific alterations. However, extrapulmonary foci (e. g., lymph nodes, bones) are more often present.

Nontuberculous Mycobacterioses

Nontuberculous mycobacterioses (synonym: atypical mycobacterioses) are mycobacterial diseases that are not caused by *Mycobacterium tuberculosis*, *M. bovis*, *M. bovis BCG*, or *M. leprae*.

Pathogens and Detection. These mycobacteria are ubiquitous. However, the incidence exhibits geographical predilections. Only a very few species are pathogenic to humans. Occasionally associated with pulmonary disease are *M. avium complex*, *M. kansasii*, *M. malmoense*, *M. scrofulaceum*, *M. xenopi*, *M. chelonae*, *M. for-*

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tuitum, and *M. genavense*. However, the detection of these species more frequently reflects colonization or contamination rather than mycobacterial disease. Therefore, in addition to appropriate clinical findings, the verification of an isolate from sterile sites or the multiple verifications from nonsterile materials and appropriate histological alterations (biopsy) is necessary for the diagnosis. In HIV-infected patients with advanced immunodeficiency, nontuberculous mycobacteria (most frequently *M. avium complex*, *M. kansasii*, *M. genavense*, or *M. hemophilum*) can be detected in the blood. Because of the extremely frequent resistance against tuberculostatics of first choice, identification and resistance screening is decisive for therapeutic success.

Clinical Features. Nontuberculous mycobacterioses mainly occur as a disease of the lungs (predisposing factors; status after recurrent tuberculosis, subtotal gastrectomy), the lymph nodes (especially children), and rarely the skin. Disseminated diseases occur only with severe underlying illnesses (e. g., advanced immunodeficiency in HIV infection) or in patients under immunosuppressive therapy.

Nocardiosis

Nocardiosis (*Nocardia asteroides*) is a rare, chronic–granulomatous inflammation that preferably invades the lungs of patients with impaired immune function. The radiological presentation is uncharacteristic. Pneumonic foci have a clear tendency to form necroses and abscesses. This tendency can lead to an empyema in foci near the pleura. From the perspective of the differential diagnosis, the clinical symptoms of night sweats, fever, and productive cough are most consistent with tuberculosis. In addition, there is an explicit tendency towards hematogenic dissemination, whereby the central nervous system is affected in one-third of the cases. CSF alterations are nonspecific in that *Nocardia* cannot be detected. In the sputum the Gram-positive, variable, acid-fast, slender rods with true branching can be detected either directly with the microscope or in an aerobic culture. The prognosis in immunocompromised patients is poor without an adequate therapy.

Pericarditis, Myocarditis

The etiology of most cases of pericarditis and myocarditis is still unknown. However, in infants, children, and adults it is frequently possible to determine that coxsackie B viruses (mainly coxsackie B2, B3, and B4 viruses) are the responsible pathogen. The disease begins with fever, malaise, and early cardiac symptoms such as retrosternal pain, pericardial rub, and cardiomegaly. A pericardial effusion can be diagnosed with echocardiography. The involvement of the myocardium expresses itself in arrhythmias and occasionally cardiomyopathy.

Noninfectious Diseases

Noninfectious causes of fever and pulmonary symptoms are pulmonary embolism, pulmonary infarction, chemical-induced pneumonitis after aspiration of gastric juice, necrotizing pulmonary tumor, allergic alveolitis, and interstitial pneumonia. In general, these diseases can be diagnosed by means of a careful medical history, chest radiograph, and pulmonary function test. In myocardial infarction and pericarditis the chest pain predominates. During the first few days, temperatures of 38 °C are frequent in infarction. Fever also can occur in viral pericarditis. ECG and enzyme values, or auscultation and echocardiography are diagnostically indispensable. Nitrofurantoin and bleomycin can cause both fever and infiltrates.

Fever and Jaundice

If these two symptoms occur, it is first necessary to determine whether the jaundice is *pre-*, *intra-*, or *post-hepatic*.

Prehepatic Jaundice

Hemolysis. Various pathogens (malaria, *Clostridium perfringens*, *Mycoplasma pneumoniae*) are able to cause *hemolysis* which can be detected by a drop in the hemoglobin value, reticulocytosis, and elevated LDH and unconjugated bilirubin values. Patients with sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, or paroxysmal, nightly hemoglobinuria also can experience a hemolytic crisis during an infection.

Hepatic Jaundice

Infectious Diseases. Fever can be a prodromal symptom of *viral hepatitis*. *Mononucleosis* and cytomegalovirus infection cause fever and abnormal liver enzymes in a high percentage of the cases. However, the hyperbilirubinemia is not very extensive. The situation is comparable in *Q fever*, *legionellosis*, and *leptospirosis*. Jaundice frequently occurs in *severe sepsis* caused by

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pneumococci, *Klebsiella*, *Salmonella*, *Bacteroides fragilis*, *E. coli*, or streptococci. In *miliary tuberculosis* liver involvement is virtually always detectable. However, it only rarely expresses itself in the form of jaundice. In contrast, liver enzyme alterations and especially cholestasis are typical. In this situation, the bioptic confirmation of a granulomatous hepatitis proves diagnostic.

Localized Bacterial Infections. It is possible for *pylephlebitis* with multiple intrahepatic abscesses to develop if a case of perityphlitis or a diverticular abscess undergoes hematogenic dissemination in the form of septic emboli via the mesenterial veins and the portal vein. These do not communicate with the bile duct system as do the abscesses which form as a result of cholangitis. The clinical consequences are hepatomegaly with jaundice, epigastric pain on the right side, fever, and chills. These symptoms are also typical for a *liver abscess* that occurs as a result of sepsis, an abdominal trauma, or idiopathically. However, a solitary abscess, but also multiple liver abscesses, can take the course of a fever of unknown origin and not present any local symptoms.

Imaging techniques are the decisive diagnostic measures. These also facilitate a targeted fine needle puncture. Cultures most frequently detect streptococci, anaerobes, and *Enterobacteriaceae*.

Parasitic Infections. After staying in tropical countries, it is possible to develop an *amebic abscess*. These are mostly solitary and larger than bacterial abscesses. The Gram stain of the abscess contents and the culture are negative. Only rarely are trophozoites found. However, antibody detection is virtually always positive.

Medications. *Hepatotoxic drug side effects* must also be mentioned. These mainly occur after taking isoniazide, rifampicin, hydantoin, halothane, and α-methyldopa.

Parallel Occurrence of Jaundice and Fever. Naturally the *association* of jaundice and fever *need not* have a *causal* connection. For example, pre-existing asymptomatic liver cirrhosis can decompensate during a severe infectious disease. Tuberculosis or lobar pneumonia can also develop in a patient with alcoholic hepatitis and result in fever and jaundice.

Posthepatic Jaundice

Bile Duct Diseases. *Cholangitis* is a feared complication of *choledocholithiasis*, which can lead to a partial or complete occlusion of the bile duct. In contrast to an obstruction by a tumor or bile duct stricture, an ascendant infection is frequent in persistent choledocholithiasis.

> Fever, chills associated with epigastric pain on the right side, and jaundice combined with a medical history of epigastric colics are very suggestive of cholangitis.

Diagnosis. Laboratory tests detect the elevated conjugated bilirubin level, the cholestasis, and the excretion of bilirubin in the urine. Decisive diagnoses can be made using ultrasound, the endoscopic retrograde depiction of the common bile duct, and possibly the pancreatic duct, and finally the percutaneous transhepatic filling of the bile duct system.

Differential Diagnosis. The differential diagnosis must also consider *cholecystitis* and *pancreatitis* in addition to cholangitis. Cholestasis can be caused by simultaneously present bile duct stones or an edema of the common bile duct in case of cholecystitis, and by edema of the head of the pancreas in patients with pancreatitis.

Pathogens. The pathogen spectrum for cholangitis mainly consists of *Enterobacteriaceae*, enterococci, and anaerobes. Exotic causes of jaundice are fascioliasis and, especially in Southeast Asia, endemic hepatic flukes. *Fasciola hepatica* initially causes parenchymatous hepatitis, elevated transaminases, hepatomegaly, and eosinophilia. Posthepatic jaundice can develop during the course of the disease.

Fever and Splenomegaly

Splenomegaly and fever frequently occur in lymphoproliferative diseases as well as infections, rarely in reticuloendotheliosis and chronic hemolytic anemia. The most important clinical pictures associated with these two cardinal symptoms are summarized in Tab. 4.**11**. Rarer causes in nontropical countries are malaria, visceral leishmaniasis, schistosomiasis, echinococcosis, trypanosomiasis, rickettsiosis, and relapsing fever. Acute pneumonia, intense headaches, splenomegaly, and fever arouse the suspicion of *psittacosis*. The noninfectious inflammatory causes of splenomegaly include *Still disease*, *Felty syndrome*, and *systemic lupus erythematosus*.

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Tab. 4.**11** Differential diagnosis of fever and splenomegaly

	Typhoid	Infective endocarditis	Miliary tuberculosis	Hodgkin lymphoma	Mono-nucleosis	Brucellosis
Onset	1 week	gradually	gradually	gradually	2–3 weeks	gradually
Erythrocyte sedimentation rate	slowly increasing	strongly elevated	moderately elevated	normal or elevated	moderately elevated	slowly increasing
Chills	rare	frequent	rare	absent	absent	absent
Leukocyte count	decreased	normal or increased	normal	normal	normal or increased	normal or decreased
Lymphocyte count	normal or increased depending on the disease stage	decreased	strongly decreased	decreased	strongly increased (monocytoid cells)	increased
Toxic changes of neutrophils	increasing	yes	absent	variable	absent	absent
Eosinophilia	always absent	decreased	decreased	increased	normal	mostly decreased
Blood cultures	positive	positive	negative*	negative	negative	rarely positive
Means of diagnosis	blood culture	blood culture	biopsy (liver, lymph nodes)	biopsy (lymph nodes)	blood count, serology	serology (blood culture)

* Except in HIV infection.

Fever and Diarrhea

The differential diagnosis of *noninfectious* diarrhea is discussed in Chapter 27.

Intestinal Infections

The differential diagnosis of intestinal infections focuses on *epidemiological* and *pathogenetic* considerations.

Pathogenesis. Pathogenetically, noninflammatory, inflammatory, and systemic intestinal infections are distinguished.

- *Noninflammatory intestinal infections.* The pathogen spectrum includes *Vibrio cholerae*, enterovirulent *E. coli* (ETEC, EPEC, EAggEC, see below), as well as bacteria which form toxins in food and viruses. *Watery* diarrhea, which usually exhibits an *afebrile* course, is caused by enterotoxins or the adherence of pathogens to the epithelium of the proximal small intestine. The stool usually does not contain any leukocytes.
- *Inflammatory intestinal infections.* The pathogens, *Shigella*, enterovirulent *E. coli* (EIEC, EHEC, see below), *Salmonella enteritidis*, *Campylobacter jejuni*, or *Clostridium difficile*, invade the intestinal epithelium or form cytokines. The infection is clinically manifest as dysentery. This is an inflammatory disease of the colon, often associated with blood and pus in the stool. Patients frequently suffer from abdominal pain, cramps, and fever.
- *Enteric fever.* The pathogens, *Salmonella typhi* and *Yersinia enterocolitica*, can penetrate the wall of the distal small intestine and lead to a systemic febrile illness.

Epidemiology. Epidemiological considerations can reduce the possible pathogen spectrum as follows:

- *Diarrhea acquired outside of the hospital, "community acquired":* in countries with a temperate climate, *Campylobacter*, nontyphoid *Salmonella*, enterovirulent *E. coli*, and viruses are the most frequent causes of diarrhea in persons without a history of international travel.
- *Nosocomial diarrhea:* this is usually caused by *C. difficile*.
- *Persons returning from having traveled abroad or diarrhea in tropical countries:* enterotoxigenic *E. coli* or *Shigella* are most frequently involved. Protozoa or worms are rare.
- *Diarrhea in children:* the most frequent causes are rotaviruses or astroviruses.
- *Diarrhea in immunocompromised persons:* patients with *cellular immunodeficiency* (HIV infection, immunosuppression after organ transplantation) frequently suffer from infections with opportunistic protozoa (*Cryptosporidia*, *Microsporidia*), nontubercular mycobacteria, and cytomegalovirus.

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Neutropenic patients are at risk for nosocomial infections and can develop the severe and life-threatening illness of neutropenic enterocolitis. A *selective IgA deficiency* with follicular nodular hyperplasia in the small intestine can lead to chronic diarrhea and malabsorption and is frequently associated with *Giardia lamblia* infections.

Pathogens Causing Diarrhea

Campylobacter. *Campylobacter jejuni*, rarely *Campylobacter coli*, causes acute, occasionally febrile, enteritis with diarrhea, abdominal cramps, nausea, and vomiting. In most cases the disease subsides within one to four days. About 20 % of the patients are symptomatic for one to two weeks. The stool contains blood or mucous. Granulocytes also can be detected microscopically. A *reactive arthritis* is observed in HLA-B27-positive patients. Other rare complications are meningitis, endocarditis, cholecystitis, and pancreatitis. Transmission to humans occurs through contaminated food and beverages, rarely through infected animals.

Salmonella. *Nontyphoid* and *typhoid Salmonella* are distinguished.

- *Enteritic (nontyphoid) salmonellosis:* This foodborne disease is a zoonosis. The clinical symptoms can occur after an incubation period of six to 48 hours including fever, nausea, vomiting, watery diarrhea (rarely with blood or mixtures of mucus), as well as cramping abdominal pain. Septic forms of the disease are rare except in infants and immunocompromised patients (especially HIV infected).
- *Typhoid.* The pathogen reservoir of *Salmonella typhi* is found only in humans. The clinical manifestations of *abdominal typhus* begin after an afebrile to subfebrile incubation period of about 10 days and typically include general symptoms such as fatigue, shivering, headaches, and a tickle in the throat. The temperature increases to 40 °C within one week. Sometimes constipation and rarely diarrhea are present. With a retained orientation to time and place, the untreated patient alternates between states of apathy or excitement, and occasionally delirium.
- The *rose spots* (pink, pale, oval, blanching maculopapular skin lesions) (Fig. 4.**14**) first occur in about one-half of the cases between day 7–10 of the illness. They are exclusively located in the lower thoracic region, above the abdomen, and on the back. An enanthema also is occasionally observed.
- Additional typical findings are splenomegaly, relative bradycardia despite a high fever, leukopenia with a distinct left shift, and absent eosinophils. Blood cultures are diagnostic. In 15–20 % of cases a relapse occurs which usually is benign.
- The clinical picture in *paratyphus B* (A is infrequent, C is a rarity) generally takes a more rapid and milder course. Bacteriological identification is important for the differential diagnosis.

Fig. 4.**14** Rose spots in a patient with typhoid.

Shigella. In shigellosis (bacillary dysentery) bloody or mucous stools are more frequent, as *Shigella*, in contrast to *Salmonella*, cause destruction of the epithelium with ulcerations. The remaining symptoms differ little from the cases of enteritis caused by *Salmonella*.

Enterovirulent *Escherichia coli*. The enterovirulent *E. coli* are divided into six pathovars. Identification occurs by molecular genetics.

- The *enterotoxigenic E. coli* (ETEC) are the most frequent cause of watery, usually afebrile, traveler diarrhea.
- Increasingly observed is the sporadic and epidemic occurrence of *verotoxin-forming* (*enterohemorrhagic*, EHEC) *E. coli* (e. g., *E. coli* O157:H7 and other serotypes) which are transmitted in food in particular. They classically cause a bloody diarrhea and can, especially in children and the elderly, sometimes lead to a *hemolytic uremic syndrome* or a thrombotic thrombocytopenic purpura. However, the clinical manifestations of the infection caused by verotoxin-forming *E. coli* often are very nonspecific and the diarrhea is not always bloody.
- The pathogenesis and clinical manifestations of *enteroinvasive E. coli* (EIEC) are comparable to those of shigellosis.
- The *enteropathogenic E. coli* (EPEC) are in particular the cause of sporadic and epidemic infantile diarrhea.
- The strains of *enteroaggregative* (EAggEC) *E. coli* have not yet been completely characterized by molecular genetics.
- *Diffusely adherent E. coli* (DAEC) have especially been associated with childhood diarrhea in developing countries.

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***Yersinia pseudotuberculosis* and *Yersinia enterocolitica*.** These anthropozoonoses become manifest in children and adolescents as an appendicitis-like clinical picture with fever, leukocytosis, and an acute abdomen. The diagnosis is made by culture (blood, stool) and serology (titer increased after one to two weeks!). In adults, enteritis symptoms (*Yersinia enterocolitica*), and very rarely, a septic course of the disease can occur. The latter is especially found in immunocompromised patients, diabetes mellitus, alcoholism, and chronic hepatic diseases. In about 10–30% of the cases *Yersinia* enteritis is followed by oligoarthritis (rarely polyarthritis) and an erythema nodosum (Fig. 4.**12**).

***Tropheryma whippelii*.** *Whipple disease* is a bacterial, multiorgan disease which is caused by *Tropheryma whippelii*. In an early phase of the disease, general symptoms, joint pain, lymphadenopathy, and often fever dominate. Manifestations that occur later are chronic diarrhea with or without malabsorption, weight loss, hyperpigmentation, endocarditis, and disorders of the central nervous system. Pathognomonic findings under the light microscope are tissue infiltrations with macrophages which contain PAS-positive inclusions. In addition to verification in intestinal biopsies, it has been possible to detect the pathogen in ocular or CNS disease, in endocarditis, as well as spondylitis by using appropriate materials and molecular genetic methods.

***Vibrio cholerae*.** After an incubation period of up to five days, on average two to three days, 25–50% of those infected with *Vibrio cholerae* or with the El Tor variant develop diarrhea without cramps or fever as a result of an enterotoxin. This diarrhea initially appears mushy brown, later watery (absent bile pigments), and in severe cases like "rice water." Stool volumes fluctuate between 1–10 L per 24 hours. Nausea and vomiting result as consequences of the fluid loss and/or the acidosis. In advanced cases the skin turgor is massively reduced (skin can be lifted in folds) and extrarenal kidney failure develops. The diagnosis of cholera can occasionally be made by microscopy (comma-shaped, rapidly moving vibriones). However, a specific diagnosis is made by stool culture. Asymptomatic carriers form the pathogen reservoir.

***Clostridium difficile*.** Pseudomembranous colitis is observed during or after antibiotic therapy and is caused by toxins produced by *Clostridium difficile*.

Food Poisoning. *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus* can produce toxins, either ex vivo in food or in vivo, which cause an acute watery diarrhea with nausea.

Neurotoxins formed by *Clostridium botulinus* cause nausea, vomiting, diarrhea, and paralysis which begins within 18–36 hours.

Tuberculosis. *Intestinal tuberculosis*, which occurs rarely today, is often accompanied by general symptoms of fever and chronic diarrhea. It is often difficult to diagnose, even with the assistance of an endoscopic biopsy.

Viruses. The widespread gastrointestinal viruses (noroviruses, rotaviruses, astroviruses, and enteric adenoviruses) cause diseases which are only occasionally accompanied by fever. However, partially as a result of massive dehydration, they are responsible for a high morbidity and also mortality rate, especially in developing countries.

Intestinal Parasites. Of the parasite-related diarrheas, severe amebic dysentery and hyperinfection syndrome with *Strongyloides stercoralis* can take a febrile course, while patients with lambliasis remain afebrile. Malaria in those returning from international travel can initially become manifest as a febrile "traveler diarrhea."

In immunodeficient (especially HIV-infected) patients, cryptosporidiosis and microsporidiosis (microsporidial species: *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*) are among the most frequent causes of chronic diarrhea. However, these parasites are increasingly being recognized as the cause of a self-limiting diarrhea in immunologically healthy travelers, as well as in children and adults living in tropical regions. *Cyclospora cayetanensis* is increasingly being diagnosed in travelers, children, and adults in tropical regions and in epidemics caused by contaminated food.

Intestinal *helminthic diseases* do not usually cause fever.

Fever and Abdominal Pain

Noninfectious abdominal diseases are discussed in Chapter 7.

Intra-abdominal Infections

The initiation of an adequate therapy when an intra-abdominal infection is suspected is often time-limited, as the mortality rate can increase very rapidly if time delays occur. Although a specific diagnosis is always desirable, therapeutic interventions before a diagnosis has been established will sometimes be unavoidable. The most important decision making criterion is the information provided in the patient's medical history, especially an exact description of the symptoms and their temporal course. The diagnosis of intra-abdominal infections is primarily based on clinical findings. Imaging techniques or laboratory tests, which are time-consuming, are frequently not helpful.

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Peritonitis

Peritonitis is an inflammation of the peritoneum or parts thereof. The peritoneal inflammatory response that leads to the sequestration of large fluid volumes and triggers the inflammation cascade is almost always accompanied by severe systemic effects and can result in sepsis, organ dysfunction, and septic shock.

Pathogens. The *pathogen spectrum* which is isolated in intra-abdominal infections predominantly originates from the intestines or associated hollow organs. It includes *aerobic* (*Escherichia coli*, other *Enterobacteriaceae*, enterococci, other streptococci, *Pseudomonas*, and others) and *anaerobic* (*Bacteroides fragilis*, other *Bacteroides species*, *Clostridia*, and others) microbes.

Clinical Features. In addition to systemic signs of inflammation, the extremely severe, unremitting abdominal pain, which intensifies upon movement, and the clinical signs of peritonitis are of key importance to the differential diagnosis. Pain that remits in its intensity can indicate a localization of the inflammatory process. Intensifying pain can indicate a generalization of the peritonitis. The temperature is usually between 38–40 °C. Loss of appetite, nausea, thirst, fever, and shivering are concomitant symptoms.

Diagnosis. The blood count shows a leukocytosis or a left shift with a normal leukocyte count. The conventional radiograph of the abdomen exhibits the signs of a paralytic ileus. Abscesses can be depicted with imaging techniques.

Primary Peritonitis. In less than 1 % of peritonitis cases a *spontaneous bacterial* peritonitis is present. The clinical picture mainly occurs in children, patients with cirrhosis of the liver (especially ascites), and in nephrotic syndrome. The most frequent pathogens are *Escherichia coli*, pneumococci, and streptococci of group A. The infection occurs by hematogenic dissemination, *per continuitatem* from the subdiaphragmatic, or retroperitoneal space, or directly from the female genital tract. The diagnosis is confirmed by culture of the pathogens from the peritoneal space. The symptoms and the clinical findings usually are less acute and develop slower than in secondary peritonitis.

Tuberculous peritonitis occurs by hematogenic dissemination, usually originating from a pulmonary focus. Abdominal pain, fever, weight loss, night sweats, and ascites are the most frequent symptoms. The diagnosis usually requires laparoscopic exploration in which multiple tubercles can be seen on the peritoneum.

Perihepatitis (Fitz–Hugh–Curtis syndrome) is caused by gonococci or *Chlamydia*.

Secondary Peritonitis. Causes of secondary peritonitis are perforations by a primary necrotizing lesion along the course of the gastrointestinal tract or another abdominal organ, a traumatic perforation, or an abdominal intervention. The pathogen spectrum usually is polymicrobial and consists of aerobic and anaerobic intestinal microbes.

Patients with *chronic, ambulant peritoneal dialysis* (CAPD) exhibit pathogens from intestinal or extra-abdominal sources.

Tertiary Peritonitis. A persistent, diffuse, so-called tertiary peritonitis presents the clinical picture of occult sepsis without any detectable focus. The patients exhibit subfebrile to febrile temperatures. Often bacteria of low pathogenicity (coagulase-negative streptococci), *Pseudomonas species*, or fungi are isolated from the peritoneal spaces which frequently have been selected during antibiotic therapy. Such infections often cannot be successfully treated with antibiotic and surgical therapy. The disorder is the consequence of a local or systemic immunosuppression.

Intra-abdominal Abscesses

Causes. Causes of intra-abdominal abscesses are:

- incomplete healing of diffuse peritonitis in which a localized infection persists and subsequently forms an abscess
- spontaneous or traumatic perforation of the intestinal tract
- a postoperative leak of a surgical anastomosis in the intestinal tract.

Clinical Features. The various locations of intra-abdominal abscesses lead to various clinical manifestations. Localized pain, nausea, vomiting, or diarrhea, as well as peritonitic signs during the examination frequently occur in intraperitoneal abscesses, splenic and hepatic abscesses, or cholecystitis. In elderly patients the symptoms can be subacute and the findings less extensive.

> Several prior illnesses predispose a patient to develop intra-abdominal abscesses. These include Crohn disease (intraperitoneal, retroperitoneal abscesses, and bacterial endocarditis), bile duct diseases (hepatic abscesses), or pancreatitis (pancreatic abscesses).

Visceral Abscesses

With an intra-abdominal focus, abscesses of visceral organs are usually polymicrobial. In hematogenic dissemination from extra-abdominal sources it is also possible for microbes that do not occur in the intestinal tract to be isolated.

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- *Pancreatic abscesses* develop as a complication of pancreatitis, after endoscopic retrograde cholangiopancreatography (ERCP), rarely after a penetrating duodenal ulcer, or after a secondary infection of a pancreatic pseudocyst.
- *Bacterial hepatic abscesses* are rarely the consequence of cholecystitis, appendicitis, diverticulitis, and peritonitis, but could develop after a liver transplant or in chronic granulomatous diseases.
- *Hepatosplenic candidiasis* is a complication in patients with long-term neutropenia, especially after treatment of acute leukemia or after bone marrow transplantation.
- Hepatic abscesses caused by *Entamoeba histolytica* are a complication of amebic colitis in 3–9% of the cases. Primary symptoms of hepatic abscesses are fever and shivering. The localized pain sometimes can be mild in nature or can even be absent.
- In cystic echinococcosis (*Echinococcus granulosus*) the symptoms of an increasing space-occupying lesion protrude from the organ. Alveolar echinococcosis (*Echinococcus multilocularis*) is a destructive infection that can exhibit a clinical course comparable to that of hepatic carcinoma.
- *Splenic abscesses* develop after bacteremia which is a complication of bacterial endocarditis, disseminated tuberculosis, or *Salmonella* infection, after trauma, or in splenic infarctions (e. g., in patients with sickle cell anemia). In most patients localizing pain and high fever are present.

Specific Causes of Intra-abdominal Infections

Localized pain, fever, and increasing peritonitic signs lead to the consideration of acute appendicitis, diverticulitis, cholecystitis, or adnexitis in the differential diagnosis. In patients with severe *granulocytopenia* a case of *necrotizing enterocolitis* comparable to appendicitis or diverticulitis can develop. Likewise, *cecal actinomycosis* can imitate the clinical picture of appendicitis.

Fever, Dysuria, and Pollakisuria

Urinary tract infections with extremely varying locations can cause dysuria and/or pollakisuria. Additional urogenital tract symptoms are urethral discharge, pain in the bladder, lumbar region, buttocks, perineum, rectum, scrotum, and labia. In addition to the clinical symptoms, the differentiated *analysis of the urine* plays an important role in the diagnosis of febrile urinary tract infections. The *microscopic* and *chemical examinations* as well as the semiquantitative *microbial count* are the most important elements.

Urethritis

A burning sensation when urinating, discharge, and leukocyturia characterize *urethritis*, which is most frequently caused by gonococci, *Chlamydia*, trichomonads, and rarely by *Candida*, herpes simplex viruses, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. Systemic signs such as fever are generally absent. The anogenital forms of gonococcal infections frequently take an asymptomatic course in women; they are rarely asymptomatic in men.

Acute Uncomplicated Urinary Tract Infections in Women

The *acute uncomplicated urinary tract infection* ("acute uncomplicated cystitis") occurs in women in particular and is characterized by dysuria, pollakisuria, and lower abdominal pain. The most frequent pathogens are *E. coli* (70–80%) and *Staphylococcus saprophyticus* (10–20%). *Klebsiella pneumoniae*, *Proteus mirabilis*, enterococci, *Pseudomonas aeruginos*, and *Chlamydia* are rare. The medical history does not indicate the presence of urological disease and the affected patients become asymptomatic with a short-term antibiotic therapy in the majority of the cases.

Asymptomatic bacteriuria requires treatment during pregnancy, in patients with a kidney transplant, and in diabetes mellitus. In all other situations asymptomatic bacteriuria does not have any clinical consequences and does not lead to urological or other complications.

In recurrent, acute, uncomplicated, urinary tract infections a detailed medical history, as well as clinical and microbiological examinations are necessary.

Acute Uncomplicated Pyelonephritis

Fever of acute onset, chills, lumbar pain, and renal beds which are painful to palpation are characteristic for acute pyelonephritis. A positive blood and urine culture—usually more than 100 000 microbes/ml (100×10^6/L) can be detected in the urine—confirm this tentative diagnosis. However, clinical courses which are asymptomatic also occur and the differentiation versus cystitis is often not possible.

The most frequent pathogens are *E. coli* (>80%), while *Staphylococcus saprophyticus*, *Klebsiella pneumo-*

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niae, *Proteus mirabilis*, and other *Enterobacteriaceae* occur rarely.

Acute Complicated Pyelonephritis

Acute complicated pyelonephritis presents the same clinical picture as uncomplicated pyelonephritis and is characterized by the presence of complicating urological diseases. These include malformations, urolithiasis, prostate hyperplasia, and uterine descensus. However, diabetes mellitus, pregnancy, and an indwelling urinary catheter also are complicating factors.

The most frequently occurring pathogens are *E. coli* (50%), but other *Enterobacteriaceae* and *Pseudomonas* also occur. In addition staphylococci, enterococci, and *Candida* are found.

Especially in staphylococcal sepsis, *intrarenal and perirenal abscesses* can cause a clinical picture similar to that of acute pyelonephritis. Both ultrasound and computed tomography analyses are suitable for localization.

Prostatitis

Acute prostatitis is associated with high fever and chills. Dysuria, pollakisuria, nocturia, pain in the perineum, buttocks, and rectum are frequent. The prostate gland is painfully enlarged and bulgingly elastic. The most frequent pathogens are *E. coli* and other *Enterobacteriaceae*, as well as enterococci. In most cases they can be detected in the urine.

Chronic prostatitis causes mostly nonspecific symptoms without fever. The differential diagnosis to distinguish *prostatodynia* requires careful microbiological examinations (Meares and Stamey localization technique).

Fever and Sepsis

Systemic Inflammatory Response Syndrome (SIRS)

The systemic inflammatory response to various infectious and noninfectious causes is uniform and includes a broad differential diagnosis. Among the noninfectious causes of a systemic inflammatory response, burns, traumatic tissue injuries or surgery, and pancreatitis must be mentioned first.

Sepsis

Definition. The term *sepsis* describes the physiological consequences of a severe infection that is accompanied by the dissemination of microorganisms or their toxins (Tab. 4.**12**). The clinical and/or microbiological documentation of an infection is part of the sepsis definition.

Clinical Features. *Sepsis* is characterized by hypothermia (temperature $< 35.6\,^{\circ}C$) or fever (temperature $\geq 38.3\,^{\circ}C$), tachycardia (> 90/min), tachypnea (> 20/min), and clinical signs of infection. In addition to hypotension (< 90 mmHg or a reduction of 40 mmHg from the initial value), *severe* sepsis also occurs with the consequences of reduced perfusion affecting at least one organ, e. g., impaired consciousness, hypoxemia ($PO_2 < 75$ mmHg), elevated plasma lactate, or oliguria (≤ 30 ml/h despite fluid replacement).

In *septic shock* the hypoperfusion of organs additionally occurs. About one-quarter of the patients develop an acute, respiratory distress syndrome (ARDS) with bilateral pulmonary infiltrates, hypoxemia ($PO_2 < 70$ mmHg, $F_iO_2 > 0.4$), and a pulmonary capillary pressure of < 18 mmHg.

Table 4.**12** Clinical and laboratory findings in sepsis

Sepsis
Two or more symptoms (mandatory)
– hypothermia ($< 35.6\,^{\circ}C$) or fever ($> 38.3\,^{\circ}C$)
– tachycardia (> 90/min)
– tachypnea (> 20/min)
– leukocytes $> 12\,000$ or $< 4000\ \mu L$ *and* documented infection
Severe sepsis
Sepsis *and* organ dysfunction
– hypotension (blood pressure < 90 mmHg or decrease of > 40 mmHg) or
– organ hypoperfusion, including
– metabolic acidosis
– oliguria (< 30 ml/hour despite adequate fluid treatment), or
– acute alteration of consciousness
Septic shock
– hypotension (despite adequate fluid treatment) *and*
– hypoperfusion of organs
Laboratory findings
– leukocytosis or leukopenia
– thrombocytopenia
– hypoxaemia ($PO_2 < 75$ mmHg)
– lactic acidosis
– coagulopathy
– electrolyte imbalance
– hypophosphataemia
– positive blood cultures

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Bacteremia

Definition. The terms septicemia and bacteremia are synonymous and mean that bacteria can be detected in a patient's bloodstream.

Blood Cultures. The optimal diagnostic signifigance is provided by three aerobic and three anaerobic blood cultures, which, insofar as possible, should be drawn before an antibiotic therapy is initiated. This number generally also permits a differentiation between bacteremia and contamination microbes. The time of the rise in temperature and the time period one to two hours thereafter appear to be best suited for the blood draws. Currently, Gram-negative and Gram-positive pathogens are roughly, equally widespread. In approximately 10% of the cases several different, mainly Gram-negative microbes, anaerobes, or fungi are isolated (Tab. 4.**13**).

Table 4.**13** Pathogens frequently causing bacteremia

Gram-positive bacteria	Gram-negative bacteria
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus viridans* Enterococci β-hemolytic streptococci Pneumococci *Clostridium perfringens* *Streptococcus bovis*	*Escherichia coli* *Pseudomonas aeruginosa* *Klebsiella* species *Enterobacter* species *Serratia* species *Proteus* species (mostly *mirabilis*) *Bacteroides* species *Salmonella* species

Sources of Sepsis, Predisposition

For therapeutic reasons, it is important to look for the *portal of entry of the sepsis pathogens*, as it is quite likely that the possible pathogens can be deduced from this information. This makes it easier to administer an empirical antibiotic therapy until the bacteriological results become available:

- In approximately 50% of cases the sepsis originates from the urinary tract. Predisposing causes are urinary catheters, instrumentation, and obstruction.
- Less frequent sites of entry are the gastrointestinal tract and the bile ducts (diverticulitis, perforation, abscesses, obstruction by tumor or stone), respiratory tract (intubation, tracheotomy, artificial respiration), and skin (burns, surgical and other wounds).
- In women of childbearing age the *genitalia* (after childbirth, after abortion) are more frequently the source.
- To*nsillitis* or *otitis* can be a port of entry for bacteria.
- *Septicemic diseases* in connection with intravasal or *implanted foreign bodies* (also called *endoplastitis*) can be found in hemodialysis shunts, intravenous catheters, artificial heart valves, intravascular foreign bodies, intracardiac pacemaker electrodes, and alloplastic vascular and joint prostheses. Whenever possible they should be removed in case of infection.
- Among the various clinical pictures in internal medicine, *leukemias*, and *malignancies* (in particular under immunosuppressive or corticosteroid therapy), but also *cirrhosis* of the liver, *diabetes mellitus*, *uremia*, and *immunodeficiency syndrome* especially predispose a patient to develop infections. In these patients, but also during parenteral hyperalimentation, or in *venous catheters* (long duration), fungi (especially *Candida albicans*) are increasingly detected as the responsible pathogens. Recurrent or continuous bacteremia frequently leads to septic metastases. Certain associations exist between the type of pathogen and the location of colonization (Tab. 4.**14**).

Table 4.**14** Typical localization of septic emboli

Pathogen	Typical localization of septic emboli
Staphylococcus aureus	skin, brain, kidney, endocardium, lung, bone, liver, testicle
β-Hemolytic streptococci	skin, joints
Pneumococci	meninges, joints, endocardium, peritoneum
Enterococci and *Streptococcus viridans*	endocardium
Salmonella	bone, soft tissue (abscesses), meninges, pericardium, joints, arteries
Meningococci	meninges, skin, joints, bone, testicle, eye, endocardium, pericardium
Gonococci	skin, joints, endocardium, meninges
Haemophilus influenzae	meninges, lung, pleura
Bacteroides	lung, pleura, liver, brain
Listeria	meninges, eye, lung, pleura, peritoneum, arteries

Selected Sepsis Pathogens

Staphylococci. In deep skin or soft–tissue infections with staphylococci, bacteremia occurs in 20–30% of the cases. Bacteremias with *Staphylococcus aureus*, which occur outside of the hospital (community acquired) without a detectable primary source of infection, and lead to septic metastases, predispose patients to endocarditis in over 50% of the cases. Likewise, *nosocomial infections* with *Staphylococcus aureus* (e. g., catheter infections) are frequently associated with septic complications if they are not treated with intravenous antibiotics for a sufficiently long period of time.

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Recurrent staphylococcal infections in children indicate the presence of rare septic granulomatosus. In adults a syndrome with recurrent, staphylococcal abscesses and allergic rhinitis as a consequence of an intermittent disorder of granulocyte chemotaxis has been described. *Coagulase-negative staphylococci* almost exclusively cause postoperative infections, nosocomial bacteremias and endocarditis after valve replacement.

Toxic shock syndrome is characterized by high fever, vomiting, diarrhea, impaired consciousness, and a skin rash. Typical is scaling of the palms and soles of the feet after approximately one week. Untreated a rapidly progressive state of shock develops.

Streptococci and Enterococci. Originating from local foci of infection, *Streptococcus pyogenes* (*streptococci of group A*) can lead to invasive tissue infections (*necrotizing fasciitis*), bacteremia, sepsis, and puerperal sepsis.

A clinical picture is increasingly being observed which is called *streptococcal toxic shocklike syndrome* and exhibits a mortality rate of 30%. It most frequently affects immunocompetent adults 20–60 years of age. Usually after a minor trauma, a soft-tissue infection develops whose inflamed border, in contrast to erysipelas, is not sharply defined. Locally the soft tissues can rapidly necrotize. The patient's general state of health is poor and a fulminant course with shock, confusion, and multiorgan failure is characteristic.

Infections with *pneumococci* (*Streptococcus pneumoniae*) usually originate from the patient's own flora. They are frequently found in alcoholics, patients with an underlying cardiopulmonary disease, malignant lymphomas, HIV infection, and after splenectomy or influenza. Severe infections are frequently accompanied by bacteremia.

Invasive infections with *Streptococcus agalactiae* (*group B streptococci*) are the cause of neonatal sepsis and meningitis, puerperal sepsis, and bacteremias, as well as organ complications in immunocompromised or elderly persons.

The oral streptococci designated as the *viridans group* can pass into the bloodstream through lesions in the oral cavity and cause a transient bacteremia. They are the most frequent cause of endocarditis on natural valves. Septicemias with *Streptococcus milleri* are frequently associated with abscesses of the internal organs, the central nervous system, and endocarditis.

Enterococci. Enterococci usually exhibit minimal pathogenicity. Nevertheless, especially in severely ill or immunocompromised patients, they are also the cause of nosocomial infections.

Pseudomonas aeruginosa. *Pseudomonas aeruginosa* almost exclusively causes *nosocomial infections*:

- septicemia, rarely endocarditis and meningitis, after diagnostic and therapeutic interventions
- pneumonia and pulmonary abscesses, especially in leukemia, cystic fibrosis, intubated, or tracheotomized patients
- urinary tract infections and urosepsis in patients wearing indwelling catheters
- disseminated infections as a result of secondarily infected burns.

Enterobacteriaceae. *Escherichia coli* is the most frequently isolated microbe in urinary tract infections, Gram-negative septicemia, and infantile meningitis.

As natural inhabitants of the respiratory and intestinal tract, *Klebsiella* are pathogens which cause pneumonias (1–4% of pneumonias), upper respiratory infections, urinary tract infections, cholecystitis, and peritonitis. In immunocompromised patients *Klebsiella* septicemia can occur.

Proteus mirabilis and *P. vulgaris*, *Providencia rettgeri*, and *Morganella morganii* are normally found in the large intestine. In addition to urinary tract infections these pathogens have been found in abscesses with purulent wounds, as well as in meningitis and septicemia.

Enterobacter (various species), *Serratia*, *Citrobacter*, and *Providencia* are additional Gram-negative bacteria that in recent years, have achieved an increased significance as pathogens of nosocomial urinary tract infections and septicemia.

Gas Gangrene (*Clostridium perfringens* and Other Species). Especially in extensive, soft-tissue injuries and complex bone fractures, *Clostridia* can cause a rapidly progressive, extremely painful, phlegmonous local infection, which as a consequence of gas formation in the advanced stage, typically crackles when touched. In patients with malignant diseases (especially leukemias, lymphomas, and colon carcinomas) frequent clostridial septicemias with a fulminant course occur, without any prior trauma or operations. The bacteriological diagnosis is primarily based on the Gram stain as the result of the anaerobic culture usually arrives too late.

Bacteroides. The bacteria of the genus *Bacteroides* are anaerobic epiphytes of human hollow organs. Septicemias generally originate from the colon or female genital tract. Peritonsillar abscesses can cause a septic jugular vein thrombosis. Pneumonias and pulmonary abscesses distal to a bronchial stenosis are caused by aerobic and anaerobic bacteria in one-third of the cases. Anaerobes alone are found in approximately 25% of the cases. Infections below the diaphragm (subphrenic or hepatic abscesses, cholecystitis, appendicitis, diverticulitis, wound dehiscence after colon operations, or endometriosis) are predominantly caused by a mixed flora of anaerobes (usually *Bacteroides fragilis*) and *Enterobacteriaceae*. The bacteriological diagnosis requires aspiration or puncture material (not superficial smears!) and growth in anaerobic transport media.

Candida. An increasing *nosocomial complication* is the colonization of intravenous catheters with *Candida* that can lead to *candidal fungemia* and, if an appropriate predisposition exists, to the clinical picture of septicemia. Septicemic metastases are found particularly in the kidneys, the heart, and the meninges of children. The clini-

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cal picture is comparable to that of bacterial septicemia or endocarditis: (hepato-) splenomegaly, fever, reduced state of general health, leukocytosis, and anemia. Fungal endocarditis on valvular prostheses frequently occurs as a result of cerebral and peripheral embolisms, whereby, in contrast to the microembolisms in bacterial endocarditis, the large vessels are preferably affected.

Fever and Heart Defects

Endocarditis

Epidemiology. The clinical finding of a heart defect (*congenital* 7–16%, *postrheumatic* 20–40%) must in each incidence of fever arouse the suspicion of infectious endocarditis. However, pathological, anatomical studies indicate that in up to 50% of the cases endocarditis is present in normal or *degeneratively* altered valves. The mitral valve is most often affected, followed by the aortic valve. Incidents of endocarditis affecting the right heart are observed in less than 10% of the cases (especially in intravenous drug abuse).

Postoperative endocarditis after heart operations, especially after using a heart–lung machine, endocarditis on *artificial valves*, and endocarditis in *intravenous drug users* have increased in significance during recent years.

Clinical Features and Course. *Acute* endocarditis is rare. *Insidious* courses are more frequent. A general feeling of malaise, ill-defined limb pain, subfebrile temperatures, and night sweats are the earliest symptoms. Initially chills are unusual. They occur more frequently later in the course of the disease.

Noninfectious endocarditis (Libman–Sacks syndrome in systemic lupus erythematosus, rheumatic fever, carcinoid syndrome) occurs without chills.

> The alteration in the character of the heart murmur is of decisive, diagnostic significance in auscultation.

Splenomegaly is particularly found in about 30% of advanced cases. *Septic microembolisms* are of pathognomonic significance (approximately 30% of the cases), which are predominantly located on the fingers and toes (Osler nodes), palms and soles of the feet (Janeway lesions), but also in the conjunctivae or subungually (Fig. 4.**15**). Microembolisms can still develop during an adequate antibiotic therapy. Larger embolisms also can cause cerebral deficits. Therefore, it is always necessary to consider infectious endocarditis in younger patients experiencing a febrile apoplectic stroke.

Cardinal Symptoms. The most important *clinical symptoms* of endocarditis are:

- fever
- chills
- pathological heart auscultation findings
- microembolisms
- renal finding
- splenomegaly.

Pathogens. *Etiologically*, streptococci and staphylococci remain the most frequent *pathogens causing endocarditis* (Tab. 4.**15**).

In endocarditis which occurs on artificial heart valves an early form is distinguished which develops six to eight weeks after surgery and is most frequently caused by *Staphylococcus epidermidis*, *Staphylococcus aureus*, or Gram-negative nosocomial pathogens. In contrast, the late form exhibits a bacterial spectrum comparable to that of endocarditis on natural valves.

The most frequent cause of *negative blood cultures* in endocarditis is prior antibiotic therapy. Special culture media and long incubation times are required to detect pathogens of the *HACEK group* (*Haemophilus* species, *Actinobacillus* species, *Cardiobacterium* species, *Eikenella* species, and *Kingella* species) as well as *Brucella*. Rare endocarditis pathogens are *Legionella*, *Coxiella burnetii* (Q fever), *Chlamydia*, and *Bartonella* (earlier *Rochalimaea* species), which can only be diagnosed serologically.

Colon carcinomas have frequently been observed in patients with *Streptococcus bovis* sepsis. In sterile endocarditis and joint pain, Whipple disease must be

Fig. 4.**15** Osler nodes in a patient with endocarditis due to *Staphylococcus aureus*.

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Table 4.**15** Prevalence (per cent) of pathogens causing infectious endocarditis (summary of various data)

Pathogen	Native valves	Prosthetic valves (onset after surgery)	
		< 8 weeks	> 8 weeks
Streptococci	60–80	11	35
– *Streptococcus viridans*	30–40	3	20
– Enterococci	5–20	5	10
– Other streptococci	15–25	3	5
Staphylococci	20–35	50	40
– *S. aureus*	10–30	20	15
– *S. epidermidis* and other	1–5	30	25
Gram-negative bacteria	< 1–2	20	10
Fungi	2–4	13	5
Polymicrobial	1–2	–	–
Other pathogens	2–5	10	10
Culture negative	< 5–25		

considered in the differential diagnosis. The pathogen, *Tropheryma whippelii*, has been detected in valve material by molecular genetic methods.

In fungal endocarditis (drug addicts and after valve replacement), blood cultures usually remain sterile. If an appropriate clinical suspicion exists, the microbiological laboratory must be informed of the tentative diagnosis.

Diagnosis. As in sepsis, *blood cultures* are of decisive importance in making the diagnosis. Although the sensitivity of transesophageal (endoscopic) echocardiography is significantly better than that of the transthoracic examination, echocardiography cannot exclude endocarditis with certainty. The detection of persistent outgrowths on the aortic or mitral valve or a subvalvular abscess in echocardiography is diagnostically and prognostically significant and supports the indication for surgical valve replacement.

The blood cell count, with a moderate leukocytosis and a distinct left shift, is usually toxically altered. Focal glomerulonephritis occurs in approximately 50% of endocarditis cases and is characterized by erythrocyturia, cylindruria, and proteinuria.

Other Endovascular Infections

In addition to infections of intravenous and intraarterial catheters, or infections of endovascular grafts, mycotic aneurysms or septic thrombophlebitis can lead to fever without a clinically manifest focus. Essential to the diagnosis are blood cultures, which must be drawn before antibiotics are administered.

Mycotic Aneurysms. This is *not* a fungal infection of the artery, but a usually bacterially infected aneurysm which can occur along the entire aorta or other arterial vessels. The infection of arteries, often previously damaged by atherosclerosis or trauma, leads to an inflammatory weakening of the arterial wall and consecutively to an aneurysmatic dilation of the artery, which can rupture. The aneurysm acts as a disseminating bacterial focus which results in continuous bacteremia. It cannot be eliminated solely by antibiotic therapy. Therefore, surgery should be performed as soon as possible.

Septic Thrombophlebitis. Trauma, implanted foreign bodies (intravenous catheters), or inflammation near blood vessels (e. g., infections near the paranasal sinus) can cause inflammation of the venous wall, thrombus formation, and subsequently bacterial colonization of the thrombi with severe septic clinical pictures. Frequently affected are superficial veins, the subclavian vein, pelvic veins, the intracranial cavernous sinus, or the portal vein (pyelophlebitis).

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4.4 Fever with Multiple Organ Involvement

Viral Diseases

Many viral infections are associated with specific organ diseases and are discussed in the previous section. However, viral diseases often occur with markedly severe, nonspecific, vegetative symptoms such as general exhaustion, vomiting, loss of appetite, or occasionally predominant arthralgia and myalgia. Particularly in hepatitis, nonspecific joint pain often can precede the onset of the disease by several days, and thereby, become the leading symptom.

Diagnosis. Viral infections cause nonpurulent inflammation. The blood count can be the clue for differential diagnosis. It shows a normal leukocyte count or no more than a slight leukocytosis. The left shift, indicative of an increase in immature leukocytes, is not well developed. Likewise, the toxic changes of the neutrophils are very minimal, insofar as there is no contributing bacterial superinfection. Many viral diseases are accompanied by a *lymphocytic reaction*, which is most highly developed in *mononucleosis*. A distinct lymphocytosis is also frequently found in measles, rubella, mumps, roseola, hepatitis, and cytomegalovirus infection.

In many viral diseases *serological tests* play an important role in the diagnosis. Virus isolation or *molecular genetic detection* is often not possible or available.

Cytomegalovirus Infection

Clinical Features. With the exception of the congenital form and the infection during childhood, cytomegalovirus can cause a mononucleosis-like clinical picture with fever, hepatosplenomegaly, and pathological hepatic functions in adults without any pre-existing illnesses. The nervous system can be affected by polyradiculoneuropathy, encephalitis, or retinitis.

Diagnosis. The diagnosis is made by serology or by means of antigenic or molecular genetic detection of the virus. The rate of endemic infection is high (IgG detection in 40–50% of the population). The detection of IgM antibodies indicates a fresh infection. However, in immunosuppressed individuals with an acute infection or reactivation of a latent infection, IgM antibodies are almost never found.

Tickborne Infections

Infections transmitted by tick bites occur in specific geographic regions. The diseases include:

- Lyme borreliosis
- tickborne encephalitis (European, Russian, spring–summer meningoencephalitis, louping ill)
- other arbovirus infections (Colorado tick fever virus, Crimean–Congo virus, and others, see Tab. 4.**10**)
- rickettsioses (Mediterranean, African, Indian, and Australian spotted fever, Rocky Mountain spotted fever, see Tab. 4.**5**)
- ehrlichiosis
- babesiosis
- tularemia
- other tickborne febrile diseases caused by relapsing feverlike spirochetes: *Borrelia hispanica* and other *Borrelia species* (Spain, North Africa), *B. lonestari* (North America: *Southern tick-associated rash illness* (STARI)), *B. hermsii* and other *Borrelia* species (North, Central and South America), *B. duttonii* (Africa), *B. persica* (Middle and Near East). In contrast, relapsing fever caused by *B. recurrentis* (Asia, Ethiopia, Central Africa, South America) is transmitted by lice.

Lyme Disease

Lyme disease is caused by spirochetes (*Borrelia burgdorferi* [USA], *B. garinii, B. afzelii* [Eurasia]), which are transmitted by a tick bite (*Ixodes* species).

Clinical Features. The clinical picture begins to develop days to months (median seven days) after the tick bite with an *erythema migrans* (previously, erythema chronicum migrans) which can be accompanied by nonspecific general symptoms with fever (more frequently in the USA and less so in Europe). Weeks to months, or even years, later *neurological*, *cardiac*, *or arthritic complications* can occur (Tab. 4.**16**).

In contrast to the early neurological symptoms (early neuroborreliosis with meningitis, cranial neuropathy, or radiculoneuropathy) which are observed at the same time as or directly after the erythema migrans, the so-called, late neuroborreliosis occurs after months to years in about 15% of the patients. The clinical manifestations include encephalopathy, radiculoneuropathy, encephalomyelitis, transverse myelitis, or an inflammatory myopathy. Arrhythmias, as a result of atrioventricular block or myopericarditis, indicate *cardiac*

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Table 4.**16** Clinical manifestations and diagnosis of Lyme borreliosis

Stage	Time since tick bite	Clinical manifestations	Diagnosis
Erythema migrans	3–32 days (median: 7–10 days)	Expanding red or bluish-red patch, often with central clearing, advancing edge typically distinct, often intensely coloured	No specific laboratory findings Lyme serology negative
Acrodermatitis chronica atrophicans	6 months to years	Long-standing red or bluish-red lesions, initially doughy swelling, eventually becoming atrophic	High specific IgG antibody titers
Early neuroborreliosis	weeks to months	Meningitis, painful meningo-radiculoneuritis, with or without facial palsy or other cranial neuritis	Lymphocytic pleocytosis in cerebrospinal fluid Intrathecal specific antibody production may be missing in early disease
Late neuroborreliosis	months to years (mostly 2–3 years)	Encephalitis, encephalomyelitis, meningoencephalitis, radiculomyelitis	Intrathecally produced specific antibodies Specific serum IgG antibodies
Lyme arthritis	2 weeks to 2 years (median: 4–6 months)	Recurrent brief attacks of objective joint swelling in one or a few large joints, occasionally progressing to chronic arthritis	Significant increase of specific IgG antibodies (early arthritis) High specific IgG titers (late arthritis)
Lyme carditis	4 days to 7 months (median: 21 days)	Acute onset of atrio-ventricular conduction disturbances, rarely myocarditis or pancarditis	Significant increase of specific IgG antibodies

involvement, which is observed in nearly 10% of the cases. After a few months up to two years, it is possible for recurrent *monoarthritis or polyarthritis* to develop in up to 60% of the cases. This affects both the large and small joints.

Diagnosis. With regard to sensitivity and specificity, the detection of antibodies against *Borrelia burgdorferi* still remains problematic. Positive results of the serological screening test must be verified with the immunoblot method. Diagnosis of the late neuroborreliosis is based on the detection of intrathecal antibody formation which is confirmed by examining the CSF. In early neuroborreliosis the CSF exhibits a lymphocytic pleocytosis. The direct detection of these pathogens by polymerase chain reaction (PCR) amplification of DNA has only proven useful in the diagnosis of Lyme arthritis (detection in synovial biopsy or synovial fluid).

Ehrlichiosis

Ehrlichia are obligate intraleukocytic bacteria which are transmitted by ticks. The *Ehrlichia*, which are pathogenic to humans, attack either monocytes (*Ehrlichia chaffeensis*, transmitted by *Amblyomma americanum* in the USA) or neutrophilic granulocytes (*human granulocytic Ehrlichia* [pathogen: *Anaplasma phagocytophilum*], transmitted by *Ixodes* species in the USA and Europe).

Clinical Features. An infection with both *Ehrlichia* species leads to identical clinical manifestations, with fever, headaches, malaise, muscle pain, shivering, sweating, nausea, and vomiting. Cough, joint pain, neurological symptoms, and, rarely, a disseminated maculopapular exanthema occur less frequently. Life-threatening complications occur rarely (pneumonitis, renal failure, disseminated intravasal clotting, seizures, coma). In contrast, many *Ehrlichia* infections probably follow an asymptomatic course. Simultaneous double infections with Lyme disease agents *Borrelia* and *Ehrlichia* have been described. Frequently occurring laboratory findings are thrombocytopenia, leukopenia, and slightly elevated transaminase levels.

Diagnosis. *Ehrlichia* can occasionally be seen under the light microscope as inclusion bodies (morula) in leukocytes (Fig. 4.**16**). The infection is diagnosed primarily by serological and molecular genetic methods. A serological cross-reaction between human granulocytic ehrlichiosis and *Ehrlichia chaffeensis* does not exist.

Babesiosis

Babesia microti and *Babesia divergens* are protozoa that multiply within the erythrocytes.

Clinical Features. The occasionally severe clinical manifestations include fever, shivering, myalgia, fatigue, and jaundice as a consequence of hemolytic anemia. Furthermore, many infections probably follow an asymptomatic course.

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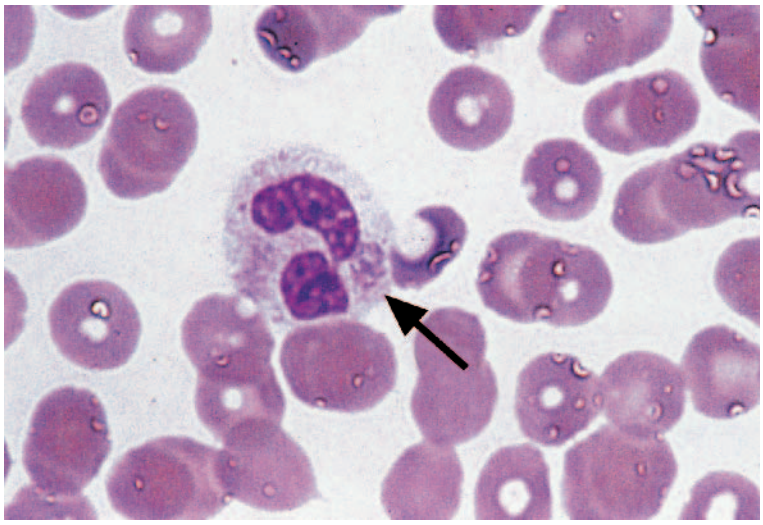

Fig. 4.**16** Human granulocytic ehrlichiosis: Morula within a granulocyte (arrow).

Diagnosis. The diagnosis can be made by visualizing the parasites in the blood with the light microscope, detecting the antibody serologically, or verifying the parasite with molecular genetic methods. The intra-erythrocytic forms of *Babesia* can be confused morphologically with malaria.

Sexually Transmitted Infections

In sexually transmitted infections, it is primarily the local symptoms in the genital area, and possibly the regional lymphadenopathy, that predominate. Extragenital manifestations can occur in gonorrhea (arthritis–dermatitis syndrome, perihepatitis), syphilis, and chlamydial infections.

Syphilis (*Treponema pallidum*)

Transmission. Syphilis is virtually only transmitted by sexual contact and rarely undergoes diaplacental transmission.

Laboratory Diagnosis of Syphilis

Treponema pallidum cannot be cultured. The *direct detection of pathogenic organisms* can be undertaken by means of dark-field microscopy or direct immunofluorescence microscopy of the extract of the primary ulcer, mucous membrane lesions, or lymph node punctures, but it is not sensitive and can only be performed in specialized laboratories. The diagnosis of syphilis is, in particular, based on *serological* methods. Two groups of tests are available for this purpose (Figs. 4.**17**, 4.**18**).

Nonspecific Tests. These tests detect reagins which do not, or only partially, originate from *Treponema*, e. g., VDRL test (Venereal Disease Research Laboratory) or RPR test (Rapid Plasma Reagin). They become reactive no sooner than five weeks after infection, and after therapy, they once again become negative within one year. However, they can also become negative without therapy or despite adequate treatment can remain reactive at a low titer level. Overall, their titer level correlates well with the syphilis activity (follow up), but are not sufficient to make the diagnosis, because they frequently give false-positive results (granulomatosis, collagenosis, infectious diseases, tumors, pregnancy).

Specific Tests. These tests detect components of *Treponema pallidum*. The TPHA (*Treponema pallidum* hemagglutination assay) has a very high specificity. It is used as a routine screening test, often in combination with the nonspecific VDRL. In case of a positive result of one of these tests, the FTA-Abs test (Fluorescent Treponemal Antibody Absorption Test) is performed as a control. Both the TPHA and the FTA-Abs test become reactive approximately 4 weeks after infection and mainly detect IgG antibodies. Since after successful therapy both tests usually remain reactive until death (serological scar), the *T. pallidum*-specific 19S IgM antibody detection test (19S IgM FTA-Abs, CAPTIA Syphilis-M™) is used to determine the current status of the disease and to monitor the course of therapy. These can become active three weeks after infection and cannot pass through the placenta. Therefore, they can confirm the presence of congenital syphilis.

Neurosyphilis. The diagnosis of neurosyphilis requires a positive syphilis reaction in the CSF as well as pathological CSF findings and/or neurological symptoms. In an untreated case of syphilis which has lasted for more than one year or in the presence of a simultaneous HIV infection, a CSF examination is indicated.

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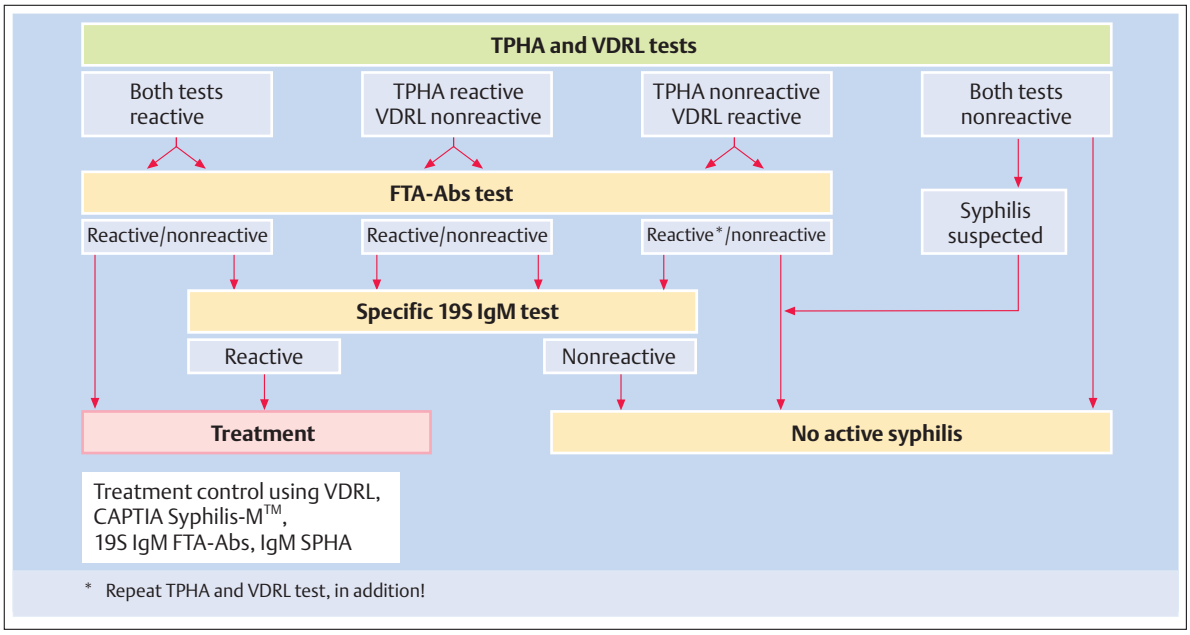

Fig. 4.**17** Flow chart in the evaluation of syphilis.

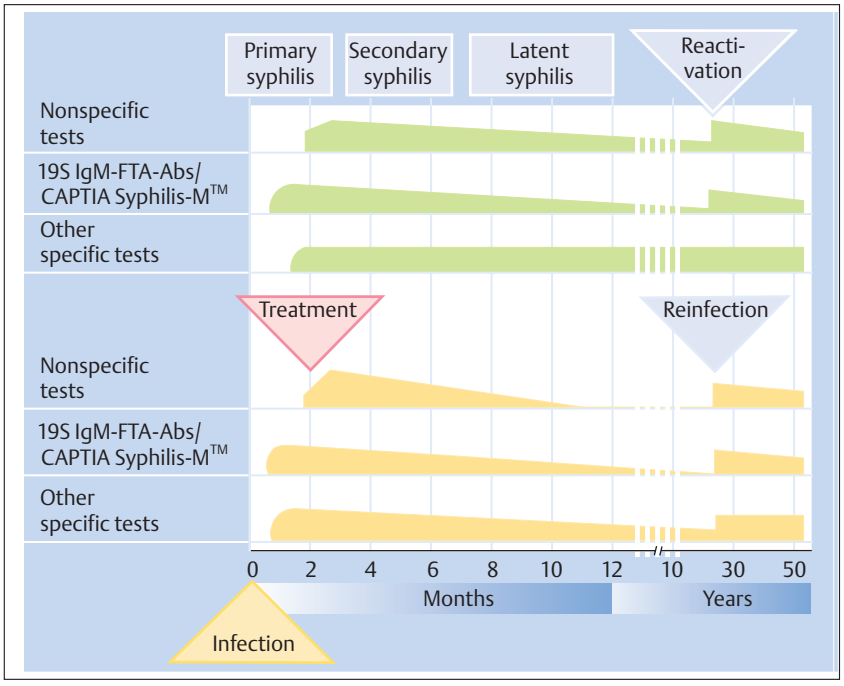

Fig. 4.**18** Serologic test results in syphilis in relation to disease stage.

Clinical Features. About three weeks after infection, a primary lesion develops (*primary syphilis*). It is seen as a coarse, nonpainful lesion at the point of entry with corresponding lymphadenopathy (primary complex). It always heals, even without therapy.

After about eight weeks the bacteremic phase begins (*secondary syphilis*) with mild general symptoms (headaches, arthralgia, possibly fever), generalized lymphadenopathy, and a recurrent, nonpruritic exanthema. This rash can become papular and typically affects the palms and soles of the feet. The flat condylomas, which contain many *Treponema*, form at moist skin locations. Additional manifestations are mucous plaques of the oral mucosa, alopecia areolata, and syphilitic leukoderma (depigmented location on the neck).

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The asymptomatic condition after the spontaneous disappearance of secondary syphilis signs is called *latent syphilis*. In about 30–50% of cases syphilis heals spontaneously and the nonspecific seroreactions as well as the *Treponema pallidum*-specific 19S IgM detection tests become negative. Without treatment an additional one-third of the patients exhibit positive seroreactions, but clinical symptoms no longer occur.

In the remaining untreated patients a latency period of up to 20 years is followed by a transition to *tertiary syphilis*. If an HIV infection is also present, the disease can follow a significantly more rapid course. The typical gummas (granulation tumors) are no longer contagious and can develop in all tissues of the body. Other organ manifestations are myocarditis, mesoaortitis, and *neurosyphilis*. Neurosyphilis includes cerebrospinal syphilis (meningoencephalitis, cerebral vasculitis), tabes dorsalis (calf pain, ataxia, rigidity of the pupil to light), and progressive paralysis (articulation disorders, epileptic seizures, personality changes).

Congenital Syphilis. *Congenital syphilis* is transmitted diaplacentally from the fifth month of pregnancy by a syphilitic mother.

Chlamydia trachomatis

Chlamydia trachomatis is a widespread pathogen that causes venereal diseases.

Clinical Features. In the temperate regions, urethritis, epididymitis, prostatitis, proctitis, cervicitis, salpingitis, perihepatitis, and peritonitis in women are the typical clinical manifestations. *Lymphogranuloma venereum*, which is characterized by a massive abscess-forming inguinal lymphadenitis, mainly occurs in Southeast Asia, Central and South America.

In Africa, the Middle East, and Southeast Asia, *Chlamydia trachomatis* is the pathogen that causes a chronic conjunctivitis (*trachoma*), and is the most frequent cause of preventable blindness. Newborn children infected during childbirth can develop conjunctivitis or pneumonia.

Diagnosis. The *diagnosis* is made using immunofluorescence techniques, direct molecular genetic detection of the pathogen, or by the serological detection of antibodies.

Zoonosis

A classification of the zoonosis based on the mode of transmission of the microorganisms can prove useful from the perspective of the differential diagnosis (and prevention):

- *Animal bites or scratches:* infections caused by *Capnocytophaga*, pasteurellosis (*Pasteurella multocida*), cat scratch disease (*Bartonella henselae*), rat-bite fever (*Streptobacillus moniliformis, Spirillum minus*), tularemia, plague, rabies, and lymphocytic choriomeningitis virus.
- *Direct contact with animal excretions:* anthrax, brucellosis, tularemia, Q fever, pasteurellosis, leptospirosis, *Mycobacterium marinum* infection, plague, herpes B virus, vesicular stomatitis virus, *Orthopoxvirus* (*Monkeypox, Cowpoxvirus*), *Parapoxvirus* (milker nodule virus, Orf virus), newly discovered paramyxoviruses in Southeast Asia and Australia (Hendra, Nipah, Menangle virus), as well as the Marburg and Ebola virus.
- *Fecal–oral transmission:* bacterial (*Campylobacter*, *Salmonella*) and parasitic (*Cryptosporidia*) pathogens that cause diarrhea, *Toxocara canis*, *Echinococcus* species, *Toxoplasma gondii*, and *Baylisascaris procyonis*.
- *Consumption of meat or animal products:* bacterial (*Campylobacter jejuni*, nontyphoid *Salmonella*, enterohemorrhagic *E. coli*) and parasitic (*Cryptosporidia*) pathogens which cause diarrhea, brucellosis, anthrax, tularemia, listeriosis, tropical helminths, and *Toxoplasma gondii*.
- *Aerogenic transmission:* anthrax, Q fever, plague, *Rhodococcus equi* infection, psittacosis, tularemia, brucellosis, pasteurellosis, rabies, influenza, lymphocytic choriomeningitis virus, various hantaviruses (Tab. 4.**7**).
- Transmission by *ticks, mosquitoes*, or other *insects*.

Brucellosis (*Brucella melitensis, B. abortus, B. suis*)

Transmission. The transmission of *Brucella* occurs directly from infected animals (goats, cattle, cows, pigs, sheep, etc.) or via their products (nonpasteurized milk and cheese products) to humans. Veterinarians and occupations engaged in the processing of milk and meat are especially at risk. Portals of entry are the respiratory and the gastrointestinal tract, as well as via skin injuries.

Clinical Features. The incubation time of five to 60 days is extremely variable. The onset of the disease can be acute or insidious. Fever of varying duration, headaches, weakness, sweats, chills, arthralgia, weight loss, and depression are observed. Rare complications are spondylitis (Fig 4.**19**) or arthritis. Splenomegaly, lymphadenopathy, or rarely hepatomegaly is found in approximately 10% of the cases. Septic metastases occur in all organ systems.

Diagnosis. Diagnosis is made by blood and bone-marrow cultures, especially in the acute phase, or by the specific detection of IgG in chronic forms.

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Fig. 4.**19** Spondylitis due to brucellosis with bone destruction and narrowing of intervertebral disk space.

Leptospirosis (*Leptospira interrogans* [Weil disease] and other serotypes)

Transmission. Leptospiroses are highly febrile, acute, infectious diseases with a *two-phase course*. The pathogen reservoir is formed by small rodents (rats, mice), domesticated animals (dogs, horses, pigs, cattle) and wild animals. Transmission occurs by direct and indirect contact with animals excreting *Leptospira* through the intact skin or mucous membrane. The most common diseases occur in late summer and fall. Sewage workers, butchers, animal breeders, and rice field workers are particularly at risk. A great number of bathing epidemics (water contaminated with the urine of infected rats) have also been described.

Clinical Features. The incubation period is seven to 12 days. The clinical picture of the *first leptospiremic phase* is characterized by an acute rise in temperature, frequently with chills, high fever for four to seven days, headaches, neck stiffness, severe myalgia (especially in the calves), conjunctivitis, episcleritis, transient exanthemas, hypotension, and relative bradycardia. After a brief, possibly afebrile interval, the disease transitions to the *phase of organ manifestation*. Depending on the serotype and virulence of the *Leptospira* and additional unknown factors, fever, jaundice, hemorrhagic diathesis, meningitis, nephritis with oliguria to anuria, and iridocyclitis occur in varying degrees.

Diagnosis. During the first week of the illness, *Leptospira* can be detected in the blood, CSF, or urine. Beginning in the second week of the disease, it is possible to serologically detect type-specific antibodies against *Leptospira*.

Toxoplasmosis (*Toxoplasma gondii*)

Transmission. Toxoplasmosis is a zoonosis found throughout the world. The most important sources of infection are cat feces contaminated with oocysts and raw or inadequately cooked meat.

Clinical Features. Both the congenital and the acquired form usually take an asymptomatic clinical course. In immunocompetent individuals an indication for therapy is given exclusively in chorioretinitis as well as the acute infection during pregnancy. Lymph node toxoplasmosis, which can be accompanied by general symptoms, occurs most frequently. The *Toxoplasma* oocysts can settle in all organs. However, the brain, chorioretina, and the musculature are preferred locations. In HIV-infected patients with advanced immunodeficiency it is possible for a reactivation in the central nervous system to occur. Chorioretinitis and the disseminated infection occur rarely.

Diagnosis. The diagnosis is mainly based on the serological detection of antibodies. In HIV-infected patients with clinically manifest toxoplasmosis IgM antibodies characteristically cannot be found.

Trichinosis (*Trichinella spiralis*)

Clinical Features. Despite a clear decline, due to meat inspection, trichinosis is the most widespread helminthic disease, which is accompanied by fever. The initial symptoms, diarrhea, vomiting, abdominal pain, are typically noticed after ingesting uncooked infected pork (frequently small epidemics). After one week, fever, muscle pain, and possibly facial edema, occur. The diaphragm, chest, arm, and leg muscles are most frequently affected.

Diagnosis. During the invasive phase of the *Trichinella* larvae into the musculature, a high-grade eosinophilia is present. The diagnosis can be made by detecting *Trichinella* in muscle biopsies taken from an especially painful location (crush preparation), or by serology.

Toxocara Infection

A rare disease which mainly occurs in children (via intimate animal contact) is the infestation with larvae of dog or cat ascarids (*Toxocara canis* or *T. cati*). The most frequent symptoms are a reduced state of general health, intermittent fever, cough, hepatosplenomegaly, muscle and joint pain. Choroiditis and iritis are occasionally observed. Useful laboratory findings are the often high grade eosinophilia, leukocytosis, and notably elevated IgG, IgM, and IgE values. Additionally, serological tests for antibody detection are available.

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Rabies (Rhabdoviruses)

Transmission. After an incubation period of about one to three months, the bite of a rabid animal can cause a nearly always fatal disease. In principle all infected domestic and wild animals can transmit rabies. However, the most frequent sources are dogs, cats, and foxes, but also martens, raccoons, badgers, squirrels, deer, cattle, as well as bats in Spain and America. If possible, the animal should be caught and shipped to a specially equipped laboratory (rabies antibody fluorescence test, virus isolation in cell cultures or mice) for examination.

Clinical Features. The clinical symptoms begin with a nonspecific prodromal phase which lasts two to four days (fever, headache, loss of appetite, dysphagia, hoarseness). A characteristic initial symptom (more than 80% of the cases) is *paresthesia* in the region of the (usually healed) bite.

The *excitation* phase is characterized by alternating mental and vegetative symptoms. Cranial nerve paralysis first expresses itself in eye movements and pupil reactions. In this phase, tonic spasms while swallowing also occur (therefore, the name *hydrophobia*). The involvement of the respiratory musculature can lead to choking fits. Insofar as death does not occur during one of these spasms, a third paralytic phase with coma and circulatory collapse follows.

Diagnosis. During the clinically manifest disease, an attempt can be made to detect the virus by examining an corneal impression smear or a skin biopsy (back of the neck or hairline) by means of a fluorescent antibody test.

Other Infections Caused by Animal Bites

Pasteurellosis (*Pasteurella multocida*). The infection in humans normally occurs within 24 hours after a dog or cat bite. Severe local cellulitis and lymphadenitis develops. Septic complications are possible. Especially in the elderly, it is possible for subacute to chronic infections of the respiratory tract to develop.

***Capnocytophaga canimorsus* (CDC group DF-2).** Up to five days after a bite, and especially in immunocompromised persons, a severe, life-threatening disease develops with cellulitis, fever, sepsis, meningitis, endocarditis, or septic arthritis. Predisposing factors are splenectomy, chronic pulmonary disease, and alcoholism. The pathogen is found in the oral cavity of healthy dogs and cats.

Infections by Arboviruses

Arbovirus infections (**ar**thropod-**bo**rne viruses) cause four groups of diseases:

Febrile Arbovirus Diseases. Most of the arbovirus infections observed in Europe are asymptomatic. If symptoms should develop, they are usually associated with benign, uncharacteristic, febrile illnesses which are accompanied by muscle and joint pain. For example, these include West Nile fever (with skin rash), pappataci fever (with conjunctivitis), and the Tahyna virus infection (with catarrhal symptoms, possibly bronchopneumonia).

Acute Arbovirus Infections of the Central Nervous System. These infections become manifest with differing severity and range from mild aseptic meningitis to severe encephalitis with potentially permanent neurological deficits, coma, or death. This group includes:

- viruses transmitted by *ticks* (e.g., spring–summer meningoencephalitis virus) (see Tab. 4.**10**)
- viruses transmitted by *mosquitos* (see Tab. 4.**10**).

Hemorrhagic Fever. This group includes infection by the Crimean–Congo virus, dengue fever, and yellow fever (see Tab. 4.**7**).

Polyarthritis and Exanthema after Arbovirus Infection. The arthritis occurs with or without fever and is of variable duration. Examples of such diseases are infections with the Sindbis virus (Africa, Asia, Australia), Ross River, and Barma Forest virus (Australia), or the Chikungunya virus (Africa, India and Southeast Asia).

HIV Infection and AIDS

Pathogen. AIDS (acquired immunodeficiency syndrome) is a disease that was first described in 1981 and is caused by HIV-1 and HIV-2 (human immunodeficiency viruses 1 and 2). These retroviruses of the genus *Lentivirus* are lymphoneurotropic viruses.

Transmission. HIV is transmitted either sexually, through parenteral contacts with blood or blood products, during childbirth, peripartally, or via breast milk.

Acute HIV Infection

Clinical Features. A primary infection can follow an asymptomatic course or be accompanied by clinical manifestations (Tab. 4.**17**). Typical is a febrile, partially mononucleosis-like, clinical picture with a maculopapular exanthema primarily on the trunk and with small aphthous lesions on the oral and genital mucosa. The differential diagnosis must first exclude an infection

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Table 4.**17** Clinical manifestations of primary HIV infection

Mononucleosis-like manifestations	Neurologic manifestations	Dermatologic manifestations
Fever Pharyngitis Lymphadenopaty Arthralgias, myalgias Headache, retroorbital pain Lethargy, malaise Anorexia, weight loss Diarrhea	Meningitis Encephalitis Peripheral neuropathy Radiculopathy Brachial neuritis Guillain–Barré syndrome Cognitive and affective disorders	Erythematous or maculopapulous exanthema Rubella-like rash Diffuse urticarial rash Desquamation Alopecia Palatinal, gingival, or genital ulcers

with herpesviruses, toxoplasmosis, syphilis, a disseminated gonococcal infection, and allergic reactions to medications.

Diagnosis. In a symptomatic, primary infection tests for the HIV p24 antigen or quantitative PCR for the molecular genetic detection of HIV are often found to be positive.

> The tentative diagnosis of a primary HIV infection cannot usually be excluded until three months have elapsed and the seroconversion of HIV antibody titers has failed to occur.

Asymptomatic HIV Infection

The majority of those infected remain asymptomatic for several years. Some individuals exhibit a prognostically insignificant, generalized lymphadenopathy. In over 95% of untreated individuals infected with HIV the process of continuous and extensive HIV replication occurs (even during the asymptomatic phase) and a progressive immunodeficiency, with a reduction of the CD4 lymphocytes, develops.

Symptomatic HIV Infection, AIDS

Clinical Features. Immunodeficiency usually becomes manifest after a period of years through the occurrence of nonlife-threatening, opportunistic diseases such as candidal stomatitis or oral leukoplakia (Figs. 4.**20**, 4.**21**).

At 10–11 years after the primary infection, 50% of untreated, infected individuals become ill with AIDS-defining, opportunistic infections and malignancies (Tab. 4.**18**, 4.**19**; Figs. 4.**22**–4.**24**). Neurological and neuropsychiatric clinical pictures are observed with greater frequency as the duration of the disease increases.

Questions in the medical history about risk factors (unprotected heterosexual and homosexual contacts, information about exchanging syringes or needles, blood transfusions before 1985, hemophilia) frequently permit the likelihood of an HIV infection to be estimated, and thereby allow the interpretation of clinical pictures in the differential diagnosis as primarily a manifestation of an opportunistic infection.

Diagnosis. The diagnostic confirmation of an HIV infection occurs serologically and by means of molecular genetic methods. To estimate the extent of the immuno-

Fig. 4.**20** Candidal stomatitis in HIV infection.

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Fig. 4.**21** Oral hairy leukoplakia in HIV infection.

Table 4.**18** HIV-associated diseases (classification according to the US Center for Disease Control [CDC] and World Health Organization [WHO], 1993).

Clinical stage		
A	**B**	**C (AIDS)**
– HIV primary infection – Asymptomatic HIV infection – Lymphadenopathy syndrome	Infectious diseases – aspergillosis – *Bartonella henselae* infection (bacillary angiomatosis, peliosis hepatis, bacteraemia) – *Candida* infections (stomatitis, vulvovaginal) – herpes zoster, multisegmental – leishmaniosis, visceral – listeriosis – microsporidiosis – nocardiosis – oral hairy leukoplakia (Epstein–Barr virus) – pelvic inflammatory syndrome – progressive outer retinal necrosis syndrome – rhodoccocus equi infection – strongyloidiasis, extraintestinal Other – cervical dysplasia, carcinoma in situ – constitutional symptoms: weight loss > 10 %, or fever > 1 month, or diarrhea > 1 month (of unknown etiology) – Hodgkin disease – myelopathy, HIV-associated – neuropathy, peripheral, HIV-associated – pneumopathy, lymphoid interstitial – pulmonary hypertension, primary, HIV-associated – thrombocytopenia, HIV-associated	Infectious diseases – candidal esophagitis – coccidioidomycosis, disseminated – cryptococcosis, meningitis, disseminated – cryptosporidial infection (persistent diarrhea > 1 month) – cytomegalovirus infection (except liver, spleen, and lymph node infection) – herpes simplex infections (persistent skin or mucosal ulcers of > 1 month duration, or bronchial, pulmonry, or esophageal infection) – histoplasmosis, disseminated – *Isospora belli* infection (persistent diarrhea > 1 month) – leukoencephalopathy, progressive multifocal (PML) – *Mycobacterium tuberculosis* infection – nontuberculous mycobacteriosis, disseminated – *Pneumocystis carinii* pneumonia – pneumonia, recurrent (≥ 2 episodes per year) – *Salmonella* septicaemia, recurrent – toxoplasmosis, cerebral Neoplasms – cervical carcinoma, invasive – Kaposi sarcoma – non-Hodgkin lymphoma – primary cerebral lymphoma Other – encephalopathy, HIV-associated (AIDS dementia complex) – wasting syndrome
Laboratory stage (CD4 cell count)		
1	**2**	**3**
> 500/μl	200–500/μl	< 200/μl

Prerequisite for classification is a confirmed HIV infection.
CDC classification: A1, A2, A3, B1, B2, B3, C1, C2, C3 (examples: asymptomatic HIV-infected person with a CD4 cell count of 523/μl = CDC stage A1; HIV-infected patient with candidal stomatitis and a CD4 cell count of 268/μl = CDC stage B2; HIV-infected patient with *Pneumocystis carinii* pneumonia and a CD4 cell count of 123/μl = CDC stage C3).

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Table 4.**19** HIV-associated diseases in resource-rich countries, grouped according to organ system and prevalence

Nervous system	
Frequent	cerebral toxoplasmosis
	peripheral neuropathy (HIV associated)
	encephalopathy, HIV associated dementia
	cytomegalovirus chorioretinitis
	myelopathy (HIV associated)
	progressive multifocal leukoencephalopathy (JC virus)
	primary brain lymphoma
	cryptococcal meningitis
Rare	viral encephalitis (CMV, HSV, VZV)
	viral myelitis (CMV, HSV, VZV)
	aseptic meningitis (acute HIV infection)
	microsporidial infection
Respiratory tract	
Frequent	*Pneumocystis carinii* pneumonia
	bacterial pneumonia (pneumococci, *Haemophilus influenzae*, and other bacteria)
	tuberculosis
Rare	Kaposi sarcoma
	Mycobacterium kansasii pneumonia
	CMV pneumonitis
	Penicillium marneffei pneumonia (Thailand, Southeast Asia)
	Rhodococcus equi pneumonia
Gastrointestinal tract	
Frequent	candidal stomatitis and esophagitis
	oral hairy leukoplakia
	anorectal herpes simplex infection
	cryptosporidiosis
	isosporiasis
	microsporidiosis
Rare	oral ulcers
	gingivitis, periodonitis
	Kaposi sarcoma
	cytomegalovirus colitis
	herpes simplex virus esophagitis
	non-Hodgkin lymphoma
Skin	
	seborrhoic dermatitis
	herpes zoster
	herpes genitalis and analis
	Kaposi sarcoma
	bacillary angiomatosis
Systemic	
Frequent	*Mycobacterium avium* complex
	Mycobacterium tuberculosis
	septicimia due to *Salmonella*
Rare	leishmaniosis, visceral
	strongyloidiasis
	histoplasmosis
	coccidioidomycosis

Fig. 4.**22** Anitis due to herpes genitalis in a patient with AIDS.

Fig. 4.**23** Kaposi sarcoma in a patient with AIDS.

deficiency, the determination of the CD4 lymphocyte count has proven useful. The activity of virus replication is measured by quantitative determination of HIV-1 RNA (quantitative PCR). These two parameters are used to determine the indication for treatment and to monitor an antiretroviral therapy. As the AIDS-defining, opportunistic diseases normally do not occur until the cell count falls below 200/μl ($< 0.2 \times 10^9$/L), it can be used in the differential diagnosis when fever is present.

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Fig. 4.**24** Interstitial pneumonitis due to *Pneumocystis carinii* infection.

Infections in Immunocompromised Persons

Classification. The *classification of infections* is based on the following predisposing factors:

- cellular immunodeficiency (HIV infection, immunosuppression after organ transplantation, chemotherapy)
- neutropenia and qualitative defects of phagocytosis (chemotherapy)
- humoral immunodeficiency and complement deficiency
- splenectomy
- special situations: e. g., therapy with anti-TNF substances.

Clinical Features. A varying, but usually "typical" pathogen spectrum is associated with these various causes of immunodeficiency. This spectrum will be discussed below.

The clinical manifestations of infections in the immunocompromised patient are often very nonspecific. Infectious diseases can take very fulminant and life-threatening courses. Severely immuncompromised individuals, especially those with neutropenia, often do not develop any, or only develop reduced, local or systemic signs of inflammation.

For example, instead of an abscess, merely cutaneous cellulitis can become visible. The classical signs of pneumonia can be absent despite an extensive invasion of the respiratory tract or meningitic symptoms are not present in meningitis.

Diagnosis. The diagnosis requires a careful study of medical history and repeated clinical examinations. The medical history must clarify risk factors such as traveling, environmental exposition, animal contacts, drug use, and medications. Initially, microscopic examinations of wound secretions, cutaneous lesions, pus, sputum, or tracheal secretions (if necessary, CSF, pleura, ascites, and urine) should be performed. In the presence of fever, cultures of blood, urine, other secretions, and if necessary, catheters, should be prepared before the antibiotic therapy is initiated.

Because of the potentially fulminant course of infections in neutropenic patients with fever, an empirical therapy according to a defined algorithm is immediately initiated before the microbiological results are received.

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Opportunistic Viral Infections

Cellular Immunodeficiency. In cellular immunodeficiency, infections caused by the following viruses are frequently observed: herpes simplex virus, varicella-zoster virus, cytomegalovirus, JC virus (a papovavirus, the cause of progressive multifocal leukoencephalopathy), Epstein–Barr virus (oral leukoplakia, non-Hodgkin lymphomas), and human herpesvirus 8 (HHV-8).

Neutropenia. Viral diseases in neutropenia are almost exclusively caused by herpes simplex viruses.

Humoral Immunodeficiency. In humoral immunodeficiency, enterovirus infections can take a chronic course and hepatitis viruses can lead to severe clinical pictures.

Cytomegalovirus (CMV). As an opportunistic infection in patients under cytostatic or immunosuppressive therapy, or after open heart surgery (multiple transfusions), cytomegalovirus infection can become manifest as a fever without any cardinal symptoms, pneumonia, myocarditis, or hepatitis. In advanced HIV disease, CMV chorioretinitis, colitis, encephalitis, or pneumonia can occur.

Human Herpesvirus 8 (HHV-8). Human herpesvirus 8 was first detected in Kaposi sarcoma lesions and appears to have a causal significance in the development of this skin tumor. Furthermore, HHV-8 probably is causally associated with multicentric Castleman disease, HIV-associated primary effusion (body cavity) lymphoma, as well as angioimmunoblastic lymphadenopathy in immunocompetent persons.

Opportunistic Bacterial Infections

Cellular Immunodeficiency. Recurrent bacterial pneumonias, pulmonary abscesses caused by *Pseudomonas aeruginosa* or *Rhodococcus equi*, as well as cutaneous or visceral bacillary angiomatosis are more prevalent in persons with cellular immunodeficiency. In addition, these patients more frequently are afflicted with tuberculosis or nontuberculous mycobacterioses, nocardiosis, listeriosis, and nontyphoid salmonelloses.

Neutropenia. Neutropenic patients more frequently become ill with infections caused by Gram-negative bacteria (*E. coli*, *Klebsiella* species, *Pseudomonas* species), staphylococci, and streptococci. Since such patients with severe neutropenia are often hospitalized, they are especially at risk of developing nosocomial infections.

Humoral Immunodeficiency and Splenectomy. In particular, these patients are at risk of infections by encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*), *Capnocytophaga canimorsus* (fulminant sepsis after dog bite), and rarely babesias.

Anti-TNF Therapy. Patients with a rheumatological or immunological underlying disease, who have been treated with anti-tumor necrosis factor medications, more frequently suffer from infections caused by intracellular (tuberculosis) or other opportunistic pathogens. Therefore, before therapy a search should be undertaken for latent tuberculosis.

Opportunistic Fungal Infections

Risk Factors. Because of the increasing survival time of patients with organ transplants, leukemias, metastatic malignancies, and immunocompromising underlying illnesses, as well as the increasing use of broad-spectrum antibiotics, corticosteroids, immunosuppressants, and cytostatics, the number of systemic mycoses has significantly increased.

Neutropenia. Patients with medicinally induced neutropenia are at risk of developing nosocomial infections caused by the colonization or endogenous reactivation of opportunistic pathogens (*Candida*), or by environmental molds (*Aspergillus*). In 10–20% of patients with neutropenia and fungal infections, novel fungal species are increasingly being identified: *Fusarium* species, *Trichosporon* species, *Pseudallescheria boydii*, *Bipolaris*, *Alternaria*, and *Scedosporium*.

Steroids, Diabetes Mellitus, Acidosis. Risk factors for a mucormycosis, in particular, are immunosuppression by steroids or metabolic diseases (diabetes mellitus, acidosis).

Cellular Immunodeficiency. Patients with cellular immunodeficiency more frequently suffer from candidal or cryptococcal infections (HIV infection) or aspergillosis (organ transplantation), as well as, depending on the geographical location, infections due to *Histoplasma* (America, Africa, Asia), *Coccidioides immitis* (America), or *Penicillium marneffei* (Southeast Asia).

Candidiasis (Various *Candida* Species). A colonization of the upper respiratory tract (including the oropharynx), the upper digestive tract, or the skin, occurs in all infants and in patients with impaired resistance to infection, but this is not the same as an infection. The latter most frequently originates from the intestines (colonization after long-term antibiotic therapy) or from indwelling venous catheters which have been implanted for a long time.

In patients infected with HIV, *candidal stomatitis* (Fig. 4.**20**) occurs frequently. Esophagitis is observed less frequently. *Oral hairy leukoplakia* must be distinguished from candidal stomatitis in the differential di-

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agnosis. This is mostly a white, mucosal alteration located on the lateral edge of the tongue which cannot be wiped off. Its patho-anatomical form is that of a hyperkeratosis and parakeratosis in whose pathogenesis the *Epstein–Barr virus* plays a decisive role (Fig. 4.**21**).

After *candidal fungemia* it is possible for septicemia to occur. Primary candidiases mainly become manifest as bronchopneumonia, pneumonia, enterocolitis, or urogenital diseases (*Candida* in the urine, especially in diabetics). A typical clinical picture for patients with long-term neutropenia is *hepatosplenic candidiasis* with multiple hepatic and splenic abscesses.

Cryptococcosis (*Cryptococcus neoformans*). Cryptococcosis is a chronic fungal infection which in particular affects the central nervous system and the lungs, rarely the skin or bones. Malignant diseases (Hodgkin disease, thymoma), immunosuppressive treatments (after organ transplantation), but also HIV infection, sarcoidosis, and diabetes mellitus predispose a person to develop cryptococcosis.

In addition to the direct detection with the microscope (CSF), and by culture, a very sensitive serological antigen test is available. The pulmonary manifestation and basal meningitis are reminiscent of tuberculosis in the differential diagnosis.

Aspergillosis (*Aspergillus fumigatus*, *Aspergillus flavus*). Like candidiasis or cryptococcosis, aspergillosis is an infection which occurs in immunodeficiency, other risk factors, or in previously damaged tissues. The respiratory tract by far is affected most frequently. The early diagnosis is based on a CT scan of the thorax, as the infiltrates often cannot be seen initially on the conventional chest radiograph. A demonstration of pathogenic organisms is only infrequently successful or could only be confirmed by very invasive examinations (biopsy) which are unjustifiable in light of the patient's condition. Serological antigen tests (galactomannan) are still controversial, but they can yield valuable results, especially during the long-term course.

Rarer locations of aspergillosis are the auditory canal and the eye. Disseminated aspergillosis has a poor prognosis. The septicemic presentation is mainly determined by renal involvement (hematuria, renal insufficiency) and the involvement of the central nervous system (headaches, seizures, focal neurological disorders). Additionally, endocarditis with the typical clinical findings occurs. Fundamentally, all organ systems can be involved.

Mucormycosis (various Zygomycetes: *Rhizopus*, *Absidia*, *Mucor*). Zygomycetes are ubiquitous, saprophytic fungi that cause mycoses essentially only in immunocompromised patients.

Clinically a distinction is made between cerebral, pulmonary, gastrointestinal, and disseminated forms. The cerebral form occurs especially in diabetics. Sinusitis with hemorrhagic, nasal secretions, and cranial nerve deficits, which in particular impair ocular function, are typical. Malignant lymphomas and leukemias predispose the patient to the pulmonary and disseminated forms. Pulmonary invasion resembles the clinical picture of pulmonary embolism.

As a culture frequently proves unsuccessful, the histological verification of large, branching, nonseptated hyphae is the only diagnostic method, aside from the clinical findings.

***Pneumocystis carinii* infection.** Recent phylogenetic analyses indicate that this pathogen, previously classified as a protozoan, actually belongs to the fungi. *Pneumocystis carinii* pneumonias are almost exclusively observed in immunodeficient patients and belong to the most frequent opportunistic infections in patients with AIDS. The clinical presentation is dominated by fever, dry cough, dyspnea, and tachypnea and stands in contrast to the absent auscultatory findings. A radiologically normal chest radiograph does not exclude the presence of *Pneumocystis carinii* pneumonia. In severe cases the typical image of a bilateral interstitial pneumonia is found (Fig. 4.**24**). In 70% of the cases the diagnosis can be made from an induced sputum sample (using 3% NaCl inhalations). In 30% of the cases the diagnosis requires a bronchoalveolar lavage.

The presence of pneumocysts can be confirmed by fluorescenctly labeled monoclonal antibodies or molecular genetics. Less sensitive techniques use Giemsa, toluidine or methenamine silver stains. Extrapulmonary diseases are rare.

Opportunistic Protozoa and Helminths

The opportunistic parasitoses associated with *cellular* immunodeficiency are listed in the section on HIV infection (Tabs. 4.**18**, 4.**19**). After organ transplantation, an infection with *Strongyloides stercoralis* can result in a fulminant, life-threatening dissemination with a hypereosinophilia syndrome. Patients with neutropenia or humoral immunodeficiency are not particularly at risk of developing parasitic infections.

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Mycoses in Localized Endemic Regions

In geographically localized regions various environmental fungi occur endemically. These include blastomycosis (United States: Mid West and South), coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis (United States, Central and South America). In immunocompetent individuals, such infections frequently are asymptomatic or lead to pulmonary, dermal, and rarely to systemic diseases. In immunodeficient patients they cause severe, disseminated, and life-threatening illnesses.

Coccidioidomycosis (*Coccidioides immitis*)

Clinical Features. The infection with *Coccidioides immitis* occurs mainly in the Southwestern USA, in Mexico, and in Central America. The disease is highly infectious. However, in humans not infected with HIV, 95% of the coccidioidomycosis infections are asymptomatic. The respiratory tract is affected most frequently. In one-third of cases erythema nodosum is observed, which further complicates the otherwise likely, differential diagnosis of tuberculosis. The disseminated form of coccidioidomycosis is very rare and begins with a respiratory illness (primary pulmonary coccidioidomycosis). Subsequently, infection can involve all organ systems, especially the skeleton (osteolyses, periostitis to subcutaneous abscesses and granulomas), spleen, and kidneys (asymptomatic), as well as the leptomeninges (CSF).

Diagnosis. Diagnostic methods are the serological detection of antibodies, and culture of the pathogen.

Histoplasmosis (*Histoplasma capsulatum*)

Clinical Features. A fungal disease that is rare in Europe, but occurs more frequently in America is histoplasmosis. The primary infection is aerogenic and affects the bronchial tree. It frequently causes a clinically asymptomatic bronchopneumonia with regional lymphadenitis. Especially in infants, adults over 50 years of age (men significantly more often than women), and immunocompromised patients (Hodgkin disease, acute and chronic lymphatic leukemias, HIV infection), it is possible for a disseminated form to develop involving all organ systems. The clinical presentation is dominated by the involvement of the lungs and the organs of the reticuloendothelial system. In order of decreasing frequency, the kidneys, oropharynx (ulcers), meninges, endocardium, adrenal glands, gastrointestinal tract, and the skin are affected.

Diagnosis. Anemia, leukopenia, or thrombocytopenia occurs in more than one-half of the cases. Diagnostically useful in the disseminated form are bone marrow biopsies; blood, CSF, sputum, or biopsy cultures, which grow very slowly. Additionally, serological antibody tests are available.

Travel and Tropical Diseases

For individuals returning from tropical regions who are suffering from fever, potentially *life-threatening* diseases should be excluded first. In addition to specific tropical diseases, differential diagnosis should in particular also consider *sexually transmitted infections*, as well as *nontropical* conditions. Depending on the endemic region visited, the exposure, and the prophylactic measures, this primarily concerns:

- malaria
- typhoid
- hemorrhagic fever
- amebic abscess of the liver
- meningitis
- encephalitis
- endocarditis
- diphtheria
- tetanus
- rabies
- hepatitis A and B
- HIV infection
- intoxications (poisonous animals, drugs).

Infectious Diseases. Most infectious diseases that occur while traveling are caused by ubiquitous microorganisms and not only by "tropical" parasites. The risk of exposure to diseases that are transmitted in food (hepatitis A, salmonelloses, intestinal protozoa) is increased when visiting tropical zones. Likewise, leisure-time activities in tropical regions (swimming, hiking, sexual contacts) are also associated with an increased risk of infection.

The diagnostic algorithm of frequently occurring, tropical infectious diseases is based on the cardinal symptoms, which are summarized in Tab. 4.**20**.

Other Diseases. Diseases which occur during or shortly after a trip must not necessarily be associated with the trip itself (e. g., acute appendicitis). These also include noninfectious illnesses (e. g., pulmonary embolism after sitting for a long time in an airplane) or can be caused by prophylactic medicinal measures (e. g., adverse effect of a drug used in malaria prophylaxis).

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Table 4.**20** Fever in returning travelers and migrants from tropical regions: frequent differential diagnoses*

	Major signs and symptoms, exposition	Important differential diagnoses*
General	Fever	Evaluation for malaria always in case of exposure in endemic region, independent of other cardinal symptoms always consider nontropical disorders
Emergency	– Meningitis, neurologic signs – Respiratory insufficiency – Shock – Renal or liver failure – Severe anemia, thrombocytopenia, neutropenia	Emergency hospitalization
Medical history	Skin exposure to fresh or brackish water Exposure to animals in the workplace Sexual contacts Hypodermic needles Consumption of unpastuerized milk products	Schistosomiasis, leptospirosis Leptospirosis, anthrax HIV, herpes, hepatitis B, hepatitis C infection HIV, hepatitis B and C infection Brucellosis, tuberculosis, foodborne bacterial infection
Cardinal symptoms	Fever without localizing signs or symptoms Maculopapular eruptions Bleeding, petechia Skin ulcers (without genital lesions) Jaundice (and/or elevation of liver enzymes) Cough, dyspnea Cough, dyspnea, and eosinophilia Sore throat Abdominal pain Diarrhea Hepatomegaly Splenomegaly	Malaria, typhoid, rickettsioses, amebic abscess of liver, Dengue fever, HIV infection, infective endocarditis, tuberculosis, cytomegalovirus, Epstein–Barr virus infection Dengue fever, rickettsioses, typhoid, measles, relapsing fever, acute HIV infection, leptospirosis Hemorrhagic fevers; Dengue virus, Crimean Congo virus, Ebola virus, Marburg virus, Lassa virus, leptospirosis Rickettsioses, bacterial skin infection, african trypanosomiasis, plague, anthrax Viral hepatitis A, B, C, typhoid, yellow fever, leptospirosis, relapsing fever Pneumonia (including legionellosis), tuberculosis, American histoplasmosis, melioidosis, typhoid, pulmonary embolism, malaria Tropical pulmonary eosinophilia, ascariasis, strongyloidiasis, ancylostomiasis, paragonimiasis, schistosomiasis Viral and bacterial pharyngitis, diphtheria, Marburg fever, Lassa fever, acute HIV infection Typhoid, amebic liver abscess Bacterial, viral, parasitic intestinal infection, typhoid Viral hepatitis A, B, C, liver fluke, amebic liver abscess, visceral leishmaniasis Visceral leishmaniasis, brucellosis, malaria, typhoid, tuberculosis, mononucleosis, infective endocarditis
Laboratory findings	Eosinophilia	Lymphatic filariasis, loasis, onchocerciasis, schistosomiasis, strongyloidiasis, ancylostomiasis, liver fluke infections, trichinosis

Modified from D'Acremont et al., 2003.
* Depending on exposure in an endemic region.

Malaria

Pathogens and Types of Malaria. The occurrence of malaria cases in temporal countries can be attributed to the increasing amount of vacation travel to tropical regions (usually with no or inadequate prophylaxis). Rarely does the transmission occur through blood transfusions and an exchange of syringes.

- The most frequent type of malaria is caused by *Plasmodium falciparum* (*tropical malaria*).
- Rarer are *quartan malaria* (*Plasmodium malariae*) and
- *Tertian malaria* (*Plasmodium vivax* and *Plasmodium ovale*). These usually exhibit a benign course. However, in order to avoid relapses with *Plasmodium vivax* and *P. ovale*, therapy directed against erythrocytic forms must be followed by treatment of the latent extra-erythrocytic stages in the liver (hypnozoites).

The expected characteristic course of the fever (periodical three day or four day peak of the fever) (Fig. **25a, b**) is rare. Usually the type of fever is irregular, continuous, or intermittent.

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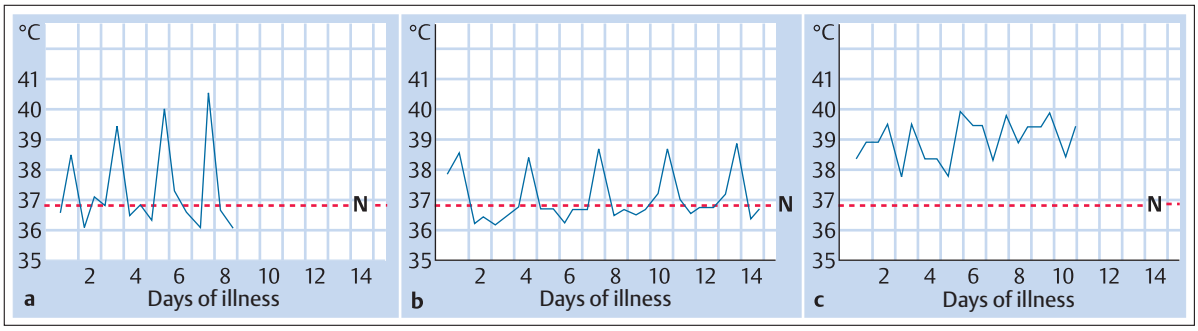

Fig. 4.**25** Course of fever in malaria:
a Tertian malaria (*P. vivax* and *P. ovale*)
b Quartan malaria (*P. malariae*)
c *P. falciparum* malaria

Clinical Features. After an incubation period of up to a few weeks, the first clinical manifestations to occur are nonspecific, prodromal symptoms, which are followed by fever attacks, each lasting several hours. Extremely intense headaches, myalgia, gastrointestinal symptoms, and herpes labialis accompany these attacks. Persons returning from tropical regions with malaria, often initially have a febrile "traveler diarrhea." With increasing duration of the disease splenomegaly (soft!) develops. The liver is also usually enlarged. The differential diagnosis should consider influenza, salmonellosis (typhoid), dengue fever, or hepatitis. The blood count shows normal, or only slightly elevated, leukocyte values during the attacks, leukopenia in the afebrile interval, as well as a mild anemia, and possibly thrombopenia.

Characteristics of *Plasmodium falciparum* Malaria. *Plasmodium falciparum* malaria can result in death within a few days. The characteristic fever attacks, alternating with an asymptomatic interval, are often absent. The course of the fever is remittent or intermittent (Fig. 4.**25c**). The rapid propagation of the intra-erythrocytic parasites causes an erythrocyte stasis and hypoxia in the capillaries of the internal organs. The clinical presentation is determined by the failure of the most damaged organ:

- In *cerebral malaria* a clouding of consciousness, coma, seizures, acute exogenic reaction type, or hyperreflexia with pyramidal signs stand in the foreground. Except for an elevated pressure and an increased protein concentration, the CSF examination yields little information.
- *Biliary forms* are characterized by intravasal hemolysis and hemoglobinuria (blackwater fever), cholestasis, elevated LDH and transaminase values, as well as urobilin bodies in the urine.
- *Renal forms* occur with renal insufficiency and oliguria.
- *Cardiac forms* occur with ECG alterations, arrhythmias, and heart failure.
- *Gastrointestinal forms* with diarrhea, possibly melena, also occur.

Diagnosis. The diagnosis of malaria requires that blood samples be drawn during the febrile phase. The pathogens can be visualized microscopically in a "*thick blood smear*" (hemolysis of the erythrocytes) or in a normal blood smear stained with May–Grünwald–Giemsa stain. Therapeutic decisions require knowledge of the *Plasmodium* species and the proportion of parasitized erythrocytes (in %, i. e., number of parasitized erythrocytes per 100 erythrocytes).

Different species of *Plasmodium* exhibit different manifestations according to their *developmental cycle* in humans. The cycle initially is extraerythrocytic (in the liver cells) and then continues in the intraerythrocytic stages (Fig. 4.**26**):

- growth as trophozoites, from ring–shaped (Fig. 4.**27a**) to ameboid forms
- nuclear division occurs in schizonts to form daughter merozoites, that are seen under the microscope as a daisylike shape (Fig. 4.**27b**)
- merozoites are released after the erythrocyte bursts and then invade new erythrocytes
- some merozoites will, after invading a new erythrocyte, develop into a male or female gametocyte (Fig. 4.**27c**).

Rapid antigen tests are not more sensitive than microscopy, cannot quantify the parasitemia, and still remain positive for several weeks after successful therapy.

Leishmaniasis (*Leishmania donovani*)

Cutaneous Form. The cutaneous forms of leishmaniasis do not result in a dissemination of the pathogens.

Clinical Features of the Visceral Form. Visceral leishmaniasis (kala azar) is an infectious disease that is endemic to Mediterranean countries, Africa, India, Bangladesh, and rarely to South America. It is transmitted by the bite of a *Phlebotomus* species (sand fly). The incubation period varies from months to years. The clinical manifestations are characterized by the involvement of the reticuloendothelial system: hepatosplenomegaly, enlarged lymph nodes, leukopenia to pancytopenia. The course of the fever is intermittent.

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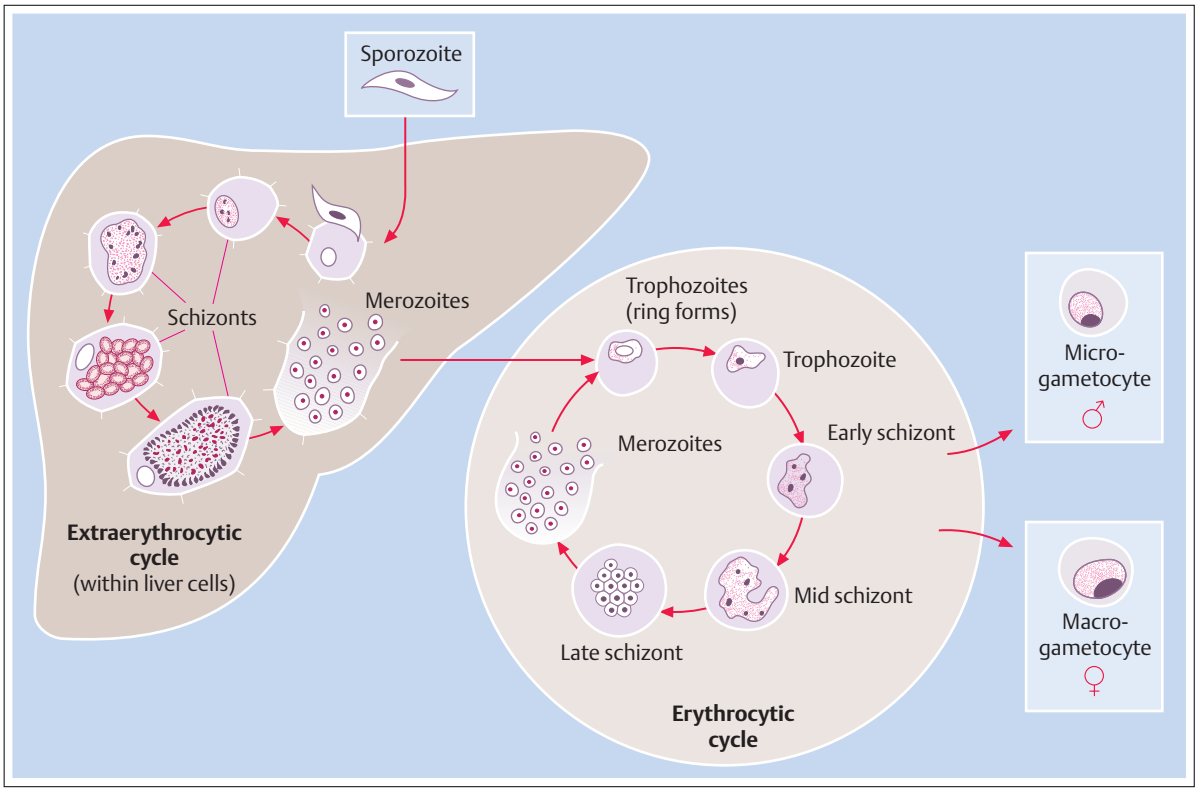

Fig. 4.**26** Life cycle of *Plasmodium* in humans.

Diagnosis. The demonstration of pathogenic organisms occurs in the bone marrow (using Giemsa stain, culture), spleen, or lymph node puncture. Furthermore, serological methods are available to detect antibodies. The cause of elevated IgG in the serum is unknown. The differential diagnosis of HIV-infected patients with an unclear fever must necessarily consider a visceral leishmaniosis in endemic regions or with a history of international travel. Bone marrow cultures are of decisive importance in this case, as the serology in those infected with HIV exhibits a sensitivity of less than 50%.

Schistosomiasis (Bilharziosis)

Transmission. *Schistosomiasis* is a helminthic disease (trematodes). The necessary intermediate hosts (snails), which live only in the waters of tropical and subtropical regions, take up the miracidia and after a propagation cycle, release the worm larvae (cercaria). In the water the larvae penetrate the healthy, human skin and reach the liver via the lungs, where they mature into adult worms (length 1–2 cm). From there they move into certain venous areas, where they can survive for up to 30 years without any further propagation. However, each female worm can release hundreds of eggs each day. It is the eggs that cause an eosinophilic, granulomatous inflammation that, as a consequence of fibrous scar formation, results in the typical chronic organ damage.

Clinical Features. The acute *Katayama fever*, which is similar to serum disease, develops during the phase of the first egg deposits (allergens!). *Schistosoma japonicum* produces the largest number of eggs.

Schistosoma mansoni and *Schistosoma japonicum* mainly reside in the mesenterial veins. *Schistosoma haematobium* is found in the veins of the urinary bladder. Accordingly, the first two, in addition to hepatopathy, primarily cause gastrointestinal symptoms. The resulting congestion in the portal circulation leads to splenomegaly and esophageal varices. However, the eggs can also disseminate via the blood into the lungs, heart, and brain and cause the described granulomas at these locations.

Consistent with its location, *Schistosoma haematobium* is characterized by dysuria and hematuria. Stenotic granulomas can lead to bilateral hydroureters and hydronephrosis.

Diagnosis. Eosinophilia of the blood can be expected in the early forms of bilharziosis. The diagnosis is made by detecting eggs in the stool or the urine which also permits the determination of the *Schistosoma* species. Occasionally a biopsy of the rectal mucosa is necessary. Serological results are often false positive or false negative and do not provide any information about the activity of the disease.

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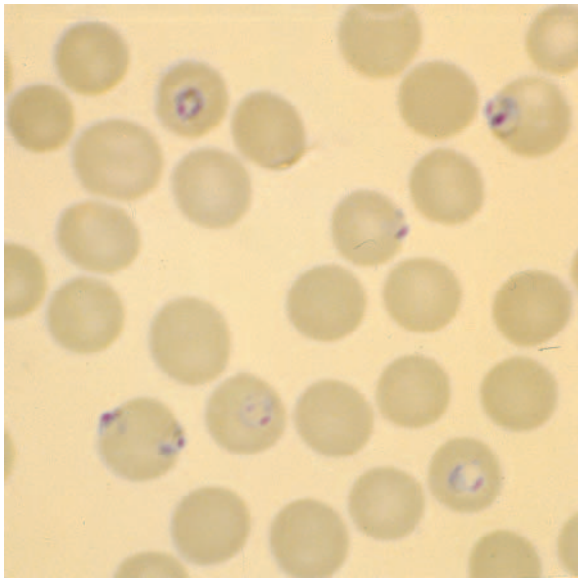
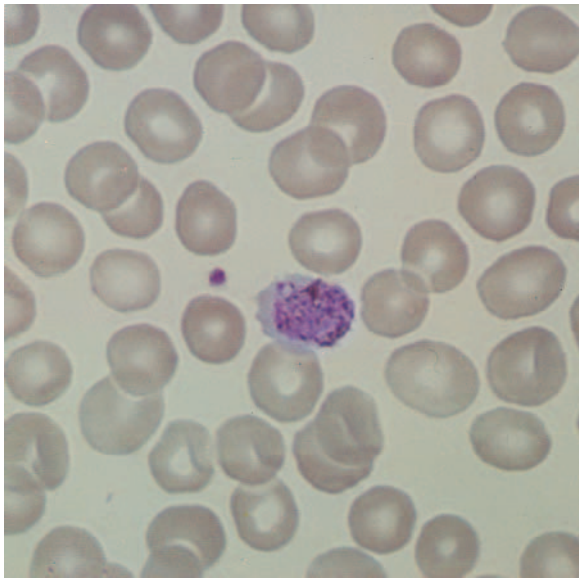


a



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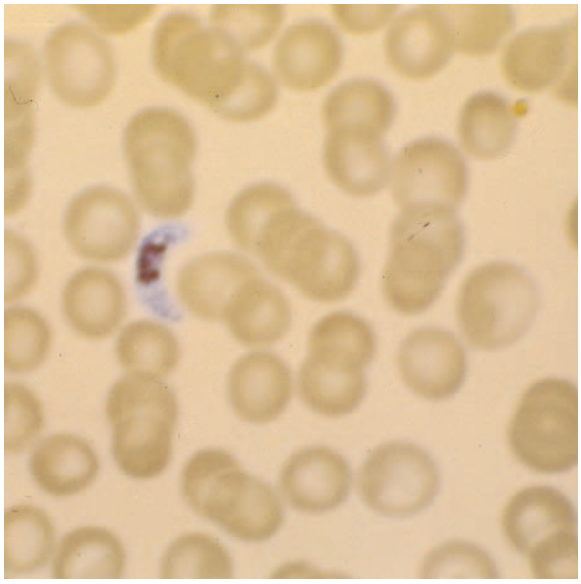

c

Fig. 4.**27** Blood smears of patients with malaria:
a erythrocytes with trophozoites (ring forms)
b erythrocyte with schizont (*Plasmodium vivax*)
c gametocyte (*Plasmodium falciparum*).

Lymphatic Filariasis

Transmission. *Lymphatic filariasis* is caused by nematodes (*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*). Adult female worms, which reside in lymph vessels, produce microfilaria which appear in the peripheral blood six to 12 months after infection and then circulate. The pathogen reservoir for all filaria species is humans. Additionally, small mammals and nonhuman primates are the pathogen reservoir for *B. malayi*. Infectious larvae are transmitted by different species of mosquitoes (*Culex*, *Anopheles*, *Aedes*). *W. bancrofti* is endemic in practically all tropical climatic zones of Latin America, Africa, and Asia. The two other species of filaria occur in localized regions of Asia.

Diagnosis. The diagnosis is based on clinical suspicion and a frequent eosinophilia caused by microfilaria. Depending on the species of filaria, these can be detected in the peripheral blood during the day or at night. Additionally, serological methods are available.

Clinical Features. The spectrum of clinical manifestations is extremely variable and includes the following patterns:

- asymptomatic and test negative for parasites after exposure to pathogens
- asymptomatic with microfilaremia
- acute, recurrent *fever*, *lymphadenitis*, and *lymphangitis* with or without microfilaremia
- chronic disease with symptoms of *chronic obstructive lymphangitis* (hydrocele, chyluria, elephantiasis of

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the extremities, breasts, or genitalia), usually with a mild or undetectable microfilaremia

- *tropical pulmonary eosinophilia* with episodic, nightly asthmatic dyspnea and chronic interstitial pneumopathy without microfilaremia.

Tissue Filariases

Loa loa infection, which occurs in the rainforest regions of Africa results in edematous skin swelling, pruritic skin nodules, and eye inflammations.

Onchocercosis, (which occurs in tropical Africa, southern Arabian countries, and several countries in Central and South America), depending on the immune status, causes skin nodules (onchocercoma), pruriginous skin changes or sclerotic keratitis, chorioretinitis, and optic nerve neuritis.

Dengue Fever

Dengue virus, which is especially transmitted in the urban areas of tropical regions by the *Aedes* mosquito, spreads rapidly and has in the meantime become endemic in nearly all tropical countries. It causes an acute febrile disease which normally lasts for three to five days and exhibits a partially biphasic course. Concomitant symptoms are severe headaches, myalgia, arthralgia, retroorbital pain, gastrointestinal symptoms, and occasionally a generalized maculopapular exanthema which develops after the febrile phase. Slight petechial hemorrhaging of the skin, epistaxis, or gingival bleeding is frequent. Usually lymphadenopathy and leukopenia can be detected. Severe thrombocytopenia and elevated transaminase levels are rare. The diagnosis is made serologically.

In life-threatening, *hemorrhagic dengue fever* or *dengue shock syndrome*, which has been more frequently observed during recent years, disorders of vascular permeability, hypovolemia, and coagulation disorders occur.

Yellow Fever

Yellow fever, which occurs in tropical Africa and Latin America, is an acute febrile viral disease that can exhibit varying clinical severity. Typical concomitant symptoms are headaches, back pain, myalgia, nausea, and vomiting. Jaundice is initially mild in nature and becomes more extensive with increasing duration of the disease. Most of those afflicted patients recuperate after this phase. After a brief and transient remission, a small number of patients develop a hemorrhagic fever with bleeding complications, and hepatic and renal failure.

The diagnosis is made by virus isolation, antigen verification in the blood, or serological antibody detection.

Other Tropical Diseases

Additional tropical diseases are considered in light of the travel history:

- *Meloidosis* (*Burkholderia pseudomallei*) is especially endemic in Southeast Asia and can become manifest as sepsis or necrotizing pneumonia.
- *African trypanosomosis (sleeping sickness)* begins with nonspecific general symptoms and lymphadenopathy. Later meningoencephalitic symptoms develop.
- The acute infection in *South American trypanosomosis (Chagas disease)* is usually asymptomatic. Rarely, but particularly in children, fever, edemas, lymphadenopathy, hepatosplenomegaly, and myocarditis occur. After a latency period of up to 20 years, the consequences of chronic damage to tissue and ganglion cells become manifest (cardiomyopathy, megacolon, neurological disorders).
- In addition, in those returning from traveling abroad *sexually transmitted infections*, including an acute *HIV infection*, often must be considered in the differential diagnosis.

4.5 Fever in Autoimmune Diseases

The immune system can distinguish between self and nonself proteins (antigens) and reacts with the generation of specific antibodies (humoral immune response) and the formation of primed lymphocytes (cellular immune response). Especially in the course of bacterial infections, the immune system can be amplified significantly by activation of both the complement system and macrophages, which produce proinflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor alpha.

Autoantigens. The immune system not only recognizes bacteria, bacterial toxins, viruses, and drugs, but also self antigens, the so-called autoantigens such as DNA, ribonucleoprotein, thyroglobulin, etc. During development, the immune system is able to eliminate lymphocyte clones which are directed to self antigens and propagate the generation of lymphocyte clones which recognize foreign antigens. In adulthood, autoreactive lymphocyte clones are suppressed (anergy). The breakdown of tolerance to self antigens can lead to the development

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of autoimmune diseases. It is not unusual to detect autoantibodies. However, such antibodies do not usually lead to autoimmune diseases. Destruction of parenchymal cells very often leads to antibodies against the destroyed parenchyma, for instance after myocardial infarction or heart surgery. However, such antibodies only rarely lead to clinical manifestations such as Dressler syndrome and postcardiac injury syndrome, both of which are associated with fever, polyserositis, and increased blood sedimentation rate.

Autoimmune Diseases. Principally, we can distinguish between:

- *systemic* autoimmune diseases, which are most commonly induced by circulating autoantigens
- *organ-specific* autoimmune diseases, in which the destructive mechanism is restricted to one or only a few organs.

However, it is not always possible to clearly distinguish between these two groups of autoimmune diseases, as smooth transition forms frequently occur.

Localized or Organ-Specific Autoimmune Diseases

The group of organ-specific autoimmune diseases includes those that harbor activated lymphocytes in individual organs and autoantibodies in the serum. The most commonly known examples are antibodies to the thyroid gland, adrenal gland, stomach, and pancreas. Further examples of localized autoimmune processes are immune hemolysis, immune thrombocytopenia, and certain forms of aplastic anemia. So-called "autoimmune polyendocrinopathy syndrome, type 1" is a familial disease of the endocrine glands, which occurs due to mutation in the "autoimmune regulator (*AIRE*) gene" on chromosome 21q22.3. Its clinical characteristics are Addison disease, hypoparathyroidism, and very often mucocutaneous candidiasis. In type 2 and type 3 autoimmune polyendocrinopathy syndrome, the thyroid gland and/or the pancreatic islet cells also become targets of the autoimmune reaction.

Generalized Autoimmune Disease, Vasculitis, and Connective Tissue Syndrome

Examples of generalized autoimmune diseases are the various forms of vasculitis and inflammatory diseases of the connective tissue (Tab. 4.**21**). The term "connective tissue syndrome" refers to inflammatory diseases with alterations of the connective tissue in which inflammation of the vessels is sometimes present. Examples are scleroderma, "mixed connective tissue syndrome" (Sharp syndrome), and dermatomyositis. Vasculitis and connective tissue syndrome are very frequently associated with immune complexes, and are clinically characterized by systemic occurrence with manifestations in various organs.

Clinical Features. The clinical manifestations involve several organs, and are associated with arthritis, skin manifestations (purpura, exanthema), glomerulonephritis, pericarditis, pleuritis, alveolitis, and mononeuritis. Diagnosis must exclude infectious diseases (sepsis, endocarditis, Lyme disease), cholesterol embolization (which occurs after vascular surgery or angiography), atrial myxoma, and tumor-associated vasculitis or vasculitis due to viral infections (hepatitis B, hepatitis C, cytomegalovirus, herpes simplex).

Diagnosis. These diseases are most commonly associated with a moderately increased blood sedimentation rate, anemia, thrombocytosis, and/or elevated C-reactive protein. From an immunological point of view, antibodies against cell nuclei, DNA, chromatin, and ribonucleoproteins (SS-A, SS-B), as well as antineutrophilic, cytoplasmic autoantibodies (ANCAs) can be detected (Tab. 4.**22**). The latter antibodies are directed against proteins in the granules of neutrophils. The so-called c-ANCAs recognize protease-3, whereas p-ANCAs are directed to myeloperoxidase. Besides these autoantibodies, also frequently seen are increased numbers of immunoglobulins and detection of rheumatoid factors and cryoglobulins.

Classification. The various forms of vasculitis can be classified in different ways. The name *infectious angiitis* refers to vasculitis which may occur in the course of acute infectious diseases such as syphilis and Lyme disease, or infections with *Rickettsia* or pyrogenic bacteria. *Noninfectious vasculitis* can be grouped according to the size of the affected vessel (large, medium, and small), and the histological characteristics (granuloma, necrosis, giant cells, eosinophilic leukocytes) (Tab. 4.**21**).

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Table 4.**21** Classification of vasculitis

Vasculitis of large vessels	Vasculitis of medium vessels	Vasculitis of small vessels
– Arteritis temporalis (giant-cell arteritis) – Takayasu arteritis – Inflammatory aortic aneurysms (in possible combination with retroperitoneal fibrosis)	– Classical polyarteritis nodosa – Buerger disease – Kawasaki disease – Primary angiitis of the central nervous system	– ANCA-associated vasculitis – Wegener granulomatosis – microscopic polyangiitis – Churg–Strauss syndrome – Immune-complex-induced vasculitis – hypersensitivity angiitis induced by drugs, malignomas, and infectious diseases – serum disease – systemic lupus erythematosus – Henoch–Schönlein disease – purpura–arthralgia–nephritis syndrome induced by chronic hepatitis C – Goodpasture syndrome – Behçet disease – hypocomplementary urticarial vasculitis – Schnitzler syndrome – Connective tissue diseases – scleroderma – mixed connective tissue disease – Sjögren syndrome – dermatomyositis

Table 4.**22** Autoantibodies in vasculitis and connective tissue disease

Disease	Autoantibodies*	Sensitivity High	Low	Specifity High	Low
Systemic lupus erythematodes	ANA	+			+
	anti-nDNA	+		+	
	anti-Sm		+	+	
	anti-chromatin	+		+	
	anti-ribosomal P protein	+ (CNS lupus)		+	
	anti-C1q	+ (lupus nephritis)			+
	anti-histone		+ (drug-induced SLE)		+
Mixed connective tissue disease	anti-U1-snRNP	+			+
Diffuse scleroderma	anti-Scl 70		+	+	
Limited scleroderma	anti-centromere	+		+	
Polymyositis	anti-Jo-1	+ (polymyositis with pulmonary fibrosis)		+	
	anti-PM-ScL		+	+	
	anti-Mi 2		+	+	
Rheumatoid arthritis	rheumatoid factor	+			+
	anti-CCP	+		+	
Wegener granulomatosis	ANCA (especially c-ANCA)	+ (with kidney involvement)	+ localized form	+	
Polyarteritis nodosa	ANCA (especially p-ANCA)	+ microscopic form	+ classical form	+	
Churg-Strauss syndrome	ANCA (especially p-ANCA)		+	+	

* Abbreviations: ANA: anti-nuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies (c-ANCA: cytoplasmic, antiprotease 3; p-ANCA: perinuclear, anti-myeloperoxidase); CNS: central nervous system; nDNA: native DNA; RNP: ribonucleoprotein; SLE: systemic lupus erythematosus; Sm: Smith antigen.

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Vasculitis of Large Vessels

Giant Cell Arteritis (Arteritis Temporalis Horton) and Polymyalgia Rheumatica Syndrome

Definition and Histology. Arteritis temporalis Horton, also referred to as cranial or *giant cell arteritis,* is an inflammation of the medium and large vessels that manifests most commonly in the temporal artery, the ophthalmic artery, and the vessels of the retina. Its histologic hallmarks are segmental necrosis, lymphocytic infiltrates, giant cells near the disrupted lamina elastica interna, and granulomatous panangiitis. Up to 10% of patients also show an involvement of the aorta, carotids, subclavia, vertebral arteries, and coronary vessels.

Arteritis temporalis is very often associated with *polymyalgia rheumatica syndrome*. However both diseases can occur separately. Both most commonly affect people over the age of 50, with a predominance in women.

Fig. 4.**28** Prominent temporal artery in arteritis temporalis (giant-cell arteritis, arteritis temporalis Horton).

Clinical Features. Characteristics of *arteritis temporalis* are headaches on one or both sides, discomfort in the scalp, and jaw claudication (often bilateral). The temporal arteries become tender to the touch, painful, and possibly pulseless (Fig. 4.**28**).

Polymyalgia rheumatica syndrome manifests as pain in the muscles of the neck, shoulders, lower back, and less commonly in the hips and thighs. The pain is amplified by movement and at night. Morning stiffness can become a hallmark of the disease. No atrophy or signs of inflammation can be identified upon examination. Only rarely does muscle weakness or joint swelling occur.

Complications. Complications develop due to vascular involvement of the disease. The ocular manifestations (ischemic optic neuritis) can lead to irreversible blindness. Moreover, stroke, myocardial infarction, and aortic aneurysm can develop.

Diagnosis. In both arteritis temporalis and polymyalgia rheumatica syndrome a high erythrocyte sedimentation rate is seen (commonly above 50 mm in the first hour) paralleled by anemia, leukocytosis, and increase in α2-globulins and possibly γ-globulins. Important: the enzymes of the muscles are not elevated and rheumatoid factors are negative.

The disease is diagnosed by biopsy of the temporal artery, which can give a positive result even when the artery is clinically not affected. It is important that the biopsy specimen be at least 4–6 cm long, and for the histological work-up cut into pieces at 3–5 mm intervals. Patients with polymyalgia rheumatica show histologically proven arteritis temporalis in one third of all cases. In both diseases, muscle biopsies do not lead to characteristic findings.

Differential Diagnosis. Diseases such as polyarteritis nodosa, thrombangiitis obliterans, dermatomyositis, paraneoplastic syndrome, and rheumatoid polyarthritis must be excluded.

Vasculitis of Medium-Sized Vessels

Polyarteritis Nodosa or Panarteritis

Definition and Histology. Polyarteritis nodosa is a necrotizing vasculitis of the small and medium arteries. Because the nodular inflammatory infiltrates along the vessels occasionally become palpable, Kussmaul and Maier introduced the term "periarteritis nodosa." But because nodular infiltrates do not occur in all cases and all the layers of the arterial wall are affected, the term "panarteritis" or "polyarteritis nodosa" is more commonly used currently. The disease may be associated with viral infections (hepatitis B, HIV, HTLV-1), drugs, or malignant tumors (the secondary forms of the disease), and affects mostly men (two to three times more often than women). If only small vessels are affected by the inflammatory process, the term "microscopic polyangiitis" is used (Tabs. 4.**23**, 4.**24**).

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Polyarteritis nodosa must be considered if symptoms of multiple organs are associated with transient and relapsing arthralgias, fever, weight loss, and an elevated blood sedimentation rate.

Etiology. Patients frequently report allergic manifestations (such as asthma, urticaria, allergies to drugs), treatment with sulfonamides or antibiotics, or recent vaccinations. Hepatitis B virus is considered one of the potential causal agents. Up to 40% of patients with polyarteritis nodosa test positive for hepatitis B antigens (20%) and/or hepatitis B surface antigens or anti-hepatitis B core antigens. Immune complexes to hepatitis B antigens can be detected in the affected arteries. These immune complexes seem to initiate the inflammatory processes.

Clinical Features. Depending on the organ involvement, the following symptoms dominate:

- Involvement of the *abdominal vessels* leads to severe abdominal pain, which can be accompanied by vomiting, bleeding, bowel infarction and perforation, and paralytic ileus.
- Increased *splenomegaly* is seen in 10% of the patients. *Involvement of the liver* is associated with an increase in serum aminotransferases AST and ALT.
- Involvement of the *coronary vessels* is manifested by angina pectoris, myocardial infarction, and congestive heart failure. Noninfectious endocarditis, as seen in systemic lupus erythematosus, is not a feature of polyarteritis nodosa.
- *Renal manifestations* of the disease are associated with abnormal findings in the urine (hematuria, proteinuria, renal casts) which can be followed by hypertension and renal failure. In contrast to systemic lupus erythematosus, nephrotic syndrome can be observed only very rarely. The kidneys are affected in 70–90% of the patients. In 30% of the patients, a focal and segmental proliferative glomerulonephritis is seen. This manifestation is the usual occurrence in the so-called microscopic form of polyarteritis nodosa which only affects the small vessels. The latter disease is characterized by the development of purpura, arthralgia, myalgia, kidney involvement, and quite commonly, pulmonary hemorrhage. This clinical picture may be difficult to distinguish from that of other forms of vasculitis of small vessels (see Tab. 4.**25**).
- *Peripheral nervous system* and *muscular involvement* may be the leading symptoms of polyarteritis nodosa, and occur due to vasculitis of the vasa nervorum. Differential diagnosis must exclude polymyositis, primary muscle atrophy, and trichinosis.
- *Cerebral manifestations* occur in the form of stroke, seizures, and focal symptoms or meningitis.
- The classical form of polyarteritis nodosa affects the lungs only rarely, a feature that distinguishes this disease from Wegener granulomatosis and Churg–Strauss syndrome. Small nodules in the chest radiograph may point to an involvement of the *pulmonary vessels* (Fig. 4.**29**), and can be falsely interpreted as infectious processes. In case of occlusion of the large branches, pulmonary infarction with hemoptysis may develop. There is no evidence of polyserositis as seen in systemic lupus erythematosus.
- *Ophthalmic manifestations* include signs of hypertension in the retina or vasculitis of the retinal vessels, both with visual disturbances.
- In case of suspicion of polyarteritis nodosa, examination for *skin changes* must not be omitted. Cutaneous or subcutaneous nodules are rarely seen. However, nonspecific skin manifestations (urticaria, purpura) are encountered much more frequently. Occasionally, Raynaud syndrome and livedo reticularis, resembling scleroderma do occur. Some patients notice testicular pain, which is due to vasculitis and is, if present, of great diagnostic importance.

Table 4.**23** Laboratory results for polyarteritis nodosa

- Elevated blood sedimentation rate
- Leukocytosis, less commonly associated with eosinophilia
- Normochromic anemia
- Thrombocytosis
- Hypergammaglobulinemia
- Elevated transaminase levels in infections with hepatitis B and C viruses
- Pathological urinary sediment (hematuria, dysmorphic erythrocytes, proteinuria, cellular casts)
- Elevated creatinine levels
- Elevated serum creatinine phosphokinase levels (CPK) in patients with vasculitis of the skeletal muscles
- Rheumatoid factors in approximately 20% of cases
- Immune complexes, often with hypocomplementemia
- Antineutrophil cytoplasmatic antibodies (ANCA)

Table 4.**24** Differential diagnosis for polyarteritis nodosa: typical and microscopic forms

	Polyarteritis nodosa	
	Classical form	Microscopic form
Glomerulonephritis	No	Yes
Hypertension	Yes (20%)	No
Pulmonary bleeding	No	Yes
Mononeuritis	Yes (70%)	Yes (20%)
Relapses of disease	Rare	Yes
Hepatitis B serology	Yes (30%)	No
ANCA	Rare	Yes
Angiography: microaneurysms	Yes	No

Diagnosis. (Tabs. 4.**22**–4.**24**) The classical form of polyarteritis nodosa is only rarely associated with antineutrophil cytoplasmic autoantibodies (ANCAs). Diagnosis can only be verified by a muscle or skin biopsy with

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Fig. 4.**29** Pulmonary involvement in polyarteritis nodosa after multiple infarctions in a 53-year-old man.

demonstration of fibrinoid necrotizing vasculitis. Angiographic examinations (e. g., of the kidneys) may show aneurysms or vascular occlusions. However, as in the case of liver and kidney biopsies, an angiographic examination is rarely done now, because of the significant changes brought about since the discovery of ANCAs.

Course of Disease. In the late phase of the disease, occlusion of the affected vessels becomes manifest mainly in the heart, the central nervous system, and the kidneys. At this stage of the disease, general symptoms seen in the acute phase are often absent. The affected vessels show intense proliferation of endothelial cells in the absence of inflammatory cell infiltrates.

Vasculitis of Small Vessels

Wegener Granulomatosis

Wegener granulomatosis is characterized by both a necrotizing vasculitis and by granulomas. Mainly affected are the upper and lower respiratory tract and the kidneys. If no signs of kidney involvement are seen the term for the limited form, "Wegener disease," is used. ANCAs are hardly ever seen in the limited form of Wegener. In Chapter 18 the clinical picture is described in detail.

Allergic Granulomatosis (Churg–Strauss Syndrome)

Clinical Features. Typically, Churg–Strauss syndrome is associated with blood eosinophilia, infiltrates of the lung with eosinophils, perivascular granulomas, and a strong association with severe asthma. Moreover, rhinitis and/or sinusitis, which develop due to an atopic predisposition, precede the disease for many years. In contrast to polyarteritis nodosa, in which eosinophilia occurs only rarely (10%), manifestations of the myocard are frequent and renal involvement is rare.

Diagnosis. As in the case of the microscopic form of polyarteritis nodosa, ANCAs, as well as rheumatoid factors and immune complexes are often detected (Tab. 4.**22**). It is occasionally difficult to distinguish Churg–Strauss syndrome patients from patients with asthma, eosinophilia, and pulmonary aspergillosis from patients with chronic eosinophilic pneumonia or hypereosinophilic syndrome, which is associated with transient pulmonary infiltrates, endocardial fibrosis, dementia, polyneuropathy, and exanthema of the skin.

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Hypersensitivity Vasculitis

Hypersensitivity vasculitis is a necrotizing vasculitis of small vessels with the histologic hallmarks of leukocytoclastic vasculitis. Clinically, various forms of vasculitis can be included here, and have in common known triggers such as viral infections, drugs, or malignant tumors.

Purpura–Arthralgia–Nephritis Syndrome

The leading symptom of this disorder is chronic purpura on the lower extremities associated with arthralgia, myalgia and, in 50% of the patients, diffuse membrano–proliferative glomerulonephritis and polyneuropathy. Rheumatoid factors, low levels of complement C4, and the detection of cryoglobulins (mostly mixed cryoglobulins, IgM–IgG) are characteristic laboratory features. Most patients have an underlying hepatitis C virus infection (Tab. 4.**25**).

Systemic Lupus Erythematosus (SLE)

Definition. Systemic lupus erythematosus, a disease of unknown origin, is caused by immune complex mediated tissue destruction and shows the occurrence of polyclonal B-lymphocyte proliferation and antibodies to nuclear proteins.

Subacute cutaneous lupus erythematosus (SCLE) shows only recurring skin lesions, whereas systemic lupus erythematosus (SLE) is a multisystemic disease.

Drug-induced SLE. Drug-induced SLE shows a direct relation of the disease with the consumption of drugs, and disappearance of the disease after discontinuation of the drugs. The drugs most commonly associated with drug-induced lupus are hydralazine and procainamide, but also hydantoins, isoniazid, and beta-blockers. The clinical symptoms of drug-induced SLE mainly include fever, arthralgia, myalgia, and pleuropericarditis. Kidney and central nervous system manifestations are rarely seen, and the laboratory complement factors C3 and C4 therefore remain normal. Anti-DNA antibodies are mostly negative. Antinuclear antibodies and antibodies to histones and chromatin are positive.

Clinical Features of SLE. The systemic form of lupus erythematosus mostly affects women between the ages of 20 and 50. The clinical manifestations vary considerably, as all organs can be affected (Tab. 4.**26**). The course of disease is equally variable. In over 75% of the patients, the overall survival is more than 10 years:

- In 10% of patients, the *joint manifestations* resemble rheumatoid arthritis. However, large joints are also affected, while erosions of the bones are rarely seen.
- *Skin manifestations* (Fig. 4.**30**) may be so characteristic that they allow a first-time diagnosis. The skin hallmark is a combination of erythema teleangiectasia, depigmentation, atrophy, and hyperkeratosis. Alopecia is usually patchy. Ultraviolet light leads to exacerbation of the skin changes, mainly in patients with antibodies to ribonucleoprotein SS–A. Light-sensitive eruptions are seen not only in the form of the butterfly rash, but also on the hands and other parts of the body unprotected from the sun.
- More than 50% of patients have *glomerulonephritis* with hematuria and/or proteinuria and possibly

Table 4.**25** Differential diagnosis of small-vessel vasculitis (data in %)

	Henoch–Schönlein disease	Purpura–arthralgia–nephritis syndrome	Microscopic polyangiitis	Wegener granulomatosis	Churg–Strauss syndrome
Cryoglobulin/rheumatoid factor/C4 ↓	< 25	> 75	< 25	< 25	< 25
Hepatitis C infection	< 25	> 75	25–75	< 25	< 25
Immunoglobulin A (IgA) deposits (skin, kidney)	> 75	25–75	< 25	< 25	< 25
ANCA	< 25	< 25	> 75	> 75	> 75
Bronchial asthma, eosinophilia	< 25	< 25	< 25	< 25	100
Skin involvement	90	100	80	40	60
Kidney involvement	50	50	90	80	45
Ear, nose, pharynx	< 25	< 25	35	90	50
Muscles, joints	75	70	60	60	50
Nervous system	< 25	40	30	50	70
Gastrointestinal tract	60	30	50	50	50

Modified from Jeannette and Falk, 1997.

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Fig. 4.**30** Skin manifestations in systemic lupus erythematosus: typical butterfly rash on nose and cheeks in a 17-year-old girl.

Table 4.**26** Clinical manifestations and laboratory results for systemic lupus erythematosus

Clinical manifestations	%
Arthralgias	92
Fever	84
Skin involvement	72
Lymph node enlargement	59
Pathological kidney and urine test results	53
Anorexia, nausea, vomiting, diarrhea	53
Joint swelling	49
Myalgia	48
Pleuritis	45
Exudative pericarditis	32
Pulmonary changes	30
Involvement of the central nervous system	26
Joint deformations	26
Hepatomegalia	23
Heart murmurs	20
Abdominal pain	19
Raynaud syndrome	18
Splenomegalia	9
Laboratory Findings	
Elevated erythrocyte sedimentation rate	84
Anemia, HB < 11 g/dL (< 110 g/L)	72
Leukopenia < 4500/mm³ (< 4.5 × 10⁹/L)	61
Thrombocytopenia < 100 000/mm³ (< 100 × 10⁹/L)	15
Positive direct Coombs test	14
Antinuclear antibodies*	99
Anti-DNA antibodies*	92
Elevation of γ-globulins > 1.5 g/dL (> 15 g/L)	77
Decrease of complement factors (in C3 and/or C4)*	75
Circulating immune complexes*	70
Rheumatoid factor	20
Anticardiolipin and anti-β2 glycoprotein antibodies	30

* = with active disease.

kidney failure. The latter develops mostly in the case of diffuse membrano-proliferative glomerulonephritis.

- *Polyserositis:* pericarditis, pleuritis, and peritonitis with ascites are seen in half of the patients.
- *Libman–Sacks endocarditis* (verrucous endocarditis) affects mostly the mitral valve, in possible combination with lesions in the aortic and tricuspidal valves, and is mostly associated with pericarditis. This non-infectious endocarditis is complicated by aortic or mitral regurgitation, rarely by stenosis, and may give rise to thromboembolism. To distinguish Libman–Sacks endocarditis from infectious endocarditis, blood cultures are required.
- *Pulmonary manifestations* display multiple forms, ranging from small pulmonary infiltrates of the lower lobe to interstitial pneumopathy, pulmonary embolism, or pulmonary hemorrhage. Antiphospholipid antibodies predispose to pulmonary embolism.
- *Central nervous system manifestations* of SLE can lead to seizures, organic brain syndrome with psychosis, focal infarct with resulting deficiencies including paraplegia or hemiplegia, or cranial nerve palsis. These manifestations may not be due to vasculitis of the cerebral vessels, but rather may be the consequences of hypertension in lupus nephritis, thromboembolism in Libman–Sacks endocarditis, thrombotic–thrombopenic purpura, or infection due to drug-induced immunosuppression. Peripheral sensorimotor neuropathy is seen only rarely.
- Various signs of other *vasculitic lesions* including secondary Raynaud syndrome, occlusion of arteries of the extremities, skin ulcers, and recurring thrombophlebitis have been observed.

Clinical Diagnostic Criteria. The American Rheumatism Association (ARA) criteria for classifying SLE patients are as follows:

- malar rash
- discoid rash
- photosensitivity
- oral ulcers
- nonerosive arthritis
- serositis
- proteinuria or cellular casts
- psychosis or seizures

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- hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
- evidence of anti-DNA antibodies or false-positive VDRL
- evidence of antinuclear antibodies.

Four or more of these 11 criteria occurring together, or accumulating over time, indicate a diagnosis of SLE.

Laboratory Diagnosis. The typical laboratory findings are summarized in Tab. 4.**26**. Leukopenia, thrombocytopenia with purpura, or hemolytic anemia may be the first manifestations of the disease.

Immunological Diagnosis. Antinuclear antibodies are the serologic hallmark, and are positive in 95% of the patients. However, these antibodies are not SLE specific, as they are also seen in many other autoimmune diseases such as Sjögren syndrome and collagen vascular diseases including scleroderma and Sharp syndrome (Tab. 4.**22**).

Unlike antinuclear antibodies, antibodies to nDNA are highly specific for SLE and are seen in 90% of patients. They are most commonly associated with antinuclear antibodies and antibodies to chromatin.

Only rarely can antibodies to nuclear DNA (nDNA) be seen without the presence of antinuclear antibodies. Equally specific for SLE are antibodies to the Sm-antigen, which is seen in 20–25% of the patients.

Antibodies to histones can be measured in patients with drug-induced SLE. High titers of antibodies to nDNA and the ribonucleoprotein SS-A are associated with HLA haplotypes DR2 and DR3, and point to a higher risk for the development of nephritis. DR4-positive patients with antibodies to both SS-A and SS-B usually show lower levels of antibodies to nDNA, as well as a lower risk for nephritis.

Direct immunofluorescence analysis shows granular deposits of immunoglobulins and complement along the basal membrane of the skin, as well as the basal membrane of the nephric glomeruli. Unlike the systemic form of the disease, discoid lupus only shows immunoglobulin deposits in skin lesions, not in normal-appearing skin. In addition to circulating immune complexes (C1q binding assay, Raji test), SLE activity is evidenced by low complement values (C3, C4).

In addition, antibodies to red blood cells, platelets, neutrophils, and coagulation factors develop in SLE. A false-positive syphilis reaction is distinctive of the presence of antibodies to phospholipids. In primary anti-phospholipid antibody syndrome (APS) or in secondary APS in lupus, the antibody is clinically associated with thrombosis, embolism, relapsing abortions, neurological and cerebrovascular injury, and thrombopenia.

Scleroderma (Progressive Diffuse or Generalized Scleroderma or Progressive Systemic Sclerosis [PSS])

Definition and Epidemiology. Progressive systemic sclerosis (PSS) is an autoimmune disease which affects the connective tissue and leads to fibrosis. The fibrosis is mainly seen in the skin (scleroderma), the lung, gastrointestinal tract, heart, and kidney (Fig. 4.**31**). Onset is between the age of 45 and 60 years of age. Women are affected four times as often as men, and their long-term prognosis is less favorable.

Clinical Features. In PSS, the following manifestations can be seen:

- sclerosis of the *skin* is typically found on the hands (sclerodactyly), with painful ulcers on the fingertips; and in osteolysis on the face, extremities, and trunk (Figs. 4.**32**–4.**36**). Patients have difficulty opening their mouth (microstomy) and complain of dryness of the mouth (xerostomia);
- *arthritis* and Sjögren syndrome;
- symptoms of esophageal involvement, with *dysphagia* and burning pain, bacterial overgrowth with diarrhea, and malabsorption;
- half of the patients complain of exertional *dyspnea* due to pulmonary fibrosis. Bilateral basilar rales are typical;
- *cardiac involvement,* with myocardial fibrosis and arrhythmia. Right heart failure occurs due to pulmonary hypertension;
- *renal failure* with hypertension is the main cause of death.

Differential Diagnosis. PSS must be distinguished from rheumatoid arthritis, SLE, Raynaud syndrome, dermatomyositis, Sjögren syndrome, and mixed connective tissue disease (MCTD) or Sharp syndrome. Many of the patients described by Sharp in 1972 later developed PSS in the course of their disease. Scleroderma-like diseases are also seen in graft-versus-host disease (GVH) after bone marrow transplantation, in primary biliary cirrhosis (PBC), and in intestinal carcinoid syndrome. An association with silicone breast implants has been suggested but remains unverified. Drug-induced scleroderma is observed from exposure to vinyl chloride. Pulmonary fibrosis is observed from exposure to busulfan, bleomycin, and trichloroethylene.
One form of PSS is Thibièrge–Weissenbach syndrome (calcinosis of the skin, tendons, bursas) (Fig. 4.**36**). Another form is CREST syndrome with subcutaneous **c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia. In CREST syndrome, manifestations of the disease in the internal organs are rare.

Diagnosis. Laboratory investigations show antibodies to centromere in CREST syndrome (60%), and anti-Scl70 antibodies in patients with PSS (40%). Diagnosis of PSS

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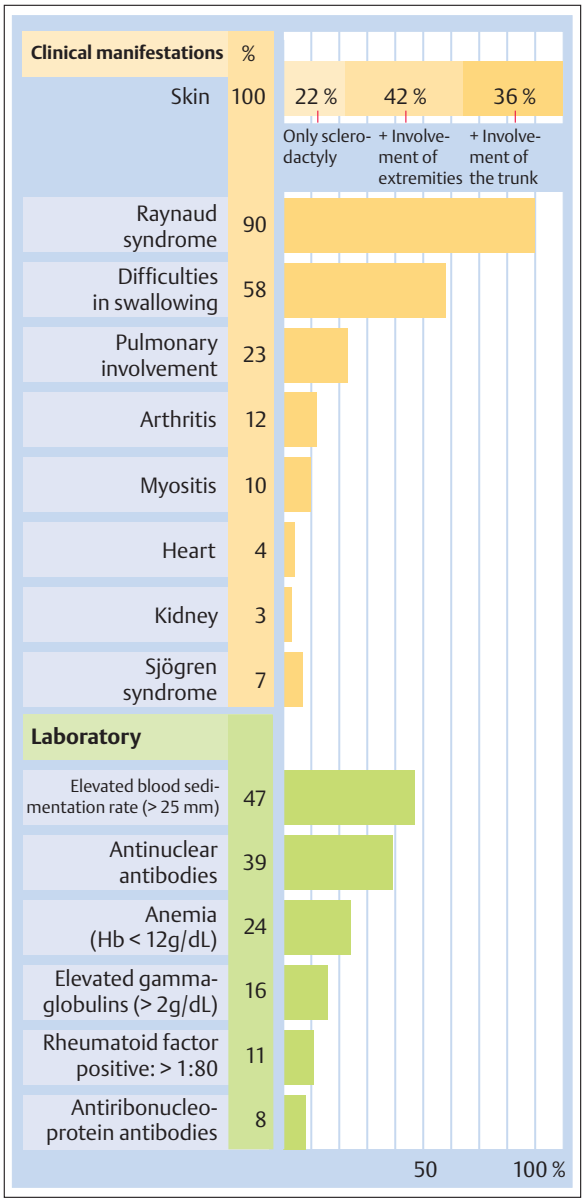

◁ Fig. 4.**31** Clinical symptoms and organ involvement in 426 patients with scleroderma.

is very likely correct if two of the three following signs occur:

- ➤ sclerodactyly
- ➤ ulcers on the fingertips (rat bite necrosis)
- ➤ bilateral basal fibrosis of the lung (chest radiograph).

Circumscribed Scleroderma

Circumscribed scleroderma (morphea) must be differentiated from progressive systemic sclerosis (PSS), as it is limited to the skin, and presents neither with acral lesions nor Raynaud syndrome. Various dermal manifestations have been described: focal forms (morphea en plaques), linear (scleroderma en coup de sabre, sword stroke), and patchy (morphea guttata). The prognosis of circumscribed scleroderma is favorable. Spontaneous remissions are frequent (50 %), and transition into PSS is rare.

Scleroederma Adultorum (Buschke Syndrome)

In both adolescents and women, a sclerodermalike disease named scleroderma adultorum, develops within one to six weeks after an infection, usually streptococci, and initially affects the throat. However, the whole body can become involved. The prognosis is favorable, and the disease resolves after six to 12 months.

Fig. 4.**32** Sclerodermic affliction of the skin of the hands: tightness of the skin ironing out all wrinkles, feeling of tautness.

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Fig. 4.**33** Ulcers on the fingertips (rat-bite necrosis) in scleroderma.

Fig. 4.**34** Resorption of the terminal phalanges in scleroderma.

Fig. 4.**35** Face in scleroderma: tight skin, telangiectases, wrinkles around the mouth, microstomy.

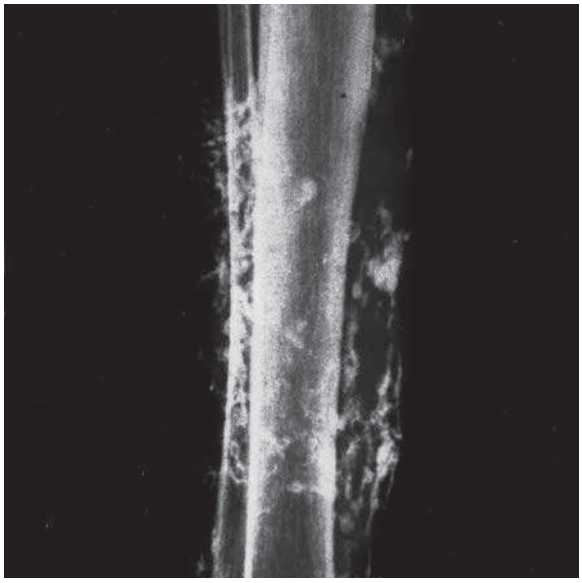

Fig. 4.**36** Subcutaneous calcinosis in scleroderma (Thibièrge–Weissenbach syndrome).

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Eosinophilic Fasciitis (Shulman Syndrome)

Clinical Features. The scleroderma-like disease called eosinophilic fasciitis (Shulman syndrome) is characterized by subepidermal, eosinophilic skin indurations of the extremities with heavily reduced agility of the joints. There is no association with Raynaud syndrome, which is very distinctive of scleroderma, nor is there any involvement of the internal organs.

Diagnosis. The hallmark of this disease is a distinct eosinophilia, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate. Antinuclear antibodies are absent. A good response to systemic treatment with corticosteroid has been observed, and the disease resolves within two to 19 months.

Eosinophilia–myalgia syndrome is triggered by L-tryptophan treatment. However, the disease is resistant to corticosteroid treatment.

Sharp Syndrome, Overlap Syndrome (Mixed Connective Tissue Disease [MCTD])

Mixed connective tissue disease (MCTD) or Sharp syndrome is characterized by a combination of clinical features of systemic lupus erythematosus, progressive scleroderma, and polymyositis. Therefore, clinicians often call it "overlap syndrome."

Clinical Features. The *primary features of* MCTD are:

- arthralgia and arthritis (96%)
- swelling of hands and fingers (88%)
- Raynaud syndrome (84%)
- myositis which mainly affects proximal muscles in the extremities (72%).

Involvement of the kidney is rare, and the response to corticosteroids is positive. After many years, however, MCTD progresses into progressive systemic sclerosis (PSS), and myositis and lupuslike symptoms are no longer the leading symptoms.

Diagnosis. High titers of antinuclear antibodies directed to ribonuclease-sensitive ribonucleoprotein (RNP) are characteristic, but they have also been reported in other connective tissue diseases (Tab. 4.**22**).

Dermatomyositis (Polymyositis)

Definition. Dermatomyositis and polymyositis are inflammatory diseases of the skeletal muscles, the skin, and the connective tissue. If only the skeletal muscles are affected, it is called polymyositis. If, in addition, characteristic skin lesions occur, the disease is termed dermatomyositis.

Clinical Features. Dermatomyositis develops at any age and in both sexes. Women are, however, affected three times as often as men. Weakness of the proximal limb muscles is mainly observed in the legs, arms, throat, and pharynx. Half of the patients report myalgias, pain on palpation, and atrophy of the affected muscles.

In dermatomyositis (40% of myositis patients) a typical, lilac rash is seen, with maculopapular eruptions which might be scaly, on the elbows, knees, knuckles, dorsal side of the fingers, eyelids, and bridge of the nose (Fig. 4.**37**). The skin lesions can be photosensitive.

Further *commonly occurring features* are fever, arthralgia, and Raynaud syndrome. Less common symptoms are pulmonary fibrosis, cardiac disease with necrosis of the myocardial fibers, and arrythmia. Patients with pulmonary fibrosis may have Jo-1 antibodies which are directed to the histidyl-transfer-RNA synthetase. There are frequent overlaps with

Fig. 4.**37** Dermatomyositis with rash on the face in a 33-year-old man.

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scleroderma. Malignant tumors (tumors of the ovary, gastrointestinal tract, pancreas, lung, and lymphoma) develop four times as often in patients with dermatomyositis or polymyositis than in normal patients.

Diagnosis. Increase of skeletal muscle enzymes (including creatinephosphokinase (CPK), aldolase, and transaminase) and of myoglobin reflect the activity of the disease. Antibodies to Jo-1 (20%) and Mi-2 (10%) are specific but show low sensitivity. Rheumatoid factors may be present, and antinuclear antibodies are seen very frequently. Diagnosis is made from biopsy of the affected muscle (Tab. 4.**22**).

Differential Diagnosis. To diagnose polymyositis, the following diseases must be excluded: polymyalgia rheumatica (in which CPK is normal), rapidly progressive muscular dystrophy (which only rarely starts after the age of 30), trichinosis, endocrine disorders (hyperthyroidism, hypothyroidism, Cushing disease, and Addison disease), alcohol-induced myopathy, myasthenia gravis, amyloidosis, and neuropathies.

4.6 Fever in Immune Deficiencies

Classification of Immune Deficiency

As the immune system is responsible for the elimination of both exogenous and endogenous antigens it is no surprise that inherited or acquired deficiencies of elements of the immune system also imply increased risk for development of infectious diseases, autoimmune diseases, and malignant tumors. The interaction of the T and B lymphocytes, antibodies, complement factors, and phagocytes leads to elimination of antigens and clearance of microorganisms. Phagocytes are attracted to the site of infection and, by a process of opsonization, take up antibody-coated microorganisms, leading to intracellular death.

Immune diseases can be initiated by disturbances of various humoral and cellular elements of the immune system. As a consequence various functions of the immune system may be altered. The clinical presenting factors and the severity of the defect depend on the extent of the deficiency and on which part of the physiological system is affected.

Immune deficiencies can be categorized in accordance with the four limbs of the immune system:

- the humoral immune system
- the cellular immune system
- the complement system
- phagocytosis.

Association of an immune deficiency with organ malformations (aplasia of the thymus, malformations of the extremities, enzyme deficiencies), the familial occurrence of the immune defect, and initial manifestations of the defect in early childhood are highly suggestive of an inherited form of immune deficiency (*primary immune deficiency*). *Secondary immune deficiencies* develop as a result of other diseases (Tab. 4.**27**).

Table 4.**27** Classification of immune deficiencies

Humoral immune deficiencies (B-cell deficiencies)	
Primary	– congenital X-linked agammaglobulinemia (Bruton syndrome) – acquired agammaglobulinemia or hypogammaglobulinemia – selective deficiency of IgA, IgM, or IgG subclasses, IgA deficiency associated with IgG2 and IgG4 deficiency
Secondary	– drug-induced: hydantoin, D-penicillamine (IgA deficiency) – loss of proteins: protein losing enteropathy, nephritic syndrome, exfoliative dermatitis, extensive burns (especially a decrease of IgG and IgA levels) – lymphoproliferative diseases: multiple myeloma, chronic lymphatic leukemia, malignant lymphoma, thymoma
Cellular immune deficiencies (T-cell deficiencies)	
Primary	– Di George syndrome (congenital thymic hypoplasia) – chronic mucocutaneous candidiasis
Secondary	– lymphoproliferative diseases: malignant lymphoma, chronic lymphatic leukemia – granulomatous inflammations: sarcoidosis, lepra, fungal infections (coccidioidomycosis, histoplasmosis) – viral infections: measles, rubella, hepatitis B – HIV infection – autoimmune diseases: lupus erythematosus, chronic polyarthritis, thyroiditis etc. – postoperative transitory immune deficiency – malignant tumors – renal and liver insufficiency – immune suppressive therapy

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Tab. 4.**27** (Continued)

Combined humoral and cellular immune deficiencies	
Primary	– severe combined immune deficiency – Nezelof syndrome – Wiskott–Aldrich syndrome – ataxia telangiectasia
Secondary	– lymphoproliferative diseases: malignant lymphoma, chronic lymphatic leukemia, multiple myeloma
Defects of the complement system	
Primary	– C1 (C1r/C1s) deficiency – isolated C2, C4, C3, C5, C6, or C7 deficiency – C1 inhibitor deficiency (angioedema)
Secondary	– membranoproliferative glomerulonephritis (decrease in C3) – partial lipodystrophy (decrease in C3) – immune complex diseases: serum disease, lupus erythematosus, rheumatoid arthritis, endocarditis associated with nephritis, shunt nephritis, cryoglobulinemia (mixed type) – autoimmune diseases: Sjögren syndrome, paroxysmal cold hemoglobinuria, hemolytic anemia, myasthenia gravis – urticaria – septicemia (especially Gram-negative septicemia) – liver insufficiency
Defects in phagocytosis*	
Primary	– Chediak–Higashi disease (C, D, K) – leukocyte adhesion deficiency (C) – Job syndrome (C, K) – Down syndrome (P) – septic granulomatosis (D, K) – myeloperoxidase deficiency (K) – glucose-6-phosphate dehydrogenase deficiency (K) – humoral immune deficiencies (O) – complement deficiencies (O, C)

Secondary	– deficient opsonization:
	  – humoral immune deficiencies (IgG, IgM)
	  – complement deficiencies (C3b, C5)
	– deficient chemotaxis:
	  – lack of chemotactic factors (C3a, C5a, C567 complex)
	  – measles
	  – diabetes mellitus
	  – rheumatoid arthritis
	  – chronic liver insufficiency
	  – drug-induced (steroids, phenylbutazone, colchicine, chloroquine)
	  – hypophosphatemia
	– inhibitors of phagocytosis:
	  – Wiskott–Aldrich syndrome
	  – chronic mucocutaneous candidiasis
	  – IgA myeloma
	  – malignomas
	– chemotactic factor inactivators:
	  – sarcoidosis
	  – Hodgkin disease
	  – lepra
	  – liver cirrhosis
	– deficient phagocytosis:
	  – quantitatively: agranulocytosis
	  – qualitatively: diabetes mellitus
	  – hemolysis
	  – lymphoproliferative diseases
	  – immune complex diseases
	  – renal insufficiency
	  – burns
	– deficient intracellular elimination:
	  – drug-induced (steroids, cyclophosphamide, colchicine)

* O, opsonization; C, chemotaxis; P, phagocytosis; K, intracellular elimination; D, degranulation.

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Humoral Immune Deficiencies (B-cell Deficiencies)

B Lymphocytes. The humoral immune system is characterized by the presence of cells of the B-lymphocyte lineage, which develop from stem cells of the hemopoetic system. B lymphocytes express membrane–bound immunoglobulins and HLA class II antigens. Various receptors recognize the following molecules:

- Fc part of immunoglobulins
- complement components (C3b and C3d)
- cytokines such as interleukin-2, interleukin-4, interleukin-5, interleukin-6, and interferon-γ
- Epstein–Barr virus.

The binding of antigens to membrane-bound immunoglobulins on the B lymphocytes and the interaction of B lymphocytes with T lymphocytes lead to both the proliferation of B cells and the maturation of the B cells into plasma cells which secrete immunoglobulins.

Function of the Humoral Immune System. Antibodies produced by B lymphocytes are crucial for the binding of antigens. Acting as opsonins, they promote phagocytosis of bacteria. Antibodies are also able to neutralize toxins, prevent absorption of virus to host cells, and initiate lysis of antigen-loaded cells by binding of complement. The secretor immune system of the mucosa is mainly composed of secretor IgA which, after oral and bronchial exposure to antigens, forms the local defense system of the mucosa in the respiratory tract, the gastrointestinal tract, and the urogenital tract. As a polymer, secretor IgA is bound to both the J chain and the secretory component produced by glandular epithelial cells.

Primary Humoral Immune Deficiencies. In primary humoral immune deficiencies the primary humoral immune system shows either hypogammaglobulinemia or agammaglobulinemia with decreased levels of all immunoglobulin classes, either seen in the serum electrophoresis or presenting with a deficiency of a single immunoglobulin class or subclass (Fig. 4.**38**).

In *X-linked agammaglobulinemia*, or Bruton syndrome, observed in children, B lymphocytes and plasma cells are absent due to failure of maturation of pre-B cells. This disease is caused by a mutation of the *ATK* gene situated on the X-chromosome long arm encodes a tyrosine kinase. *Acquired hypogammaglobulinemia or agammaglobulinemia* are the equivalent diseases in adults resulting in either diminished or increased numbers of B lymphocytes. These defects are generated either by suppressor T cells, which inhibit B-cell maturation or by the lack of T-helper lymphocytes, which promote B-cell maturation. These diseases can occur in people of any age, are often familial, and affect both sexes equally.

The clinical manifestations of *acquired hypogammaglobulinemia or agammaglobulinemia* resemble the picture observed in *selective IgA deficiency*, the most common primary immunodeficiency state. IgA deficiency as a hereditary disease is seen sporadically, or rarely, only occurring in 0.1 % of the population. *Selective deficiency of IgM* or *single IgG subclasses* is rarely seen (Tab. 4.**27**). IgA deficiency can be associated with low IgG2 and IgG4 subclasses. In the latter case, clinical symptoms are frequent and include chronic infections with decreased antibodies to polysaccharide antigens.

Clinical Features. The prominent clinical feature of humoral immune deficiency states is increased susceptibility to bacteria, especially to staphylococci, streptococci, pneumococci, and *Haemophilus influenzae*. The sites of infection are:

- upper respiratory tract with sinusitis, otitis, bronchitis, and pneumonia
- infections of the gastrointestinal tract with diarrhea and malabsorptions (Spruelike syndrome)
- septicemia with abscesses in the skin, bones, meninges and/or joints.

Besides infections, there is increased frequency of atopic disorders (allergic rhinitis, bronchial asthma, and eczema). Rarely, an association with autoimmune disease is observed, especially pernicious anemia. The occurrence of malignant tumors is even rarer.

Secondary Humoral Immune Deficiencies. Secondary humoral immune deficiencies include IgA deficiency in epileptics treated with hydantoins, IgA deficiency occurring during treatment with D-penicillamine, and immunodeficiencies caused by either a viral infection or a protein-losing syndrome (nephrotic syndrome, exudative gastroenteropathy, exfoliative dermatitis, extensive burns). Humoral immune deficiency states associated with malignant lymphoma, or in the course of treatment with cytotoxic drugs, are accompanied by altered T-lymphocyte numbers and functions. 10 % of patients with thymoma show hypogammaglobulinemia, with absence of both pre-B cells and B cells due to abnormalities of the stem cells.

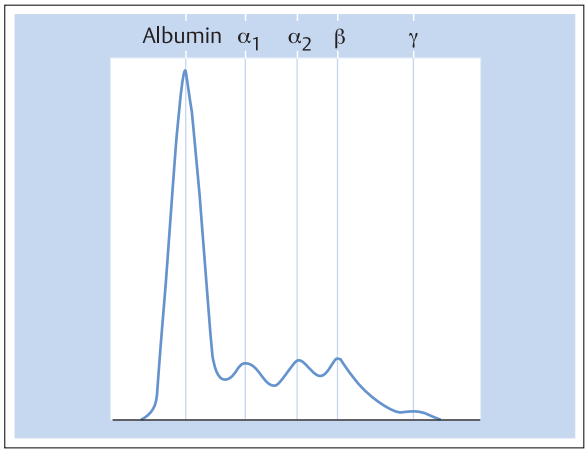

Fig. 4.**38** Electrophoresis in agammaglobulinemia (γ-globulin peak almost absent).

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Cellular Immune Deficiencies (T cell Deficiencies)

T Lymphocytes. T lymphocytes are regarded as the key element of the cellular immune system. Under the influence of thymic epithelial cells and thymic hormones, T lymphocytes develop from pluripotent hemopoetic stem cells, cross the medulla of the thymus, and travel into the thymus cortex. They then invade the paracortical regions of the lymph nodes, the perivascular areas of the spleen, and the interfollicular areas of the intestinal lymphatic tissue, and from there they return to the blood stream.

Function of the cellular immune system. Maturation of T lymphocytes is paralleled by the expression of functionally important membrane structures such as the CD3 molecule. The latter is linked to the so-called T cell receptor, which is the antigen recognition structure of T cells. T helper lymphocytes express the CD4 molecule and are able to recognize antigen on antigen-presenting cells in the context of MHC/HLA class II proteins, whereas cytotoxic T lymphocytes express the CD8 molecule and are able to recognize the antigen on MHC/HLA class I proteins. Antigen-presenting cells secrete cytokines such as interleukin-1, interleukin-6, and interleukin-12, which promote activation of the immune system.

Primary Cellular Immune Deficiencies. In children, the main primary immune deficiency diseases are *Di George syndrome* and *chronic mucocutaneous candidiasis:*

- *Di George syndrome.* This disease results from maldevelopment of the third and fourth pharyngeal pouches, and is associated with congenital cardiac defects, failure of parathyroid development, and an abnormal thymus.
- *Chronic mucocutaneous candidiasis.* This immunodeficiency state is characterized by a singular defect in the recognition of *Candida* antigens by T cells, with normal T cell responses to other antigens. In addition to chronic *Candida* infections of the skin, the mucosa, and the nails, presenting features also include endocrine abnormalities such as primary hypoparathyroidism, Addison disease, pernicious anemia, and type 1 diabetes mellitus (Tab. 4.**27**).

Secondary Cellular Immune Deficiencies. Secondary T cell deficiencies in adulthood are mainly due to lymphoma, granulomatous inflammations (sarcoidosis, leprosy, fungal infections), viral infections (measles, rubella, hepatitis B, HIV), autoimmune diseases, major surgery, malignant tumors, kidney and liver failure, and immunosuppressive treatment (Tab. 4.**27**).

Clinical Features. Functional abnormalities of the cellular immune system are evidenced by decreased circulating T lymphocytes, and altered functions of T lymphocytes when exposed to mitogens or antigens in vitro. This results in lower skin reactivity to ubiquitous antigens (anergy of the skin). The number of circulating B lymphocytes and the number of immunoglobulins are both normal.

Severe viral infections (varicella, herpes, cytomegalovirus, measles, and adenovirus), fungal infections (*Candida*, *Aspergillus*), protozoan infections (*Pneumocystis carinii*, *Toxoplasma*) and bacterial infections (*Mycobacteria*, *Listeria*) are characteristic of a deficient cellular immune system. Complications arising from use of live virus vaccines (generalized vaccinia, BCG disease), as well as the development of malignant tumors (lymphoma, thymoma) have been reported.

Diagnosis. Monoclonal antibodies to various subsets of T lymphocytes have been established including antiserum to CD3, which recognizes all T cells, CD4 (T helper lymphocytes), and CD8 (cytotoxic T lymphocytes). The ratio of CD4 to CD8 positive cells is usually ≥ 1.2. Decreased CD4/CD8 ratios are seen in AIDS, hemophilia, and in patients showing viral infections after organ transplantation (cytomegalovirus, Epstein–Barr virus).

Combined Humoral and Cellular Immune Deficiencies

Lymphopenia, agammaglobulinemia, and lack of responsiveness of T lymphocytes to antigens are diagnostic of X-chromosomal- or autosomal-inherited severe combined immunodeficiency. Some patients show an inherited enzyme deficiency with absence of adenosine deaminase. Other patients present deficiencies in the interleukin-2 receptor γ-gene or in the transcription factors that regulate the expression of MHC/HLA class II genes. Differentiation from other immunodeficiency states seen in children is based on distinctive clinical and immunological presentations.

- *Nezelof syndrome* is characterized by lymphadenopathy, hepatosplenomegaly, and Coombs-positive hemolytic anemia.
- The occurrence of eczema, thrombocytopenia, and repeated infections are diagnostic of X-chromosomally inherited *Wiskott–Aldrich syndrome*. Immunization with polysaccharide antigens does not generate specific antibodies. Low IgM levels are usually detected. Besides complications due to infections and bleeding, all patients with this syndrome develop lymphoreticular malignancy (e. g., in the central nervous system). Mutations of the *WASP* gene (Wiskott–Aldrich syndrome protein gene) have also been reported. However, the relation of this mutation to the clinical symptoms remains unexplained.
- In *ataxia teleangiectasia,* chronic infections of the respiratory tract are associated with teleangiectases

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in the skin and conjunctiva. Progressive neurological symptoms with ataxia, choreoathetosis, and extrapyramidal symptoms rapidly become dominant. Two-thirds of patients present with an IgA deficiency (Tab. 4.**27**). This disease occurs due to mutation of the *AMT* gene on chromosome 11q22–33, a gene that is involved in regulating oxidative stress mechanisms.

Defects of the Complement System

The complement system is activated by immune complexes, bacteria, and endotoxin, and produces a great number of biological effects directed at promoting inflammation, phagocytosis, neutralization of viruses, and cell lysis. Inflammation is triggered by chemotactic and anaphylactic complement components.

Primary Deficiencies. Inherited deficiencies of a single complement factor, out of the 19 that are known, are only rarely associated with increased susceptibility to infections (deficiency of C1r and of terminal components C5–C8). Complement defects are more commonly involved in the pathogenesis of systemic lupus erythematosus and related diseases (deficiency of C1, C4, and C2) and of glomerulonephritis (deficiency of C1r and C2).

Deficiency of C1 inhibitor leads to *angioedema.* This is an autosomal dominant hereditary disease. Diagnosis can be made by observation of episodes of edema of the skin (especially on the face) and the mucosa. In the latter case laryngeal edema can develop, and leads to death in up to 25% of the patients. Recurrent gastrointestinal attacks of colic develop through mucosal edema. Deficiency of the C1 inhibitor results in overshooting activation of C1 with consumption of C2, C4, and occasionally C3. Triggers of the disease in women are menstruation and pregnancy. An acquired form of angioedema with antibodies binding C1 inhibitor is seen in lymphoproliferative diseases.

Secondary Deficiencies. The so-called C3 nephritic factor, one example of a secondary complement deficiency, leads to consumption of C3 which forms the basis for mesangiocapillary glomerulonephritis and/or partial lipodystrophy. Low levels of serum complement factors can be observed in immune complex diseases, autoimmune diseases, urticaria vasculitis, septicemia, and hepatic failure (Tab. 4.**27**).

Defects of Phagocytosis

Physiologic Basis. Neutrophils and monocytes can opsonize bacteria and fungi by expressing receptors for IgG and complement factors, and thereby phagocytose infectious particles. Inside the cells, the phagosome merges with the granulas, which leads to intracellular lysis of the infectious agents and, eventually, to cell death.

During this process, a burst of oxygen consumption and activation of the hexose-monophosphate shunt are required. Lysis of the infectious particles also involves other components of cellular granules such as myeloperoxidase, antimicrobial peptides, and enzymes.

Dysfunction of Chemotaxis and Opsonization. In inherited or acquired deficiencies with absence of chemotactic complement factors (C3a, C5a, C5, C6, C7), complement receptors (iC3b receptor), or opsonins (IgG, IgM associated with C1–C4, C3b, and C5), impairment of chemotaxis or opsonization is observed.

- In inherited lazy leukocyte syndrome (LAD), which is caused by mutation of the beta chain of the adhesion molecule LFA-1 and the complement receptor 3 (MAC-1), neutrophils fail to invade the tissue due to impaired adherence and chemotaxis.
- Isolated *deficiencies of chemotaxis* are seen in patients with chronic eczema, bacterial infections of the skin with formation of abscesses, and relapsing pneumonia. IgE serum concentrations are often increased.
- *Reduction of chemotaxis* is seen in various diseases, such as measles infection, diabetes mellitus, rheumatoid arthritis, kidney failure, and hypophosphatemia (during parenteral hyperalimentation).
- *Inhibitors of chemotaxis* acting on phagocytes are encountered in Wiskott–Aldrich syndrome, chronic mucocutaneous candidiasis, IgA myeloma, and malignant tumors. Factors which *inactivate chemotactic factors* and thereby inhibit chemotaxis are seen in sarcoidosis, Hodgkin disease, lepra, and cirrhosis of the liver.
- *Multiple defects in chemotaxis, opsonization, and phagocytosis* are distinctive of some rare diseases in childhood (Job syndrome, Chediak–Higashi syndrome). Diminished intracellular elimination of microbes is caused by deficiencies of the enzymes glucose-6-phosphate dehydrogenase and glutathione peroxidase, which both result in an altered hexose-monophosphate shunt. In septic granulomatosis, *impairment of intracellular elimination of microorganisms* is induced by NADH-oxidase deficiency, which leads to diminished production of H_2O_2.
- Various medications impair chemotaxis (corticosteroids, phenylbutazone, colchicine, chloroquine) or *intracellular elimination* of microorganisms (corticosteroids, phenylbutazone, sulfonamide) (Tab. 4.**27**).

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Dysfunction of Phagocytosis. Acquired forms of impaired phagocytosis include quantitative diminution of phagocytes (neutropenia), disturbed function of phagocytes in diabetes mellitus, immune complex diseases (lupus erythematosus, rheumatoid arthritis), hemolysis, leukemias, kidney failure, burns, and severe bacterial infections.

4.7 Fever in Various Noninfectious Conditions

Periodic Fever

Definition. This term refers to fever attacks of one to four days duration, which occur over a period of years at more or less regular intervals.

Clinical Features. While the rise in temperature is the obligatory symptom, the secondary symptoms (arthralgia, myalgia, impairment of general health) can vary.

Diagnosis. In addition to fever the objective parameters that can be determined are an elevated ESR, CRP, a moderate leukocytosis with left shift, rarely joint swelling, skin manifestations, as well as an acute abdomen.
After excluding infectious and neoplastic diseases as well as collagenosis, recurrent fever attacks over a period of years lead to the consideration of several clinical pictures (Tab. 4.**28**).

Familial Mediterranean Fever

This is an autosomal recessive disease which is caused by a mutation in the pyrin gene. The disease has primarily been described in Jewish, Armenian, Turkish, and Arab populations and occurs throughout the Mediterranean region. In addition to recurrent fever attacks at two to four week intervals, which last 12–72 hours, the typical clinical presentations include arthritis (60%), myalgia, mostly unilateral pleural thoracic pain (30%), erysipeloid erythema, and often severe abdominal pain with peritonitis (90%), which can lead to laparotomy if an acute abdomen is suspected. Amyloidosis is described as a late-occurring complication.

Mutation of the pyrin gene in leukocytes is of pathogenetic significance and results in the uncontrolled activation of various mediators of inflammation, such as complement factor C5a. During an attack the ESR, CRP, and fibrinogen levels are elevated (Tab. 4.**28**).

Hyper-IgD Syndrome

The *hyper-IgD syndrome* has a clinical picture that is similar to that of familial Mediterranean fever. Starting in newborns or infants, fever attacks develop which last three to seven (maximally 14) days and recur at intervals of four to eight weeks. The fever is accompanied by lymph node enlargement, splenomegaly (50%), arthralgia or arthritis, abdominal pain, peritonitis with secondary adhesions, and erythematous skin alterations.

In addition to leukocytosis and an elevated ESR, repeated, elevated IgD values are crucial to the diagnosis (possibly combined with elevated IgA). A mutation of mevalonate kinase has been confirmed. This leads to a

Table 4.**28** Differential diagnosis of familial Mediterranean fever (FMF), hyperimmunoglobulinemia D syndrome (HIDS), and tumor necrosis factor (TNF) receptor-associated periodic fever (TRAPS)

	FMF	HIDS	TRAPS
Mutation	pyrin gene	mevalonate kinase gene	TNF receptor1 gene
Mode of inheritance	autosomal recessive	autosomal dominant	autosomal dominant
Age at time of first clinical manifestations (years)	< 20	< 1	< 20
Attack duration of fever	0.5–3 days	3–7 (maximally 14) days	1–2 (maximally 10) days
Clinical manifestations	sterile pleuritis and peritonitis arthritis	lymphadenopathy arthritis peritonitis maculo-papular rash	myalgia periorbital edema pleuritis arthralgia
Laboratory findings	leukocytosis, CRP ↑	leukocytosis, CRP ↑ IgD ↑ (possibly IgA ↑)	leukocytosis CRP ↑ soluble TNF receptor 1 ↓

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slight reduction of serum cholesterol and an elevated mevalonic acid concentration in the urine. The relationship of the mevalonate kinase mutation to the elevated IgD value and inflammation is unclear. Elevated IgD values also can be found in chronic infections (HIV, tuberculosis), aspergillosis, sarcoidosis, lymphomas, and in smokers (Tab. 4.**28**).

Tumor Necrosis Factor Receptor-associated Periodic Fever Syndrome (TRAPS)

The autosomally dominant inherited mutations in the tumor necrosis factor receptor 1 gene (especially observed in Ireland and Scotland) exhibit a recurrent fever that lasts for one to two (maximally 10) days, notably severe myalgia, abdominal pain with possible diarrhea, periorbital facial edemas with conjunctivitis, exanthema, pleuritis, and arthralgia. The CRP and leukocyte values in the serum are elevated and the soluble TNF receptor 1 is reduced (Tab. 4.**28**).

"PFAPA" Syndrome

The etiologically unexplained "PFAPA" syndrome (**p**eriodic **f**ever, **a**denitis, **p**haryngitis, and **a**phthous stomatitis) can cause long-lasting, periodic fever in infants. The attacks, which last for three to five days, are partially accompanied by headaches and abdominal pain, and elevated parameters of inflammation are present. The prognosis is good and permanent consequences apparently do not occur.

Other recurrent periodic fevers and *cyclic neutropenia* must be excluded.

Fever in Endocrine Disorders

Elevated temperatures are known to occur in *hyperthyroidism*, namely when an underlying case of *subacute thyroiditis* is present. In *thyrotoxic crises* the fever increases to over 40 °C. Fever is also a frequent symptom in an *Addisonian crisis*. This must especially be considered when discontinuing long-term steroid therapy. In contrast other *steroids (e.g., progesterone)* are themselves pyrogenic. Individual patients with *pheochromocytoma* also exhibit elevated temperatures. The rare combination of hyperglycemia and fever is also attributed to elevated catecholamines. Also worth mentioning are cases of hyperthermia in *acute hyperparathyroidism* with extremely high calcium values. These are due to lesions near the thermoregulation center of the *hypothalamus*.

Fever in Vegetative Dystonia

Differentiation between *hyperthyroid* rises in temperature and *vegetatively* caused febrile conditions is often very difficult, because the symptoms frequently overlap. However, the specific hyperthyroid symptoms such as fine tremor, constant resting tachycardia, warm moist skin, ocular symptoms, and struma do not belong to vegetative dystonia. In doubtful cases, determination of thyroid gland hormone values can facilitate a differentiation.

Chronic Mercury Intoxication

The differential diagnosis should also consider chronic mercury poisoning. Persons with a long-term and concentrated exposure to mercury vapors in industry and certain laboratories can present with the following symptoms: loss of appetite, weight loss, gastric symptoms, sleeplessness, increased salivation, stomatitis, diarrhea, neurological disorders (fine tremor of the hands, eyelids, lips, and tongue, ataxia, dysarthria), mental disorders (depression, irritability, anxiety, exaggerated emotional reactions), and vegetative disorders (dermographism, blushing and turning pale, sweating). A detailed work history and multiple determinations of mercury excretion values in the urine can confirm the diagnosis.

Chronic Fatigue Syndrome

Chronic fatigue syndrome is a controversial entity whose etiology is unknown.

Clinical Features. The clinical manifestations are very nonspecific, variable, and include chronic fatigue, sleep disorders, states of diffuse pain, and fever. The possible causes which are being discussed include chronic infections, immune dysfunctions, muscle diseases, neurobiological dysfunctions, or psychogenic disorders. Various viral diseases (Epstein–Barr virus, cytomegalovirus,

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enteroviruses), have been ruled out as possible causes.

Diagnostic Criteria. The case definition of the American Centers for Disease Control requires:

- ➤ the exclusion of a somatic, mental, or psychiatric underlying disease or addiction
- ➤ severe fatigue lasting for six months
- ➤ four or more of the following symptoms:
  - impaired memory or reduced level of concentration
  - sore throat
  - painful cervical or axillary lymphadenopathy
  - myalgia
  - polyarthralgia
  - headaches (newly occurring)
  - sleep disorders
  - a feeling of malaise which lasts for 24 hours after physical exertion.

Fever in Tumors

In some tumors, unexplained febrile states often remain in the foreground of the clinical presentation for a long period of time. These rises in temperature are already present at an early stage, and therefore, can hardly be explained by tumor lysis. Among solid tumors, it is mainly hypernephroma and carcinomas of the pancreas, liver, and stomach that are associated with fever. In bronchial carcinoma the tumor itself, as well as secondary pneumonic processes can cause fever. An additional cause is atrial myxoma (changing findings on auscultation, recurrent embolisms, joint pain). Tumors of the lymphoreticular system, such as malignant lymphomas or leukemias, frequently cause recurrent febrile states. In 5–10% of patients with lymphogranuloma a characteristic periodic type of fever (Pel–Ebstein) is observed (Figs. 4.**39**, 4.**40**).

In Hodgkin disease and non-Hodgkin lymphoma *A-symptoms* are present if general symptoms are absent. *B-symptoms* are present if a weight loss of more than 10% within a six-month period and/or an inexplicable fever of more than 38 °C and/or night sweats are observed. Pruritus and alcoholic pain do not count as B-symptoms.

Fever in Tissue Degradation

Frequent causes of fever include: myocardial infarction, pulmonary infarction, renal infarction, gangrene of the extremities, pancreatitis, cirrhosis of the liver, resorbent hematomas in body cavities or in the gastrointestinal tract, or intracranial hemorrhages. However, in these cases it is virtually always the primary clinical event and not the fever which is in the foreground.

Fever in Hemolysis

Additional causes of fever are *hemolytic crises*, especially in sickle cell anemia, intravascular hemolyses, and *transfusion incidents*.

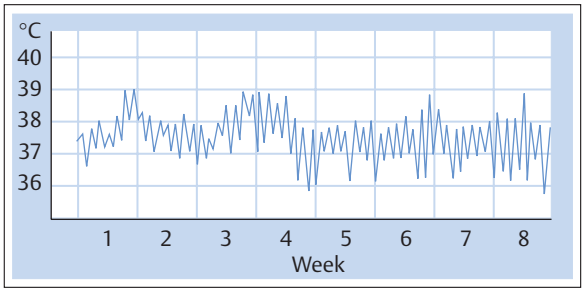

Fig. 4.**39** Fever curve of a patient with a malignant lymphoma showing a remittent–intermittent pattern of body temperature.

Fig. 4.**40** Periodic fever (Pel–Ebstein) in a patient with lymphoma.

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Hemophagocytosis Syndrome

Hemophagocytosis syndrome (also called hemophagocytic lymphohistiocytosis) is a rare, but often very severe, multiorgan disease with a high mortality rate. It is associated with malignant or autoimmune diseases or can develop after activation of macrophages (probably infection related). The clinical picture has been associated with a great variety of microorganisms, but most frequently with Epstein–Barr, cytomegalovirus infection, hepatitis, or HIV infections.

In the bone marrow and other lymphoepithelial tissues an increased number of histiocytes phagocytose erythrocytes, leukocytes, and thrombocytes. The histiocytes and other blood cells are morphologically mature. The clinical presentation is characterized by fever, splenomegaly, lymphadenopathy, hepatomegaly, jaundice, and sometimes an exanthema or neuropsychological deficits. The cardinal symptom is pancytopenia and there is often a massive elevation of the ferritin value, an intravascular coagulation disorder, and hepatic dysfunction.

Fever in Thrombosis and Thrombophlebitis

Thrombosis, phlebitis, and thromboembolisms can be accompanied by fever even in the absence of any significant clinical findings. Of these, especially recurrent pulmonary embolisms are of great practical significance. After long-term infusion therapy, thrombophlebitis frequently occurs in the arms. The differential diagnosis in these cases must also exclude endoplastitis with bacteremia or septicemia.

Fever in Allergic Reactions

In this group *drug fever* is of greatest significance. Nearly all medications can cause fever if the patient is hypersensitive. Sometimes (but not obligatorily) this fever reaction is accompanied by skin manifestations, which make the diagnosis easier. The drug eruptions exhibit an extremely varied morphology. The most frequently occurring are maculopapular exanthemas and urticaria. Scarlatiniform (e. g., quinine), morbilliform (e. g., barbiturates), bullous, eczematous, and purpuralike exanthemas also occur.

A febrile *erythema nodosum* or a Stevens–Johnson syndrome is observed after taking diphenylhydantoin or sulfonamides.

In *drug fever*, eosinophils are usually present in the peripheral blood, but eosinophilia exists only in approximately 20 % of the cases. The ESR or CRP values can be significantly elevated and often leukocytosis and slightly elevated transaminase levels are also present. One to two days after discontinuing the responsible medication, the fever generally can be expected to remit. A renewed exposure to the responsible medication can possibly cause an anaphylactic reaction.

Simulated Fever

Simulated fever is usually recognized in persons with psychosocial or psychiatric problems by the atypical course and the disproportion between the magnitude of the temperature and the pulse rate. A thorough medical history and the discrepancy between the oral and rectal temperature makes it possible to detect these cases.

4.8 Significance of Individual Findings for the Differentiation of Febrile States

Course of the Temperature

Some febrile clinical pictures exhibit a characteristic course of the fever. The knowledge of these fever courses is extremely instructive in the differential diagnosis, even if during the first days of the disease, in which the diagnosis must be made, the typical characteristics usually are not yet discernible. Furthermore, antibiotics or antiinflammatory analgesics frequently falsify the typical fever courses:

- In *continuous fever* the morning and evening temperatures only fluctuate, insignificantly, by 1 °C.

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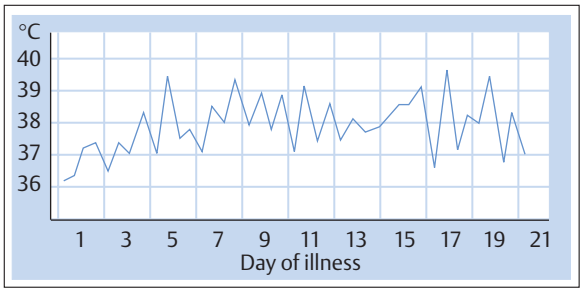

Fig. 4.**41** Remittent fever in tuberculous peritonitis.

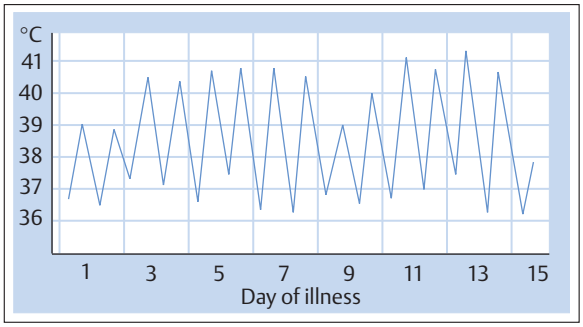

Fig. 4.**42** Intermittent fever in septicemia.

Continuous fever is, for example, typical in *pneumococcal pneumonia*, *typhoid*, *paratyphoid*, *spotted fever*, and *erysipelas*.

- The *remitting fever type* exhibits a considerable difference (up to 2 °C) between the morning and evening temperature, whereby the morning temperature usually does not reach afebrile values (Fig. 4.**41**). This temperature course is observed in many diseases, e. g., *tuberculosis*, *circumscribed suppuration*, *septic processes*, *bronchopneumonia*, some *viral diseases*, and *rheumatic fever*.
- In the *intermittent fever type* the differences between the morning and evening temperatures are even greater. The morning temperature also falls below 37 °C. This type of fever occurs, for example, in acute *pyelonephritis*, *pleuritis*, and *sepsis* (Fig. 4.**42**).
- *Irregular*, *wavelike (undulating) fever courses* are seen in brucellosis (however, not pathognomonic). A fever course of a special form is the Pel–Ebstein fever type in lymphogranuloma (Fig. 4.**40**).
- Regular, periodic rises in temperature are typical for malaria, trench fever (quintana fever due to *Bartonella quintana*), and relapsing fever.
- *Periodically* occurring higher temperatures at *irregular intervals* can be found in diseases with a tendency to develop inflammatory recurrences such as *bronchiectasis*, *cholelithiasis*, *prostate diseases*, etc.

Chills

Frequently, true chills are observed in the following conditions:

- bacteremia of various origins
- sepsis, subacute bacterial endocarditis
- bacterial pneumonia
- meningococcal meningitis
- erysipelas
- malaria
- acute pyelonephritis
- Weil disease
- allergic reactions (intravenous drugs, radiograph contrast media, or blood products).

Chills occur *rarely* in tuberculosis, paratyphus, typhus (even rarer than in paratyphus), rickettsiosis, and viral diseases and *never* in rheumatic fever.

Inflammation Parameters

Erythrocyte Sedimentation Rate (ESR)

An elevated sedimentation rate primarily depends on an increase in the quantities of fibrinogen and the globulins at the expense of the albumins. Such shifts of the plasma proteins can occur not only in inflammatory processes, but also in many other pathological conditions, most extensively in tumors with tissue disintegration.

In diseases with acute onset elevation of the sedimentation rate is generally absent, because a preliminary phase of about 30 hours is necessary. On the other hand, elevation of the sedimentation rate often persists for weeks after an illness. This must especially be considered in the evaluation of sedimentation values during convalescence.

- The *sedimentation rate is significantly elevated* in all circumscribed, *purulent processes* (important exception: appendicitis in the early stage), most *bacterial infections* (pneumonia, meningococcal meningitis, pyelonephritis), the *leptospiroses*, *moderately signifi-*

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cant also in brucelloses and *tuberculosis* (not obligatory). Especially high values can be found in *rheumatic fever*, vasculitis, collagenoses, noninflammatory processes, which are accompanied by *dysproteinemia* (malignant tumors, hepatic diseases, etc.), and often in drug fever. The highest values are found in multiple myeloma (Tab. 4.**29**).

- Despite the presence of *febrile states*, the sedimentation rate is *not or only slightly accelerated in many viral diseases*. In tuberculosis (even in open forms) low sedimentation rates can be found.
- If the values obtained are inconsistent with the remaining clinical findings, it should always be determined whether other factors are present that, for example, could explain an abnormally low sedimentation rate. These primarily include erythrocytosis, heart failure, or treatment with corticosteroids. In contrast, a moderate acceleration of the sedimentation rate occurs in anemia.
- An elevated sedimentation rate in individuals who do not exhibit any disease symptoms (either because the elevation has not regressed during convalescence or the elevation was discovered during a checkup) can pose very difficult problems in the differential diagnosis.

C-reactive Protein (CRP)

In the differential diagnosis of fever increased interest has been shown in CRP, because a significantly elevated value indicates a bacterial infection, but not a viral infection. However, in a clinical emergency the sensitivity or specificity of CRP may prove inadequate and mislead the differential diagnosis. In the early phase of peracute, systemic, bacterial infections, CRP can still be low and is often still low in bacterial abscesses, even in an advanced phase. In contrast, CRP can be clearly elevated in viral infections and can be significantly elevated in rheumatological diseases or in tissue damage (trauma, operation). In cases of systemic vasculitis a CRP elevation reflects the disease activity, without a bacterial infection needing to be present.

CRP responds rapidly to short-term changes of inflammatory activity, while the sedimentation rate plays the main role in the diagnosis and monitoring of long-term inflammatory changes.

Procalcitonin

Precursors of calcitonin, including procalcitonin, are significantly elevated in severe bacterial infections, but usually are only slightly or moderately elevated in viral infections or noninfectious inflammatory diseases. Compared with CRP, procalcitonin values rise earlier in bacterial infections.

Table 4.**29** Selected causes of an elevated erythrocyte sedimentation rate (ESR)

Inflammatory diseases
– Tonsillitis
– Inconspicuous sinusitis
– Dental granuloma (slight elevation of BSR)
– Phlebitis
– Cholecystitis
– Unnoticed tuberculosis
– Brucellosis
Rheumatic diseases
– Collagen vascular and hypersensitivity diseases
Liver and kidney diseases
Neoplasms
– Hypernephroid carcinoma
– Neoplasms of the gastrointestinal tract
– Neoplasms of the urogenital tract
– Neoplasms of other location
– Malignant lymphoma
Dysproteinemias
Anemia

Sensitivity and Specificity. Procalcitonin has been most successfully validated in severely ill patients receiving intensive care (ICU) in whom infectious and noninfectious complications normally can be readily distinguished by measuring the procalcitonin value.

Procalcitonin has been less systematically examined in many other settings and clear cutoff values are presently unavailable. The sensitivity and specificity of procalcitonin for the diagnosis of a bacterial infection are significantly under 100 %. For example, procalcitonin can be elevated in noninfectious diseases, and even in a severe bacterial infection, including infectious sepsis, can remain low. The predictive value of procalcitonin is especially limited or unusable in neutropenic patients with fever or after allogenic, bone marrow transplantation:

- The procalcitonin value can be *very high* in the newborn, malaria, fungal infections, within one to three days after trauma, after burns, and one to two days after surgery (especially after cardiopulmonary bypass).
- The value is also *high* in patients with a medullary carcinoma of the thyroid gland, small cell bronchial carcinoma, carcinoid tumor, and occasionally in neuroendocrine tumors.
- *Mild to moderate* elevations of procalcitonin were determined in various inflammatory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, pulmonary tuberculosis, regional ileitis, or ulcerative colitis.

Procalcitonin, like other markers of inflammation, is not a substitute for a detailed medical history, clinical examination, and comprehensive clinical assessment.

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Blood Count

Leukocytes

Analysis of leukocytes has always had a special significance in differential diagnosis. However, in doing so the *stage of the disease* should always be considered.

Leukocytosis. In general, all *bacterial infections*, with or without a circumscribed formation of pus, exhibit leukocytosis. Its absence in these diseases indicates a mild form or an especially severe toxic course. Even in *rheumatic fever* the elevation of the leukocyte count is usually obligatory.

Especially severe leukocytoses (*leukemoid reactions*) with an extensive left shift (where even myelocytes and myeloblasts can be present in peripheral blood) can be found in bone metastases, miliary tuberculosis, carbon monoxide intoxication, diabetic and uremic coma, scarlet fever, pneumonia, disseminated form of fungal diseases (coccidioidomycosis, etc.), herpetiform dermatitis, as well as in the recovery phase after agranulocytosis. Even in severe hemorrhaging with shock, high leukocyte values are observed. In isolated cases, high leukocytoses ($>50\,000$/mL, $>50 \times 10^9$/L) have also been described in carcinomas (e. g., bronchial carcinoma) without notable metastasis into the bones. If immature white blood cells are present in these carcinoma-related hyperleukocytoses, this finding does not indicate the simultaneous existence of myelosis.

> An increase in the number of neutrophilic leukocytes is the earliest detectable sign in the course of many diseases.

Therefore, the finding of leukocytosis should never be equated with an infection. Leukocytosis is also found in many noninfectious processes, e. g., *myocardial infarction*, *tumors*, *gout*, *uremia*, and *diabetic coma*.

Stab Cells. Apart from an increase in the neutrophilic leukocytes, the number of *stab cells* (or band cells) must also be observed. If all neutrophils without a filament bridge between the individual segments are counted as stab cells, the number of stab cells is normally $\leq 16\,\%$. In contrast, if only neutrophils with segment bridges measuring more than one-third of the largest segment diameter are counted, then the number of stab cells is $\leq 5\,\%$.

A notable increase in the number of stab cells, also called a *left shift*, likewise indicates an increased demand being placed on the myeloid system.

If *all* neutrophils exhibit only two segments, the familial Pegler–Huet leukocyte anomaly must be diagnosed. This anomaly can demonstrate a particularly extensive left shift in blood film (Fig. 4.**43**).

Toxic Neutrophils. Likewise, of comparable importance to the differential diagnosis are the toxic alterations of the neutrophils (Fig. 4.**44**). *Toxic neutrophils* meet the following criteria:

- the nuclei of the neutrophils are pycnotic
- the granules are found to be moderately coarse or coarse
- basophilic striae (so-called, Doehle inclusion bodies) occur in the plasma
- the plasma is vacuolized.

Toxic changes (especially characterized by coarse granules) are observed in *bacterial infections* that have lasted for two to three days. Vacuolization of the plasma has a special relationship to *hepatic afflictions* (hepatic abscess, hepatic coma).

Rarely one must differentiate May–Hegglin cytoplasm anomaly and the familial Alder granulation anomaly from toxic alterations.

Toxic alterations are *absent* or are only indicated in *viral infections*, *spirochetosis*, *brucellosis*, *rickettsiosis*, and *tuberculosis*, insofar as a secondary bacterial infection does not exist (cavities, intestinal ulcers).

> A neutrophilic leukocytosis is not exhibited by malaria, viral diseases, and many forms of tuberculosis.

Leukopenia (Granulocytopenia). Leukopenia occurs in *typhoid* and *paratyphoid*, *brucellosis*, other *septicemias*, *viral diseases* (e. g., AIDS, measles, rubella, mumps, influenza, mononucleosis, dengue fever), *kala azar*, *splenomegaly*, also in Felty syndrome, *lupus erythematosus*, and *histoplasmosis*. Occasionally severe *miliary tuberculosis* is accompanied by a pronounced leukopenia (<1000/mL, $<1 \times 10^9$/L):

- An even more pronounced granulocytopenia or even *agranulocytosis* (depending on the definition, leukopenia with a leukocyte count <500 or 500–1200/mL (0.5×10^9–1.2×10^9/L) and absence of granulocytes) occurs as a side effect of certain *medications*.

There are two causes:

- *Toxic* leukopenia (e. g., cytostatics, benzene, radioactive medications), is independent of the individual, but dependent on the dose.
- *Allergic* leukopenia (e. g., aminopyrin, phenylbutazone, sulfonamides, chloramphenicol, gold, thyrostatics, tranquilizers, antiepileptics, antihistamines, antidiabetics), depends on the individual, but is essentially independent of the dose.

Rare manifestations are *autoimmune granulocytopenia*, *isoimmune granulocytopenia* after multiple blood transfusions, and *cyclic neutropenia* or *agranulocytosis*. Fi-

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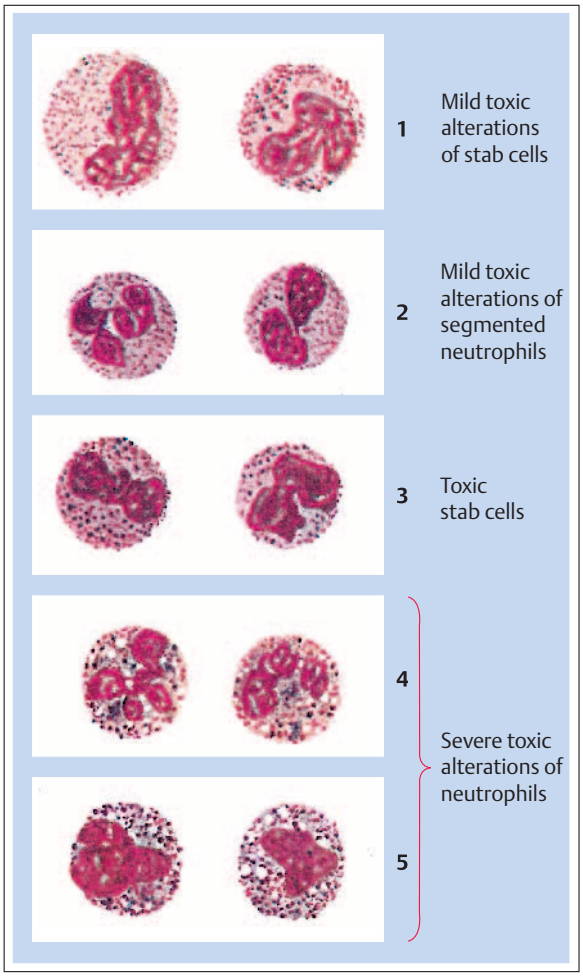

Fig. 4.**44** Toxic changes of neutrophils (modified from Frick).

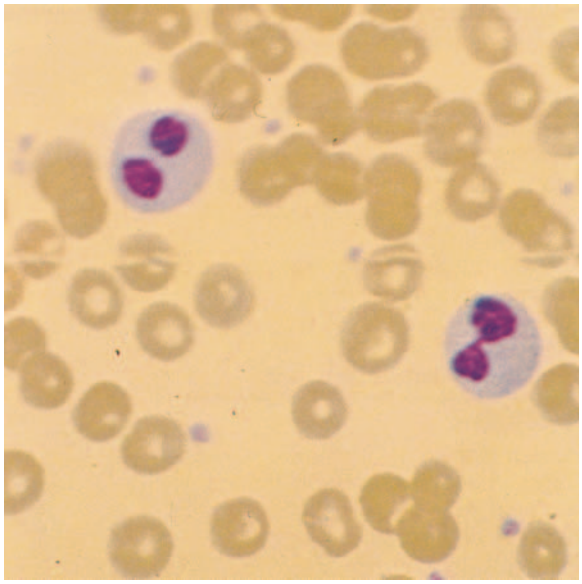

Fig. 4.**43** Pelger–Huet nuclear anomaly.

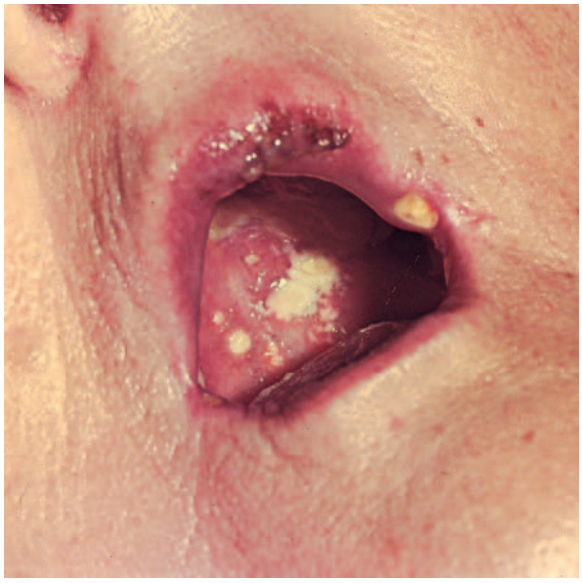

Fig. 4.**45** Mucosal ulcers of the palate and lips in a patient ▷ with agranulocytosis.

nally, leukopenia can be a manifestation of aleukemic *leukemias* (e. g., hairy cell leukemia). Granulocytopenia or agranulocytosis must always be considered, if a fever develops without a discernible cause. This is especially the case if the fever is accompanied by a purulent angina or ulcerations of the oral mucosa (Fig. 4.**45**).

Eosinophils

Eosinophilia. In infections eosinophilia is generally a prognostically favorable sign. The reappearance of eosinophils has been called the dawn of convalescence (postinfectious eosinophilia, e. g., in abdominal typhoid).

Pronounced eosinophilia is found in:

- *allergic* diseases (serum disease, bronchial asthma, etc.)
- *parasitic diseases*, especially if the parasites penetrate the tissue: *Trichina*, *Echinococcus*, filaria, *Toxocara*, *Ankylostoma duodenale*, *Schistosoma* (bilharziosis), and less markedly in intestinal parasites
- Löffler eosinophilia (pulmonary infiltrates)
- fibroplastic endocarditis (Löffler)
- diseases of the hematopoietic system
- *collagen diseases* such as periarteritis nodosa
- tumors, mainly of the ovaries, but also in other locations.

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Mild eosinophilia occurs in scarlet fever, lymphogranuloma, and hypernephroma, and also can indicate the presence of Addison disease.

Eosinopenia or the Absence of Eosinophils. The absence of eosinophils is of diagnostic value. The percentage of eosinophils declines in most infectious diseases. In *typhoid* the disappearance of eosinophils is so pronounced that the diagnosis of typhoid becomes very unlikely if eosinophils can be found in the blood smear. Eosinophils are also absent in measles. Eosinopenia is typical in Cushing disease and during therapy with glucocorticoids.

Monocytes

Monocytosis. Infectious monocytosis occur in syphilis, brucelloses, listeriosis, trypanosomiosis, subacute bacterial endocarditis, and tuberculosis. Monocytosis also occurs in other inflammatory diseases, in collagenoses, sarcoidosis, granulomatous intestinal diseases, and myeloproliferative syndromes.

Unclear monocytoses in elderly patients may be a sign of a preleukemic condition.

Lymphocytes

Lymphocytoses. These frequently occur during the course of infectious diseases. From a diagnostic perspective, three different forms can be distinguished:

- The *lymphocytic response* is seen with mostly old, small lymphocytes.
  - It occurs in the recovery phase of many infections (typhoid, bacterial pneumonia, etc.) and has no great diagnostic significance.
  - *Lymphocytosis due to brucellosis* can achieve values of up to 60% and is diagnostically more important.
  - *Chronic infectious diseases* (tuberculosis, syphilis) can be accompanied by lymphocytosis.
- The *lymphocytoid response* is seen with large cells.
  - The cells are very typical in mononucleosis, whereby they can achieve values of up to 70%. Usually a simultaneous leukocytosis is also present.
  - Comparable findings are made in acute infections with cytomegalovirus and HIV.
  - Less pronounced, these cells also can be found in other viral infections (viral pneumonia, hepatitis) (so-called virocytes).
- The *plasmacellular response* is seen with typical plasma cells having cartwheel nuclei and deep, cornflower-blue plasma.
  - Such cells are especially observed in rubeola and hepatitis.

Lymphopenias. Pronounced lymphopenias are a regular finding in the presence of high leukocyte values and as *relative lymphopenias* they have little diagnostic value. *Absolute lymphopenias* (with or without mild leukocytosis) are often present in *miliary tuberculosis* and also in extensive *lymphogranuloma*. In miliary tuberculosis the symptom is of such importance that this disease essentially can be excluded if the lymphocyte count is normal. In advanced HIV infection (AIDS) lymphocytopenia with values $< 1000/\text{mL}$ ($< 1 \times 10^9/\text{L}$) is considered to be characteristic.

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5–11

5 Head and Facial Pain and Neuralgia of the Head Area
K. Hess

6 Chest Pain
F. R. Eberli and E. W. Russi

7 Abdominal Pain
D. Moradpour and H. E. Blum

8 Neurogenic Arm and Leg Pain
K. Hess

9 Pain due to Vascular Disease
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10 Pain in Joint Diseases
P. Greminger and B. A. Michel

11 Localized Bone Lesions
A. Aeschlimann and M. E. Kraenzlin

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5 Head and Facial Pain and Neuralgia of the Head Area

K. Hess

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5.1 Introduction

Importance of the Medical History. Head and facial pain (see below), as well as neuralgia of the head area, are a typical domain of the accurate medical history. The main points of the medical history are summarized in Tab. 5.**1**, and the nature of the onset of the pain, as an important differential diagnostic element, in Tab. 5.**2**. The case history makes it easy to distinguish between *headache (in the narrower sense)* and *neuralgia*, which is defined as a pain of a particular category, "neuralgiform" in the *propagation area of a nerve*.

Differential Diagnosis. From the *time course*, and to a lesser degree, from pain localization and its main characteristics, the *key* differential diagnoses of *symptomatic or idiopathic headache* (Tab. 5.**3**) or *neuralgia*, can often be determined immediately. In addition, the usual

Table 5.**1** The medical history in head and facial pain including neuralgias

Main elements of the medical history	
Onset	acute to insidious/awakening
Localization	diffuse, helmet, nuchal, temple, unilateral, face, etc.
Character	dull, pressing, burning, pulsating, electrifying, etc.
Intensity	numeric pain scale 0–10 (10 = unbearable)
Duration	sting, attack, episode, lasting pain
Periodicity	singular, repetitive, episodic
Concomitant symptoms	nausea, vomiting, light, noise, and smell hypersensitivity, dizziness, diplopia, malaise

Table 5.**2** Onset of pain as a differential diagnostic element

Peracute (onset within seconds to minutes)
- Subarachnoid hemorrhage
- Dissection
- Intracerebral hemorrhage/insult
- Hypertensive crisis
- Barosinusitis
- Thunderclap headache
- Trigeminal neuralgia

Acute (onset within minutes to hours)
- Meningitis, encephalitis, abscess
- Occlusive hydrocephalus
- Pituitary apoplexy
- Sinusitis
- Acute glaucoma
- Cervicocephalic syndrome
- Intracerebral hemorrhage
- Migraine
- Cluster headache

Insidious
- Subdural hematoma
- Venous sinus thrombosis and cerebral venous thrombosis
- Chronic, intracranial hypertension/pseudotumor
- Giant cell arteritis
- Refractive anomaly
- Chronic sinusitis
- Sinus/pharynx carcinomas
- Mandibular joint affections
- Tension headache

Table 5.**3** Two main categories of headaches

Symptomatic ("secondary," i. e., diagnosable, underlying disease)
- Subarachnoid hemorrhage
- Meningitis, neoplastic meningitis, meningoencephalitis, encephalitis, brain abscess
- Intracerebral hemorrhage
- Carotid and/or vertebral artery dissection
- Ischemic brain lesions
- Acute, occlusive hydrocephalus
- Venous sinus thrombosis and cerebral venous thrombosis
- Pituitary apoplexy
- Subdural hematoma
- CSF leak (intracranial hypotension)
- Intracranial hypertension/pseudotumor
- Giant-cell arteritis and other vasculitis
- Sleep apnea syndrome
- Epileptic seizures
- Posttraumatic headache
- Cervicogenic headache
- Head and facial pain in ophthalmologic, otorhinologic, and orthodontic diseases
- Headaches of organic origin
- Hypertonia, hypoxia, sleep apnea syndrome, bone diseases

Idiopathic ("primary," i. e., no underlying disease)
- Migraine with/without aura
- Basilar migraine and other special forms
- Tension headache
- Cluster headache and hypnic headache
- Chronic, paroxysmal hemicrania, hemicrania continua, SUNCT
- Thunderclap, exercise-induced, and orgasm headache

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associated findings, which define symptomatic headache and neuralgia, are typically absent in idiopathic forms (Tab. 5.**4**). The most important diagnostic criteria are meningism, pain when tapping or pressing the skull (including the trigger points), pupillary and papillary anomalies, loss of trigeminal and facial nerve functions, and abnormal blood pressure, as well as pathological findings in the cranial computed tomography (CCT), lumbar puncture, and other laboratory tests.

Table 5.**4** Typical findings in symptomatic headache (danger signals)

- Meningism
- Horner syndrome
- Papilloedema/retinal bleeding
- Cranial nerve loss of function and other focal deficits
- Hypertonia
- Pressure pain (sinus, temple, etc.)
- Pathologic murmurs (neck, head, eyes)

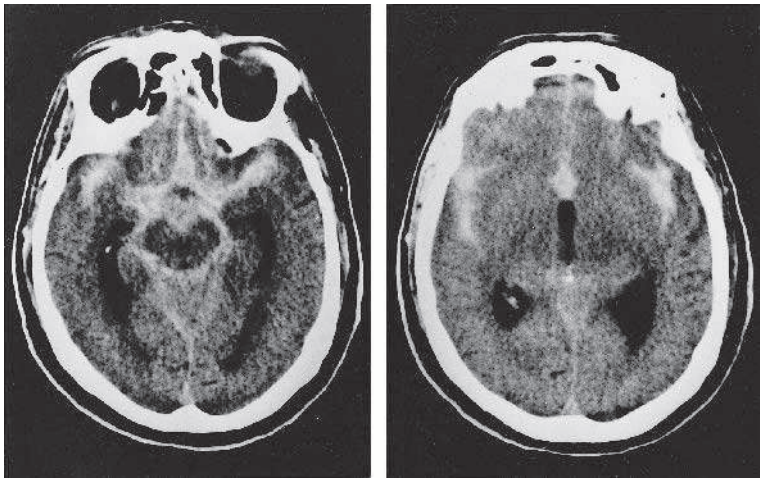
5.2 Symptomatic Headache

The symptomatic headache is usually a singular event in the life of a patient, who previously either never had a headache or had one of a completely different kind. Depending on the cause, they either accompany or dominate an illness. According to the acuity and perceived level of severity of the concomitant headache, subarachnoid hemorrhage and bacterial meningitis are the worst, followed by acute, occlusive hydrocephalus, vascular dissection, and intracerebral bleeding. In addition, high pain scores are found in barosinusitis (sinusitis sphenoidalis), acute glaucoma, acute otitis, and cluster headache. The characteristic pain feature (burning, dull, boring, pulsating, etc.) is often not as helpful and important in the differential diagnosis as the localization of the pain, even when indicated as vague (see Tab. 5.**3**).

Subarachnoid Hemorrhage

Clinical Features. A *sudden, agonizing headache* "like never before" is the hallmark of a subarachnoid hemorrhage following a ruptured aneurysm. Sometimes, migrainelike headache attacks ("sentinel leakage") may precede the event. The pain is diffusely located throughout the whole head and only eases off slowly over hours or days. Even with opiates, the pain is difficult to alleviate. Meningism often follows only hours later. However, in one-third of the patients it does not occur at all. Vomiting, clouding of consciousness, focal central nervous system findings (pareses, aphasia, hemianopia), and/or loss of cranial nerve functions are typical signs. Unilateral, oculomotor nerve palsy with mydriasis and ptosis or bilateral abducens nerve palsy is characteristic for aneurysms in the basilar region. Fundus hemorrhages (Terson syndrome) occur mostly in the peripapillary region with heavy bleeding and support the diagnosis of subarachnoid hemorrhage. Contrary to meningitis, fever arises only secondarily and does not exceed a 39.5 °C core temperature on the first day.

Diagnosis. Immediate hospitalization and a *CCT* (Fig. 5.**1**) are essential. A lumbar puncture is indicated only if the CCT does not reveal blood. A negative CCT on the first day and normal spinal fluid 12 hours after and not later than two weeks after the onset of the headache, to a great extent exclude a subarachnoid hemorrhage.



a **b**

Fig. 5.**1** Subarachnoid hemorrhage in a ruptured aneurysm of the anterior communicating artery.
a Blood (white) in the basal cistern and the entire, anterior, cranial fossa.
b Blood in the interhemispheric and Sylvian fissures.

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Differential Diagnosis. The most important differential diagnoses include fulminant meningitis, intracerebral bleeding, barosinusitis (in particular, with a sinusitis sphenoidalis), occlusive hydrocephalus (aqueductal stenosis), and basilar migraine. The uncommon, spontaneous, and mostly orgasm-associated idiopathic "thunderclap" headache and the agonizing, but benign, exertional headache may mimic a subarachnoid hemorrhage. Initial, severe agitation may falsely lead to psychiatric hospitalization.

Meningitis, Neoplastic Meningitis, Meningoencephalitis, Encephalitis, and Brain Abscess

Clinical Features. Bacterial meningitis (*Pneumococcus* and *Meningococcus*, in particular) may begin shortly after a preceding malaise and nearly as rapidly as the onset of serious subarachnoid bleeding, with a strong, diffuse headache, vomiting, and rapid clouding of consciousness. Coughing or any kind of physical effort will exacerbate the pain (as is true for every irritation of the meninges). With rare exceptions, fever is high from the outset, and the classical signs of meningitis (meningism, Kernig sign, Brudzinski sign, and adopting a curled-up position ["position en chien de fusil"]) are clearly manifested, although they may disappear in cases involving deep coma.

> If bacterial meningitis is suspected, then antibiotic treatment must be started immediately after cranial computed tomography (CCT) and blood culture, before confirmation by lumbar puncture.

Viral meningitides as well as tuberculous meningitis and neoplastic meningitis usually begin less dramatically and must, particularly with only slight meningism, be differentiated from sinus and cerebral vein occlusions, subdural hematomas, or vascular dissections, rather than from subarachnoid hemorrhage. Here, fever and other inflammatory signs usually provide a clear distinction.

Differentiation of Encephalitis. The transition of meningitis to the clinically evident encephalitis is fluid. Epileptic seizures, focal neurological symptoms, delirious conditions, and mental clouding are indicative. If encephalitis (as observed in *herpes simplex* infections) or cerebritis (i. e., preliminary state of a brain abscess) dominate during septic spreading, then the various signs of meningism, and often also the headache, are reduced, as compared to the more prevalent, central nervous system symptoms/findings and potential signs of raised intracranial pressure (see Brain Tumor, p. 211).

Intracerebral Bleeding

A sudden, but usually less agonizing, and often localized headache is accompanied by focal central nervous system symptoms such as hemiplegia, hemianopsia, and acute mental states. Frequently, a focal epileptic seizure precedes the event. Vomiting and clouding of consciousness may indicate increased brain pressure, particularly with infratentorial bleeding or invasion of blood into the ventricles. Meningism is absent or negligible, except with bleeding into the subarachnoid space.

Differential Diagnosis. The most important differential diagnoses which can be clarified by means of emergency CCT are vascular dissections with ischemic cerebral infarct, bleeding, brain tumor, sinus or cerebral vein thrombosis, hypertensive crisis, and the rare basilar migraine. The various potential causes of bleeding (hypertonia, metastases, vascular malformations) must be evaluated carefully.

Carotid and Vertebral Artery Dissection

With a carotid dissection, the sudden and often violent headache is normally located on one side of the neck and/or face, and usually accompanied by an ipsilateral Horner sign. With a vertebral dissection, the pain is located more or less on one side of the neck and in back of the head. An accompanying transient focal ischemia or a cerebral infarct is not obligatory. Carotid dissection rarely causes ipsilateral caudal cranial nerve losses (IX–XII, in various combinations) as a consequence of perivascular bleeding in the base of the skull region. Often a CCT is already diagnostic. Otherwise, magnetic resonance imaging, with inclusion of the neck, must be carried out. In the beginning, Wallenberg syndrome can also occur with acute facial pain, ipsilateral Horner sign, and ipsilateral caudal cranial nerve losses. However, Wallenberg syndrome has an obligatory contralateral dissociated reduction of sensation in the trunk and extremities, the presence of which must be carefully ascertained.

Ischemic Brain Lesions

Intensive unilateral facial pain, as well as dissociated loss of sensation in the trigeminal area (central trigeminal areas) (Fig. 5.**2**), is characteristic of *Wallenberg syndrome*. Unilateral pain, including the face, is also typical for thalamic infarctions (*Déjerine–Roussy syndrome*). Both are examples of a rare centrally generated facial pain (see Neuralgia in the Head Region, p. 215).

It is unclear to what extent ischemic brain lesions can cause headaches outside of pain-related structures. *Transient ischemic attacks* and even *lacunar infarcts* are

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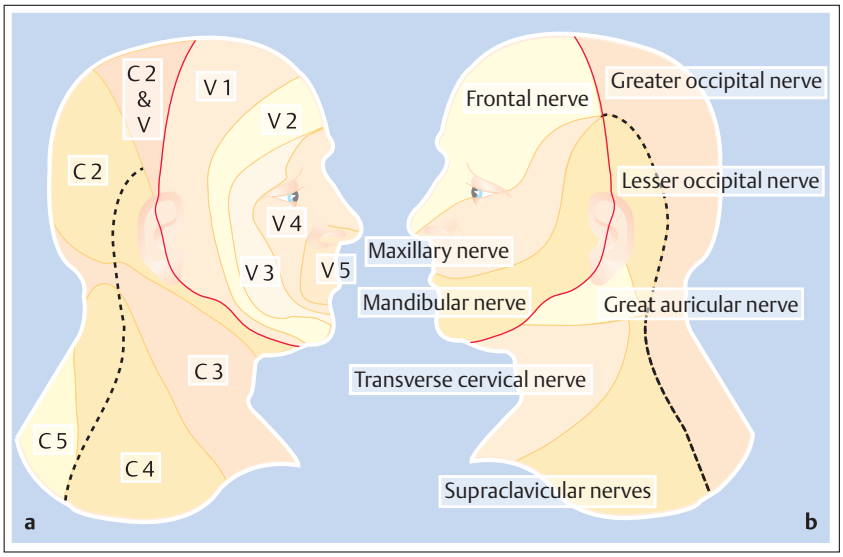


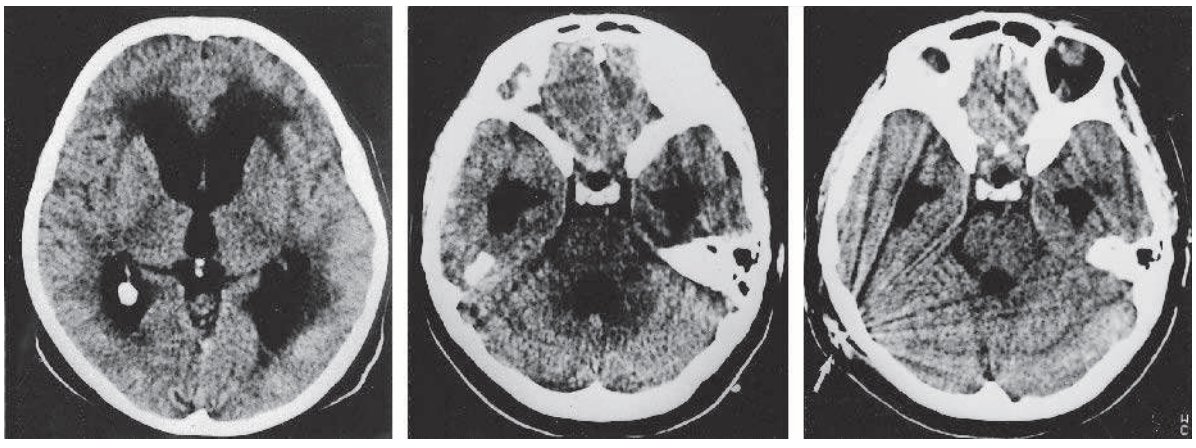
Fig. 5.**2** Innervation areas of the head and neck according to spinal nerves (back of the head, neck) and central trigeminal representation (face).
a The onion-skin-like distribution of the Soelder's lines (V 1–V 5)
b According to cutaneous nerves.

frequently accompanied by an occasionally pulsating and localized headache (for hours) without the presence of a vascular occlusion or a dissection. Moreover, *territorial infarcts* may occasionally be accompanied by an annoying, persistent headache (without localizing predilections), which however, hardly reaches the level of a headache associated with a brain hemorrhage.

Acute Occlusive Hydrocephalus

Clinical Features. A sudden delirious or psychologically agitated state of emergency, often together with a violent headache (and vomiting), is typical for acute hydrocephalus due to an obstruction in the third ventricle e. g., with a colloid cyst or parasite infestation (cysticercosis, *Echinococcus*), with aqueduct occlusion (after latent, congenital stenosis), or with Arnold–Chiari malformation.

Differential Diagnosis. The more frequent subarachnoid hemorrhage or bacterial meningitis begins similarly, whereby the headache may sometimes not be noticed in view of the often spectacular state of emergency. The diagnosis is easily made by CCT. Partial or insidious, obstructive hydrocephalus occurs with a chronic brain pressure syndrome (see below). Chronic nonresorptive hydrocephalus (normal pressure hydrocephalus) does not cause headache, while acute malabsorptive hydrocephalus after subarachnoid bleeding (Fig. 5.**3**) may hardly be differentiated due to the bleeding.



a **b** **c**

Fig. 5.**3** Acute malabsorptive hydrocephalus, three weeks after subarachnoid hemorrhage (aneurysm of the anterior communicating artery).
a Wide lateral ventricles (black) with periventricular "zones of resorption."
b Wide temporal horns of the lateral ventricles, and fourth ventricle.
c After ventriculoperitoneal shunt. Shunt valve (arrow) in parietal calotte with radiating artifacts due to the metal.

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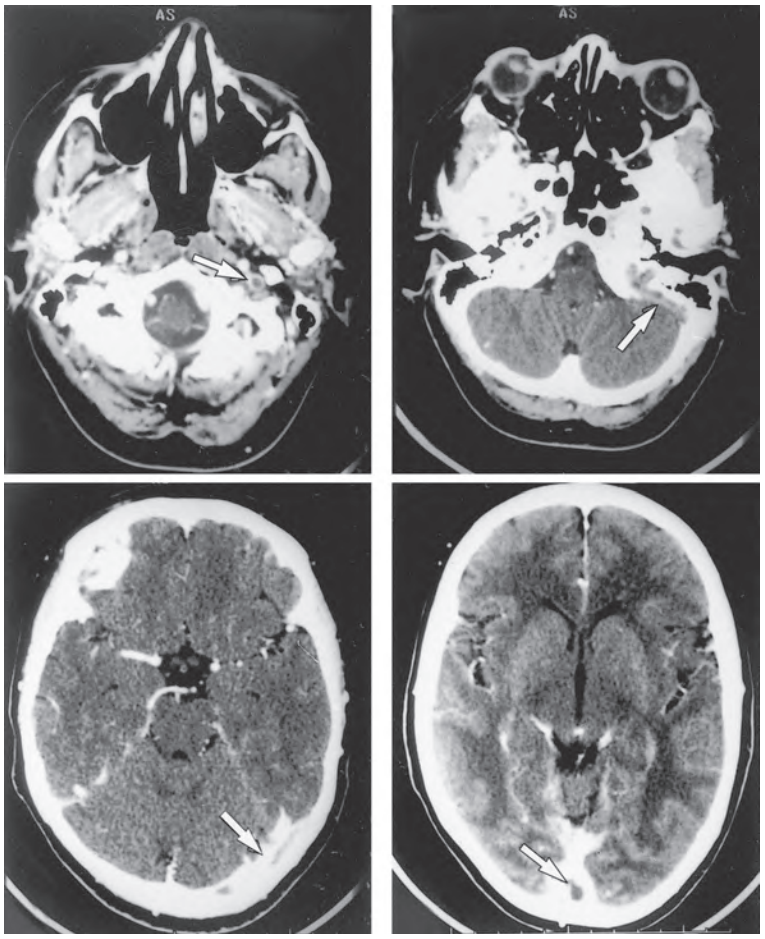

Fig. 5.**4** Aseptic venous sinus thrombosis. Axial contrast enhanced CCT scan of a 47-year-old woman with diffuse, persistant headache (three weeks, acute onset, behind left ear).
a Thrombosed left jugular vein (arrow).
b Sigmoid sinus (arrow)
c Transverse sinus (arrow)
d Confluence of the sinuses (arrow).

Venous Sinus and Cerebral Venous Thrombosis

A more insidious and continuously persistent headache over days and weeks, normally more on one side, with a more diffuse and somewhat bearable but constant pain, mark the aseptic sinus and/or cerebral vein thrombosis (Fig. 5.**4**). Younger women are relatively more affected, often without further hormonal or hematological risk factors. The diagnosis is easily made by CCT. Complicating hemorrhagic venous infarcts are frequent and may cause epileptic seizures or cerebrovascular infarcts. Secondary septic sinus and cerebral vein thrombosis, with severe meningitis or encephalitis, may be missed clinically or regarded as an encephalitic exacerbation. A first manifestation of Behçet disease is possible, which is why the presence of aphtha, mucosal ulcers, and signs of iritis should be investigated.

Pituitary Apoplexy

With an acute and continuous, at first unexplainable, (frontal) *postpartum or puerperal* headache, one must consider a pituitary apoplexy. This is sometimes the first manifestation of a pituitary adenoma, but rarely occurs spontaneously. This rare condition must be diagnosed rapidly by a CCT scan, MRI or by the fasting serum cortisol level, since endocrine insufficiency follows within days if untreated.

Subdural Hematoma

Because of the large spectrum of headaches (from insidious to acute episodic, from diffuse to well-localized, the acute and chronic) the possibility of subdural hematoma must be evaluated with all unusual headaches. Position dependence is sometimes remarkable when a CSF leak is present (subdural hematoma as a consequence of a chronic CSF leak). Focal neurological indicators are usually absent. However, a general slowing, lack of motivation, and an increased need of sleep are ominous symptoms of increased brain pressure. Frequently, a trauma cannot be determined. The diagnosis is confirmed by a CCT scan.

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CSF Leak (Intracranial Hypotension)

The clear position dependence of otherwise dull and diffuse headaches, which become intolerable within minutes in an upright position, and often are associated with nausea, but disappear within minutes when lying down, is the hallmark of this condition. If it continues for several weeks, the history may sometimes falsely describe a continuous headache.

The most frequent cause is a temporary dural fistula after lumbar puncture (so-called postpunctional syndrome). Other causes are rare. Before further investigations are carried out (e. g., for spontaneous fistula, other depletion in volume of the cerebrospinal fluid space) the diagnosis must be confirmed by magnetic resonance imaging of the head.

Tumor and Pseudotumor Cerebri (Idiopathic Cranial Hypertension)

Space-occupying processes such as meningioma, glioblastoma, or brain metastases manifest themselves more frequently with epileptic seizures or focal neurological symptoms than with continuous head pressure or localized headache.

Even with a complicating insidious *intracranial hypertension*, a headache is not usually obvious. Confusion and vomiting are more indicative. Papilloedema, central scotoma or visual field deficits, amblyopic attacks, pupillomotor disturbances, and bradycardia are alarming signals.

However, with a pituitary adenoma, chronic frontal headaches (together with loss of libido and impotence/amenorrhea) can occur long before the appearance of severe endocrine disturbances, visual field losses, or headache exacerbation with pituitary apoplexy.

Pseudotumor cerebri denotes a chronic increase in intracranial pressure without a space-occupying lesion. Pathogenetically, a venous occlusion is the most likely cause. Sometimes the condition occurs with an obstructive venous sinus thrombosis. Typically, young obese women are affected. Moreover, hormonal birth control pills and tetracycline are risk factors. After chronic, moderate, continuous head pressure lasting for weeks, loss of vision and often abducens palsy ensue. The CCT scan shows narrow ventricles, and the pressure of the cerebrospinal fluid is increased (more than 30 cm H_2O). Lowering the pressure reduces headache and improves vision.

Giant Cell Arteritis and Other Vasculitis

Giant Cell Arteritis (Arteritis Temporalis Horton). is autoimmune disease is characterized by chronic, nagging, often fluctuating headaches, predominantly in the temple region of older patients who feel ill and depressed, and behave accordingly. Circumscribed, painful, often swollen arteries in the entire head area, not only on the temple (arteritis temporalis), together with a significantly elevated erythrocyte sedimentation rate, confirm the diagnosis. A biopsy of the temporal artery is necessary in ambiguous situations due to the high risk of long-term treatment with steroids (see Chapter 4).

Tolosa–Hunt Syndrome. Typical of this focal inflammatory (perhaps autoimmune) disease is a constant "boring" pain around or behind an eye, with nocturnal exacerbation, which is accompanied or followed a few days later by one or more eye nerve pareses, sometimes sensory disturbance in the first branch of the trigeminal nerve (ophthalmic), and visual disturbance (optic nerve). Inflammatory changes in the cavernous sinus are the predominant cause. When not treated, the episode usually lasts for weeks. However, substantial improvement may occur within one day following treatment with systemic steroids. In contrast to giant cell arteritis, the erythrocyte sedimentation rate is not, or only marginally, increased. Relapses are possible.

Other Vasculitis. With other vasculitides such as nodular periarteritis, Wegener granulomatosis, systemic lupus erythematosus (SLE), Sjögren syndrome, eosinophilic angiitis, granulomatous angiitis of the nervous system, Behçet disease, and with infectious vasculitis (meningovascular syphilis, neuroborreliosis), headache usually is not the main symptom.

Sleep Apnea Syndrome

Dull, frontal headaches for hours in the mornings with irritable behavior combined with daytime sleepiness, nocturnal snoring, obesity, and/or narrow or obstructed upper airways (polyps, pharyngeal tonsils, macroglossia), may indicate sleep apnea syndrome and should prompt further neurological and pneumological investigations (see Chapter 17).

Epileptic Seizures

Rarely, epileptic seizurelike "attacks" occur (painful parietal seizures, hemicrania epileptica) with holocephalic or hemicephalic painful sensations of hot, cold, cramping, stinging, or pulsating, which last for seconds or minutes and usually spread to the whole body. They are accompanied by mental alterations or other typical signs of an epileptic seizure.

Moreover, migrainelike or unclassified headaches can provoke or accompany focal epileptic seizures. They must be delineated from migraines with aura, which normally is readily achieved via a careful medical history.

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Posttraumatic Headaches

This heterogenous group of headaches, which follow a serious head and/or brain injury, requires the investigation of possible neurological side effects such as chronic subdural hematoma, occlusive hydrocephalus, chronic brain abscess, or meningeal fistula. Moreover, a trauma of the cervical vertebrae, the occipital, and/or the mandibular joints with secondary degenerative changes, and accompanying complaints such as dizziness, lack of concentration, and other behavioral disturbances including depression, also must be excluded. Finally, the history of headaches before the accident, the onset of the headache after the accident, the occupational and family environments, the exact nature of the accident, and the insurance situation should be analyzed carefully. It should be noted that severe craniocerebral trauma in general causes remarkably few headaches, whereas mild traumas often entail persistent, severe, and unrelenting headaches. Altogether, this points to the complexity of the domain of headaches.

Cervicogenic Headache

Cinical Features. The main area and origin of the usually movement-dependent pain is the neck. Pain radiation into the forehead and eyes (so-called *cervicocephalic syndrome*) occasionally diverts diagnostically, as the transition to the tension headache is fluid. In particular, the upper cervical syndrome often is associated with, or mistaken for an *occipital neuralgia* (see below). Active and passive movement restrictions, local cervical and/or occipital pain on pressure, as well as tense neck musculature are diagnostically decisive.

Differential Diagnosis. In contrast to meningitis with painful, blocked flexion, passive rotation/abduction is restricted with the vertebral syndromes, and flexion is relatively easy. Radiographs of the cervical vertebrae are rarely productive, diagnostically (decreased cervical lordosis), but are justified to exclude subluxations, spondylodiscitis, or metastases.

The rare *retropharyngeal tendonitis* creates a continuous, increasing neck pain over weeks, sometimes accompanied by signs and symptoms of a systemic inflammation. Throughout the examination, pain during retroflexion of the cervical spine is most prominent. Nonsteroidal antiinflammatory drugs bring rapid improvement.

Headaches and Facial Pain in Ophthalmologic, Otorhinologic, and Orthodontic Diseases

Ophthalmology

The following ophthalmic diseases are part of the differential diagnosis of head and facial pain:

- *Acute glaucoma* is the classical differential diagnosis of acute, unilateral, frontal headache or facial pain. The common red eye is a defining feature.
- Acute or chronic *iritis/iridocyclitis* can be similarly painful.
- Rubeosis iridis, as well as a bruit (subjective or objective), is typical for the *cavernous sinus fistula*, together with chemosis or exophthalmus for the *cavernous sinus thrombosis*. Early onset of diplopia is common to both.
- In cases of uncorrected, because unidentified, *refraction anomalies and heterophoria,* a frontal headache is provoked by reading and often is accompanied by blurred vision or diplopia.
- Bilateral, usually chronic or fluctuating eye pain, and eye redness together with fluctuating diplopia, can indicate an *eye muscle myositis*.
- Acute pain in the eye without ophthalmologic findings is a guiding symptom in the Tolosa–Hunt syndrome and giant cell arteritis, and is prodromal to diabetic (ischemic) oculomotor palsy.

Otorhinolaryngology

- An acute or chronic sinus headache, or rather facial pain, is easy to locate except in cases of *sinusitis sphenoidalis*, where it can radiate frontward, laterally, or diffusely. Tilting the head forward often aggravates a sinusitis. Most significantly, however, chronic or acute sinusitis can dramatically exacerbate into *barosinusitus* (negative pressure due to swelling of the ostia) and falsely lead to suspicion of meningitis or subarachnoid hemorrhage. Pain to pressure and tapping as well as a dripping nose are diagnostically helpful. If necessary, also perform a throat inspection (mucus, pharyngitis), diaphanoscopy, and radiographic procedures.

Odontology

- Tooth diseases such as *pulpitis*, *periodontitis*, or *tooth neck abscesses* occasionally cause poorly localized facial pain or headache, and, therefore, may diagnostically be misleading for a long time. However, they escape the dental examination only in the earliest stages.
- On the other hand, persistent facial pain is misinterpreted frequently as being of dental origin. Many

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teeth become victims of idiopathic trigeminal neuralgia! In addition, metastases and osteitis of the mandibular joint, sinusitis maxillaries, and sinus and tonsillary carcinomas can imitate a toothache.

- *Arthropathy and dysfunction of the mandibular joint* in numerous variations, together labeled as Costen syndrome, cause pain in the mandibular joints themselves or in the temple region. The pain usually increases when chewing, speaking, and pressing the teeth together. Movement restriction, local pain to pressure, and movement noises are indicative. Myofascial pain syndrome is diagnosed most frequently with an often poorly identifiable, oromandibular dysfunction.
- As a differential diagnosis, giant cell arteritis with ischemic muscular pain on chewing (masseter claudicatio) must not be missed.

Headaches of Organic Origin

Arterial Hypertonia. Headache attacks and continuous headaches can be due to hypertonia. Therefore, measuring the blood pressure must be part of each examination. However, a mild or moderate hypertonia is not a direct cause of headache. Instead, what is pathogenetically crucial is an acute rise in the diastolic blood pressure (over 25%). Frequent and often pulsating, diffuse headaches in the early morning hours (differential diagnosis of migraine) and upon rising, as well as prolonged headaches after physical exercise, are suspected as being related to arterial hypertonia. Headache attacks during hypertensive crises (differential diagnosis of malignant hypertonia, pheochromocytoma, preeclampsia/ eclampsia) can be accompanied by signs of hypertensive encephalopathy, the most ominous manifestation of which is bilateral amaurosis. Other symptoms are light-headedness to somnolence and occasional grand mal seizures. Effective antihypertensive treatment eliminates the headache within hours.

Metabolic/Toxic Etiologies. Metabolically or toxically induced headache episodes are known to occur with hypoglycemia, dialysis, and hypoxia (elevator headache, CO intoxication, sleep apnea syndrome), after excessive consumption of alcohol, after nitrate/nitrite (hot dog headache) or glutamate intake, as well as after drug withdrawal. Headache in the context of anemia, infections, and severe intoxications is self-evident. Skull diseases are rarely accompanied by headache (and/or pain to tapping), e. g., *myeloma* and *Paget disease*. Radiology or CT of the head are diagnostically crucial.

5.3 Idiopathic Headache

Repetitive and *stereotypical* are common descriptives of most idiopathic headaches (Tab. 5.**3**). It must be noted, however, that symptomatic headaches can likewise be episodic and uniform, for example, with toxic exposition (nitrate/nitrite, glutamate), relapsing sinusitis, Mollaret meningitis, cervicogenic vertebral syndromes, hypertensive crises (pheochromocytoma), and transient ischemic attacks. Also, headache with giant cell arteritis often fluctuates considerably, up to a nearly intermittent, periodic, time course. Characteristic for migraine syndromes is the often strong familial affliction, consistent with autosomal dominant diseases.

Migraine without Aura

Definition. Migraine without aura is defined by recurring attacks of often unilateral, pulsating headaches, lasting for many hours, which are increased by physical effort and associated with nausea and/or vomiting as well as general irritability with photophobia and phonophobia. Common *triggers for an attack* are red wine, relaxation after stress, menstruation, acute neck stiffness, mild head injuries, and simple flulike infections.

Clinical Features. The attack gives the impression of a systemic illness. The need to retreat is typical, in contrast to the cluster headache. Sleep does not always end the migraine. Diagnostic subtleties should be taken from the criteria of the International Headache Society.

Diagnosis. The question is controversial: to what extent does a typical migraine need to be investigated neurologically? Large series of patients have been evaluated by imaging, with only a small fraction showing vascular or other anomalies. With a positive family history and normal neurological findings, the diagnosis can be settled without CCT. However, the diagnosis should be reevaluated if atypical auras and time courses of the attacks occur, or with treatment resistance.

Differential Diagnosis. The *first migraine attack*, which may occur at any age and without a positive family history, is not always easily differentiated from symptomatic headache and must sometimes be investigated.

In addition, even with an established migraine, there may be a diagnostic problem. Naturally, migraine patients are not protected against meningitis or a subarachnoid hemorrhage with acute headache. Keeping this in mind, one should always be alert to the possibility of meningism or central nervous system signs and symptoms.

> Every migraine of unusually long duration or unusual severity must be scrutinized.

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Typically, acute systemic diseases as well as certain brain diseases, for example, a cerebral infarct or multiple sclerosis, begin with a severe and prolonged migraine attack. Between episodes, multiple sclerosis patients suffer frequently from migraine and tension headaches. Carotidynia is a loosely defined syndrome with migrainelike, often prolonged, unilateral neck and facial pain, with a tender, dilated, and swollen carotid artery.

Migraine with Aura

Clinical Features. The classical pattern is a focal, central nervous system symptomatology, most frequently a scintillating scotoma (teichopsia), which expands from an initially small point in the visual field, lasts for approximately 20 minutes, and is followed immediately by a headache of acute onset and autonomous disturbances as observed in the migraine without aura. Other aura symptoms, which may occur in parallel or follow each other, consist of unilateral sensory disturbances (tingling/numbness), speech arrest, and rarely, a unilateral paresis. The aura is highly variable, and the headache is not always unilateral and may even be perceived as contralateral.

Differential Diagnosis. The differential diagnosis is similar to that of migraine without aura. In particular, if an aura lasts for an abnormally long time (over 60 min) and/or outlasts the headache, one must consider other central nervous system diseases, including a migraine infarct, a multiple sclerosis episode, a cerebral venous thrombosis or a vascular malformation with bleeding.

An aura changing sides of the affected visual field or the body effectively excludes an underlying structural anomaly, as well as two important differential diagnoses with repetitive disturbances: focal epilepsy and transient ischemic attacks.

- *Focal epileptic seizures* are identifiable by their more frequent recurrence, by the occasional transition to generalized seizures, by prolonged central nervous system symptoms (Todd paresis), and by the usually minor nature of the headaches. Of course, with an EEG they are more readily identifiable. The "marching", which is the slow propagation of focal symptoms, is, although pathophysiologically different, similar to the migraine aura (spreading depression) and an epileptic seizure (expanding epileptic discharges).
- During *transient ischemic attacks* (TIA) the "marching" is absent to a large extent and the headache is, if present at all, completely in the background relative to the focal signs. In addition, paralysis more frequently indicates a TIA than a migraine aura. Exceptions are some rare forms of migraine: basilar migraine, familial hemiplegic migraine, and ophthalmoplegic migraine.

Isolated scintillating scotomas (teichopsia), known as "migraine sans migraine" or migraine aura without headache, are often difficult to distinguish from transient ischemic attacks, especially in older patients. If in doubt, they must be investigated and treated like TIA. The long-term course usually confirms the diagnosis.

In addition, the rare monocular aura (retinal migraine) is difficulty to verify and must be carefully distinguished from TIA (amaurosis fugax) and retinal diseases.

Basilar Migraine and Other Special Forms of Migraine with Aura

Clinical Features and Differential Diagnosis. Characteristic of basilar migraine is the aura, comprising a bewildering variety of signs and symptoms of the visual cortex and the brain stem (oscillating vision, dizziness, buzzing in the ear, diplopia, tingling sensation in the face, slurred speech, unsteady gait), which often evolve into somnolence or even coma. The whole evolution including the headache may then be lost due to the subsequent amnesia. Since they frequently occur in young people and are often the first, dramatic manifestation of migraine in a patient's life, they pose particularly difficult differential diagnostic problems, whereby CNS intoxication is an important consideration. In addition, basilar thrombosis, fulminant meningitis, herpes encephalitis, and subarachnoid hemorrhage are to be considered. Usually, different migraine types follow later, and the basilar migraine attack remains singular or the rare exception.

Other Special Forms. *Familial hemiplegic migraine* is a rare, dramatic disease of children and young adults, with autosomal dominant inheritance (chromosome 19). Besides heredity, it is characterized by hemiplegia or signs of hemiparesis during the aura. Often, the hemiparesis is very prolonged, like a *migraine with prolonged aura*, i. e., over 60 minutes up to seven days. In these cases, differentiation versus a migrainous infarction is essential. Another important differential diagnosis is "strokelike episodes", which are found in a form of *mitochondrial cytopathy* (MELAS).

The very rare *ophthalmoplegic migraine* is characterized by diplopia (due to eye muscle palsy), which lasts for hours or days after a headache episode. As, in most cases, a structural lesion (e. g., aneurysm) is responsible for such a clinical entity, this diagnosis is to be made by exclusion only. Tolosa–Hunt syndrome (see above) and diabetic oculomotor palsy have very similar onsets; however, they typically last for weeks if not treated.

Tension Headache

Signs and Symptoms. In some ways, tension headache is the opposite of migraine because its onset is rather slow, it is usually more prolonged, its pain intensity is nearly always mild (to moderate), and it is not influenced by physical activity. Stress and tiredness exacerbate the dis-

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comfort; analgesics of all kinds improve it rapidly. The oppressive or constricting diffuse pain lasts for hours or often up to several days; the number of "headache days" distinguishes episodic from chronic (> 180 days per year) tension headache (*chronic daily headache*).

Differential Diagnosis. Many migraine patients also suffer from frequent tension headaches, and there are flowing *transitions* with a blurring of the typical migraine time course, which sometimes makes the evaluation more difficult. Phonophobia and photophobia are not typical for the tension headache, nausea is unusual, and vomiting indicates either the transition to a migraine or a wrong diagnosis. Systemic diseases, chronic sinusitis, chronic glaucoma, giant cell arteritis, chronic meningitis/neoplastic meningitis/brain abscess, and cerebral vein thrombosis are to be considered with newly occurring, persistent tension headaches. Contrary to popular belief, brain tumors such as meningioma or metastasis are believed to manifest themselves more frequently with epileptic seizures than with chronic headaches.

Most people tolerate a tension headache as an annoying, yet harmless disturbance of their quality of life. A minority of patients, however, suffers to the extent that they continuously mobilize the entire medical instrumentation and also demand the specialist's time to the extreme. These patients should be occasionally examined clinically, as they are at risk that a newly developed neurological or internal disease might be missed.

A still larger problem is the *chronic abuse of medication* to which many of these patients succumb. This abuse itself produces headache and, thus, maintains a vicious circle.

Cluster Headache (Bing–Horton Headache) and Chronic Paroxysmal Hemicrania

Clinical Features. The differentiation from (more frequent) migraine is usually clear, if attention is given to the *time course as the most crucial criterion*: In a period of one to many weeks (cluster), the attacks relentlessly follow one after the other, up to eight times in 24 hours, but at least once in 48 hours, often regularly and typically waking the patient from sleep. The increase in pain is much faster compared to the migraine; the plateau is reached after 20 minutes, and its duration is shorter than that of a migraine. The pain is located in the temple or face, almost never changes side, is agonizing, and often resistant to opiates. Cluster headaches compel the patient to walk around the room with their hands firmly pressed against their head, and often drive him or her to abuse pain medication or even to suicide. Additional signs, such as an ipsilateral red eye, a tearing eye, a clogged nose, and Horner syndrome, may be helpful diagnostically, but cluster headaches may sometimes also occur with a migraine or other headache type (see below). The presence of Horner syndrome, particularly during the very first attack, requires the exclusion of a carotid artery dissection or the very rare Raeder syndrome.

Most commonly, the time course of the cluster headache is characteristic to such an extent that there are few differential diagnostic overlaps with symptomatic headache.

Chronic Paroxysmal Hemicrania. Chronic paroxysmal hemicrania, an illness affecting only women, is characterized by more frequent and shorter attacks compared to a cluster headache, the corresponding illness for men. A usually rapid easing of the pain after intake of indomethacin is diagnostically important. The same applies to *hemicrania continua*, a unilateral continuous pain with exacerbation, which is distinguished from chronic paroxysmal hemicrania. SUNCT (**s**hort–lasting **u**nilateral **n**euralgiform headache with **c**onjunctival injection and **t**earing) denotes the indomethacin-negative form of chronic paroxysmal hemicrania with many attacks and strong autonomous disturbances.

Cluster headache in coexistence with ipsilateral, metachronous or synchronous trigeminal neuralgia is its own entity and is called *cluster-tic syndrome.*

Hypnic Headache. Like the cluster headache, this rare *holocephalic* pain, always out of sleep, causes the patient to pace around all night with their hands pressed against their head over weeks or months. Both eyes can be red and watery. During the day the patient is free of pain. Indomethacin, when taken in the evening, usually promptly alleviates this condition.

Thunderclap, Exertional, and Orgasm Headache

These special forms of idiopathic headaches are of particular importance in the differential diagnosis of *subarachnoid hemorrhage* and are mentioned above.

5.4 Neuralgia in the Head Region

Definition. Neuralgia denotes a pain in the area of a sensory nerve with a special characteristic: lancinating, often electric (neuralgia in the strict sense) or "neuralgiform," i. e., continuously burning, stinging or cutting. Several typical neuralgia occur in the head region (Tab. 5.**5**), which are usually easily distinguishable from

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Table 5.**5** Neuralgia of the head area/facial pain

- Idiopathic/symptomatic trigeminal neuralgia
- Idiopathic/symptomatic glossopharyngeal neuralgia
- Occipitalis major/minor neuralgia
- Rare neuralgia/neuralgiform pain in cranial nerve syndromes
- Traumatic neuralgia, painful anesthesia and facial pain of central origin
- So-called atypical facial pain

other forms of head or facial pain. Neuralgia and neuralgiform facial pains typically are sequels of a peripheral nerve lesion and only rarely of central nervous system origin (see below).

Idiopathic and Symptomatic Trigeminal Neuralgia

Clinical Features. The serially lancinating, sharp, and often electric pain, which is stereotypically unilateral, and always in the same place, usually in the middle and/or lower face (second/third trigeminal branches [maxillary/mandibular], see Fig. 5.**2**), are clear indications of trigeminal neuralgia. *Trigger points* in the pain zone are typical. Most commonly, attacks are initiated by chewing or speaking, which is why the patients often lose weight and become isolated. In the intervals between attacks, patients are pain free. Rarely, particularly after violent attacks, they may be troubled by tingling or boring sensations at the same location. In older patients, and in those with normal neurological findings, the neuralgia is "probably idiopathic." After an initially fluctuating course with one or two spontaneous remissions, the illness usually turns into an intolerable, continuous suffering, which can only be cured neurosurgically.

Trigeminal neuralgia in younger patients, in the first trigeminal branch, and with sensory disturbances within the trigeminal area, are usually symptomatic, i. e., the result of a structural lesion. Symptomatic trigeminal neuralgia often have a moderate and protracted pain character. The pain is often chronic and dull or boring ("neuralgiform") with exacerbations, but, in contrast to the idiopathic form, hardly ever lancinating.

Differential Diagnosis. A bout of multiple sclerosis is most likely in younger patients; this neuralgia is self-limiting after weeks to months. Postherpetic neuralgia is characterized by skin changes. Moreover, neuralgiform pain frequently accompanies different *trigeminal neuropathies*, either of idiopathic (viral) origin, pressure induced in the case of bone metastases or neurinoma, or due to autoimmune inflammatory processes and often bilateral, e. g., in scleroderma.

Idiopathic and Symptomatic Glossopharyngeal Neuralgia

This rare condition features a pain character and strict unilateral nature similar to that of idiopathic trigeminal neuralgia, but in a different location. In the "external form" the attacks are located under/behind the mandibular angle; in the "internal form" they are located deep in the ear, throat, or base of the tongue. *Triggers* are predominantly swallowing and coughing, and, less frequently, speaking. Inflammatory and space-occupying processes at the base of the skull and carotid dissection, both usually with additional neurological findings, are causes of symptomatic glossopharyngeal neuralgia.

Occipitalis Major/Minor Neuralgia

The fashionable diagnosis of "*occipital neuralgia*" summarizes entrapment neuropathies of these nerves (see Fig. 5.**2**), as well as the hardly distinguishable cervical disk syndrome C2 (C3). The diagnosis is very often incorrect, because spondylogenic pain due to a cervical syndrome, which radiates to the back of the head, is very similar and is also eliminated temporarily by exeresis of the occipital nerve. Indeed, "occipital neuralgia" is often associated with a cervical syndrome, and the movement-provoked, lancinating, neurogenic pain is not easily distinguished from a rheumatologic pain at the same place. The pain with occipital neuralgia is more stereotypical, strictly unilateral, marked by abnormal Tinel sensitivity of the nerves, and often characterized by tingling or dysesthesia in the area of these nerves. Local anesthesia at the Tinel point eliminates the symptoms for a while and supports the assumed diagnosis.

Rare Facial Neuralgias. Neuralgiform Pain in Cranial Nerve Syndromes

Optic neuritis, as well as diabetic *oculomotor palsy*, is often heralded and accompanied by intense pain in the eye or upper facial area without participation of the trigeminal nerve. A similar onset is observed in *Tolosa–Hunt syndrome* (painful ophthalmoplegia), giant cell arteritis, cavernous sinus fistula or thrombosis (in the early stage), and *Gradenigo syndrome* (petrositis with involvement of the trigeminal and abducens nerves).

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Raeder Syndrome manifests itself similarly with unilateral pain in the eye or forehead. However, it is additionally marked by a sensory loss in the area of the frontalis nerve (see Fig. 5.**2**) and by an ipsilateral Horner syndrome.

Differential diagnoses are *abortive Wallenberg syndrome*, an incipient *cavernous sinus process*, and *carotid dissection* with a typical, acute, facial pain on the side of the Horner syndrome (see Carotid and Vertebral Artery Dissection, p. 208).

The rare *auricolotemporal neuralgia* does not really deserve its name, as the burning pain sensations in the chin area are predominantly caused by abnormal hidrosis due to aberrantly re-innervated otic ganglion efferent nerve fibers (skin instead of parotid gland).

On the other hand, premonitory or accompanying lancinating pain, which radiates deep into the acoustic meatus in cases of herpes zoster oticus, or rarely, of facial hemispasm, indicates a *neuralgia of the intermedius nerve* (Hunt neuralgia). Sensory loss and/or trigger points located at the acoustic meatus confirm the diagnosis. It is not known whether this neuralgia is connected to the continuous pre-auricular and retro-auricular pain found in Lyme disease or in idiopathic *facial palsy* (Bell palsy).

The rare *superior laryngeal neuralgia* is defined by lancinating pain into the lateral neck triangle, which is triggered by swallowing, screaming, or movement. A trigger point at the lateral lower larynx confirms the diagnosis. Differentiation from glossopharyngeal neuralgia is difficult.

Traumatic Neuralgia, Painful Anesthesia, and Central Facial Pain

Traumatic Neuralgia. Lesions due to pressure or contusions, as well as rare ischemic (e. g., after angiography), or inflammatory (e. g., with sinusitis), affections of individual trigeminal branches, are easily diagnosed based on the medical history and accompanying findings (e. g., scars). They always exhibit a sensory loss in the area of neuralgiform pain and often an abnormal Tinel sign at their respective nerve exits.

Painful Anesthesia. More painful is the often continuous, causalgiform pain in trigeminal regions after unsuccessful thermocoagulation of the Gasser ganglion, after rhizotomy, or after other trigeminal lesions (e. g., infiltration by a tumor), which may become unbearable. The term painful anesthesia (anaesthesia dolorosa) expresses the apparent paradox of severe sensory deficit in an area of likewise severe pain.

Central Facial Pain. Intense unilateral facial pain and ipsilateral dissociated sensory loss in the trigeminal region (see Fig. 5.**2**), together with other brainstem signs, are typical in Wallenberg syndrome. Thalamic lesions can also produce such central, usually quadrantic or unilateral, pain syndromes (see Ischemic Brain Lesions, p. 208). Syringobulbia and tabes dorsalis are other rare examples of central facial pain, which should not be missed, given the additional neurological context. In isolated pain syndrome, i. e., without neurological signs the differential diagnosis versus psychogenic pain is very difficult and the transition to so-called atypical facial pain (see below) is fluid. Without evidence (imaging) of a lesion, an organic origin of such facial pain is difficult to substantiate.

5.5 Atypical Facial Pain

Differentially, circumscribed or diffuse facial pain may sometimes be very difficult to define more precisely, despite all neurologic, rhinologic and ophthalmologic investigations. For lack of better knowledge, these are called atypical facial pain. Most likely, somatoform disturbances often play a distinct role. The symptoms are episodic or chronically similar to tension headaches, and frequently respond to the same treatment.

It is still open to debate whether some forms, i. e., unilateral pain in the lower facial region and neck area, are due to *carotidynia* (see above) or not, and may be linked pathogenetically to the carotid artery.

If the point of maximum pain is located in the orbit and associated with a trigger point at the inner and upper orbital margin, local application of anesthetics or steroids to the trochlear area may relieve the pain (*primary trochlear headache*).

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6 Chest Pain

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Differential Diagnosis of Chest Pain

Introduction. Patients often associate any chest pain with pain originating from the heart. Indeed, serious cardiovascular diseases such as acute myocardial infarction or aortic dissection cause chest pain. Chest and thoracic pain, however, can originate from all organs of the thorax. The most serious lung diseases that cause chest pain are massive pulmonary embolism and pneumothorax. Apart from the many cardiac, vascular, and lung diseases, diseases of the gastrointestinal tract and of the musculoskeletal apparatus can also cause chest pain. Chest pain often induces anxiety in the patient. In addition, anxiety and emotions are often the causes of chest pain.

Importance of Medical History and ECG. A careful medical history, noting the character, duration, and location of the chest pain, in most cases allows the identification of the affected organ system (Tab. 6.**1**). For a more precise differential diagnosis it is essential to inquire as to details of pain-precipitating or pain-relieving factors (e. g., change of pain with change of position) and accompanying symptoms (e. g., nausea, fever, hyperventilation). An electrocardiogram (ECG) should be taken early in the evaluation process of unclear chest pain. The ECG is an important tool to quickly diagnose, or rule out, acute myocardial ischemia as a cause of chest pain. Establishing the correct diagnosis, and therefore the correct cause of chest pain, in a timely fashion is crucial for initiating the correct therapy.

Table 6.**1** Differential diagnosis of chest pain

	Character	Duration	Location
Heart			
Angina pectoris (myocardial ischemia)	Chest heaviness, tightening, constricting, choking, burning	Stable angina pectoris: short duration < 5 min; unstable angina pectoris: often prolonged 5–10 min, sometimes lasting hours with changing intensity	Center of chest, over sternum or just to the left of it, sometimes ring-like; radiation to shoulder/arms (left > right, usually ulnar side), neck/jaw, epigastrium (seldom back)
Myocardial infarction	Excruciating, severe constriction and tightening, dyspnea	Building up over minutes; most often persistent (> 30 min)	Precordial, radiating as in angina pain
Pericarditis	Sharp, severe, stabbing, tearing, varying with respiration, position, and motion (increasing pain in recumbency and with deep inspiration or coughing)	Persistent	Often precordial; not infrequently radiating to neck and shoulders
Aortic stenosis	Exercise-induced chest heaviness or tightening, often accompanied by dyspnea	Short duration 5–10 min	Similar to angina pectoris
Arrhythmias	Sharp pain at rest	Ending with stop of arrhythmia	Precordial, radiating to throat
Mitral valve prolapse	Sharp	Often of longer duration	Left side of chest
Aorta			
Aortic dissection	Excruciating pain, ripping, tearing	Abrupt onset, persistent	Precordial and/or interscapular; often migrating
Lungs/pleura			
Massive, pulmonary embolism	Blunt, chest heaviness, accompanied by dyspnea	Abrupt onset, persistent	Precordial
Pulmonary embolism accompanied by lung infarction	Tearing, rubbing, varying with respiration, occasionally resembling angina pectoris; typically associated with tachycardia, hemoptysis	Persistent	Center of chest and/or affected chest side
Pneumothorax	Sharp, tearing, variable with respiration, accompanied by dyspnea, tachycardia	Sudden onset, persistent	Unilateral
Pleuritis	Sharp, tearing, variable with respiration	Persistent (sometimes for days)	Unilateral, radiating to shoulder or epigastrium
Pneumonia	Sharp, variable with respiration, accompanied by fever, cough	Persistent	Unilateral, radiating to shoulder or epigastrium

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Table 6.**1** (Continued)

	Character	Duration	Location
Esophagus			
Gastro-esophageal reflux, esophagitis, esophageal spasm	Burning, dull, tightening, mimicking angina; provoked by bending, straining, or lying down	Lasting minutes to hours	Precordial, epigastrium
Rupture of esophagus	Excruciating, sharp pain, usually after vomiting; followed by fever and shock	Persistent	Precordial, radiating to back
Musculoskeletal apparatus			
Vertebral pain, rib fracture/injury, intercostal muscle injury, tumors of chest wall	Varying, dull to sharp (more often sharp), often provoked or worsened by motion, position, pressure	Variable, often beginning after exertion, motion	Unilateral, sometimes localized, occasionally along intercostal space
Nervous system			
Intercostal neuralgia; spinal cord compression; herpes neuralgia; thoracic outlet syndrome	Tearing, burning, electrifying. Accompanied by sensory disorders (paresthesia, numbness)	Persistent; resistant to therapy	Dermatome
Functional chest pain	Sharp, tearing, often associated with hyperventilation	Often persistent	Precordial; punctuated localized

6.1 Pain Originating from the Heart

Angina Pectoris

Definitions

Typical and Atypical Angina Pectoris. Angina pectoris is, until proven otherwise, the result of myocardial ischemia, secondary to coronary artery disease. Angina pectoris can be divided into typical and atypical angina pectoris. In typical angina pectoris, the discomfort or pain is located substernally and often radiates. It is precipitated by exertion or emotion and promptly relieved by rest.

Atypical chest pain is located in the left chest, sometimes confined to a small area, does not radiate, and is described as sharp, stabbing, or tearing. In atypical angina pectoris the pain can occur repetitively for short periods of time (seconds) or last for hours. It is unrelated to exercise and not relieved by rest or nitroglycerin. Atypical chest pain is often noncardiac in origin (Tab. 6.**2**).

Table 6.**2** Differential diagnosis of ischemic pain

	Ischemic cardiac chest pain	Noncardiac chest pain
Character	Tightening, squeezing, choking, burning, constricting, chest heaviness	Sharp, stabbing, tearing
Location	Precordial, central diffuse to ringlike	Unilateral, localized, peripheral
Radiation	Shoulder, arms (left > right), neck, jaw, epigastrium, back	Other or no radiation
Precipitating factors	Exertion, emotion, heavy meals, cold, windy weather	Spontaneous, provoked by posture, motion, coughing, palpitations
Relieving factors	Rest or after nitrates (within 5 min)	Not relieved by rest; slow or no response to nitrates

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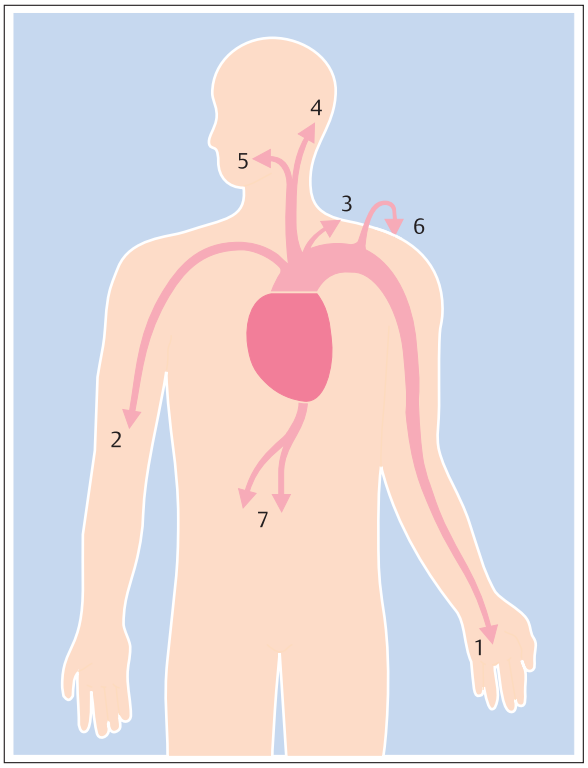

Fig. 6.**1** Radiation of angina pectoris: 1 = left arm, 2 = right arm, 3 = left shoulder, 4 = neck, 5 = jaw, 6 = back, 7 = epigastrium.

Stable and Unstable Angina Pectoris. The distinction between stable and unstable angina pectoris is of great clinical importance. In chronic stable angina pectoris the discomfort is predictably provoked by exertion and relieved by rest. A chronic stable coronary stenosis is, in most cases, the pathophysiological explanation of chronic stable angina pectoris.

Unstable angina pectoris occurs with minimal exertion or at rest. The pain is new in onset or increasing in intensity. Character and location are typical, however the intensity is often more severe and the duration longer than in chronic stable angina pectoris. Pathophysiologically, unstable angina pectoris is associated with ruptured plaques and thrombi, which obstruct the coronary lumina. Occasionally, coronary vasoconstriction or spasms contribute to the typical dynamic clinical manifestation of unstable angina pectoris.

It is important to note that myocardial ischemia may present itself in forms other than angina pectoris. Particularly in elderly patients, myocardial ischemia may cause nausea and stomach ache without chest pain.

About one-third of patients, predominantly diabetic patients, do not experience any discomfort with myocardial ischemia.

In those patients the first manifestation of coronary artery disease may be an acute myocardial infarction, heart failure, or cardiac arrest.

Clinical Characteristics of Angina Pectoris

Pain Characteristics. The discomfort or pain of angina pectoris is typically dull and tightening. It is often described as "pressing," "tearing," "constricting," "squeezing," "burning," or as chest heaviness, a "band across the chest," or "weight in the center of the chest" (Tab. 6.**2**). Angina pectoris is often accompanied by *dyspnea*. Dyspnea is caused by pulmonary congestion, secondary to increased left ventricular filling pressures. In fact, occasionally dyspnea may be the only symptom of myocardial ischemia and may represent an "angina equivalent." Radiation of angina pain is common. Angina pain radiates most typically to the left shoulder and arm, although many other locations are possible (see Fig. 6.**1**). Occasionally, the pain is only felt at the radiation point, e. g., in the jaw or the arm. Angina pectoris pain occurs with physical exertion and abates promptly (less than five minutes) at rest. Angina can *also be provoked by* exertion, emotions, heavy meals, and cold, windy weather. Not infrequently, patients wake up from sleep having angina pain and quite often the pain occurs with the first physical activity in the morning. Stable, and most often also unstable angina pectoris is promptly relieved by nitrates. The response to *nitroglycerin* may be used to differentiate angina pain from other causes of chest pain. However, keep in mind that pain originating from a hiatal hernia, esophageal spasm, or mild biliary colic may abate after nitroglycerin, too. The severe pain in acute myocardial infarction is often preceded by episodes of typical and atypical chest pain. This is an expression of the intermittent flow obstruction, secondary to the varying thrombus size at the site of the ruptured plaque.

Differential Diagnosis of Angina Pectoris. Emotional distress is a very common cause of atypical chest pain (Tab. 6.**2**). *Functional chest pain* should be considered, if the pain lacks a reasonable relationship to precipitating factors or features of anxiety and neurosis are present. Functional pain occurs at rest, lasts from seconds to hours, and is often localized to one point in the left chest. However, be aware that ischemic chest pain causes anxiety and therefore it may be at times difficult to differentiate between ischemic and functional pain.

Pericarditis can result in severe chest pain originating from the heart. Pericardial pain is sharper and more tearing than ischemic pain. Pericardial pain lasts for hours and the intensity can be aggravated by changing body position or by breathing.

Aortic dissection is suggested by sudden onset, sharp, tearing chest pain, felt in or radiating to the back.

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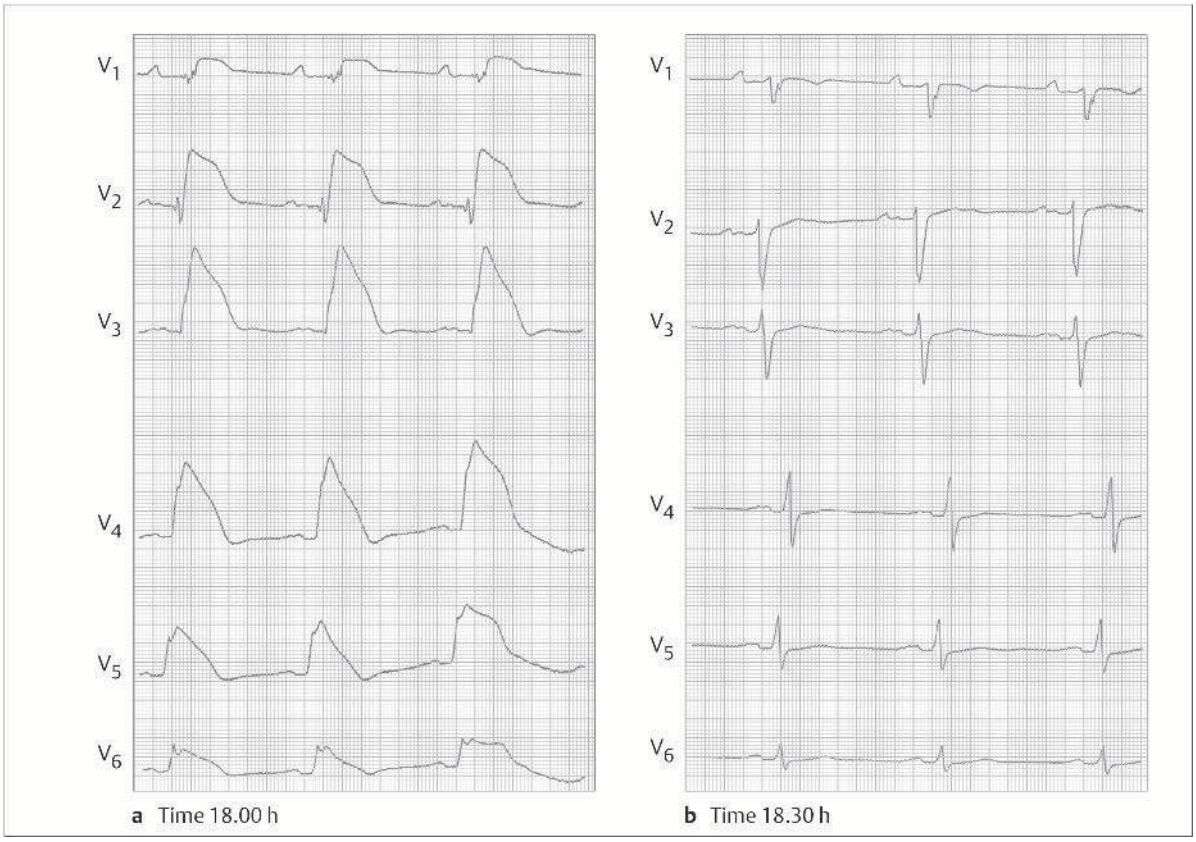

Fig. 6.**2** ECG of a 60-year-old patient with typical Prinzmetal angina pectoris.
a During attack
b 30 minutes after the attack. Coronary angiography revealed normal coronary arteries.
V_1 to V_6: chest wall leads according to Wilson.

Musculoskeletal pain of the chest is a very common problem. Chest wall pain is usually located to one site of the chest and can be provoked by posture, motion, or pressure. Sometimes a local tenderness is present. The most common causes of *chest wall pain* are arthritis, chondritis, intercostal muscle injury, and coxsackie virus infection (e. g., Bornholm disease).

Special Forms of Angina Pain

Prinzmetal Angina. Prinzmetal angina occurs at rest and is (sometimes) associated with grotesque ST segment elevations (Fig. 6.**2**). Prinzmetal angina is caused by a focal vasospasm of one of the coronary arteries and is therefore also called vasospastic angina. In the vast majority of patients with Prinzmetal angina, minimal atherosclerotic changes are present. However, in about 10% of patients the coronary arteries are normal. Prinzmetal angina is sometimes associated with migraine or Raynaud disease. Apart from this extreme form of vasospastic angina, vasospasm may contribute to many angina pectoris attacks:

- In nocturnal angina pectoris the increased vagal tone may induce vasospasm.
- Angina pectoris provoked by cold or emotion is most certainly secondary to a general vasoconstriction and possibly a vasospasm at the site of an eccentric coronary lesion.
- Hyperventilation can result in vasospasm and angina pectoris.

"Walking-through" Phenomenon. Walking-through describes the phenomenon that exercise-induced angina can abate despite, or because of, continued exercise. The pathophysiological explanation of this phenomenon is the recruitment of collaterals during exercise. Increasing blood flow via collaterals provides enough oxygen, such that ischemia decreases and the pain subsides.

Angina Pectoris, Secondary to Left Ventricular Hypertrophy. Patients with aortic stenosis, aortic insufficiency, hypertension, or hypertrophic obstructive cardiomyopathy often experience typical exercise-induced angina pectoris. The cause of angina pectoris in these cases is a transient myocardial ischemia of the hypertrophied left ventricle. Ischemia is the result of a

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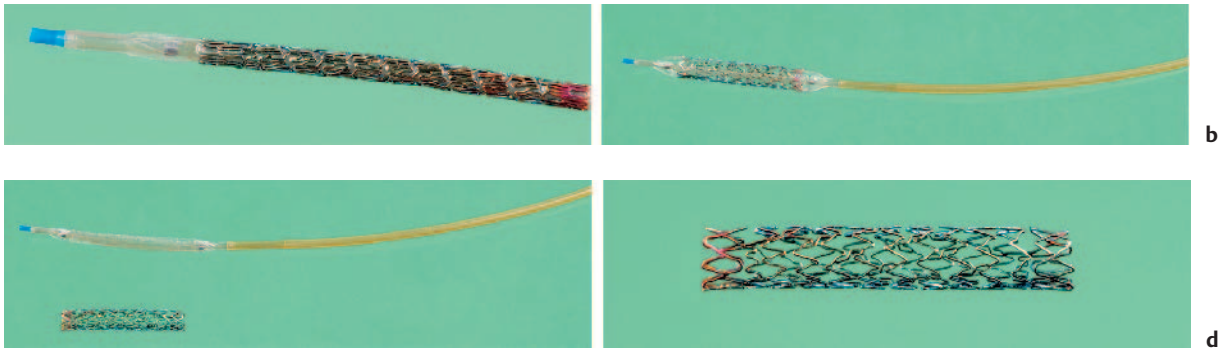

Fig. 6.**3** Technique of stent implantation.
a The stent is mounted onto a balloon catheter, which is advanced over a guiding wire into the coronary stenosis.
b Balloon inflation expands the stent.
c After withdrawal of the balloon, the expanded stent remains in the vessel.
d The deployed stent prevents elastic recoil of the dilated stenosis and protects against an acute or subacute occlusion of the vessel in case of an intimal tear. Restenosis is prevented by a drug that is eluted from the stent surface.

decreased coronary flow reserve and an impaired vasomotion of the resistance vessels (arterioles). In a normal (nonhypertrophied) ventricle, the coronary blood flow can be increased four- to fivefold with physical activity. In left ventricular hypertrophy, coronary flow at rest is already increased (to meet the needs of the increased demand) and cannot be further increased during exercise. This results in a relative underperfusion of the hypertrophied ventricle and causes ischemia in the subendocardium.

Angina Pectoris after Percutaneous Coronary Interventions (PCI). PCIs are performed to alleviate angina pectoris. The technique involves the dilation of coronary stenosis with a balloon catheter. Over 90% of the dilations are completed with the implantation of a stent to prevent early reocclusions and decrease restenosis rate (Fig. 6.**3**). Despite this, chest pain may reoccur after a PCI. Early (i.e., usually within the first 30 days after an intervention) crushing chest pain associated with ST segment elevations may occur. The cause is an acute thrombotic occlusion of the coronary artery at the dilated lesion. The clinical presentation of this so-called subacute stent thrombosis is that of a myocardial infarction. Late after an intervention (i.e., within three to nine months) typical and atypical angina pectoris may reoccur. The discomfort usually resembles the discomfort before the intervention. It is caused by a renewed narrowing of the dilated stenosis, the so-called restenosis. Restenosis is the result of an extensive intimal hyperplasia at the site of the intervention. Angina pectoris necessitating reinterventions (i.e., clinically driven reintevention after PCI) had to be performed in 10–12% of patients treated with bare metal stents. The new drug–eluting stents have decreased this rate to 2–3%.

Cardiac Syndrome X. In cardiac syndrome X, patients with normal epicardial coronary arteries suffer from angina pectoris. The cause is a decreased coronary flow reserve, which in this case is the result of a dysfunction of the resistance vessels.

Angina Coerulea. Dyspnea is the leading symptom of severe pulmonary hypertension. However, patients with pulmonary hypertension sometimes report an exertional chest pain, which can persist for some time at rest. The cause of this angina pectoris is most likely a relative underperfusion of the hypertrophied right ventricle resulting in myocardial ischemia during exercise.

Decubitus Angina. In severe coronary artery disease, angina pectoris may be provoked in recumbency. It is thought that the increased return of blood to the heart, and the resulting increase in filling pressures, precipitates angina pectoris. Similarly, the symptoms of an acute myocardial infarction can be aggravated in the recumbent position.

Silent Myocardial Ischemia. Myocardial ischemia that does not cause angina pectoris is called "silent" ischemia. The prognosis of silent ischemia is similar to that of symptomatic myocardial ischemia.

Angina Pectoris Caused by Myocardial Ischemia

Classification. According to its clinical presentation, ischemic heart disease is categorized as chronic stable or unstable angina pectoris and/or acute coronary syndrome (ACS), including acute myocardial infarction. Severity of chronic stable angina pectoris is classified according to the Canadian Cardiovascular Society (Tab. 6.**3**). Unstable angina pectoris is a clinical syndrome, which is defined by one of the following fea-

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tures: severe chest pain of new onset, pain at rest or minimal exertion, or pain with crescendo pattern. Unstable angina pectoris is classified according to Braunwald (Tab. 6.**4**). Unstable angina pectoris is part of ACS (see Fig. 6.**13**).

Risk Assessment. When approaching a patient with suspected coronary artery disease the risk for coronary artery disease should be assessed according to the number of cardiovascular risk factors present and through careful history taking. In a second step, the risk of a ruptured plaque as the cause of the symptoms should be evaluated. A ruptured plaque often results in ACS. For prognostic reasons, ACS needs to be treated with greater urgency than chronic stable angina pectoris.

Table 6.**3** Canadian Cardiovascular Society classification of stable angina pectoris

Class	Definition
0	Silent ischemia
I	Angina pectoris with strenuous exercise (e. g., mountain climbing)
II	Slight limitation of ordinary activity (e. g., climbing stairs rapidly)
III	Marked limitation of ordinary physical activity (e. g., angina after walking two blocks or climbing one flight of stairs)
IV	Angina pectoris with minimal physical activity or at rest

Chronic Stable Angina Pectoris

A careful study of the medical history, including the history of the pain, is the key to the differential diagnosis of ischemic chest pain. The physical examination in a patient with chronic stable angina pectoris is often unrewarding. The most common finding is arterial hypertension. In addition, features of general atherosclerosis may be present.

The higher the number of cardiovascular risk factors, the more likely is the presence of coronary artery disease. Lack of cardiovascular risk factors decreases the likelihood, but does not exclude coronary artery disease.

Table 6.**4** Braunwald clinical classification of unstable angina pectoris*

Class	Definition
Severity	
Class I	New onset of severe angina or accelerated angina; no rest pain
Class II	Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)
Class III	Angina at rest within 48 hours (angina at rest, acute)
Clinical circumstances	
A	Secondary angina; develops in the presence of extracardiac condition (such as anemia, hypotension, tachyarrhythmia) that intensifies myocardial ischemia
B	Primary angina; develops in the absence of extracardiac condition
C	Postinfarction angina; develops within two weeks after acute myocardial infarction

* From *Braunwald's Heart Disease*, 7th edition, p. 1244.

Risk Factors of Coronary Artery Disease

Endothelial dysfunction and a chronic inflammation resulting in lipid deposition in the arterial wall are part of the initial pathophysiological processes of atherosclerosis. The chronic process of atherosclerosis then progresses from fatty streaks, to atherosclerotic plaques, to diffuse coronary sclerosis and calcification. The development of atherosclerosis is, in many cases, caused or initiated by a genetic predisposition and/or various cardiovascular risk factors (Tab. 6.**5**). Cardiovascular risk factors often accelerate the process of atherosclerosis. Nonmodifiable, genetic risk factors are responsible for more than half the individual risk factors. The so-called modifiable risk factors contribute to the residual risk factors. Successful control of the modifiable risk factors will decrease the risk for atherosclerosis and will slow the process in the case of established atherosclerosis.

Table 6.**5** Some important risk factors for atherosclerosis

Nonmodifiable factors:
Family history
Age
Gender
Modifiable factors:
Lipid disorders
Hypertension
Diabetes mellitus
Tobacco
Obesity
Other possible factors:
Sedentary lifestyle
Diet
Hyperhomocysteinemia
Psychosocial stress and personality traits
Prothrombotic hemostatic variables
Chronic inflammation

Nonmodifiable Risk Factors:

- *Family history:* a genetic predisposition not only exists for atherosclerosis, but similarly for the most important, cardiovascular risk factors (hyperlipidemia,

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diabetes, hypertension). In addition to this combination of genetic risk factors, many families share a common high-risk lifestyle with respect to diet, smoking, and sedentary lifestyle.

- *Age and sex:* age is the most powerful independent risk factor. Premenopausal women have a lower incidence of coronary artery disease than men. After menopause, this gender-related difference decreases with increasing age.

Modifiable Risk Factors:

- *Dyslipoproteinemia:* apart from the genetically caused primary forms of hyperlipidemia, the secondary forms of hyperlipidemia due to diet, lifestyle, drugs, and diseases are the most important modifiable risk factors (see below). High levels of total cholesterol and/or LDL cholesterol and, to a lesser degree, high levels of triglycerides and lower HDL cholesterol, are associated with an increased risk for atherosclerosis. Since abnormal lipid metabolism is a key element in the development of atherosclerosis, treatment of hyperlipidemia is an essential part of primary and secondary prevention of atherosclerosis and coronary artery disease.
- *Hypertension:* the higher the blood pressure, the higher the risk. Systolic and diastolic hypertension carry similar risks.
- *Diabetes mellitus:* diabetes, but also insulin resistance and decreased glucose tolerance, cause a substantial increase in atherosclerosis. Very often atherosclerosis is not confined to the coronary arteries; the whole vascular system may be affected.
- *Tobacco:* the risk for a myocardial infarction can be decreased by 65% with smoking cessation. After a myocardial infarction, smoking cessation improves the prognosis substantially.
- *Obesity:* obesity, particularly if central or truncal, is an independent cardiovascular risk factor. This type of obesity is characterized by an increased ratio of waist to hip circumference. Obesity is often associated with insulin resistance, dyslipidemia, hyperglycemia, hypertension, and hypercoagulability.
- *Metabolic syndrome:* a state in which in addition to increased waist circumference (men > 94 cm [37 in], women > 88 cm [35 in]) there is an increase in blood pressure (> 130/85 mmHg), plasma triglycerides (> 1.7 mmol/L [> 150 mg/dL]), fasting blood glucose levels (≥6.1 mmol/L [> 110 mg/dL]), and HDL cholesterol is decreased (< 1.0 mmol/L [< 40 mg/dL]), is called metabolic syndrome. For the diagnosis, three of these five diagnostic criteria must be fulfilled. Metabolic syndrome is associated with a substantially increased cardiovascular morbidity and mortality. Metabolic syndrome is one of the biggest health problems of modern society.

Other Risk Factors. Sedentary lifestyle doubles the risk for coronary artery disease and stroke. Long-lasting psychosocial stress can be a risk factor. Short episodes of stress, however, do not influence the development of atherosclerosis. Nevertheless, extremely stressful situations (such as natural disasters, strong emotions) can precipitate a myocardial ischemia. Some personality traits (impulsive personality, depression) are associated with increased incidence of coronary artery disease. The rare, inherited hyperhomocysteinemia is accompanied by atherothrombosis. Whether a more modest hyperhomocysteinemia (> 15 μmol/L) results in an increased risk is not clear. Diet can influence the risk for atherosclerosis. A diet high in saturated fat increases the risk, a diet high in ω-3 polyunsaturated fat decreases the risk. Modest intake of alcohol also decreases the risk. The importance of prothrombotic, hematologic factors, such as an elevated fibrinogen or a decreased fibrinolytic activity, is uncertain. Chronic inflammation contributes to atherosclerosis. The more active the inflammation, as assessed by proinflammatory cytokines and C-reactive protein, the higher the risk.

Dyslipoproteinemia

Water-insoluble lipids are transported in the blood encapsulated in phospholipids and special proteins (called apolipoproteins). These lipid–protein particles are called lipoproteins. Lipoproteins are categorized according to their density, size, lipid content, and main apolipoprotein (Tabs. 6.**6**, 6.**7**). The large chylomicrons and very low density lipoproteins (VLDL) form the "milky" supernatant over the serum after centrifugation (Fig. 6.**4**). Apart from high levels of lipoproteins (hyperlipoproteinemia), the ratio of the lipoproteins can cause an increase in the risk for atherosclerosis, in particular the ratio of total cholesterol to HDL cholesterol. Therefore, it is better to describe lipid disorders not as hyperlipidemia, but as dyslipidemia or more precisely as dyslipoproteinemia.

Diagnosis of Dyslipoproteinemia. In clinical routine, patients are screened for dyslipoproteinemia by a standard lipid profile. Included in a lipid profile is the measurement of total cholesterol, triglycerides, and the cholesterol of high density lipoproteins (HDL-C). Cholesterol of low density lipoproteins (LDL-C) is either measured or calculated from the above measured parameters. In most cases an accurate diagnosis of the dyslipoproteinemia can be achieved with the standard lipid profile. Occasionally, the exact diagnosis or classification of the dyslipoproteinemia requires further testing, such as measurement of apolipoprotein composition or measurement of LDL particle size. For practical, clinical reasons dyslipoproteinemias are commonly divided, independent of etiology or phenotype, into hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, and low HDL cholesterol disorder (Tab. 6.**8**).

Clinical Features. The most important clinical manifestation of a dyslipoproteinemia is atherosclerosis. Severe hyperlipidemia, particularly primary forms of hyper-

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lipidemia, can be associated with lipid deposits in the skin and in joints. However, a corneal arcus, an arcus lipoides, and xanthelasma (Fig. 6.**5**) may be present with normal cholesterol levels after the fourth decade. Tendon xanthoma and palmar xanthoma (Figs. 6.**6**, 6.**7**) occur in some of the primary dyslipoproteinemias (Tab. 6.**9**). Tubero-eruptive xanthoma may itch and the lesions may be reddened due to inflammation and scratch effects (Fig. 6.**8**). Lipid deposits in the skin are typically absent in familial combined hyperlipidemia and familial hypertriglyceridemia. Patients with homozygotic, familial hypercholesterolemia may develop acute or subacute polyarthritis of the large joints. Recurrent episodes of pancreatitis are typical of familial chylomicronemia.

Primary Forms of Dyslipoproteinemia. The most important primary forms of dyslipoproteinemia are listed in Tab. 6.**9**. In addition, several rare genetic defects exist that result in similar phenotypes. The rare, familial hypo-α-lipoproteinemia increases LDL levels. It is interesting to note that some disorders affecting the HDL cholesterol protect against atherosclerosis. One mutation of the apolipoprotein A1, the apoA-I_{Milano}, severely reduces HDL-C levels, but does not increase the risk for atherosclerosis and is associated with longevity.

Secondary Dyslipoproteinemias. The recognition of secondary causes of dyslipoproteinemias is important, as on the one hand dyslipoproteinemia may be the leading

Fig. 6.**4** Hyperchylomicronemia with "creamy" chylomicrons over the serum.

Table 6.**6** Structure and function of the main lipoproteins

Lipoprotein	Cholesterol	Triglycerides	Main apolipoproteins	Function
Chylomicron	3 %	90 %	B_{48}, A-I, C-II, E	Main transporter of dietary triglycerides; not present in normal fasting plasma
VLDL (very low density lipoprotein)	15 %	65 %	B_{100}, C-II, E	Main transporter of endogenous triglycerides, synthesized in liver; precursor of LDL
LDL (low density lipoprotein)	45 %	10 %	B_{100}	Main cholesterol carrier in blood; synthesized from VLDL in the blood
HDL (high density lipoprotein)	20 %	5 %	A-I, A-II	Transport of cholesterol from peripheral tissue to liver for excretion

Table 6.**7** Structure and function of some apolipoproteins

Apolipoprotein	Molecular weight	Site of synthesis	Metabolic function
A-I	28 000	Liver, intestine	Main HDL protein; activator of lecithin cholesterol acyltransferase (LCAT1)
B_{100}	549 000	Liver	Main structural protein of VLDL and LDL; important for synthesis and excretion of VLDL from liver, ligand of LDL receptor
B_{48}	254 000	Intestine	Protein of chylomicrons involved in synthesis and excretion of chylomicrons from intestine
C-II	8 850	Liver	Activator of lipoproteinlipase (LPL)
E	34 000	Liver, intestine, macrophages, glial cells	Ligand of LDL receptor and also of other specific liver receptors

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Fig. 6.**5** Arcus lipoides and xanthelasma in a 43-year-old patient with hypercholesterolemia.

Fig. 6.**6** Tendon xanthoma in hyperlipidemia.

Fig. 6.**7** Plantar xanthoma in hyperlipidemia.

Fig. 6.**8** Eruptive xanthoma in hyperlipidemia.

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Table 6.**8** Classification of dyslipoproteinemia

	Hypercholesterolemia	Hypertriglyceridemia	Mixed Hyperlipidemia	Low HDL-cholesterol
Blood levels	Total cholesterol ↑ LDL-cholesterol ↑	Triglycerides ↑ VLDL ↑ possibly chylomicrons ↑	Total cholesterol ↑ triglycerides ↑ HDL-cholesterol ↓ /→	HDL-cholesterol ↓ total cholesterol →/ ↑
Secondary causes	Hypothyroidism Cushing disease nephrotic syndrome chronic cholestasis drugs: glucocorticoids	Estrogens drugs: – corticosteroids – immuno suppressants – recinoids – contraceptives alcohol excess	Diabetes mellitus, metabolic syndrome, chronic renal insufficiency, sedentary lifestyle drugs: – protease inhibitors – betablockers – thiazides	Smoking, sedentary lifestyle
Inherited diseases (primary causes)	Familial hypercholesterolemia, familial defective Apo-B_{100}, polygenic hypercholesterolemia	Familial hypertriglyceridemia, familial chylomicronemia	Familial combined hyperlipidemia, familial type III hyperlipidemia (dysbetalipoproteinemia)	Apo-A-1 deficiency familial HDL deficiency (e. g., Tangier disease) familial LCAD deficiency

Table 6.**9** Most important primary hyperlipidemias

Disease	Mechanism/ Defect	Cholesterol (mmol/L)	Triglycerides (mmol/L)	Lipoproteins	Clinical manifestation
Hypercholesterolemia					
Polygenic hypercholesterolemia	Genetic disorders of several genes, total cholesterol ↑	6.5–9.0	normal	LDL ↑	Atherosclerosis
Familial hypercholesterolemia, heterozygote	Absent or deficient LDL-receptor	7.0–13.0	normal	LDL ↑, HDL ↓	Atherosclerosis (third to fifth decade), xanthomata, xanthelasma
Familial hypercholesterolemia, homozygote	Absent or deficient LDL-receptor	> 13.0	normal	LDL ↑, HDL ↓	Atherosclerosis (in childhood), xanthomata over tendons, aortic stenosis, arthritis
Familial defective Apo-B_{100}	Reduced affinity of LDL for LDL-receptors; slowed clearing of LDL	7.0–13.0		LDL ↑	Atherosclerosis, xanthomata
Hypertriglyceridemia					
Familial hypertriglyceridemia	Hepatic overproduction of triglycerides	normal	2.8–8.5	VLDL ↑	Atherosclerosis(?)
Familial chylomicronemia	Impaired lipolysis due to deficient LPL (or Apo-C-II)	normal	> 10.0	chylomicrons ↑, VLDL ↑	Pancreatitis (in childhood), eruptive xanthomata, hepatosplenomegaly
Combined hyperlipidemia					
Familial combined hyperlipidemia (FCH)	Excessive synthesis of Apo-B_{100}	6.5–13.0	2.8–12.0	VLDL ↑, LDL ↑, HDL ↓	Atherosclerosis
Familial dysbetalipoproteinemia, remnant type III hyperlipidemia	Defective Apo-E	6.5–13.0	2.8–8.5	remnants ↑, IDL ↑, VLDL ↑	Eruptive xanthomata and planar xanthomata, Atherosclerosis

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symptom of the disease, and on the other hand therapy of the underlying disease may correct the disorder. Metabolic and hormonal disorders, diseases of the kidney and the liver, drugs, and an unhealthy lifestyle can all cause dyslipoproteinemias. The main metabolic disorders causing dyslipoproteinemias are diabetes and metabolic syndrome. In both cases a resistance of the peripheral tissue to insulin exists and this contributes predominantly to the increase in lipids in the blood. Hypothyroidism is another important cause for hypercholesterolemia. Estrogens may cause an increase of triglycerides and HDL cholesterol. In contrast, growth hormone decreases LDL cholesterol and increases HDL cholesterol. An acute glomerulonephritis can cause an extensive increase in LDL cholesterol, while chronic, renal failure is associated with decreased HDL cholesterol. The most important drug-induced dyslipoproteinemias associated with premature atherosclerosis are induced by corticosteroids, immune-suppressant drugs, and protease inhibitors used as antiviral therapy in HIV-infected patients. Obesity, high fat diet, and sedentary lifestyle may all contribute to dyslipoproteinemia.

Pathophysiology of Lipoprotein Metabolism

Lipoprotein metabolism is a complex system of enzymes, receptors, and transport mechanisms, which may be thought of as three interconnected transport pathways. The exogenous pathway is responsible for the absorption and distribution of alimentary fat and the endogenous pathway for the production of cholesterol in the liver. The third pathway accomplishes the cholesterol transport to the peripheral tissue and the reverse cholesterol transport back to the liver for excretion.

Exogenous Pathway. Alimentary fats are taken up by intestinal enterocytes in the form of micelles and resynthesized to triglycerides and cholesteryl esters and incorporated into chylomicrons. Chylomicrons are then secreted in the portal circulation. In the capillaries of adipose tissue, heart, and skeletal muscle, triglycerides are removed from chylomicrons by the action of lipoprotein lipase, an enzyme located on the luminal side of the endothelial cells of these capillaries. The liberated fatty acids are rapidly taken up by adipose tissue or muscle cells by an insulin-dependent mechanism. In case of insulin resistance, free fatty acids increase in the blood and more free fatty acids are recirculated to the liver.

Endogenous Pathway. Through the above described process chylomicrons are depleted of triglycerides and this leaves two main residual particles of chylomicrons: a so-called chylomicron remnant and a precursor of HDL. The remnant particle is taken up by the liver and either used for synthesis of VLDL or excreted in the bile acid. In the fasting state, the liver synthesizes triglycerides as an energy source and secretes them as triglyceride-rich VLDL. Similar to the chylomicrons, the VLDL is depleted of triglycerides by the action of the endothelial lipoprotein lipase. The resultant VLDL remnants are called intermediate density lipoproteins (IDL). From IDL, the cholesterol-rich low density lipoproteins (LDL) are synthesized. LDL will eventually be removed from the circulation by the LDL receptor pathway in the liver and peripheral tissue. In addition, through a pathway that is less specific and less well understood, LDL can also be incorporated in atheromatose plaques.

Third Pathway. High density lipoproteins are synthesized in the liver and intestine and also in part by lipolysis of chylomicrons and VLDL. One of their functions is to remove cholesterol from the peripheral tissues and transport it to the liver for excretion. This cholesterol-lowering effect of HDL is considered atheroprotective.

Apolipoproteins. Apolipoproteins are important structural components of the lipoproteins and have important functions as activators and coactivators of many enzymatic pathways of the lipoprotein metabolism (see Tab. 6.**7**). The main apoprotein of HDL, the apolipoprotein A-I, for example, is an activator of the enzyme lecithin cholesterol acyltransferase, which catalyses the transfer of fatty acids from peripheral tissue into the HDL. A mutation of the LDL apolipoprotein, apo-B_{100}, results in hypocholesterolemia because the mutant apoprotein can no longer mediate the binding of LDL to the LDL receptor.

Diagnostic Methods in Coronary Heart Disease

Noninvasive and invasive tests are routinely used for the diagnosis of coronary artery disease (Fig. 6.**9**).

Resting ECG. The standard 12-lead electrocardiogram (ECG) and the exercise (stress) ECG are the most important screening tests in coronary heart disease diagnosis. The resting ECG is, however, often normal. In only about one-third of patients with chronic stable coronary artery disease specific and unspecific changes are observed, including negative or biphasic T waves, ST segment depressions, or in the case of an old infarction, loss of R waves, and occurrence of Q waves.

Exercise ECG. The exercise ECG is recorded during exercise on a bicycle or a treadmill. It is the most important and most widely used noninvasive test to diagnose coronary disease (Fig. 6.**9**). The test is clinically positive if angina pectoris occurs. It is electrocardiographically positive if there is either an ST segment depression of at least 0.1 mV (subendocardial ischemia) (Fig. 6.**10**) or a transient monophasic ST segment elevation (transmural ischemia) (Fig. 6.**11**). Extensive ST segment depressions in several leads, simultaneous with a drop in blood pressure, or the occurrence of anginal symptoms at a low exercise level, are indications of a severe coronary artery disease. The electrocardiographic parameters for a positive test do not apply in patients with left bundle,

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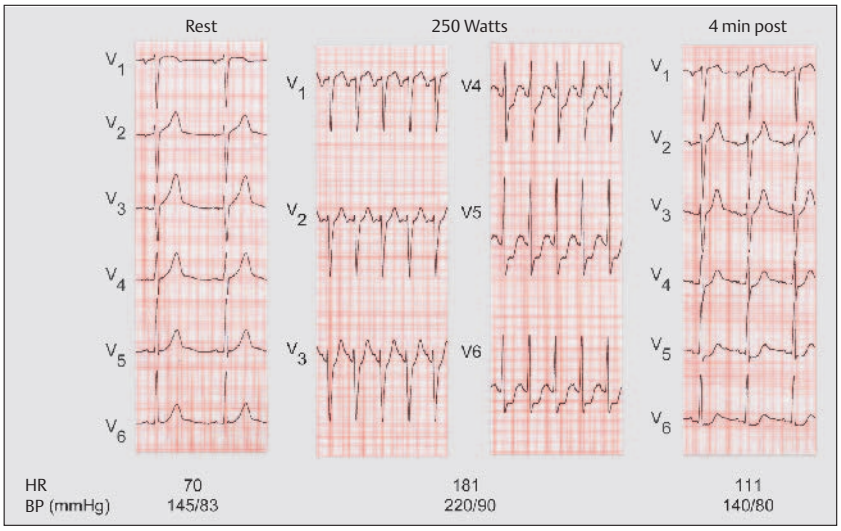
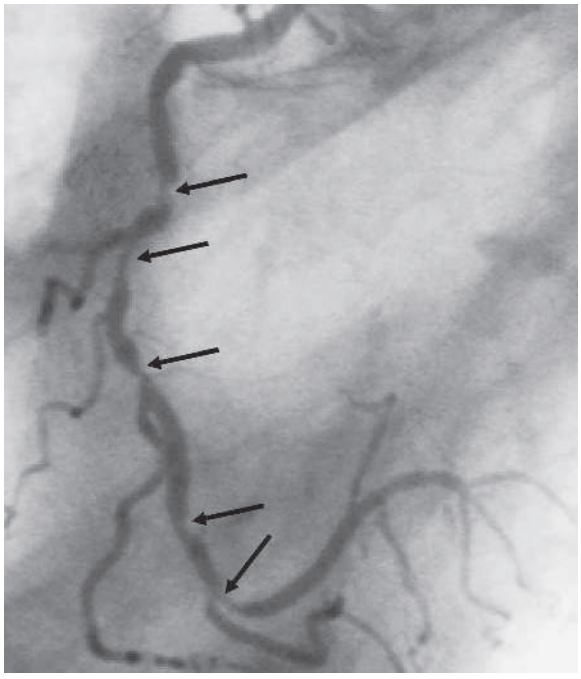


a

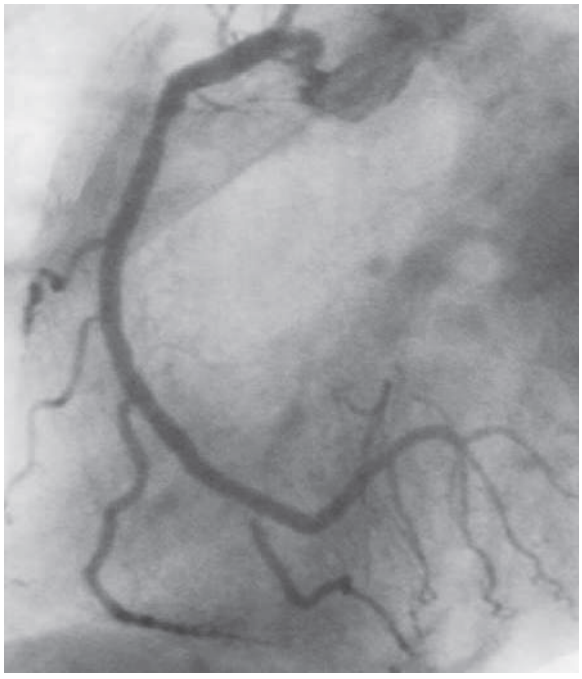
Fig. 6.**9** Stress ECG and percutaneous coronary intervention.

a Exercise ECG in a 50-year-old patient with a status post percutaneous revascularization of the left anterior descending (LAD) and circumflex arteries 6 years ago. For several months the patient had been complaining of chest pain during strenuous exercise. The patient was in good shape and achieved a maximal workload of 250 watts in a bicycle test. In the stress ECG horizontal ST segment depressions of 0.3 mV are noted, which persist into four minutes of recovery. He also experienced chest pain. The patient was referred for coronary angiography. V_1 to V_6 : chest wall leads according to Wilson.



b

b Coronary angiography reveals a diffusely diseased, right coronary artery with a subtotal stenosis proximally and two significant stenoses more distally.



c

c The stenoses are successfully treated with percutaneous coronary intervention and stent placement.

Fig. 6.**9 d** ▷

branch block, left ventricular hypertrophy, patients on digoxin, or with hypokalemia, severe anemia, and in cases of hyperventilation. A stress test is not reliable if for noncardiac reasons an adequate exercise can not be performed (adequate exercise = increase of the product of blood pressure times heart rate by a factor of three).

The exercise ECG is less reliable in women than in men. In young women the exercise test has been reported to be falsely positive in 20–40 % of cases.

Echocardiography. In coronary artery disease the two-dimensional echocardiography allows the visualization of heart wall motion abnormalities caused by a chronic or acute ischemia, and scars of old infarcts. In chronic stable angina pectoris, stress echocardiography is used to look for stress-induced heart wall motion abnormalities as a sign of a significant ischemic coronary artery disease. Dobutamin in increasing doses is infused to stress the heart in a stress echocardiography.

Myocardial Scintigraphy. Radionuclide tracers allow the visualization of regional differences in coronary flow during exercise. Thallium 201, technetium ^{99m}Tc-labeled sestamibi and ^{99m}Tc-labeled tetrofosmin are radio-

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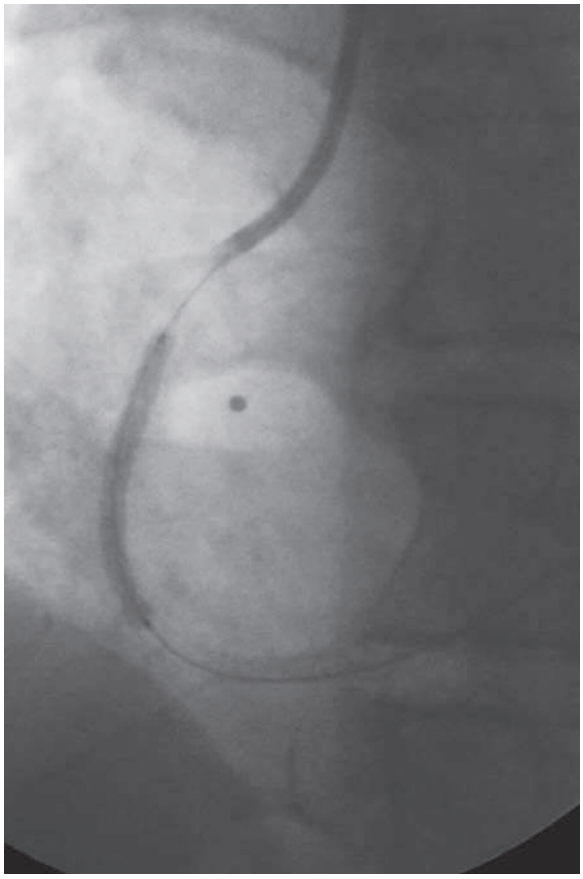


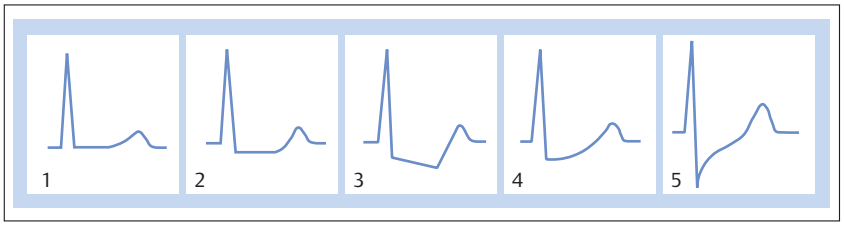
d

Fig. 6.**9** **d** Balloon dilatation and implantation of two drug eluting stents.

nucleotide tracers currently in use. The tracers are taken up by myocardial cells in proportion to coronary flow. A fixed defect is recorded in regions of an old infarct, i. e., in a scar. Regions with exercise-induced ischemia exhibit reversible uptake deficits. Thallium 201 has the property to accumulate in the myocardial cells over several hours. This allows to test whether the myocardium in the area of a defect is still viable. Late accumulation of thallium (12–24 hours after initial test) is an indication for viability of the myocardium, despite reduced coronary flow.

Positron Emission Tomography (PET). Myocardial scintigraphy detects only relative differences in perfusion. PET allows the measurement of absolute coronary flows. In addition to the detection of perfusion deficits, viability can be tested with tracers that are incorporated in metabolic pathways of the myocardial cells. Therefore, PET has become the "gold standard" to test for viability in hypoperfused, hypocontractile myocardial areas. In addition, PET can now be combined with high-resolution computed tomography. Thus, a coronary stenosis can be visualized and the physiological effect of the stenosis can be assessed simultaneously.

Magnetic Resonance Imaging (MRI). MRI not only discloses the anatomical structures of the heart and coronary arteries, it is also capable of measuring absolute coronary blood flow. Changes in MR properties of ischemic myocardium allow the detection of a significant number of coronary artery diseases (Fig. 6.**12**). In addition, scar tissue can be unequivocally identified and precisely quantified.



4 Ascending ST segment, concave transition into T wave: not typical for ischemia.
5 Ascending ST segment: not caused by ischemia.

Fig. 6.**10** ST segment changes of the ECG in subendocardial ischemia.
1 Normal ECG
2 ST segment flat, rounded angle towards T wave: sign of ischemia.
3 Descending ST segment, pointed transition into T wave: sign of ischemia.

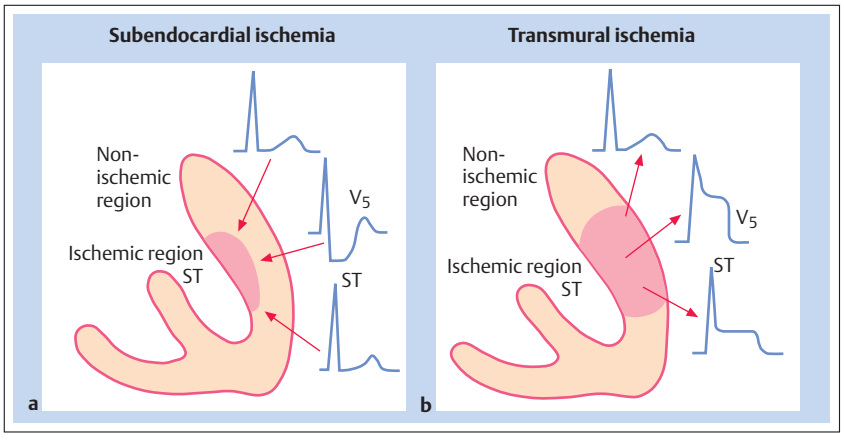


Fig. 6.**11** ECG changes in subendocardial and transmural ischemia.
a In subendocardial ischemia ST segments are depressed, because the ST vector (arrows) points toward the inner wall of the ventricle. The ECG leads positioned over the ischemic region show an ST segment depression.
b In transmural ischemia the ST vector (arrows) points to the outside of the wall. The ECG leads positioned over the ischemic region show an ST segment elevation.

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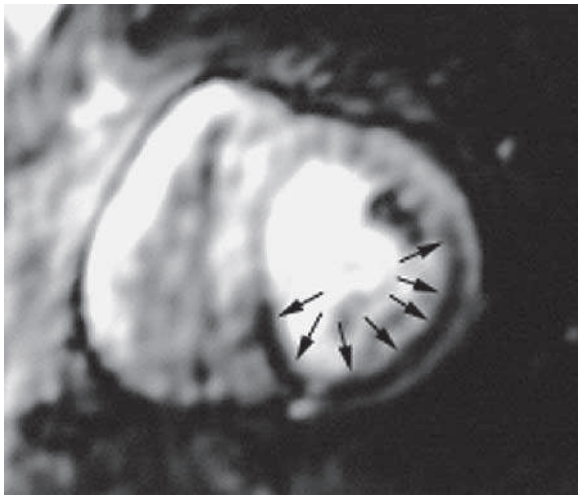

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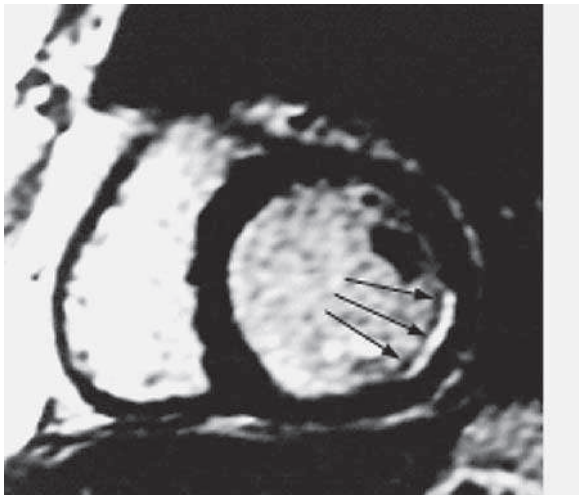

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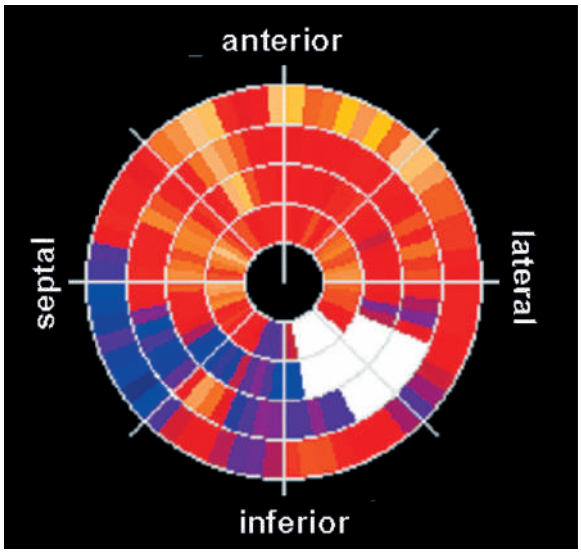

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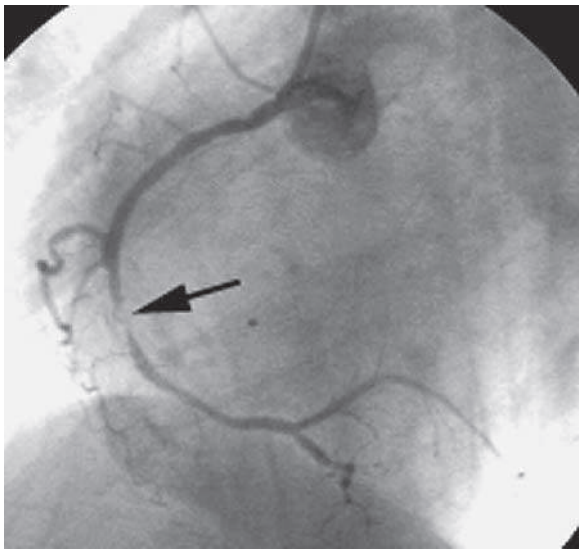
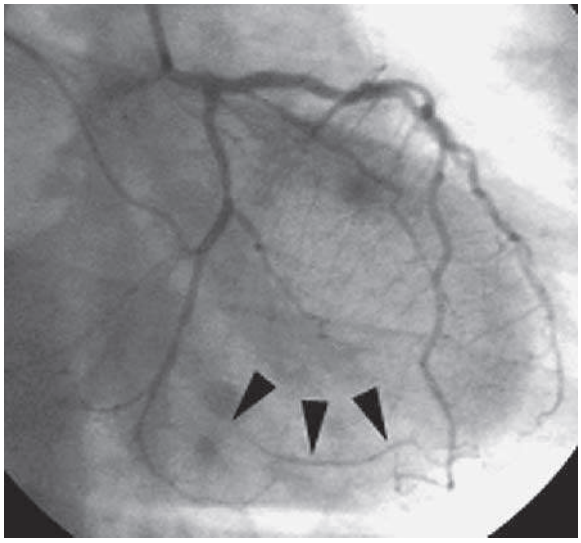


d



e

Fig. 6.**12** MR perfusion for detection of myocardial ischemia.

a 46-year-old patient with exercise-induced angina pectoris and dyspnea. MR perfusion during vasodilation shows a perfusion deficit in the inferior wall with a delayed enhancement of contrast dye (arrows, dark regions in the short axis).

b Detection of scar and viability reveals an additional subendocardial infarcted area in the lateral wall (bright region in the short axis, arrows).

c The polar view reveals the extent of the flow inhibition in the endocardium (regions with delayed enhancement are coded blue, normal perfusion is coded red/orange). In addition, the scar in the endocardium of the lateral wall is visible as a white area. In the polar view the apex is located in the center and the base at the periphery.

d Coronary angiography. The decreased coronary flow in the endocardium of the inferior wall in **a** is explained by the stenosis of the right coronary artery (arrow).

e The scar in the endocardium of the lateral wall is caused by a total occlusion of the second marginal branch of the circumflex artery, which is filled by a collateral flow (arrows).

Images kindly provided by Jürg Schwitter, MD.

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Coronary Angiography. In case of proven or suspected myocardial ischemia, coronary angiography is indispensable for visualization of the coronary anatomy and stenoses (see Figs. 6.**9**, 6.**12**). The anatomic severity of a coronary stenosis is, however, not always predictive of its physiologic effect. In a stenosis of unclear significance the physiologic effect, and therefore the clinical relevance, can be assessed by measuring the fractional coronary flow reserve. This is done by measuring the drop in pressure and/or flow over the stenosis at rest and after maximal vasodilation with adenosine.

In chronic stable angina pectoris a coronary angiography is performed if a coronary revascularization is considered. A diagnostic coronary angiography should also be performed if the noninvasive tests are not equivocal and in all patients with heart failure. In patients with unstable angina pectoris a timely invasive evaluation is advisable. In acute myocardial infarction immediate (< 90 minutes after presentation) invasive evaluation and reperfusion therapy by percutaneous intervention is nowadays the preferred treatment.

Therapeutic Implications

Coronary artery disease is divided into one-, two-, or three-vessel coronary artery disease. The prognosis with respect to myocardial infarction or survival depends on the number of diseased vessels. A three-vessel coronary artery disease or a coronary artery disease involving the left main artery should be revascularized for prognostic reasons. A one- or two-vessel coronary artery disease is usually revascularized for symptomatic reasons. A one-vessel coronary artery disease may sometimes be treated medically. PCI and coronary artery bypass grafting are the two available revascularization procedures. PCI is now the method of choice in all lesions that are anatomically suitable, even in multivessel disease. In anatomically unfavorable situations (e. g., chronic total occlusions) and in severe three-vessel coronary artery disease with left main involvement bypass surgery is still the preferred revascularization method. The use of stents have made PCI safer and applicable in a wider clinical spectrum, such that PCI can currently be offered for symptom relief to patients who are not operative candidates because of comorbidities or old age.

Acute Coronary Syndrome (ACS)

Classification. ACS includes the clinical manifestations of coronary artery disease, which share a common clinical presentation (chest pain), ECG changes, and, in most cases, an increase in cardiac biochemical markers. The spectrum spans from unstable angina pectoris to transmural myocardial infarction (Fig. 6.**13**). The underlying pathophysiology is, in almost all cases, a coronary flow obstruction, secondary to a ruptured atherosclerotic plaque with variable amount of thrombus material.

ACS is divided into two large categories, which each require a specific treatment strategy (Fig. 6.**13**).

- *ACS with ST segment elevation (ST segment elevation myocardial infarction, STEMI) or new, left bundle branch block (LBBB):* in these patients the coronary artery is most likely totally occluded. The therapy consists of rapid reperfusion, either by primary PCI or fibrinolysis.
- *ACS without ST segment elevation (Non-STEMI):* the ECG changes include transient ST segment elevation, ST segment depression, T wave inversions, and other changes of repolarization. This category also includes patients who do not show any ECG changes despite ischemic chest pain and, conversely, patients who show ischemic ECG changes but do not complain of chest discomfort.

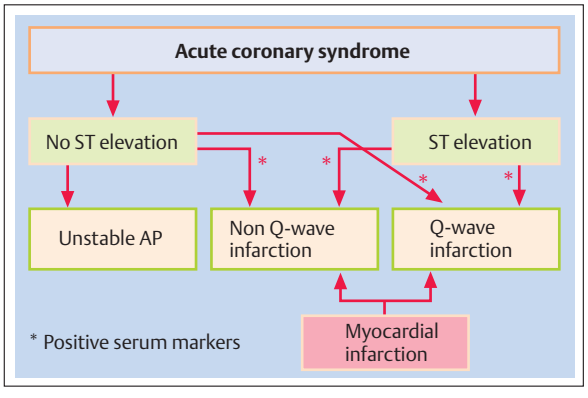

Fig. 6.**13** Spectrum and classification of the ACS.

Acute Coronary Syndrome (ACS) without ST Segment Elevation (Non-STEMI)

Risk Assessment. The leading symptom of an ACS without ST segment elevation is chest pain. Evaluation and diagnosis is based on history of pain, physical examination, electrocardiogram, and cardiac biochemical markers. In ACS without ST segment elevation, risk assessment should be performed (Tab. 6.**10**). The risk assessment has the following prognostic implications: High-risk patients have a 10% risk of developing an acute myocardial infarction or of dying within the next 30 days. Therefore, patients with a high risk should be evaluated invasively, preferably within 48 hours.

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Table 6.**10** Risk stratification in acute coronary syndrome without ST segment elevation

	High risk	Low risk
Symptoms	– prolonged angina pectoris (> 20 min) – angina at rest – nocturnal angina – recurrent angina – early, postinfarction, unstable angina	– isolated episode of angina – no recurrence of angina within observational period
ECG	– dynamic ST segment changes: – transient ST segment elevation – dynamic ST segment depression – dynamic T wave inversion	– no ST segment depression – negative T waves – flat T waves – normal ECG – unchanged ECG
Cardiac biochemical markers	– elevated cardiac biochemical markers (troponin, CK, CK-MB, myoglobin)	– no elevation of troponin or other cardiac biochemical markers – troponin, twice negative within observational period
Other clinical characteristics	– diabetes mellitus – left heart failure – hemodynamic instability – major arrhythmias (ventricular tachycardia or fibrillation)	– no signs of left heart failure

Patients with a low risk can be further evaluated with noninvasive tests.

Chest Pain. The change in character and intensity of chest pain is the most reliable and predictive factor regarding the short-term risk and the long-term prognosis. Pain at rest, nocturnal pain, and prolonged pain confers a high risk. Patients with just one episode of chest pain, which does not reoccur during the observation period, have a low risk.

Clinical Examination. Physical examination of patients with ACS includes a careful search for signs of other causes of acute chest pain (e. g., aortic dissection) and for signs of pulmonary congestion. A third heart sound and basilar rales upon lung examination indicate extensive myocardial ischemia or a decrease of left ventricular function and are prognostically unfavorable.

ECG. Proof of dynamic ECG changes is essential to establish the diagnosis of ACS. Whenever possible, an ECG recorded during chest pain should be compared with an ECG recorded during a symptom-free period. Dynamic ST segment elevations, depressions, or dynamic T wave inversions indicate a dynamic obstruction of the coronary artery and confer a high risk for myocardial infarction. The prognosis is directly related to the number of ECG leads with signs of ischemic changes: the greater the number of involved leads, the larger the ischemic area, and the higher the risk. ST segment depressions, which are followed by negative T waves in the precordial leads are associated with a lesion in the left anterior descending (LAD) artery in a high percentage of patients and carry a high risk for the development of a myocardial infarction.

Unfortunately, the ECG recording is inconclusive in about one-third of ACS patients. In particular, a posterior ischemia or an ischemia in the region of the left circumflex artery are often not visible on a normal standard 12-lead ECG. The patient with suspected ACS should be monitored for several hours. If during this observation period any dynamic ST–T segment changes are recorded, the patient carries a high risk.

Biochemical Markers. Currently, the following biochemical markers are routinely measured: creatine kinase (CK), its isoenzyme MB (CK-MB), myoglobin, and troponin I or T. CK-MB has good sensitivity and specificity whereas for troponin I and T both are high. Therefore, troponin (I or T) is currently the most widely used screening test. Troponin is sensitive enough to indicate ischemic injuries secondary to microemboli from thrombus of an activated plaque. It is important to note that troponin increases four to six hours after the injury. Therefore, to definitely diagnose, or rule out myocardial ischemia, troponin must be measured six hours after the onset of chest pain.

Acute Coronary Syndrome (ACS) with ST Segment Elevation

ACS with ST segment elevation identifies the acute ST segment elevation myocardial infarction (STEMI) caused by a transmural (epicardial) ischemia that, without adequate treatment, results in a transmural scar.

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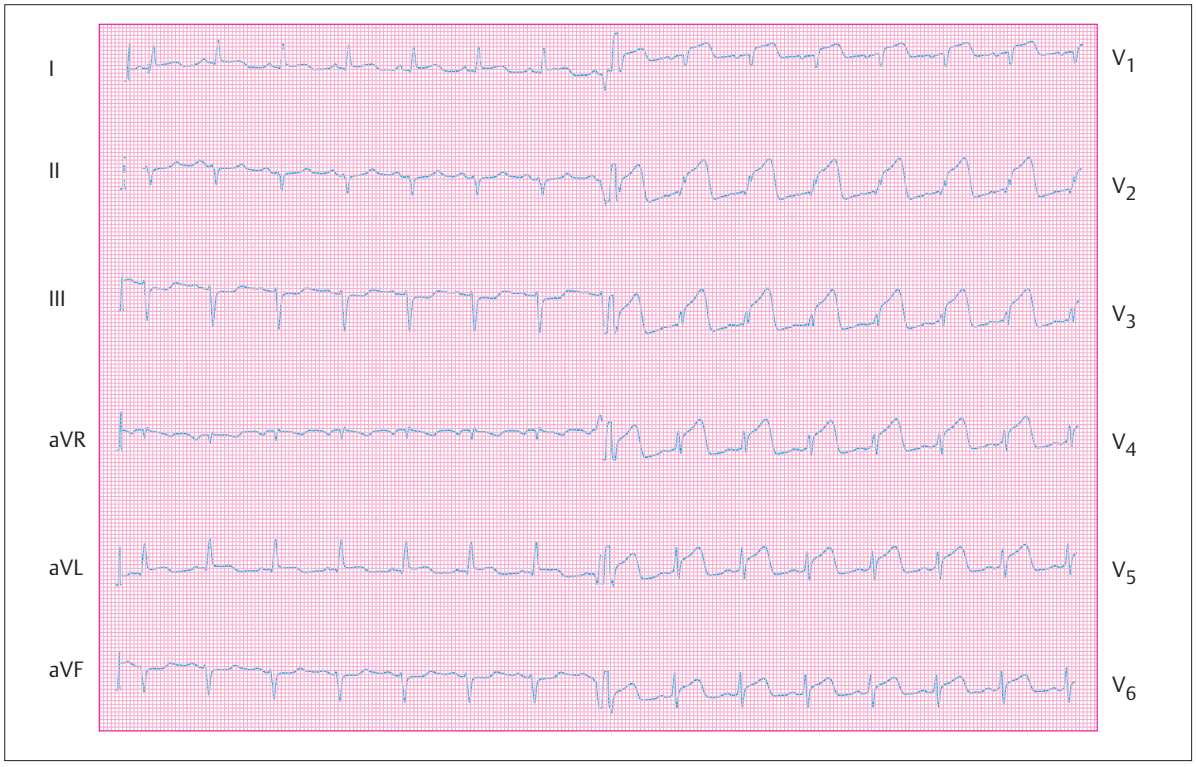

Fig. 6.**14** Acute anterior myocardial infarction, secondary to an occlusion of the left anterior descending artery (LAD) in a 70-year-old patient. The ECG shows the typical ST segment elevations in the leads V_1 to V_6. V_1 to V_6: chest wall leads according to Wilson.

Clinical Features. The main symptom of an acute myocardial infarction is chest pain, which usually lasts for 30 minutes or longer. The character of the chest pain is similar to that of angina pectoris pain but, in general, is more severe and often accompanied by anxiety and a sense of impending doom. The *pain is located* precordially, occasionally described as a ring around the chest, constricting, and tightening. Radiation is similar to angina pectoris pain (Fig. 6.**1**). In inferior or posterior myocardial infarction the pain is occasionally felt in the epigastrium, suggesting an acute abdomen, a perforated ulcer, acute cholecystitis, or pancreatitis. Some patients experience a silent myocardial infarction. Myocardial infarctions not causing pain or other symptoms are more predominant in elderly patients and in diabetics. Most patients with myocardial infarction also complain of dyspnea. In many patients, vagal stimulation results in nausea and vomiting. Vagal stimulation is common in inferior myocardial infarction. Patients with myocardial infarction may also collapse or *syncope*. The syncope is in most cases secondary to *arrhythmias*. 40–60% of all myocardial infarction patients suffer arrhythmias. The most common arrhythmias are ventricular extrasystoles, followed by bradycardias with AV-blockade, atrial fibrillation, ventricular tachycardia, or fibrillation.

Physical examination in uncomplicated myocardial infarction may not be very revealing. Upon auscultation, unspecific signs such as a presystolic or protosystolic gallop rhythm and distant heart sounds may be heard. In contrast, a large myocardial infarction is associated with cold, clammy periphery, diaphoresis, and tachycardia. In acute left heart failure, inspiratory crackles and rales at the lung bases can be heard. If right heart failure is present, jugular venous distention is the predominant sign and often a pulsus paradoxus can be found. Early in acute myocardial infarction, leukocytosis and hyperglycemia are detected. An increase in the sedimentation rate and C-reactive protein is noted after one to two days. An extensive myocardial infarction is often associated with fever up to 39 °C, usually starting the second day and lasting for several days.

Electrocardiogram (ECG). As indicated by its name, an ST segment elevation myocardial infarction (STEMI) is associated with an ST segment elevation (Fig. 6.**11**). A transmural ischemia may manifest itself as a new left bundle branch block or as a true posterior infarction with a huge R wave in V_1 and an ST segment depression in V_1 and V_2. In some cases, the initial ECG is nondiagnostic. ECG changes in ST segment elevation myocardial infarction often follow a typical pattern:

- *signs of ischemia:* the first sign of an acute myocardial infarction are tall, symmetric T waves ("hyperacute T waves"), followed by ST segment elevations in the infarct area and ST segment depressions in the reciprocal, noninfarcted zones (Figs. 6.**14**, 6.**15**).

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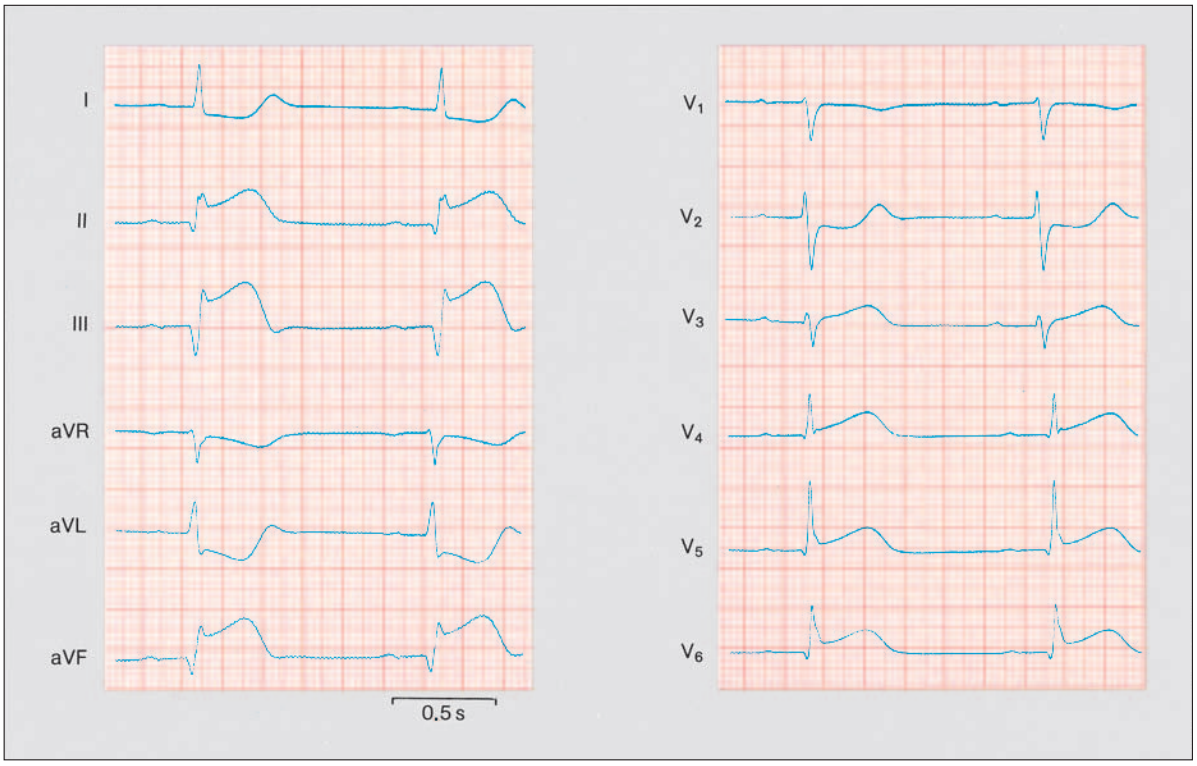

Fig. 6.**15** Acute inferior myocardial infarction in an 80-year-old patient. In the leads II, III, and aVF the typical ST segment elevations and in the leads I and aVL the reciprocal ST segment depressions are present. V_1 to V_6: chest wall leads according to Wilson.

- *signs of necrosis:* occurrence of pathologic Q waves and loss of R waves in the infarcted area (Fig. 6.**16**).
- *signs of a scar:* in the subacute phase of an acute myocardial infarction the T waves become negative over the infarcted area. Persistent ST segment elevations suggest aneurysm formation (Fig. 6.**16**).

This infarct pattern is typically recognized in ECG leads positioned over the infarct region. Therefore, the 12-lead ECG allows, in many cases, a relatively exact localization of the infarct (Tab. 6.**11**).

In contrast to transmural lesions, subendocardial ischemia is associated with changes only in the ST segment and Q waves do not appear. In some cases, a loss of the R wave can also occur in subendocardial ischemia. It is a typical ECG pattern in a nontransmural infarction after an acute, coronary syndrome without ST segment elevation.

There are reasons for ST segment elevations in the ECG other than myocardial ischemia. The most important differential diagnosis is acute pericarditis. In acute pericarditis ST segment elevation occurs in many, sometimes nearly all, leads (see Fig. 6.**18**). The ST segment elevation is followed by a positive T wave. In the acute phase of pericarditis the ST segment elevation is associated with a depression of the PQ segment. ST segment elevations also occur as a norm variant and are then called "early repolarization." In early repolarization the ST segment elevation is most pronounced in the leads V_4 and V_5 and is also followed by a positive T wave. The lack of a ST segment depression in reciprocal leads is the most helpful criterion to differentiate between early repolarization and acute myocardial infarction. Bundle branch blockades are associated with ST segment elevation, particularly the left bundle branch block. Furthermore, ST segment elevations can be found in more rare disorders, such as myocarditis, trauma of the heart, tumor of the left ventricle, hypothermia, after cardioversion, with intracranial bleeds, hyperkalemia, Brugada syndrome, and after some antiarrhythmic medication.

Table 6.**11** Localization of infarction in the ECG

Localization	Lead showing changes
Anteroseptal	V_2 to V_4
Anterior	V_1 to V_6, I, aVL
Apex	V_5, V_6
Lateral	I, aVL
Inferior	II, III, aVF
Posterior	R/S > 1.0 in V_1

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Fig. 6.**16**
a Status of a 49-year-old patient two years after anteroseptal myocardial infarction. Note the typical loss of R waves, the slight ST segment elevation, and the negative T waves in the precordial leads.
b Status post inferior myocardial infarction one year previously in a 53-year-old patient. Typical Q waves are visible in the leads II, III, and aVF.

Enzymes in Acute Coronary Syndrome (ACS)

In ACS the clinical presentation and the ECG lead to a working diagnosis. In the case of an acute ST segment elevation, myocardial infarction reperfusion therapy must be initiated immediately and before the results of enzyme measurements are available. In ST segment elevation, myocardial infarction measurement of enzymes confirms the diagnosis and myocardial infarct size can be assessed by the amount of released enzymes. In ACS without ST segment elevation the measurement of enzymes is necessary, not only for diagnosis but also for risk assessment. Positive biochemical markers indicate a high risk and require more aggressive treatment.

Biochemical Markers. Four biochemical markers are currently used for diagnostic purposes. Myoglobin, creatine kinase (CK), and its "cardiac-specific" isoenzyme, the MB-fraction (CK-MB), troponin T and troponin I (Fig. 6.**17**). Myoglobin increases after two to four hours, but has a low specificity for cardiac muscle. The other four biochemical markers are detectable four to six hours after myocardial ischemia. CK is relatively sensitive and specific. However, CK is also elevated after intramuscular injections, strenuous physical activity, seizure, severe intoxications, cardioversion, or trauma to the muscles. CK-MB is less sensitive but more specific. However, CK-MB is also present in the diaphragm and in the tongue. Therefore, CK-MB may also be elevated after a seizure accompanied by tongue bite, attacks of asthma, or profound hyperventilation. The most sensitive and specific markers are the troponins.

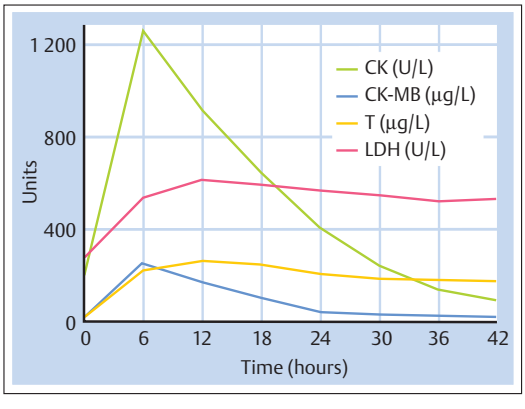

Fig. 6.**17** Typical pattern of enzyme release in a patient with acute myocardial infarction. CK = creatine kinase; CK-MB = MB fraction of creatine kinase; T = troponin T; LDH = lactate dehydrogenase.

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They increase four to six hours after an ischemic injury and remain elevated for one to two weeks. Troponin is also able to detect myocardial injury, which is not caused by coronary artery disease (Table 6.**12**). Troponin may also be elevated in some rare, noncardiac diseases. Most importantly, a false positive elevation of troponin T can be present in renal insufficiency.

Additional enzymes used in the diagnosis of an infarction are alanine aminotransferase (ALT), aspartate amylotransferase (AST), and lactate dehydrogenase (LDH). LDH increases much more slowly than CK and reaches its maximum after two to four days. An elevation of ALT or LDH is not specific for myocardial infarction. Also, ALT elevations are found in liver and muscle diseases, and LDH is elevated in a number of diseases.

Infarct Diagnosis. The dynamic increase and decrease of enzymes is the essential point for the diagnosis of a myocardial infarction. A myocardial infarction is present when there is an increase and decrease of cardiac biomarkers (troponin or CK-MB) plus one of the following findings:

- typical symptoms of myocardial ischemia
- Q waves in the ECG
- ST segment elevation or depression in the ECG
- following a percutaneous intervention.

This definition includes not only the classical ST segment elevation myocardial infarction, but also infarction associated with ST segment depression or no ECG changes, the so-called non-ST segment elevation myocardial infarction (non-STEMI). Following successful thrombolysis or primary PCI, CK rapidly increases and decreases. This CK release is called CK washout. As CK decreases within one to two days, CK and CK-MB changes are better suited for the diagnosis of a reinfarction than troponin, which might still be elevated. Conversely, troponin and LDH remain elevated for days and allow diagnosis of an infarction that has occurred three to five days prior.

Differential Diagnosis of Acute Myocardial Infarction. In general, all causes of precordial and chest pain have to be considered in the differential diagnosis of an acute myocardial infarction (see Tab. 6.**1**). In persistent chest pain, which is associated with symptoms such as nausea, diaphoresis, and dyspnea, the following acute diseases are the most important to consider in the differential diagnosis:

- *Pulmonary embolism:* a massive pulmonary embolism can simulate a myocardial infarction. Chest pain and the imminent sense of doom are main symptoms of a massive pulmonary embolism, too. A sinus tachycardia, hypotension, and peripheral vasoconstriction are typical signs found during physical examination. In addition, tachypnea, distended jugular veins, and cyanosis are often present. In the ECG a rotation of the frontal QRS axis to the right (resulting in a S_I/Q_{III} type), a clockwise rotation of the horizontal axis, and often unspecific ST–T changes are typical signs of pulmonary embolism. The chest radiograph may show wedge-shaped or linear opacities of any size or shape, a pleural effusion, or an elevated hemidiaphragm. Blood gases show a low PaO_2 and a low $PaCO_2$. D-dimers are elevated in the plasma (> 500 ng/L). The diagnosis of pulmonary embolism is most often confirmed by a spiral CT, occasionally by lung scintigraphy, or pulmonary angiography.
- *Pericarditis:* the changes of the intensity of chest pain with posture or breathing, in addition to the typical signs in the ECG, are most helpful to differentiate pericarditis from myocardial infarction (Fig. 6.**18**).
- *Aortic dissection:* an aortic dissection has to be considered in case of chest pain in the back or radiating to the back. The diagnosis is confirmed or excluded by computed tomography (see Fig. 6.**21**), transesophageal echocardiography, or MRI.
- A *spontaneous pneumothorax* (see Fig. 6.**25**) or a tachycardic arrhythmia can result in precordial tightening and a tendency for collapse or syncope.

Table 6.**12** Causes of elevated serum levels of cardiac troponin

Ischemic myocardial injury
Nonischemic myocardial injury
– Myocarditis
– Pulmonary embolism
– Tachycardic atrial fibrillation
– Acute heart failure, acutely decompensated chronic heart failure
– Pulmonary edema
– Primary ventricular fibrillation
– Cardiac trauma (e. g., blunt chest trauma)
Noncardiac causes
– Renal insufficiency
– Neoplasm
– Rhabdomyolysis
– Elevated fibrin
– Positive rheumatoid factor
– Human mouse antibody

Differential Diagnosis of Complications in the Course of a Myocardial Infarction

Chest Pain after a Myocardial Infarction:

- *Reinfarction caused by an acute reocclusion of the infarct related artery:* such an event occurs in about 10 % of patients reperfused with thrombolytic therapy and in about 1–2 % of patients treated with primary percutaneous coronary intervention.
- *Pericarditis:* usually occurring the second or third day after a myocardial infarction. Pericarditis following a myocardial infarction is often accompanied by a pericardial rub. The patient is often able to distinguish the pericardial pain, which changes with position and breathing, from the pain during the myocardial infarction.
- *Postinfarction angina pectoris:* as in many cases a significant residual stenosis is present in the infarct related artery after lytic therapy, postinfarction angina

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pectoris is present in about 50% of patients treated with fibrinolysis.

Hypotension in the Course of a Myocardial Infarction:

- *Acute left ventricular pump failure:* patients with left ventricular pump failure show signs of cardiogenic shock with hypotension, cold extremities, cyanosis, signs of pulmonary congestion, and a third heart sound on auscultation. About 5% of infarct patients will suffer a cardiogenic shock. Protracted cardiogenic shock lasting for several days is always associated with fever, increased inflammatory parameters in the plasma, and tachycardia. In most cases increased peripheral resistance will eventually decrease and a hyperdynamic hemodynamic state will ensue, mimicking a septic shock.
- *Right ventricular myocardial infarction:* the combination of hypotension, distended jugular veins, and clear lung fields suggests right ventricular infarction. A right ventricular infarction can be recognized in the right-sided ECG lead V_4 as ST segment elevation during the first hours of a myocardial infarction. However, those ECG changes are transient and disappear within several hours.
- *Pericardial tamponade:* the clinical signs of pericardial tamponade are hypotension, distended jugular veins, distended liver, and pulsus paradoxus. A massive and instant tamponade of the pericardium occurs with a rupture of the free wall after myocardial infarction. Such a rupture of the free wall usually leads to electromechanical dissociation and death. However, about one-third of the myocardial ruptures take a subacute course. Two mechanisms for a subacute rupture are possible: an epicardial or intramural thrombus can transiently seal the rupture, or in a massive infarction, a diffuse slow trickle of blood to the epicardium may occur. This phenomenon is termed "bleeding heart." The combination of confusion, nausea, chest pain, bradycardic rhythm disturbances, or a transient electromechanical dissociation may suggest a subacute ventricular rupture. If the ventricular rupture is contained or enclosed by the pericardium and epicardium, it results in the formation of a pseudoaneurysm. Diagnosis is made by echocardiography and therapy consists of surgical removal of the pseudoaneurysm and the suture of the ventricular rupture.
- *Ventricular septal defect:* the cardiogenic shock resulting from a ventricular septal defect is characterized by biventricular pump failure, whereby right ventricular failure is predominant. A new, loud, holosystolic murmur at the left sternal border is heard on auscultation. In about half of the cases a precordial thrill is palpable.
- *Papillary muscle rupture and mitral insufficiency:* in about 50% of myocardial infarctions a mild to moderate mitral insufficiency can be found and is the result of papillary muscle dysfunction or left ventricular geometry changes. However, a severe mitral insufficiency caused by papillary muscle rupture is rare (1–3%). The clinical manifestation of acute, severe mitral insufficiency is sudden onset left ventricular failure and pulmonary edema. Massive orthopnea occurs and the patient is unable to lay flat. A new, holosystolic, regurgitant murmur may be heard at the apex. The murmur may be short or distant, secondary to an early equalization of pressures between the left ventricle and left atrium. For all mechanical complications, echocardiography is the diagnostic tool of choice.

Pericarditis and Pericardial Effusion

Clinical Features of Acute Pericarditis. Acute pericarditis causes typical precordial pain, which in general increases with deep inspiration, coughing, or swallowing. The retrosternal pain may vary from a slight chest oppression to severe tearing pain. The differential diagnosis between myocardial infarction and acute pericarditis is sometimes difficult. The pain of pericarditis is typically increased in recumbency and makes the patients sit up and lean forward slightly. Patients often breathe rapidly to avoid deep, painful inspirations.

The *clinical examination* should focus on the cardinal and diagnostic signs of a *pericardial rub*. The rub is usually best heard at the left sternal border during a deep inspiration with the patient leaning maximally forward. The pericardial rub consists in general of two components (atrial and ventricular systolic rub, locomotive sound). The pericardial rub may decrease in loudness with increasing pericardial effusion. A low-grade fever is often associated with pericarditis.

Apart from acute myocardial infarction the *differential diagnosis* of pericarditis includes pleuritis, pneumonia, chest wall pain, and lung infarction.

ECG in Pericarditis. ECG changes are present in 90% of cases and are important for the differential diagnosis. The ECG is most typical in the early phase of the disease. ST segment elevations are often found in many, if not all, ECG leads. In contrast to myocardial infarction the ST segment elevation is often upwardly concave (Fig. 6.**18a**). Typical for the early phase of acute pericarditis is the depression of the PQ segment. In the aVR lead, the ST segment and PQ changes are inverted, i. e., in aVR, PQ is elevated and the ST segment is depressed. In the course of pericarditis ST segment elevation abates and the T wave becomes flat or normal (Fig. 6.**18b**). After normalization of the ST segment, diffuse T wave inversions are occasionally recorded. With the development of a *pericardial effusion* a peripheral low-voltage and electric alternans that is caused by floating of the heart in the large pericardial effusion, may be registered. In the absence of simultaneous myocardial ischemia, changes in the QRS complex, such as broadening of the QRS, or rhythm disturbances, such as AV blockade or extrasystole, suggest a *myocarditis*.

The *differentiation* of these changes from an acute *myocardial infarction* might be difficult. In myocardial

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Fig. 6.**18** ECG changes in acute pericarditis in a 27-year-old patient.
a ECG before onset of therapy.
b ECG following 10 days of treatment with steroids. The typical horizontal ST segment elevations, which were present in all leads before therapy, are no longer detectable.
V_1 to V_6: chest wall leads according to Wilson.

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a

b

Fig. 6.**19** Chest radiograph in a 47-year-old patient with 500 mL pericardial effusion after a myocardial infarction.
a Before pericardiocentesis the heart silhouette is enlarged and pear shaped.
b After pericardiocentesis the heart silhoutte is normal.

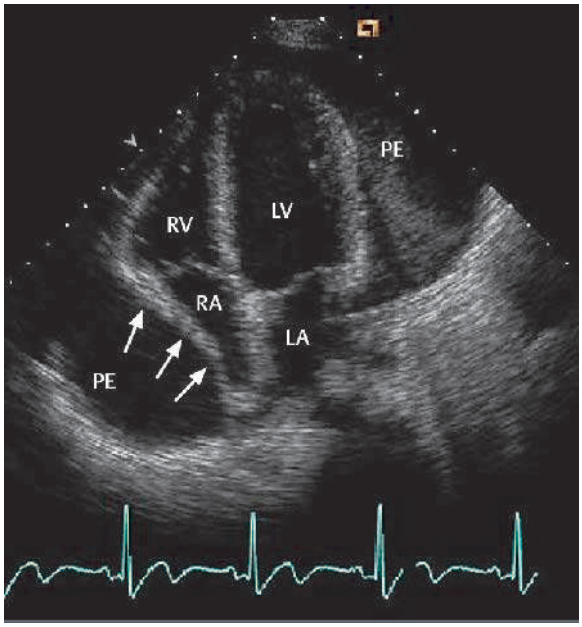

Fig. 6.**20** Echocardiography in a patient with chronic pericardial effusion. The apical four-chamber view shows a large circumferencial pericardial effusion (PE), in which the heart is "floating." Compression of the right atrium (RA, arrows) is a sign of tamponade. LV = left ventricle, RV = right ventricle, LA = left atrium.

infarction ST segment elevations are often monophasic or convex upward, in general, higher and localized over the infarct region (see Figs. 6.**15**, 6.**16**). In addition, in pericarditis no pathologic Q waves develop. In "early repolarization" the ST segment elevations resemble that of acute pericarditis. However, there is in general no PQ segment depression and the T waves are tall and pointed.

Pericardial Effusion. A pericardial effusion develops in many cases of pericarditis. A large pericardial effusion will be noticed as enlargement of the cardiopericardial silhouette in the chest radiograph (Fig. 6.**19**). The cardiopericardial silhouette may be described as pear shaped or triangular. The diagnosis of pericardial effusion and the estimation of the amount of effusion are made by echocardiography (Fig. 6.**20**). In addition, a compression of the atria and/or the right ventricle indicates tamponade. Aspiration of the pericardial effusion is performed for diagnostic purposes and must often be performed for relief of tamponade.

Etiology of Acute Pericarditis. *Idiopathic or viral pericarditis* is present in 75–80 % of cases (Tab. 6.**13**). The idiopathic or subacute, benign pericarditis is predominantly found in young men and is often preceded by catarrhal prodromi. Viral pericarditis is most often caused by coxsackieviruses A and B, echovirus, adenovirus, and HIV. However, many other viruses may also cause pericarditis. An undiagnosed viral etiology may

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also be the cause of many idiopathic pericarditis cases. A bacterial pericarditis is a very rare disease. After a myocardial infarction a pericarditis may develop early, within days, or late, within weeks. The pericarditis early after myocardial infarction is caused by an acute inflammatory reaction, whereas the late pericarditis is caused by an immunologic reaction to the myocardial injury. A similar immunologic reaction can occur after open heart surgery. This late immunologic form of pericarditis is associated with fever and pericardial effusion and occasionally with extensive polyserositis. It is then called Dressler syndrome. This late form of pericarditis after myocardial infarction has almost disappeared in the era of reperfusion.

Neoplasms are responsible for about 6% of pericarditis cases. Radiation therapy may cause pericarditis, which over many years can result in restrictive or constrictive pericarditis.

Pericardial effusion caused by an *injury to the heart wall* may occasionally occur after an accident. Much more common, however, are iatrogenic pericardial effusions caused by perforation of pacer wires, infusion lines, or catheters. Several metabolic disorders can cause a pericardial effusion. The most frequent cause is *uremia*. Systemic lupus erythematosus and rheumatoid arthritis are two of the systemic, *connective tissue diseases*, which may occasionally cause pericarditis.

Table 6.**13** Etiology of acute pericarditis

Common
– Idiopathic (after common cold)
– Viral (coxsackieviruses A and B, echovirus, adenovirus, HIV)
Less common
– Neoplastic (breast cancer, lung cancer, lymphoma)
– Metabolic (uremia)
– Radiation
– Acute myocardial infarction
– Connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis)
– Trauma
Rare
– Tuberculosis, bacterial infection
– Drugs (procainamide, isoniacide, phenytoin)
– Inflammatory bowel disease

Chronic Pericarditis. Idiopathic pericarditis may become chronic and recurrent in 10–30% of cases. The etiology and the mechanism for this development are usually unclear and are generally assumed to be immunologic. A chronic thickening of the pericardium or calcification of the pericardium following a chronic pericarditis results in a pericarditis constrictiva. The hard and thickened pericardium encases the heart and impairs its filling. The cause of pericarditis constrictiva used to be almost exclusively tuberculous pericarditis. Currently, it is much more commonly a consequence of radiation therapy, hemopericardium, or viral pericarditis.

Arrhythmias

Acute tachycardic arrhythmias may be associated with chest heaviness, chest pain, dyspnea, anxiety, and vegetative symptoms. After conversion into sinus rhythm changes of the repolarization may persist in the ECG. The most common findings are T wave inversions. This cardiac memory is called the *Chatterje phenomenon*.

Patients sometimes experience extrasystole as very unpleasant sensations. The sensations are caused by postextrasystolic potentiation of the stroke volume.

6.2 Pain Originating from Diseases of the Large Vessels

Aortic Aneurysm

An aortic aneurysm is an *abnormal dilatation* of the aortic wall. The thoracic aortic aneurysm may occasionally be accompanied by chest pain, which is related to the extension of the aneurysm. Aortic insufficiency as a result of an aortic aneurysm may cause oppression of the chest or dyspnea. An aortic aneurysm may also cause symptoms if it compresses the trachea or main stem bronchus or the superior vena cava. In most cases, however, the aortic aneurysm causes no symptoms and is discovered incidentally on a chest radiograph or by echocardiography. Rare causes of aortic aneurysms include fusiform aneurysms or aneurysm spurium as a consequence of bacterial endocarditis, and aneurysms of the sinus valsalva.

Etiology. The most common cause of aortic aneurysm is *atherosclerosis*. Less common etiologies include connective tissue disorders (Marfan syndrome, Ehlers–Danlos, cystic medial necrosis), vasculitis (Takayasu disease, Reiter syndrome, giant cell arteritis), and infections (syphilitic aortitis). All aneurysms causing symptoms should be surgically corrected. Operation should be considered in asymptomatic aneurysms larger than 5.5 cm.

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Aortic Dissection

Definition. Aortic dissection results from a tear in the intima, such that blood penetrates between the intimal layer and the media of the aortic wall. This creates a false lumen in the arterial wall. Typically a second tear of the intima creates the exit for the blood. This exit site can be located in the ascending aorta, in the descending aorta, or the iliac vessels.
The Stanford classification divides aortic dissections into two types:

- type A: all dissections involving the ascending aorta, regardless of the site of origin
- type B: all dissections not involving the ascending aorta.

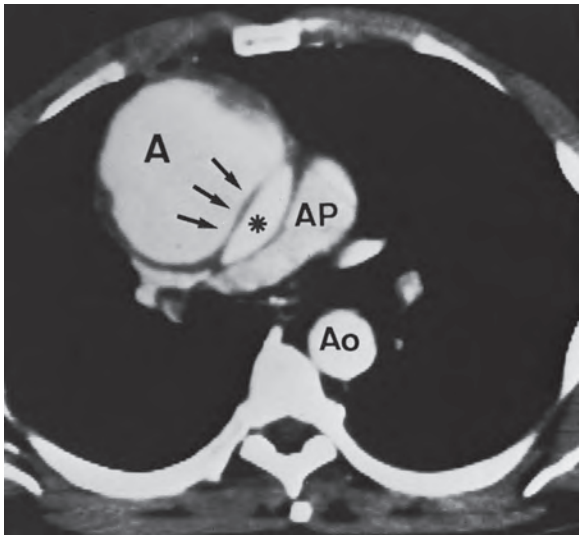
Clinical Features. The patient usually complains of a severe "tearing" chest pain, which may originate in the back or radiate from the precordium to the back. The localization of the pain may hint towards the origin of the dissection. A retrosternal pain radiating to the back suggests a dissection in the ascending aorta. An interscapular pain suggests a dissection in the descending aorta, and an abdominal pain may hint at a dissection in the abdominal aorta. Pain onset is typically abrupt and persistent, and collapse is common. The sudden onset and the lack of ECG changes help to differentiate between an aortic dissection and a myocardial infarction. The following additional symptoms may be associated with aortic dissection:

- Dissection of the *carotid* arteries may result in cerebral hypoperfusion with neurologic symptoms (e. g., hemiplegia).
- In about half of the patients with aortic dissection, shape changes of the *aortic root* result in acute aortic insufficiency.
- Compression of the *truncus brachiocephalicus* results in a pulse deficit and blood pressure difference between right and left arm. Such a pulse deficit is almost pathognomonic for aortic dissection, since only arterial emboli or Takayasu disease can cause a similar sign.
- Other *less frequent complications* are the compression of the coronary arteries resulting in myocardial infarction, rupture of the dissection into the pericardial space with pericardial tamponade, hematothorax, rupture of the descending aorta with bleeding into the mediastinum or abdomen, a compression of the renal arteries with subsequent acute renal failure, mesenteric infarction with an acute abdomen due to compression of celiac and/or superior mesenteric artery, and acute limb ischemia secondary to obstruction of the flow in the arteria iliaca.

Atypical Aortic Dissection. Occasionally (approximately 5 %) the intimal tear does not progress and no intraluminal hematoma develops. Conversely an intraluminal hematoma may develop without intimal tear. It is generally believed that such an intramural hematoma is the result of a rupture of the vasa vasorum. In addition, an atherosclerotic plaque may rupture and the blood flow into the ruptured plaque may result in a local hematoma of the aortic wall.

Diagnosis. Aortic dissection must be suspected in patients presenting with typical symptoms and signs and pathologic chest radiograph (Fig. 6.**21a**). Diagnosis is confirmed by transesophageal echocardiography or computed tomography (Fig. 6.**21b**) or MR-angiography.

a



b

Fig. 6.**21** Aortic dissection of the ascending aorta (type A) in a 57-year-old patient.
a Clearly visible is the grotesquely dilated ascending aorta (arrows).
b Computed tomography in the same patient shows the aneurysm and the dissection membrane (arrows). A = aneurysm, AP = pulmonary artery, Ao = aorta descendens, * = true lumen of the ascending aorta.

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Etiology. Aortic dissection occurs most commonly in the sixth or seventh decade of life. Hypertension, which is present in 80% of the patients, is a predisposing factor. It is believed that *hypertension* contributes to medial degeneration by compression of the vasa vasorum of the aorta. *Atherosclerosis* of the aorta and, in some cases, previous surgery of the aorta (e.g., coronary bypass operation or aortic valve replacement) may contribute to the pathogenesis of aortic dissection. Aortic dissection may, however, occur in younger patients. In these cases *aortic diseases with medial degeneration* are considered the main predisposing factors. The most important disease causing aortic dissection is Marfan syndrome. Other diseases include Ehlers–Danlos syndrome, coarctation of the aorta, or fibromuscular dysplasia. In younger women, about 50% of cases of aortic dissection occurs during pregnancy. If a patient with Marfan syndrome becomes pregnant, there is a high likelihood of aortic dissection, typically occurring in the third trimester. Aortic dissections can also be caused by trauma or iatrogenic injuries, by catheters, or an intra-aortic balloon pump.

Management. The mortality of an aortic dissection type A is about 1% per hour. The rupture of the aorta is the most common cause of death. The risk of a rupture can be reduced by decreasing the blood pressure (using nitrates or beta-blockers). Therefore, aortic dissection type A requires immediate surgical repair. In contrast, surgical repair of aortic dissection type B is performed only when complications occur such as vital organ or limb ischemia.

6.3 Pain Originating from the Pleura

The intensity of pleural pain typically fluctuates while breathing. Pain increases during inspiration and diminishes or disappears during expiration.

The parietal pleura is supplied by segmental nerves and when inflamed gives rise to pain, which is referred to superficial regions supplied by the intercostal nerves and the thoracic segments (dermatomes). This explains why pain originating from the pleura covering the diaphragm (central part) may be referred either to the shoulder or even more commonly (peripheral part) to the upper abdomen.

Pleural Friction Rubs. A patient with pleuritic chest pain may have shallow breathing, and there may be lesser excursion of the affected hemithorax than of the unaffected side (splinting). However, a hallmark finding is a pleural friction rub that has a harsh, scratchy quality and is heard throughout the respiratory cycle. It is maximal toward the end of inspiration and early in expiration. These sounds disappear when pleural fluid accumulates.

Pleuritis

Pleural inflammation occurs with or without apparent underlying pulmonary disease. As mentioned, pleural friction rub is present before fluid accumulates due to an *exudative pleuritis*. In young individuals, pleural friction rubs may be due to coxsackievirus infections (Bornholm disease) or other viral illnesses, particularly if they are heard in both lungs. Furthermore, pleural friction rubs may be caused by a pulmonary embolism.

Pleural Effusion

Etiology. The most common causes for pleural effusions are congestive heart failure, malignancies, and pulmonary embolisms.

Clinical Features. Dullness to percussion, diminished breath sounds, and egophony at the upper border of the effusion are suspicious findings. The breath sound intensity diminishes with increasing fluid accumulation. If the lung becomes compressed, the character of the breath sounds becomes bronchial ("compression breathing").

If the amount of pleural fluid is less then 300 mL it may not be visible on a chest radiograph. Smaller amounts of effusion may become visible on the chest radiograph at expiration and particularly in a lateral decubitus (affected side down) position. Large effusions are characterized by an upward concavity of the liquid layer (Fig. 6.**22**). Occasionally, effusions may accumulate between lung lobes and produce a rounded opacity on the chest radiograph that resembles a tumor. Since such a finding disappears with resolution of the effusion, it is referred to as a "phantom" or "vanishing" tumor (Fig. 6.**23**). Localized and chronic effusions may have an atypical radiological presentation. Ultrasound examination is the most appropriate method to detect small amounts of pleural fluid and can also reveal septations

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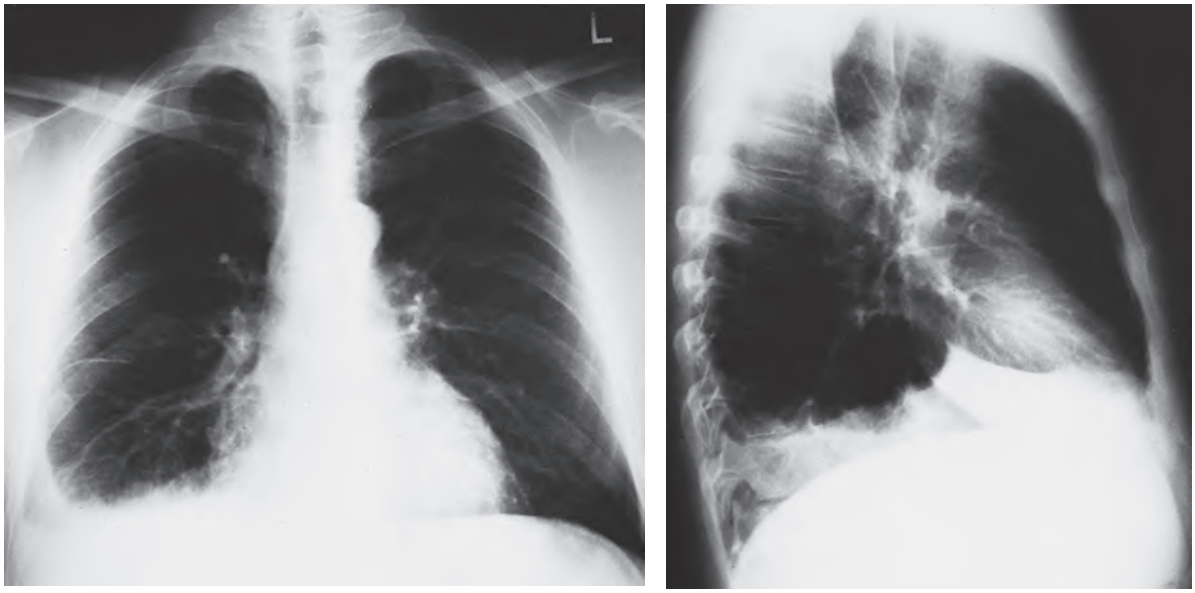

a b

Fig. 6.**22** Typical chest radiograph in right-sided pleural effusion.
a postero-anterior view.
b lateral view.

a b

Fig. 6.**23** Interlobar effusion in congestive heart failure.
a Before therapy.
b After therapy with diuretics: "vanishing tumor."

or pleural thickening. Computed tomography gives additional information, particularly in the mediastinal region. If the pleura appears thickened and shows an enhancement after intravenous contrast, pleural empyema should be suspected.

Differential Diagnosis. Diagnostic considerations are based primarily on clinical presentation and a chest radiograph:

➤ The presence of *fever* is suspicious for *inflammation*, and in patients without fever a pleural effusion is suspicious for malignancy.

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- Fever is also absent in patients presenting with a *pleural effusion* due to left heart failure and pulmonary congestion. The leading symptom is *dyspnea (shortness of breath)* while pain is absent. In the presence of other clinical signs for heart failure the diagnosis is straightforward.
- Pleural effusion due to congestive heart failure is usually bilateral and if unilateral it occurs more commonly on the right side. In *pulmonary embolism* pleural effusion occurs concurrently with a lung infarction.
- The detection of a *parenchymal pathology of the lung* gives important clues for various etiologies of a pleural effusion, e. g., pneumonia, tuberculosis, or tumors.
- It is important to exclude an upper abdominal pathology as a potential etiology.

Aspiration of the pleural effusion under local anesthesia should always be performed if the etiology of the effusion is in doubt.

Pleural Fluid Analysis

Inspection. A putrid pleural aspirate is typical for a pleural infection and a hemorrhagic fluid for cancer or pulmonary emboli.
A pleural fluid hemoglobin concentration of more than half of the blood hemoglobin is diagnostic for bleeding in the pleural space. A hematothorax, which is due to a chest trauma, may also occur as a complication of a pleural tap, a pleural biopsy, or after the insertion of a subclavian line.
If the pleural fluid is a milky white liquid, a chylothorax or pseudochylothorax is present. In chylothorax elevated levels of triglycerides are found, whereas in pseudochylothorax the cholesterol content is elevated.

Transudate and Exudate. A transudate is caused by changes of the hydrostatic or colloidoncotic pressure. Exudates occur in situations with altered membrane permeability. Therefore, exudates have a higher protein content than transudates (Tab. 6.**14**). This distinction is important since in the presence of a transudate, a further diagnostic work-up is usually not necessary. The most common causes are congestive heart failure, hypoproteinemia due to liver cirrhosis, or a nephrotic syndrome. Such diseases are usually diagnosed without difficulty. If an exudate is found additional diagnostic work-up is compulsory.

Laboratory Findings. The laboratory analysis of pleural fluid is based on:

- microbiological and cytological investigations
- parameters for the differentiation between transudate and exudate such as protein and LDH
- glucose, amylase, triglycerides, leukocytes, and erythrocytes
- the pH in the pleural fluid can be measured by a blood gas apparatus under anaerobic conditions. It is helpful to assess the fluid of a parapneumonic effusion. A pH below 7.20 is diagnostic for a so-called complicated parapneumonic effusion, which needs drainage.

If the pleural fluid has a high LDH (lactic dehydrogenase) concentration, a high protein content, an elevated cholesterol concentration, and a high pleural fluid/serum LDH ratio, then an exudate is present (Tab. 6.**14**). However, the protein content of the pleural fluid may be elevated in congestive left heart failure if the patient has received diuretics. Also of diagnostic importance are the leukocyte count and its differentiation. Massively elevated numbers of leukocytes (> 50 000–100 000/μL) can usually be recognized as pus (see pleural empyema, below). A low number of leukocytes does not distinguish between infectious and noninfectious etiologies and is present in a variety of diseases (e. g., parapneumonic effusion, pulmonary embolism, cancer, viral pleuritis, pancreatitis, and active tuberculosis). A high number of lymphocytes is seen in pleural effusions due to tuberculosis or cancer. The presence of eosinophils is unspecific.

Pleural Biopsy. If the analysis of the pleural fluid aspirate remains nondiagnostic, pleural biopsy is an option. If the pleura is diffusely involved, transthoracic needle biopsy has a high diagnostic yield. Excellent diagnostic results are obtained by thoracoscopy, whereby biopsies can be obtained under visual inspection from the parietal as well as from the visceral pleura.

Table 6.**14** Distinction between transudate and exsudate based on pleural fluid finding

	Transudate	Exudate
Pleura/serum protein ratio	< 0.5	> 0.5
Pleura/serum LDH ratio	< 0.6	> 0.6
Cholesterol	< 45 mg/dL [1.16 mmol/L]	> 45 mg/dL [1.16 mmol/L]

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Tuberculous Effusion

Pathogenesis. Postprimary tuberculous effusions occur as isolated pleural effusions in the absence of radiologically demonstrable parenchymal disease and occur within months of primary subclinical infection. This type of tuberculosis preferentially occurs in adolescents and young adults. The patient may be asymptomatic or, more commonly, has fever, malaise, and weight loss. A majority of patients have a positive tuberculin skin test.

Diagnosis. The pleural fluid is an exudate with > 50% lymphocytes. The glucose level is low and mycobacteria are rarely visible under the microscope. Fluid cultures will grow mycobacteria in about 20% of cases, the yield is higher with cultures of bacteria from pleural biopsies. Granulomas and/or growth of mycobacteria are found in up to half of the cases.

Neoplastic Pleural Effusion

Etiology. Metastatic lung and breast cancer are the most common primary tumors. If the primary tumor has already been detected, a diagnosis is simple. If a primary tumor is not known diagnosis may become difficult, since almost every metastatic tumor may be the cause for neoplastic pleural effusions.

Diagnosis. Neoplastic pleural effusions are usually exudative with or without blood. Pleural liquid cytology will confirm the diagnosis in up to 70% of cases. If cytology remains nondiagnostic, the next step is thoracoscopy, allowing inspection of the pleural space and biopsies for histologic examination.

Pleural Effusion in Abdominal Diseases

This type of pleural effusion may be caused by various abdominal pathologies:

- In *pancreatitis* a left-sided pleural effusion may be present in up to 15% of patients with acute pancreatitis or pancreatic pseudocysts.
- Effusions are typically exudative and have a high amylase concentration. A high amylase concentration may also be found in cases of esophageal rupture where the amylase is of salivary origin.
- Signs and symptoms referable to the chest very frequently accompany *subphrenic (subdiaphragmatic) abscesses*. In liver cirrhosis, ascites may pass through small clefts in the diaphragm into the right pleural space.
- Pleural effusions and ascites in association with nonmetastatic pelvic tumors in women have been designated as *Meig syndrome*. After the operative removal of the pelvic tumor, ascites and pleural effusion dramatically resolves.

Pleural Effusion in Myxedema

Rarely, pleural and pericardial effusions with high protein concentrations are found in patients suffering from myxedema.

Pleural Effusion in Collagen–Vascular Diseases

Pleural effusions occur in *rheumatoid arthritis* and *systemic lupus erythematosus (SLE)* (Chapter 4). Particularly in rheumatoid arthritis, an extremely low glucose concentration may be found in pleural fluid. The most common laboratory abnormality found in SLE is the presence of autoantibodies. High titers of antibodies to nuclear antigen (ANA) are found in patients with an active disease.

Yellow Nail Syndrome and Pleural Effusion

Yellow nail syndrome is an extremely rare condition. It presents with yellow nails, lymph edema of the lower extremities, and pleural effusion. It is due to an impaired lymphatic fluid drainage of unknown etiology.

Eosinophilic Pleuritis

Eosinophilic pleuritis is diagnosed when the pleural fluid contains more then 10% eosinophils. The presence of eosinophils is an unspecific finding and may be observed in malignancies, after a pneumothorax, after bleeding in the pleural space, and as a side effect of certain drugs.

Chylothorax and Pseudochylothorax

Chylothorax may be due to a traumatic laceration of the thoracic duct (injury, surgery), by destruction due to malignancies (lymphoma, pancreatic cancer, gastric cancer, etc.), or other changes of the lymphatic drainage (e. g., lymphangioleiomyomatosis).

Chylothorax needs to be distinguished from a so-called *pseudochylothorax*. The fluid appears opaque and milky in both situations due to its high lipid content. The lipids found in chylothorax are *triglycerides* (> 110 mg/dL [> 1.25 mmol/L]) in the form of chylomicrons and reach the pleural space through a leak from the thoracic duct.

In contrast, pseudochylothorax is due to an accumulation of cholesterol. The etiologies are different:

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- *chylus:* trauma, injury of the thoracic duct (surgery, puncture)
- *malignancies:* lymphoma, metastatic cancer, lymphangiomyomatosis
- *pseudochylothorax:* chronic inflammation (e. g., tuberculosis).

Pleural Effusion and Pulmonary Infarction

The limited fluid may contain small amounts of blood.

Pleural Effusion and Pneumonia

For the differential diagnosis of pleural complications due to pneumonia see Chapter 18.

Pleural Empyema

Diagnosis. Pleural empyema is diagnosed based on its putrid appearance, and bacteria are usually detectable. A foul smell is characteristic for anaerobes. If the usual cultures of pus remain sterile, tuberculosis should be suspected. Empyemas in a subacute stage are often capsulated. Computed tomography reveals an enhancement of the empyema membrane after intravenous contrast. If the drainage, possibly also after instillation of streptokinase, remains unsuccessful, a surgical intervention may become necessary.

> Any effusion accompanying pneumonia, i. e., a parapneumonic effusion, not responding to antibiotics should be aspirated and analysed. A low pH (< 7.20) is typical for a complicated parapneumonic effusion and needs drainage as an empyema.

Etiology. Pleural empyema is caused by a bacterial infection that originates in the lung and spreads to the pleural space. A primary infection of the pleura is much less common. The bacteria found are the same as in pneumonia (i. e., pneumococci, mixed flora with aerobes, and anaerobes). The *Streptococcus milleri* group are typical bacteria causing a primary pleural infection.

Pleural Neoplasms

Pleural Mesothelioma

Clinical Features. The diagnosis of pleural mesothelioma is often missed. The most common symptoms are constant chest pain and shortness of breath during exercise, when the accompanying pleural effusion or the tumor itself impairs the excursions of the hemithorax. The chest radiograph shows a unilateral pathology consisting of diffuse or localized pleural thickening, a pleural mass, and eventually a pleural effusion. (Fig. 6.**24**). Calcified pleural plaques are markers for previous asbestos exposure. Pleural mesothelioma typically occurs in occupations with asbestos exposure (mechanics, electrician, etc.). The latency between asbestos exposure and manifestation of the tumor is between 25–35 years.

Diagnosis. Computed tomography of the thorax supports the clinical suspicion if the following findings are present: diffuse or circumscribed thickening of the pleura, with or without effusion, and shrinking of the involved hemithorax. The pleural fluid is often hemorrhagic. Cytological findings may be diagnostic but quite often surgical pleural biopsies are necessary.

Benign Pleural Tumors

Fibroma, Lipoma, Chondroma, Angioma, Myxoma, Neurinoma. These tumors are rare and may cause uncharacteristic pain on the involved side. On the chest radiograph the tumors are sharply demarcated and dense.

Malignant Lymphoma

Pleural effusions are seen in Hodgkin and non-Hodgkin lymphoma, usually in advanced stages (stage IV).

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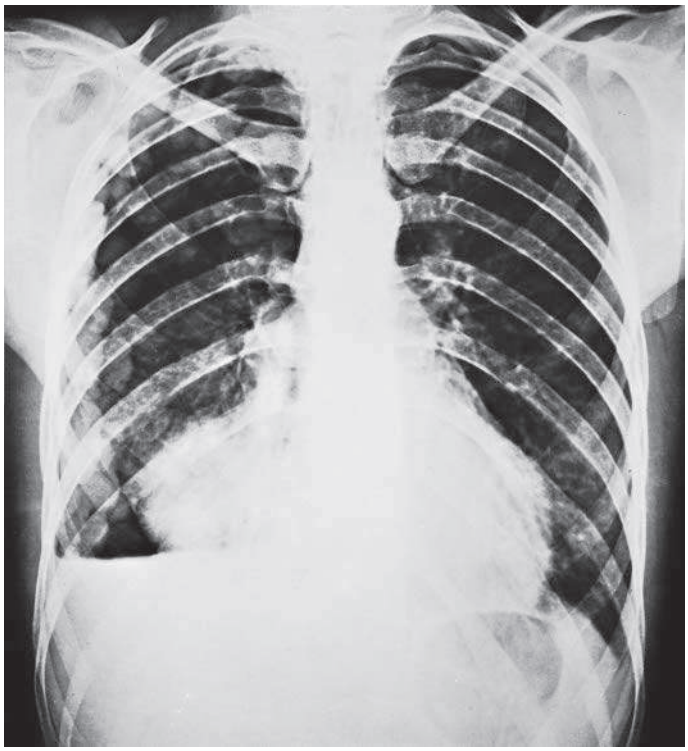

Fig. 6.**24** Characteristic, but rare, presentation of malignant mesothelioma with multinodular pleural thickening. Cytology of the pleural fluid: repeatedly negative for malignant tumor cells.

Spontaneous Pneumothorax

Etiology. The symptoms of a spontaneous pneumothorax are chest pain and shortness of breath. A distinction is made between a primary and secondary pneumothorax:

- A *primary pneumothorax* occurs in young, tall men and no underlying lung disease can be detected by lung function tests or by a chest radiograph. Nevertheless, small blebs may be found in the lung apices by computed tomography or during thoracoscopy, which is performed for the treatment of a pneumothorax after a first ipsilateral recurrence.
- A *secondary pneumothorax* occurs in lung diseases such as pulmonary emphysema, lung fibrosis, lymphangiomyomatosis, etc.
- *Iatrogenic pneumothorax* may be a typical complication of a transthoracic puncture or a puncture of the subclavian vein.
- *Mediastinal emphysema* is due to a passage of air from the lung to the mediastinum and may occur during coughing or during an extreme Valsalva maneuver. It is suspected when subcutaneous emphysema occurs at the upper chest and the neck.

Diagnosis. A small pneumothorax may be missed by clinical examination since the breath sounds are not decreased and hyperresonance is absent. The leading symptoms are sudden unilateral chest pain followed by shortness of breath. A diagnosis may be suspected from the medical history and if the pneumothorax is large enough it may be diagnosed by clinical examination. The diagnosis is eventually confirmed based on classical radiological findings such as a thin line caused by the visceral pleura, which is separated from the parietal pleura (Fig. 6.**25**). A first recurrence occurs in about one-third, and a second recurrence in about half of the cases.

Tension Pneumothorax. This complication is life-threatening and should not be missed. A tension pneumothorax is suspected when the intensity of dyspnea does not decrease as in an uncomplicated pneumothorax but increases. If the pressure inside the pneumothorax rises above atmospheric, as may occur with a one-way leak into the pleural space or occurs as a complication of positive pressure ventilation, a tension pneumothorax is present. The mediastinum shifts toward the unaffected side, and cardiac output may be severely compromised due to the positive intrathoracic pressure decreasing venous return to the heart. Clinical findings consist of dilated neck veins, tachycardia, and hypotension. A tension pneumothorax may occur after thoracotomy when the chest tube does not drain or has been removed too early. Spontaneous tension pneumothorax is an extremely rare event and usually occurs in lungs with a distinct underlying pathology.

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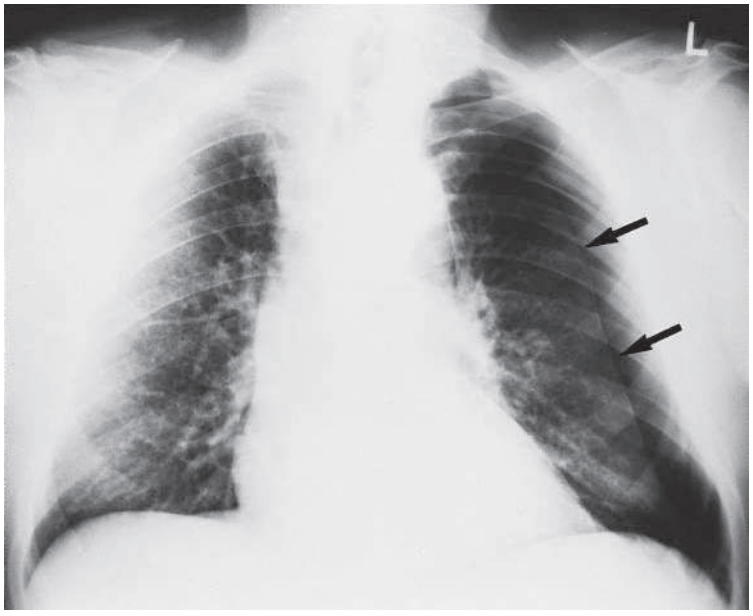

Fig. 6.**25** Idiopathic, spontaneous, left-sided pneumothorax.

6.4 Intercostal Pain

Etiology. Intercostal pain occurs frequently after thoracic surgery, particularly when the intercostal nerves become injured during thoracoscopy. Further causes of intercostal pain are radicular irritations due to vertebral column pathology or a neurinoma (e. g., in neurofibromatosis).

Differential Diagnosis. Herpes zoster is a frequent cause of pain. Pain that is localized to the areas served by the affected nerves may begin several days before, or be concomitant with the appearance of the skin eruptions. The herpes lesions are arranged unilaterally in characteristic bandlike clusters which follow radicular lines. Postherpetic neuralgia may last for several months or years and become the most troublesome part of the disease (see Chapter 4).

Bornholm disease or pleurodynia (devil grip) (see Chapter 4) is frequently diagnosed as intercostal neuralgia. Pain is sharp, severe, and paroxysmal over the lower ribs or substernal area and may be assumed to be due to pleuritis.

6.5 Pain Originating from Joints and the Vertebral Column

See Chapters 8 and 10, respectively.

6.6 Musculoskeletal Thoracic Pain

This type of pain, originating from muscles and bones, is diagnosed, as a rule, without difficulties based on localized trigger points. In the presence of muscle pain, *polymyalgia rheumatica* or *dermatomyositis* is a potential diagnosis. *Myalgia* occurs after strenuous exercise and is limited in duration. Circumscribed, painful muscle indurations are called myogelosis (see Chapter 10). Additional causes for chest pain are: rib fractures after vigorous coughing, fibromyalgia, infiltrative processes, eosinophilic granuloma, metastases to the ribs (see Chapter 11), or malignant mesothelioma.

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6.7 Pain Originating from the Esophagus

See Chapter 26.

6.8 Other Causes for Thoracic Pain

SAPHO Syndrome. This syndrome (sternocostoclavicular hyperostosis) most commonly affects the anterior chest wall (also see Chapter 10). Patients complain of painful swelling in this area. Pain may precede the physical findings, making a diagnosis difficult. Radiological findings consist of a thickening of the clavicles.

The syndrome is, by definition, associated with other symptoms (SAPHO: **s**ynovitis, **a**cne, **p**ustulosis, **h**yperostosis, **o**steitis). Its pathogenesis remains unknown.

Tietze Syndrome. Tietze syndrome consists of swelling, pain, and tenderness in the upper costochondral cartilages and mainly affects young adults. The involved costochondral joints are swollen and tender. Single joints are frequently involved, and multiple joint involvement tends to be unilateral (Fig. 6.**26**).

"Slipping-rib" or "Rib-tip" Syndrome. This term designates a thoracic and particularly abdominal pain syndrome of unknown etiology. It affects mostly young adults and the pain can be provoked and reproduced by levering the lower rib cage. Occasionally a clicking sound may be heard.

Mondor disease is characterized by superficially localized phlebitis of the lateral thorax veins (see Chapter 3).

Breast Cancer. Breast cancer may cause mild pain sensations, but is most commonly completely asymptomatic. Therefore, the diagnosis is usually made at a late stage of the disease. Women may detect a localized firm nodule in their breast by chance. Occasionally the nipple becomes retracted.

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Fig. 6.**26** Tietze syndrome: swelling at the left sternal border in the region of the insertion of the second rib.

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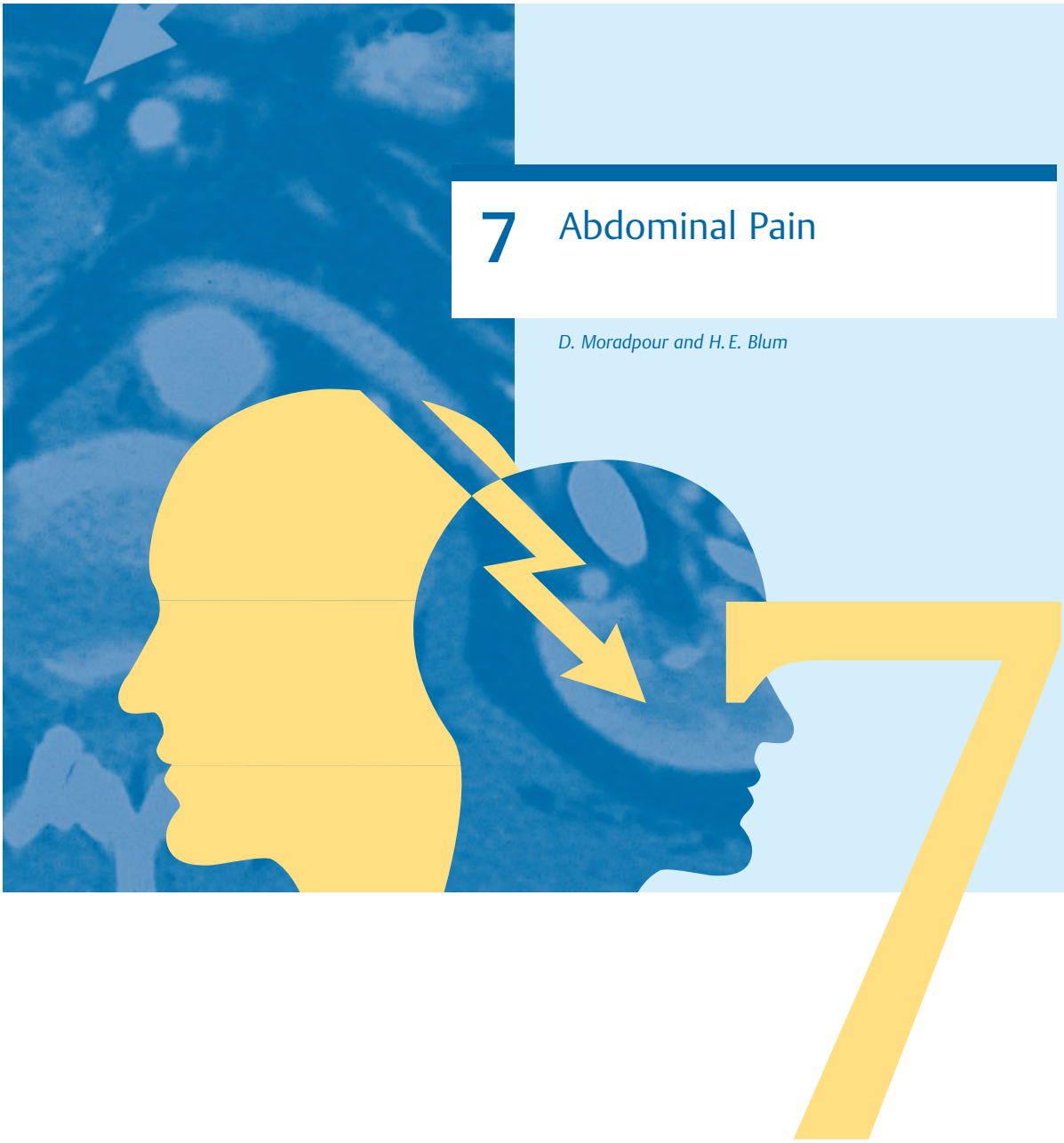

7 Abdominal Pain

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Difference Between Visceral and Somatic Pain

Nervous System in the Abdominal Organs. The abdominal organs have two different types of pain perception: via fibers of the autonomic nervous system (ANS) originating from the intestine and peritoneum (visceral pain) and via fibers of the central nervous system (CNS) originating from the abdominal wall, including the parietal peritoneum and mesenteric portion of the small intestine (somatic pain). The characteristic symptoms of visceral and somatic pain are summarized in Tab. 7.**1**.

Visceral Pain. The main causes of visceral pain are fast pressure increase in hollow organs, capsule tension, and intensive muscular contractions. Visceral pain is typically felt in or near the median line of the abdomen. Visceral pain of the hollow organs, primarily of the intestine, is generally characterized by colics, i. e., intermittent attacks of pain that vary in intensity, similar to labor pains, with pain-free intervals. Pain associated with visceral pain radiates to regions that belong to the same neurologic segment as the diseased organ (Tab. 7.**2**).

Somatic Pain. Somatic pain primarily occurs as a result of irritation of the parietal peritoneum (e. g., peritonitis) or the mesenteric portion of the small intestine. This pain is localized at the site of maximum inflammation (e. g., right lower abdominal region in appendicitis) and is typically continuous. In practice, a distinction is drawn between acute and chronic or recurring abdominal pain.

Table 7.**1** Differential diagnosis of visceral versus somatic pain

Characteristics	Visceral pain	Somatic pain
Origin	Primarily abdominal hollow viscera	Primarily parietal peritoneum including abdominal wall and retroperitoneum
Referral	Bilateral splanchnic nerves	Segmental sensitive fibers unilateral
Trigger	Primarily stretching and spasm	All forms of tissue damage
Sensation	Cramps, acute or gnawing pain	Dull to sharp continuous pain
Localization	Undetermined, symmetric, near the median line	Circumscribed, asymmetric, often lateral
Other symptoms	Restlessness, nausea, vomiting, pallor, sweating	Dependent on position and movement
Relief	Walking around, twisting, bending	Rest, relaxed position
Aggravation	Rest	Shaking, coughing, sneezing, movement

Table 7.**2** Localization of visceral pain

Organ	Segment	Dermatome
Diaphragm	C3–C5	Throat to deltoid region
Heart	C5–C6	Arm to xiphoid
Esophagus	T1–T6	Little finger to xiphoid
Upper abdominal organs	T6–T8	Xiphoid to epigastrium, lower scapular region
Small intestine and right colon	T9–T10	Periumbilical
Left colon	T11–T12	Lower abdomen

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7.1 Acute Abdominal Pain

The onset and intensity of abdominal pain and the local and general signs and symptoms are most important for the initial assessment of patients with acute abdominal pain. These criteria are particularly important for distinguishing between diseases that primarily require surgery and clinically similar pain that can be treated conservatively. This differential diagnosis can be difficult and requires close cooperation between physicians and surgeons. Chronic abdominal pain that recurs in waves with less intense local and general signs and symptoms and no indication of an emergency surgical situation must be distinguished from acute abdominal pain.

Acute Abdomen

Definition. An "acute abdomen" is defined as severe abdominal pain of *unclear etiology* lasting for several hours, which is considered a surgical emergency because of the clinical signs and symptoms and effect on the general health status.

Clinical Features, Local Symptoms. The main symptom is spontaneous pain, which is felt as either colic or continuous pain. The "surgical acute abdomen" often involves local or diffuse peritoneal irritation (*peritonitis*) or signs of an ileus. Conversely, these signs are generally not present in the "medical acute abdomen." Unlike colicky (visceral) pain (e. g., with cholelithiasis or mechanical ileus), in which the patient bends over with pain and cannot rest quietly, patients with continuous somatic pain, as a result of peritoneal pain symptoms (e. g., acute peritonitis), remain immobile lying on the back and avoid any type of vibration. Particularly important signs of peritoneal irritation are the *défense musculaire* or *rebound tenderness*, i. e., pain of short duration but increased intensity after sudden removal of the palpating hand, and the *pain on percussion* in the region of the maximal peritoneal irritation. During the clinical examination it is important to remember percussion of the hepatic dullness (generally not present with pneumoperitoneum), auscultation of the intestinal sounds (dead silence in peritonitis, high pitched metallic sounds in mechanical ileus), and the digital rectal, and if applicable, gynecologic examination.

Clinical Features, General Symptoms. The local signs and symptoms are often accompanied by general signs and symptoms that narrow down the differential diagnostic spectrum: fever, leukocytosis with or without toxic granulations, vomiting, gas and stool retention, tachycardia, threadlike pulse, dry tongue, reddening of the face with sunken cheeks and pointed nose (referred to as facies hippocratica), restlessness, cold sweat, hypertension, acute thirst, and exsiccosis.

Causes of Acute Abdomen. The following causes must be considered in patients with acute abdomen (Fig. 7.**1**).

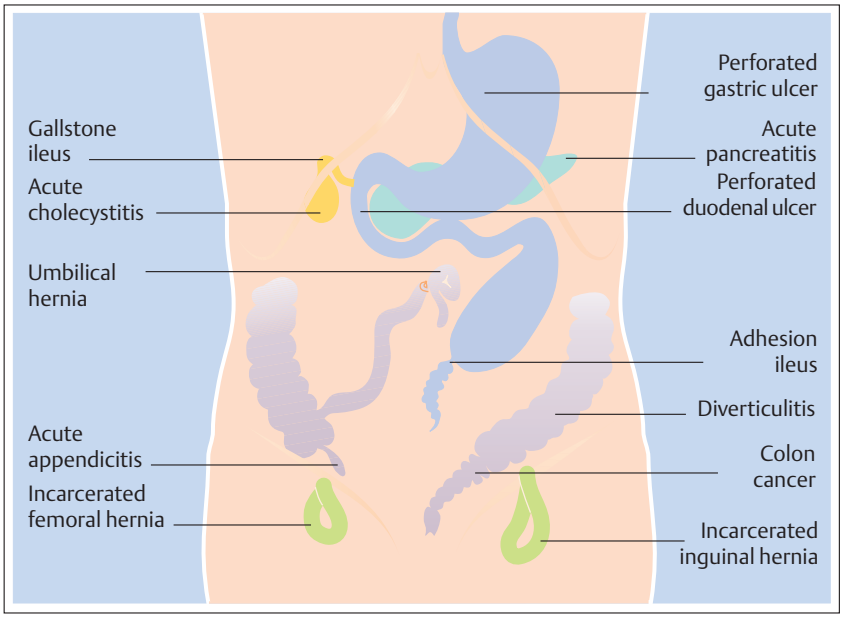

Fig. 7.**1** The most frequent causes of acute abdomen. These must be excluded before considering rarer causes (see Tab. 7.**6**).

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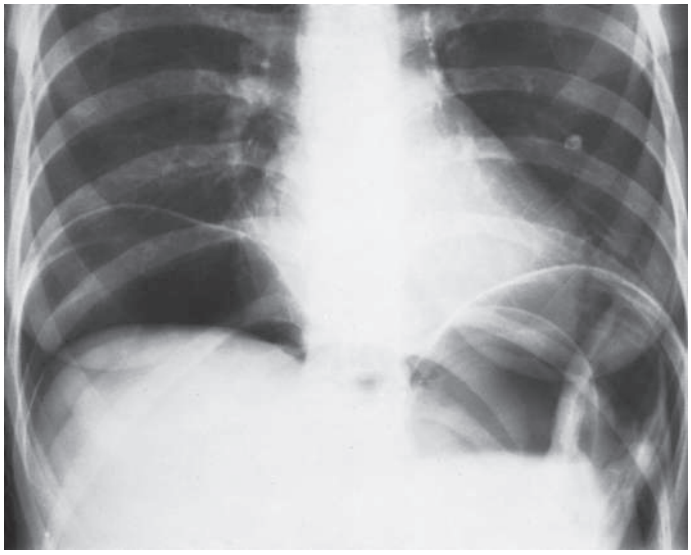

Fig. 7.**2** Radiograph showing free air under left and right diaphragm in a patient with a perforated duodenal ulcer.

Abdominal pain, generally with indication for emergency surgery:

- ➤ acute appendicitis
- ➤ acute mechanical ileus
  - – incarcerated hernia
  - – adhesions after abdominal operations
  - – tumors or inflammatory stenoses
  - – invagination, volvulus
  - – foreign body or gallstone obstruction
- ➤ perforation, primarily gastric or duodenal ulcers (Fig. 7.**2**), diverticulitis
- ➤ acute cholecystitis with peritonitis
- ➤ torsion (ovarian cysts, genital tumor, omentum)
- ➤ rupture of the fallopian tube with extrauterine gravidity
- ➤ abdominal trauma (e. g., rupture of hollow organs, spleen, pancreas, liver)
- ➤ vascular problems (mesenteric vascular occlusion, aortic aneurysm, embolism of the aortic bifurcation)

Abdominal pain, generally without indication for emergency surgery:

- ➤ acute pancreatitis
- ➤ acute inflammation or colic
  - – stomach (acute gastritis)
  - – intestine (acute enterocolitis, acute diverticulitis, Crohn disease, ulcerative colitis, irritable colon)
  - – gall bladder (cholecystolithiasis)
  - – liver (acute hepatitis, alcohol-induced hepatitis, acute congestion of the liver)
  - – urogenital organs (nephrolithiasis, cystopyelitis, adnexitis, ovulation pain)
- ➤ mesenteric lymphadenitis
- ➤ idiopathic intestinal pseudo-obstruction
- ➤ allergic abdominal crisis
- ➤ familial paroxysmal polyserositis
- ➤ acute perihepatitis (Fitz–Hugh–Curtis syndrome)

Abdominal pain mimicking an acute abdomen:

- ➤ see Tab. 7.**6** (Extraabdominal causes).

The differential diagnoses of acute abdominal pain based on pain localization are listed in Tab. 7.**3**.

Complications of Acute Abdomen. Cardiovascular failure resulting from electrolyte and/or fluid imbalance or septic complications are life-threatening in association with acute abdomen. When assessing an acute abdomen alarm symptoms must always be taken into account, particularly hypertension, oliguria, peritonitis, protracted symptoms over 24 hours, and history of abdominal trauma within the last eight days.

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Table 7.3 Differential diagnosis of acute abdominal pain based on pain localization

With rebound tenderness	Without rebound tenderness
Diffuse abdominal pain	

– diffuse peritonitis	– acute ileus of
	  – small intestine (colic, vomiting, scaphoid abdomen with high occlusion/tympanites with deep occlusion; examination for hernia and surgical scars)
	  – large intestine (wind–stool ratio, strong meteorism, no vomiting or subsequent symptom)

Epigastric region	
– circumscribed peritonitis, e. g., ulcer perforation (hard abdomen) – acute pancreatitis (soft defense)	– porphyria, collagenous colitis etc. – acute gastritis – pancreatitis – appendicitis (migration of pain to appendix region in a few hours) – coronary heart disease – pleuropneumonia, pericarditis – aneurysm – poorly controlled diabetes
Umbilical region	
	– acute enterocolitis – epigastric or umbilical hernia – irritable colon – mechanical ileus
Right hypochondriac region	
– acute cholecystitis – duodenal ulcer with penetration or perforation – acute appendicitis – acute perihepatitis – pancreatitis of head of pancreas	– cholelithiasis – liver abscess – acute congestion of the liver – hepatitis – pleuropneumonia – herpes zoster – renal colic
Left hypochondriac region	
– ulcer perforation – pancreatitis – rupture of the spleen – rupture of the esophagus	– spleen–kidney affection (e. g., infarction) – pancreatitis – myocardial infarction – incarcerated hiatus hernia – pleuritis
Right iliac fossa	
– appendicitis – adnexitis, rupture of fallopian tube – torsion of ovarian cysts	– nephrolithiasis – regional enteritis – Meckel diverticulitis – acute ileitis – adnexal disease (e. g., mittelschmerz) – pelvic vein thrombosis – pancreatitis – inguinal hernia – acute coxitis
Left iliac fossa	
– acute diverticulitis	– colon diverticulosis – irritable colon – as in right iliac fossa
Suprapubic region	
	– cystitis – aneurysm

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Intestinal Pain

Ileus

Ileus can be classified into two main types (Tab. 7.**4**):
- mechanical ileus
- paralytic ileus

Mechanical Ileus

Clinical Features. Mechanical or *obstruction ileus* causes *colicky abdominal pain*, frequently with periumbilical localization. Intestinal colic, which results from painful contraction of the intestine to overcome an obstruction, lasts from seconds to a few minutes. It can easily be distinguished from urethral or gallstone colic, which lasts much longer. Acute gas and stool retention always indicates ileus and represents one of the most important early symptoms together with pain and possibly vomiting. Palpation of the abdomen frequently triggers a colic. Initially, provided the intestinal wall is not more seriously damaged, there are almost no signs of peritonitis, i. e., the abdominal pain is mild and rebound tenderness is only minor. Signs of inflammation are absent or mild (no or only mild leukocytosis, normal ESR). The clinical picture changes in later stages. The colicky pain becomes continuous pain, and symptoms of abdominal wall necrosis appear (peritonism, leukocytosis, shock).

An *asymmetric abdomen* indicates a localized intestinal distension resulting from an organic obstruction (DD: acute urinary retention).

Diagnosis. The bowel sounds are initially increased at *auscultation*, and disappear when, with time, the mechanical ileus progresses to the paralytic stage.

Abnormal intestinal movements (stiffness), which are caused by intestinal stenoses, can be palpated in some cases or can be directly observed during inspection of the abdomen. The inconstant character is particularly typical.

Radiologically the plain abdominal radiograph shows distended intestinal loops with fluid levels at an early stage (Fig. 7.**3**). With colonic stenosis, the proximal intestine is distended and the haustra can be detected. Distal to the stenosis there is no air in the intestine.

Sonography can be helpful diagnostically by demonstrating pathologic intestinal motility and distended intestinal loops.

The character of the following four main symptoms enables localization of the mechanical ileus (Tab. 7.**5**).
- vomiting
- pain
- meteorism
- gas and stool retention

Complications. If perfusion of the intestinal wall is impaired due to mechanical ileus, *paralytic ileus* with continuous pain, localized peritonitis, shock, and leukocytosis will occur (see Tab. 7.**4**). The blood pressure is reduced, the pulse becomes rapid and weak. Facies hippocratica with sunken cheeks develops. Vomiting occurs in all stages. With complete ileus fecal vomiting (*copremesis*) occurs. Gas and stool retention are observed in most cases. However, some patients also have diarrhea.

Causes of Mechanical Ileus. The most common causes of mechanical ileus are previous abdominal surgery (i. e., adhesions), neoplasms, sliding hernia, volvulus, invagination, and various other factors (e. g., foreign bodies, Crohn disease, diverticulitis, mesenteric artery infarction).

Table 7.**4** Differential diagnosis between paralytic and mechanical ileus

	Paralytic ileus	Mechanical ileus
Medical history	Frequent ulcer or gallstone pains or other abdominal complaints, appendicitis, extrauterine gravidity	History of carcinoma, gallstones, hernias, previous laparotomy
Onset	Sudden (perforation) or gradual (laparotomy) depending on the underlying disease	Always gradual
Pain	May not be present depending on underlying disease	Generally colicky
Meteorism	Diffuse, very obvious	Reversal
Peristalsis	None (complete stasis)	Increased, intestinal stasis
General condition	Highly affected, frequently shock	Slightly affected, no shock

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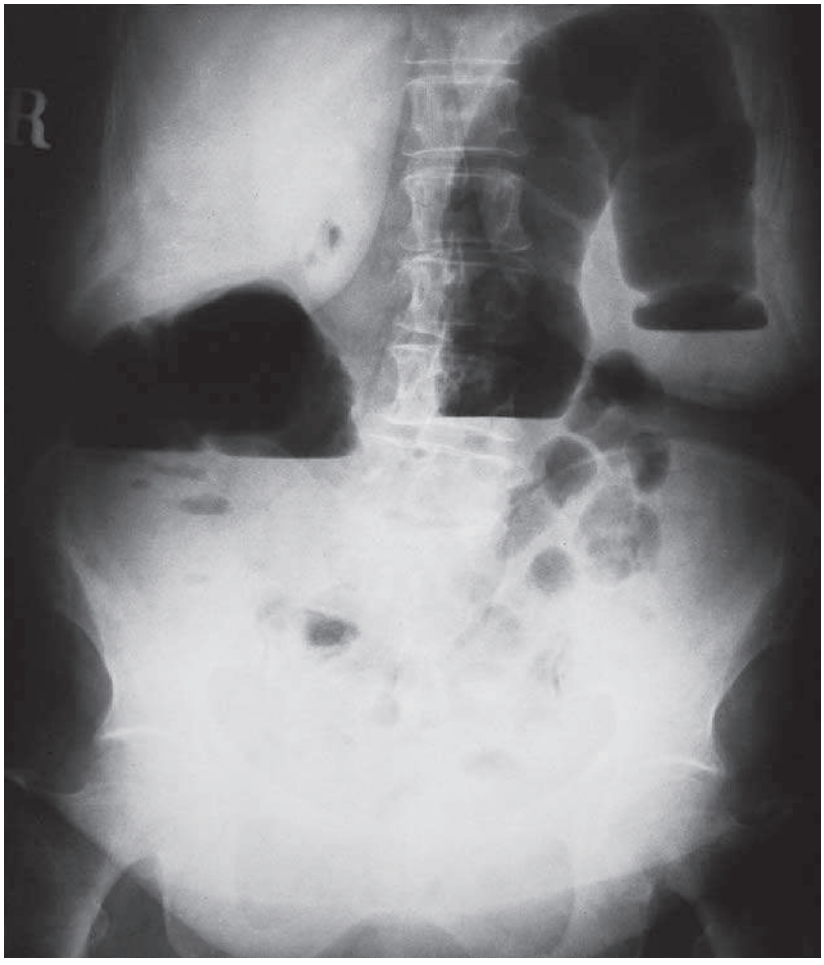

Fig. 7.**3** Mechanical ileus with seriously distended colon in 73-year-old woman with carcinoma in the descending colon. Distal to the stenosis there is no air in the intestine.

Sliding hernias (Fig. 7.**4**), postoperative *adhesions* (e. g., after appendectomy [Fig. 7.**5**]) or other surgical interventions (Fig. 7.**6**), are frequent causes of a mechanical ileus. Therefore, sliding hernia and surgical scars must be considered in patients with an ileus. In children, and less frequently in young adults, an *invagination* and torsion of the intestine (*volvulus*) must also be considered. In both cases bloody stools are generally encountered.

Obstruction of the intestine in adults is generally caused by a *colorectal carcinoma*. Carcinomas of the small intestine, that also cause ileus are rare.

In older patients with an acute abdomen a *mesenteric infarction* must be considered, which initially often presents with a clinical picture similar to that of mechanical ileus. Typical radiologic signs are gas-free intestines and later gas in the intestinal wall and portal vein.

Table 7.**5** Localization of mechanical ileus

	Vomiting	Pain	Tympanites	Gas and stool retention
High small intestine	Early, intensive	Around the navel, intermittent, intense	None or minimal	None
Low small intestine	Later, only after pain, less profuse, feculent	Intense, cramping, around the navel	Marked, center of abdomen	Initially stool passage and flatulence possible
Iliac colon	Rare, delayed symptom	Less intense, cramping	Marked, flanks	Complete, possible alternating obstipation and diarrhea

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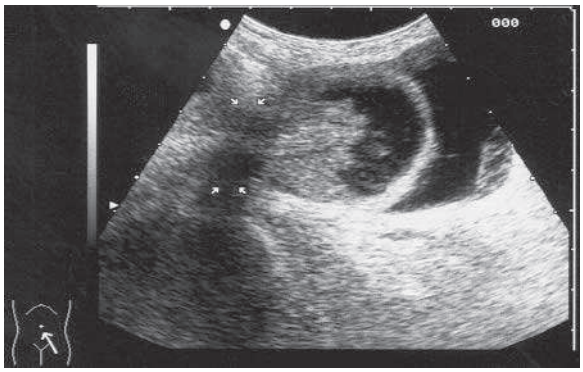

Fig. 7.**4** Abdominal ultrasound showing an incarcerated inguinal hernia. The arrows indicate the hernial canal.

Fig. 7.**5** Mechanical ileus of the small intestine due to adhesions after appendectomy in a 50-year-old woman. The colon is essentially without air. The small intestine is significantly dilated with air–fluid levels. ▷

Rare Causes of a Mechanical Ileus

Rarely, the horizontal part of the duodenum is obstructed by the Treitz ligament and the mesenteric arteries (superior mesenteric artery; *superior mesenteric artery syndrome* or mesenteric artery duodenal compression). Postprandial vomiting of bile, increased when standing or lying down, is the most important indicator. Radiologic demonstration of duodenal compression without typical clinical symptoms is not sufficient to diagnose duodenal obstruction. In adults the diagnosis must be made only with great caution and after exclusion of all other possible causes (including irritable stomach).

Very rare causes of a mechanical ileus are a large *Meckel diverticulum* or endometriosis, which is generally localized in the sigmoid colon. In endometriosis the temporal association between menstruation and occurrence of the symptoms will result in the correct diagnosis.

Passage of gallstones into the intestine (biliary-digestive fistula or more rarely via the common bile duct) can cause an ileus (*gallstone ileus*). Lodging of these gallstones most often occurs in the distal or middle ileum, rarely in the jejunum, and primarily affects older patients. Sonographic or radiologic confirmation of air in the bile ducts (pneumobilia) indicates a biliary-digestive fistula and probably gallstone ileus.

The clinical–radiologic picture of the mechanical small intestine (and colonic) ileus can also be rarely caused by *idiopathic intestinal pseudoobstruction*, which often occurs in waves. Slow-onset abdominal colic with vomiting and increasing meteorism and tendency to diarrhea are typical symptoms. Radiologic diagnosis shows distended intestinal loops and fluid in the small and possibly the large intestine. However, there are no signs of an intestinal stenosis with no air distally. The episode frequently subsides spontaneously within a few days.

Paralytic Ileus

Clinical Features. In paralytic ileus the intestinal musculature is paralyzed while the intestinal lumen is not obstructed. The inhibition of the motor intestinal activity prevents transport of the contents of the intestine. Distension of the abdomen occurs and it is painful upon pressure. Gases are not emitted and intestinal sounds cannot be detected by auscultation (deathly silence). In later stages feculent, bilious and liquid stomach contents may be vomited.

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Diagnosis. Distended bowel loops with smooth wall contours and fluid levels throughout the entire gastrointestinal tract can be demonstrated by radiography.

Complications. Respiration is accelerated as a result of the intestinal intoxication and excessive distension (diaphragm under high pressure). Tachycardia, hypotension, and exsiccosis occur. The face is sunken with halos around the eyes and pale corners of the mouth being particularly evident.

Causes of Paralytic Ileus. Common causes of paralytic ileus are:

- postoperative (reflex intestinal atonia)
- peritonitis (e. g., after intestinal perforation)
- strangulation ileus
- serious infections (Gram-negative sepsis)
- metabolic disorders (uremia, diabetic coma)
- electrolyte disorders
- pelvic or spinal fracture
- retroperitoneal diseases (e. g., pancreatitis, hematoma)
- mesenteric ischemia
- neurologic disorders

Fig. 7.**6** Mechanical small intestine ileus due to adhesions in a 70-year-old man (image taken in supine position).

Acute Appendicitis

In patients with abdominal pain acute appendicitis must always be considered in the differential diagnosis. In classical cases diagnosis is simple, but it may be very difficult in patients with atypical symptoms.

Clinical Features. The *pain* initially starts epigastrically and is only localized in the right lower quadrant after some hours. It is rarely very strong. The pressure point depends on the localization of the appendix, which can be very variable. The *McBurney point* (middle of a line drawn between the navel and anterior superior iliac spine) is most frequently sensitive to pressure. Another pain localization in the right lower quadrant or even the right epigastric region (with a highly displaced appendix) does not preclude appendicitis (consider situs inversus in rare cases). With a pelvic position of the appendix, rectal examination, which should always be part of the clinical examination for suspected appendicitis, is decisive. Rebound tenderness is always present, except in very early stages, and reflects the degree of peritoneal involvement.

Diagnosis. Leukocytosis is generally present. Nausea and vomiting are common. Fever is generally not high with the rectal temperature being significantly higher than the axillary temperature. Obstipation is generally present; diarrhea is rarely encountered initially. Sonography is frequently helpful.

Differential Diagnosis of Pain in the Right Lower Quadrant

In cases of pain with acute onset in the right lower quadrant the first considerations should be hernia and nephrolithiasis. In women, gynecologic diseases must also be considered in the differential diagnosis. In rare cases acute infections with involvement of the mesenteric lymph nodes (particularly in children) may mimic appendicitis (e. g., viral infections, yersiniosis). Other causes are diverticulitis (Meckel, cecum), Crohn disease, ileocecal tuberculosis, carcinomas, and invagination. Diseases of neighboring organs are occasionally localized in the right ileocecal region: cholecystitis, pancreatitis, gastric or intestinal perforation, pyelitis, and hypostatic abscess in spinal tuberculosis. It may be more difficult to distinguish a right pelvic vein thrombosis if there is no thrombosis of the lower extremities. Further, diseases such as pneumonia, pleuritis, etc. that can initially present with pain in the right lower quadrant before the classical symptoms develop must always be considered.
Undetermined epigastric complaints that gradually become midabdominal, hypogastric or ileocecal pain may be a manifestation of lymphadenitis from toxoplasmosis. The liver and spleen may also be slightly enlarged. Leuko-

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penia is typical; sometimes cervical lymph nodes are palpable. Fever is sometimes absent. The diagnosis must be serologically confirmed.
Certain *drugs* (e. g., NSAIDs or potassium chloride tablets) may cause circular stenosing small-intestine ulcers with typical clinical symptoms. Colicky abdominal pain, primarily postprandial, with nausea and vomiting, is the leading symptom. This pain may persist for days, weeks, or even months if the medication is continued. Intestinal perforations may occur.

Differential Diagnosis of Hypogastric Pain

Hypogastric pain is generally caused by urogenital diseases. Hernias and hip-joint diseases must also be considered. Mucous colitis (a category of Irritable Bowel Syndrome [IBS]) can also present with intense pain, primarily localized in the left or right lower quadrants. A contracted iliac colon and absence of any peritoneal irritation with the excretion of mucosa and membranes point to this diagnosis, which however, like IBS, represents a diagnosis by exclusion.
Colorectal cancer and diverticulitus are the leading causes of hypogastric pain in patients over 40 years of age.

Peritoneal Pain

Peritonitis

Clinical Features. Diffuse, *bacterial* peritonitis usually presents no differential diagnostic difficulties. The high pressure-sensitive, distended abdomen, which is painful at the slightest touch, and a marked *rebound tenderness* are the hallmarks of peritonitis. Facies abdominalis can be clearly seen in these patients. Patients suffering from peritonitis avoid all movement, have shallow breathing, and do not try to relieve the pain by pressing the abdomen. Legs are often drawn up and motionless. This behavior has characteristic differences from that associated with abdominal pain resulting from spasms of visceral organs (e. g., cholelithiasis, nephrolithiasis, onset of mechanical ileus).

Diagnosis. Intestinal sounds are absent upon auscultation. Fever (rectal temperature = 1–2 °C higher than axillary) and leukocytosis are typical.

Causes. The most common cause of diffuse peritonitis is *gastric* or *duodenal ulcer perforation*. Intestinal perforations from typhus, tuberculosis, carcinoma or appendicitis are less common. Pneumococcal, chlamydial, and gonococcal peritonitis present less dramatically. The infections are primarily ascending (in girls and women) or hematogeneously spread (primarily in children). In older immunocompromised patients the symptoms of pneumococcal peritonitis may recede so that they cannot be distinguished from the symptoms of the underlying disease. An *oligosymptomatic* or *asymptomatic peritonitis* is also observed in spontaneous bacterial peritonitis, in patients with decompensated cirrhosis of the liver (see Chapter 25), and in peritonitis tuberculosa. In sexually active women *acute perihepatitis* (*Fitz–Hugh–Curtis syndrome*) as a result of *gonorrhea* or *chlamydia* infection must be considered (peritonitis-like findings primarily in the right epigastric region). A chemical peritonitis with a similar clinical picture to bacterial peritonitis can be caused by bile leaking into the peritoneum (biliary peritonitis [e. g., after accidental puncturing of bile ducts or gall bladder, posttraumatically, or after perforation of the gall bladder, or by leakage of contrast medium into the abdominal cavity]). Rarely, peritonitis can be triggered by the rupture of an ovarian cyst or by an intraperitoneal hemorrhage (e. g., from hepatoma, vascular rupture, extrauterine gravidity).

See Tab. 7.**6** for a summary of the most common causes of abdominal pain.

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Table 7.6 Most common causes of abdominal pain

Intra-abdominal causes	Extra-abdominal causes
With generalized peritonitis – perforation of a hollow organ (e. g., esophagus, ulcer, gall bladder, appendix, diverticulum) – primarily bacterial peritonitis (e. g., *Chlamydia*, pneumococci, tuberculosis) – nonbacterial peritonitis (e. g., bile peritonitis, hemoperitoneum, extrauterine gravidity) – familial paroxysmal polyserositis	**Retroperitoneal** – renal and urinary tract – aortic aneurysm – hematoma – neoplasia – Ormond disease
With localized peritonitis – abdominal trauma – appendicitis – cholecystitis – ulcer – colitis, Crohn disease – diverticulitis – abdominal abscesses – pelvic peritonitis/ovulation pain – acute perihepatitis – pancreatitis	**Thoracic** – pneumonia (pleuritis) – embolism – empyema – myocardial infarction – pericarditis – esophagitis, rupture of the esophagus – esophageal spasm
Pain from massive pressure (hollow organs, capsule tension) – mechanical ileus – intestinal hypermotility (e. g., gastroenteritis, IBS, parasites) – biliary obstruction – urinary tract obstruction – liver capsule tension – uterus obstruction	**Neurogenic** – neuritis/neuralgia – pain from spinal affections – herpes zoster – tabes dorsalis
Ischemic pain – incarceration of a hernia – abdominal angina – thromboembolic processes (mesentery, liver, spleen) – torsion of organs (e. g., intestinal volvulus, ovarian cysts) – hemorrhage of the intestinal wall – tumor necrosis	**Metabolic disorders** – porphyria – endocrine diseases (e. g., pheochromocytoma, hyperparathyroidism, diabetic ketoacidosis) – hemochromatosis – hyperlipidemia **Intoxication** – lead, arsenic, thallium – uremia **Miscellaneous** – collagen diseases – hypersensitivity reaction (e. g., serum disease) – acute hemolysis – abdominal wall affections (e. g., trauma, hematoma) – hip joint processes (e. g., coxarthrosis, coxitis)

Rare Cause of Peritonitis

The rare *familial Mediterranean fever* (FMF, paroxysmal polyserositis or periodic peritonitis) is an autosomal recessive inherited disease with recurring episodes of fever, peritonitis, and/or pleuritis, which primarily affects people of Middle Eastern origin (Arabs, Turks, Armenians, Sephardic Jews). Chronic arthritis and painful erythema are also observed occasionally. A complication may be amyloidosis with renal failure. Mutations of the MEFV gene are associated with FMF and can be identified by molecular diagnosis.

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Pain from Vascular Causes

Mesenteric Infarction and Abdominal Angina

Clinical Features. The most severe abdominal pain is caused by an acute occlusion of the mesenteric arteries (mesenteric infarction). The pain is continuous, but usually with significant colicky exacerbation and in general is more diffuse than pain from cholelithiasis, nephrolithiasis, or ulcer. The abdomen is initially very tense but easily compressible and there is no particular rebound tenderness. Later, intestinal ischemia dominates the clinical picture. Leukocytosis, fever, peritonitis, intestinal atonia, and bloody diarrhea occur.

Diagnosis. Typical changes can frequently be detected in a plain radiograph of the abdomen: initially the gas-free intestine, then thickening of the intestinal wall, hairpin loops, and, in later stages, gas in the intestinal wall and the portal vein branches. Duplex sonography and angiography confirm the diagnosis.

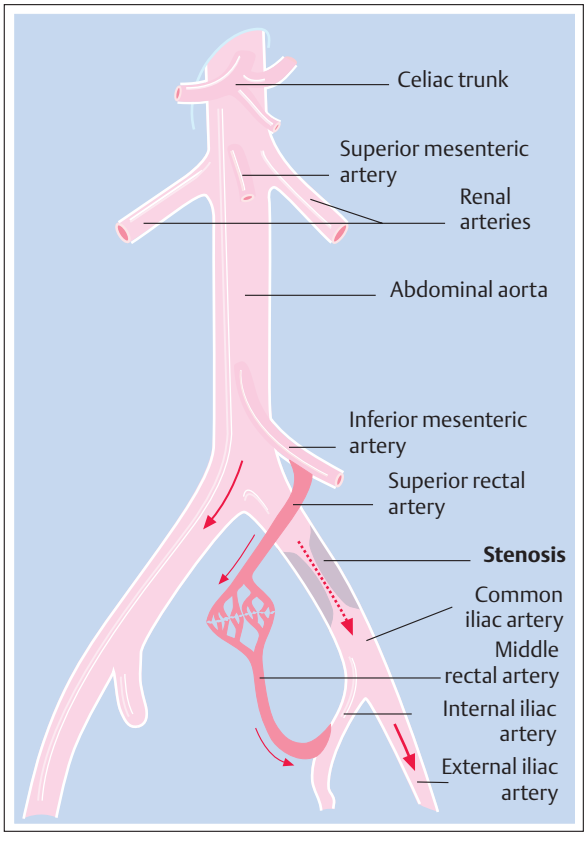

Fig. 7.**7** Schematic view of inferior mesenteric artery steal syndrome due to stenosis of the common iliac artery. If the blood supply from the external iliac artery is not sufficient because of the stenosis, it can be compensated (via inferior mesenteric artery →superior rectal artery → medial rectal artery → internal iliac artery) resulting in hypoperfusion of the inferior mesenteric artery.

Causes and Pathogenesis. The arterial vascular occlusion is frequently embolic (preexisting valvular heart disease, atrial fibrillation, cor bovinum, post myocardial aneurysm, endocarditis) or arteriosclerotic–thrombotic. Occlusions of the splenic or renal arteries are less dramatic. A nonocclusive mesenteric infarction is observed in low cardiac output syndromes, with shock or serious hypoxemia.

Abdominal Angina. *Abdominal angina* is caused by arteriosclerosis of the abdominal arteries. The pain tends to occur 20–30 minutes after rich meals and last 1–2 hours. The age of the patients (usually over 50 years), additional vascular manifestations (coronary heart disease, peripheral arterial occlusive disease), negative gastrointestinal history, and negative gastrointestinal findings are suggestive of abdominal angina. It can be confirmed by duplex sonography or angiography. Episodes of pain similar to abdominal angina are observed in panarteritis nodosa.

Abdominal pain, occult blood loss (anemia), and diarrhea during active exercise can be due to mesenteric ischemia (jogging anemia or runner's stomach).

Aortoiliac Steal Syndrome

If indeterminate abdominal pain occurs after walking, an aortoiliac steal syndrome should be considered. The cause is an obstruction of the pelvic arteries and the aorta distal from the inferior mesenteric artery. The pathomechanism is shown in Fig. 7.**7**. The clinical hallmark is abdominal pain that precedes claudication of the lower extremities.

Aortic Aneurysm

Clinical Features. An aneurysm of the abdominal aorta can cause very severe pain, particularly when rupture is imminent. In many cases a pulsating swelling of the aorta, up to the size of a small fist can be palpated in the region of the left midabdomen. Compression or occlusion of the arteries originating from the aneurysm causes mesenteric and/or renal ischemia, occasionally paraparesis or arterial emboli.

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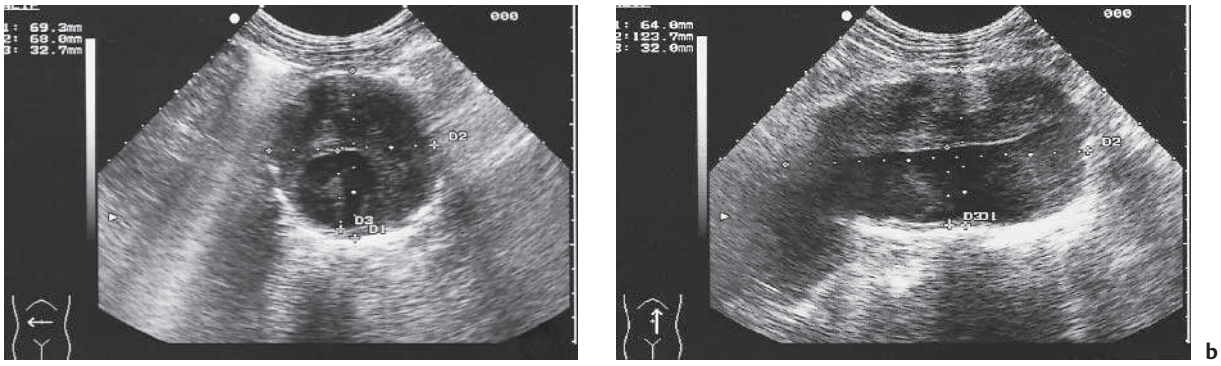

Fig. 7.**8** Ultrasound showing a partially thrombosed, infrarenal aortic aneurysm. Cross section diameter 6.8 cm.

a Cross section
b Longitudinal section

Diagnosis. A systolic murmur can occasionally be detected by auscultation above the aneurysm. The diagnosis is confirmed by sonography, CT, or aortography (Fig. 7.**8**).

The most frequent cause of infrarenal aortic aneurysm in older people is arteriosclerosis. It is about three times more common in men than in women. The symptoms are indeterminate: palpation of a pulsating swelling and unclear back pain. The most important complication is rupture with hemorrhage into the retroperitoneum, the abdominal cavity or the gastrointestinal tract, particularly in the third part of the duodenum.

Aortic dissection, which mostly starts from the thoracic aorta, causes abdominal symptoms in about 25% of cases. The type of symptom depends on the localization. High blood pressure (despite a shock-like clinical picture) and acute epigastric pain are signs of aortic dissection (see Chapter 9).

Thrombosis of the Mesenteric and Portal Veins

The onset of pain in *mesenteric venous thrombosis* is generally less acute than in arterial occlusion. The pain is continuous and can be very severe. Intestinal necrosis manifests itself after some days. In contrast, melena appears immediately, earlier than with arterial occlusion. The diagnosis is frequently made during surgery.

Acute portal vein thrombosis is rare, and almost always associated with abdominal diseases (surgical procedures, appendicitis, pancreatitis, etc.). It often causes a high fever, severe, uncharacteristic abdominal pain, primarily in the right epigastric region, low-grade defense, bloody diarrhea, and splenomegaly.

Splenic Pain

Splenic Infarction. Acute abdominal symptoms are observed with splenic infarction, due to endocarditis, atrial fibrillation as a manifestation of embolic disease, or in marked splenomegaly from various causes. Sudden pain and moderate tension of the abdominal wall in the left upper quadrant, intensified by respiratory excursions, and shoulder pain (phrenalgia) are suggestive of splenic infarction. Circumscribed pain upon palpation and perisplenic friction sounds, occurring after 1–2 days, are useful diagnostic criteria.

Splenic Rupture. Rupture of the spleen (e. g., in malaria, abdominal typhus, after trauma) manifests itself by severe left upper quadrant pain, shoulder pain, and hemorrhagic shock.

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Retroperitoneal Pain

Pain that originates from the retroperitoneal region generally radiates to the back, the lumbar region on both sides of the spinal column, and, more rarely, to the flanks and ventrally.

Spinal diseases must be excluded first.

Classification. Retroperitoneal pain can be classified as follows:

- acute or chronic
- caused by benign or malignant diseases
- caused by renal or nonrenal diseases.

The transitions are smooth, particularly because ureteral blockage is a very common cause of retroperitoneal pain, and can generally be diagnosed by sonography, intravenous urography, CT or MRI.

Causes. Important causes are:

- nephrolithiasis or urolithiasis with typical ureteral colic
- papillary necrosis
- hydronephrosis of various etiologies.

Retroperitoneal Fibrosis

The clinical picture of retroperitoneal fibrosis can be associated with severe lower back pain.

It can be classified into:

- *the idiopathic form:* Ormond disease
- *symptomatic retroperitoneal fibrosis:* Ormond-like alterations resulting from:
  - inflammatory processes (e. g., pancreatitis, distal ileitis, diverticulitis, tuberculous spondylitis, appendicitis, inflammatory aortic aneurysm)
  - tumors (malignant lymphomas, lymph node metastases [e. g., testicular tumors, consequences of radiation therapy])
  - certain drugs (e. g., methysergide).

The fibrosis may result in unilateral or bilateral *ureteral obstruction* with the corresponding consequences.

Differential Diagnosis. If there is no ureteral obstruction, the following causes of retroperitoneal pain must be considered:

- acute appendicitis of retroperitoneal appendix
- psoas abscess
- renal infarction
- retroperitoneal hematoma (e.g., in patients receiving anticoagulants)
- Wilms tumors (in children)
- aortic dissection
- vertebrogenic causes (disk disease, spondylitis).

Abdominal Pain from Intoxication and in Systemic Diseases

Intoxication

Severe colicky diffuse abdominal cramp pain occurs in *lead poisoning*. The abdomen may be tense but remains compressible and there is no particular pain upon palpation. There is no rebound tenderness. In principle, all heavy metals can cause abdominal pain.

Abdominal pain associated with *thallium poisoning* is similar to that of lead poisoning and porphyria, which is characterized by persisting obstipation and an intermittent pattern (see below).

Porphyrias

Porphyria should be considered in patients with unclear recurring abdominal pain. A positive family history and intermittent occurrence are typical. In some cases the pain can be triggered by drugs and is associated with neurologic and dermatologic manifestations (photosensitivity). Abdominal colic due to porphyria is frequently misinterpreted, resulting in a surgical intervention.

Pathogenesis. Porphyrias are hereditary disorders of heme metabolism (Fig. 7.**9**). Porphyrias are classified according to the site of overproduction and accumulation of porphyrin precursors into hepatic and erythropoietic forms (Tab. 7.**7**). Similar abdominal colics are observed with acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). All three forms can be triggered by *drugs*. Signs of cutaneous *photosensitivity* are found with HCP, VP, porphyria cutanea tarda (PCT), and the erythropoietic

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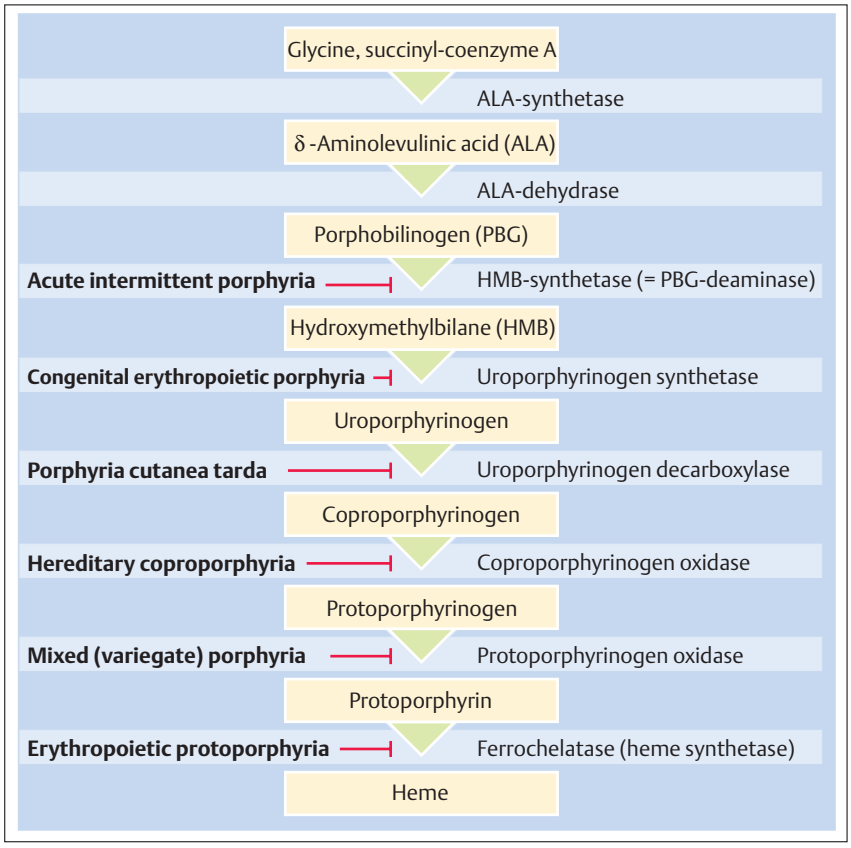

Fig. 7.**9** Heme synthesis and enzyme defects causing hepatic and erythropoietic porphyrias.

Table 7.**7** Differential diagnosis of porphyrias (modified from Desnick and Anderson 1995)

Porphyria	Enzyme defect	Inheritance	Cutaneous photosensitivity	Neurovisceral symptoms	Erythrocytes	Urine	Stool
Hepatic porphyrias							
– acute intermittent porphyria	HMB synthetase	AD	–	+	–	ALA, PBG	–
– hereditary coproporphyria	Coproporphyrinogen oxidase	AD	+	+	–	ALA, PBG, coproporphyrin	Coproporphyrin
– mixed (variegate) porphyria	Protoporphyrinogen oxidase	AD	+	+	–	ALA, PBG, coproporphyrin	Coproporphyrin, protoporphyrin
– porphyria cutanea tarda	Uroporphyrinogen decarboxylase	AD	+	–	–	Porphyrins (ALA and PBG normal)	Porphyrins
Erythropoietic porphyrias							
– congenital erythropoietic porphyria	Uroporphyrinogen synthetase	AR	+++	–	Uroporphyrin I	Uroporphyrin I	Coproporphyrin I
– erythropoietic protoporphyrias	Ferrochelatase	AD	+	–	Protoporphyrin	Protoporphyrin	

Abbreviations see Fig. 7.**9**; AD, autosomal dominant; AR, autosomal recessive.

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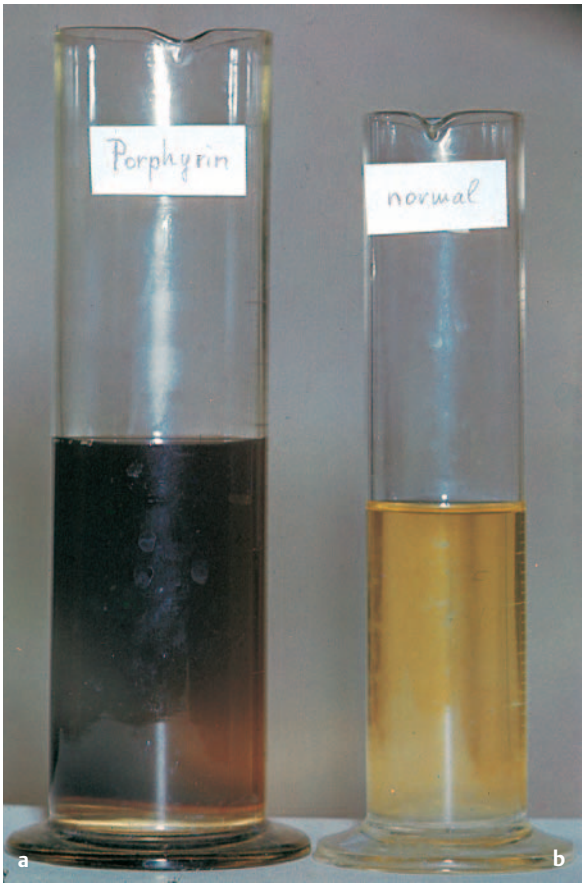

Fig. 7.**10** Urine
a Porphyrinuria
b Normal

porphyrias. In recent years the enzyme defects and underlying genetic mutations responsible for the various forms of porphyria have been identified.

Hepatic Porphyrias

The most important forms of hepatic porphyria are AIP, HCP, VP, and PCT.

Acute Intermittent Porphyria. AIP generally becomes symptomatic in the third decade of life, very rarely before puberty, and is uncommon after the age of 60. The ratio of men to women affected is 2 : 3. *Abdominal colic* (patients are frequently subjected to laparotomy several times before diagnosis), often accompanied by constipation or ileus, nausea, vomiting without palpation-sensitive abdomen, *motor paralysis* as part of a primarily peripheral neuropathy, and *cerebral symptoms* characterize the variable clinical picture. Often only a slight muscular weakness can be noted. All muscles, including the facial muscles, may be affected. Ascending paralysis occurs. Affection of the respiratory muscles may cause respiratory insufficiency. Paresis may recede. Epileptiform attacks and psychiatric symptoms (anxiety attacks, sleeplessness, depression, hallucinations, etc.) are not unusual. Additional symptoms are *tachycardia*, *hypertension*, fever, and moderate leukocytosis.

Typically, acute attacks are triggered by *barbiturates* and other drugs (e.g., sulfonamides, pyrazolone, ergotamine preparations, succinimide, carbamazepine). Alcohol, weight-reduction diets, and endogenous or exogenous sex hormones can also trigger an episode. The urine excreted during an attack darkens and does not lighten after a few hours, in contrast to normal urine with urobilirubin (Fig. 7.**10**). Increased excretion of δ-aminolevulinic acid (ALA) and porphyrobilinogen (PBG) in the urine during an acute episode are diagnostic. Unlike HCP and VP, porphyrin excreted in the stool in AIP is generally normal.

In the latent stage diagnosis can be made by the detection of reduced hydroxymethylbilane (HMB) synthetase activity in the erythrocytes.

Hereditary Coproporphyria. Triggering factors, as well as neurovisceral and other symptoms, correspond to those of AIP. Skin photosensitivity is similar to that of VP and PCT. The excretion of coproporphyrin in urine and stool is increased during acute attacks, but often also in the interval. ALA and PBG excretion in the urine is increased during the attacks.

Variegate Porphyria. The incidence of VP among the white population in South Africa is 0.3 %, but it is rare in the Western world. Triggering factors and neurovisceral and other symptoms are similar to those of AIP. Cutaneous photosensitivity is similar to that of HP and PCT. The excretion of ALA, PBG, and coproporphyrin in urine and of coproporphyrin and protoporphyrin in the stool is increased.

Porphyria Cutanea Tarda. PCT is the most common form of porphyria and is observed almost exclusively in men. The skin manifestations (photosensitivity) are dominant (Fig. 7.**11**). Neurologic manifestations and abdominal pain are not observed. Different types are distinguished, but all have a defect of the hepatic uroporphyrinogen decarboxylase in common. Various factors can contribute to reduced enzyme activity, particularly alcohol use, hepatic iron overload, and estrogens.

Chronic liver diseases (fatty liver, fibrosis, cirrhosis) are frequent and may dominate the clinical picture. Patients with PCT have an increased risk of development of hepatocellular carcinoma. An association with chronic hepatitis C has been described.

Porphyrins in the urine and stool are increased. ALA and PBG excretion in the urine is typically normal.

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Erythropoietic Porphyrias

The most important erythropoietic porphyrias are congenital erythropoietic porphyria (CEP) and erythropoietic protoporphyria (EPP).

Congenital Erythropoietic Porphyria. This is an autosomal recessively inherited disease characterized by hemolytic anemia, high-grade photosensitivity of the skin, and accumulation of the type I isomers of uroporphyrin and coproporphyrin. Marked skin changes with blisters, followed by scars and dystrophic changes of body parts exposed to the light dominate the clinical picture, and occur shortly after birth. The red urine contains primarily uroporphyrin I and somewhat less coproporphyrin I. The ratio is reversed in the stool. ALA and PBG excretion is normal. Hemolytic anemia with ineffective erythropoiesis and splenomegaly are typical.

Erythropoietic Protoporphyria. EPP is the second most common form of porphyria after PCT. It is an inherited autosomal dominant disease caused by a defect of ferrochelatase. Protoporphyrin accumulates in the erythrocytes and in the plasma and is excreted in bile and stool. The symptoms are generally mild, transitory skin changes after exposure to sunlight (itching, burning, reddening, urticaria) but may vary from patient to patient and during the course of the disease. Blisters are rare compared with other porphyrias with skin photosensitivity. Hemolysis or anemia is generally not present or only mild. In some patients the accumulation of protoporphyrin causes chronic liver disease. Increased protoporphyrin in the erythrocytes and protoporphyrin in the stool are diagnostic. The urine is normal.

Lead Poisoning. Lead poisoning causes a special form of porphyrinuria. In children, encephalopathy is dominant, whereas in adults colics and neuromuscular manifestations predominate. The lead seam on the gums is also typical. Lead anemia is due to hemolysis, caused by direct damage of erythrocytes and inhibition of erythropoiesis. The relative involvement of these two mechanisms is variable. Reticulocytosis can be marked or absent. The characteristic basophile punctation of the erythrocytes corresponds to altered ribosomes. Longer-lasting subclinical intoxication can cause deficiencies in intellectual development in children and renal insufficiency in adults. Lead inhibits heme synthesis at various levels (ALA synthetase, ALA dehydrase, ferrochelatase). Increased ALA excretion is a typical symptom. Coproporphyrin III excretion is also increased. PBG excretion is generally normal, or at most moderately increased. Erythrocyte protoporphyrin is markedly increased. Diagnosis is confirmed by an increased lead level in the blood or an increased lead excretion in the urine and stool.

Fig. 7.**11** Porphyria cutanea tarda; blistering, crust formation with healing blisters, changing pigmentation on the back of the hand.

Abdominal Pain in Other Medical Diseases

Abdominal pain occurs not only with local diseases, but can also be the leading symptom of many general diseases. The most frequent general diseases that must be considered here are listed below.

Metabolic and Endocrine Diseases. *Diabetic precoma* is frequently accompanied by severe abdominal pain primarily localized in the epigastric region, and accompanied by severe vomiting. The differential diagnoses, therefore, include perforated ulcer, cholecystitis, and acute pancreatitis. Leukocytosis is common in all these conditions.

Patients with acute *endocrinologic disorders* also frequently experience abdominal cramps, often associated with vomiting or diarrhea. In particular, thyreotoxicosis, acute hyperparathyroidism, and pheochromocytoma must be considered in the differential diagnosis of abdominal cramps.

Very severe abdominal pain can also be observed in familiar *hyperlipidemia* (type I, IV, V). If hyperlipidemia is associated with a surgical abdomen, the clinician must search for additional signs: xanthomas, lipemic retinitis, and rarely hepatosplenomegaly. Triglycerides are significantly increased in serum, giving rise to its milky appearance.

Transient hyperlipidemia in alcoholics associated with jaundice and hemolytic anemia (*Zieve syndrome*;

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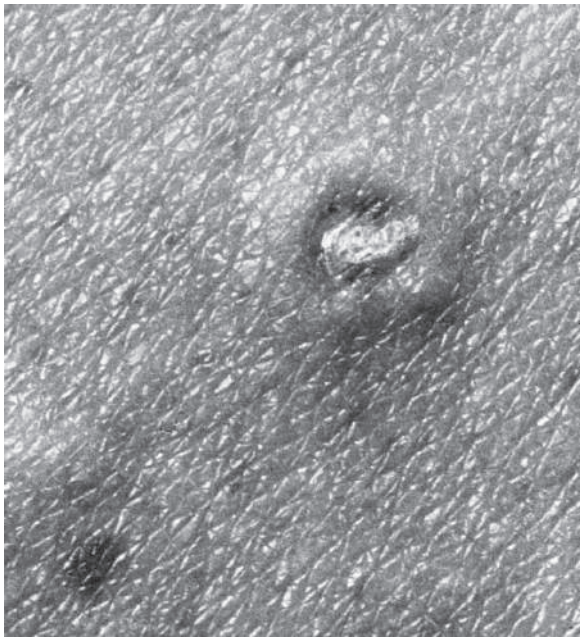

Fig. 7.**12** Skin changes with Köhlmeier–Degos syndrome (malignant atrophic papulosis). Late stage with pale center and clearly visible elevated borders.

see Chapter 25) may also lead to severe epigastric pain. Similar acute pain is observed with *alcoholic hepatitis* (see Chapter 25).

Chest Diseases. Pain radiating to the epigastric region is frequent with *myocardial infarction*, particularly with posterior myocardial infarction. The diagnosis is straightforward if chest pain is concomitant. It is often overlooked, however, if the pain is exclusively localized in the epigastric region. ECG and laboratory tests usually confirm the diagnosis.

Acute pulmonary diseases, particularly pleuritis, pneumonia, spontaneous pneumothorax, and pulmonary embolism (infarction), can cause abdominal pain. A chest x-ray is usually diagnostic.

Small amounts of free air under the diaphragm can be better detected in the chest x-ray than in the abdominal view.

Vascular Diseases. See Chapter 9.

Liver Diseases. Severe epigastric pain is observed occasionally with various liver diseases, particularly with acute right-sided heart failure, alcoholic hepatitis, and neoplasias of the liver.

Collagen Diseases. These can cause abdominal pain by involving small and medium-sized vessels. Vascular occlusion in *systemic lupus erythematosus* or *panarteritis nodosa* results in infarctions (e. g., splenic, pancreatic) or ulcers in the gastrointestinal tract, and corresponding complications (e. g., hemorrhage, perforation, stenosis).

Abdominal pain is also observed with various rheumatic-allergic diseases, such as *Henoch–Schönlein purpura* and in *Behçet syndrome*.

Indeterminate gastrointestinal complaints and signs of ileus, perforation, and peritonitis may be observed primarily in young men with *Köhlmeier–Degos syndrome*. Diagnostic hallmarks are skin changes (*malignant atrophic papulosis*) that usually precede gastrointestinal symptoms. The reddish papillae appear on the trunk and the proximal parts of the extremities over days to weeks, they become pale in the center and are surrounded by a slightly raised violet ring with teleangiectasia (Fig. 7.**12**). The cause of the underlying obliterating endothelial reaction of the small arteries, arterioles, and veins is unknown. This rare disease is usually lethal.

Hematologic Diseases. Abdominal pain in patients with primary hematologic diseases is often caused by complications such as cholelithiasis in congenital spherocytosis, nephrolithiasis in leukemia, splenic infarction in polycythemia, retroperitoneal or intestinal hematoma in coagulation disorders.

Allergic Diseases. With severe allergic reactions (e. g., serum sickness) abdominal pain may precede other allergic symptoms (e. g., skin changes) in the form of severe continuous pain in the kidney region or as cramplike pain in the epigastric and hypogastric regions.

Infectious Diseases. Abdominal symptoms are frequent in most acute infections and range from loss of appetite to severe pain. The pain associated with Bornholm disease may occasionally be localized primarily in the abdominal region. Abdominal pain may occur in various parasitic infections, particularly trichinosis, ascaridiasis, trichiuriasis, and tapeworm infection (see Chapters 4, 27).

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Neurogenic Abdominal Pain

Abdominal pain may also be a manifestation of a neurologic disease. The following syndromes should be considered:

- tabes dorsalis (tabetic neurosyphilis)
- intercostal neuralgia
- proximal asymmetric diabetic neuropathy
- entrapment neuropathy of an anterior ramus of a spinal nerve (T7–T12)
- pudendal neuralgia
- coccygodynia
- radicular syndrome
- herpes zoster

Clinical and Differential Diagnostic Considerations. Neurogenic abdominal pain can best be distinguished by the type of pain.

- The stereotypical shooting pain of *tabes dorsalis*, mostly in the mammary region, is rare.
- As indicated by its name, *intercostal neuralgia* primarily manifests itself with shooting pain, always at the same site. Coughing and sneezing or pressure on the lateral cutaneous ramus sometimes causes pain at its passage. The cause of the pain may be a benign chronic compressive radiculopathy from spinal vertebra that have fused due to degenerative processes, from thoracic disk hernia, rib fracture or thoracotomy. Malignant compressive radiculopathy from metastases, meningeal carcinoma, Schwannoma, or a tuberculous lesion should be considered.
- Only in the rare *"shingles without shingles"* will the acute herpes zoster pain pose diagnostic problems. The abdominal pain precedes blister formation by days. *Borreliosis* also causes intensive and acute pain in the midsection but without skin changes and can be diagnosed by serology.
- *Asymmetric diabetic proximal neuropathy* (*radiculopathy*) is frequently not diagnosed. Like borreliosis radiculitis, it frequently begins unilaterally and later appears contralaterally, and tends to occur segmentally, to be localized in the abdominal region and often lasts for months. Many abdominal signs and symptoms are mistakenly attributed to borreliosis because of the frequent severe pain upon touching the skin, with allodynia or hyperpathia. Importantly, diabetes may be only mild. Asymmetric diabetic neuropathy is often associated with a distal symmetric polyneuropathy.
- A *neuropathy of the anterior rami of spinal nerves T7–T12* by compression of the rectus abdominis muscle or by overextension (e.g., during pregnancy) may cause pain near the abdominal midline. A predisposing polyneuropathy must be considered with such unusual pressure or compression neuropathies.
- Perineal and genital lancinating or burning pain with itching, numbness, or painful sensitivity to touch indicate *pudendal neuralgia* due to a lesion of one or both pudendal nerves, rarely also with an initial caudal or plexus process. Sitting becomes painful and sexual activity impossible. Etiologic factors are obstetric procedures, gynecologic, urologic or proctologic conditions, surgery, perforating trauma, and excessive horse or bicycle riding. Unlike pudendal neuralgia, genitofemoral neuralgia (ventrally) and coccygodynia (dorsally) do not affect the perineal region.
- *Coccygodynia*, burning pain at the coccyx caused in part by (secondary) arachnoidal growth of sacral nerve roots, has primarily mechanical causes such as a direct fall on the coccyx, microtraumatization (television bottom), or surgical procedures. Nerve blockade or local anesthesia often allow differentiation of this pain.
- Pain in the abdominal region is also frequently part of a *radicular pain syndrome* in various spinal disorders, particularly spondylarthritis, discopathy, Bechterew disease, osteoporosis, etc.

7.2 Chronic or Recurring Abdominal Pain

More than half of all patients with chronic abdominal pain suffer from functional disorders, particularly irritable bowel syndrome (IBS). Years of intermittent abdominal in healthy, frequently younger, patients, occurring during daytime only and often combined with other functional disorders, indicates IBS.

> The diagnosis of functional disorders requires exclusion of somatic diseases.

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General Considerations on the Character of Long-Term Epigastric Pain

The medical history of most patients with abdominal pain suggests the probable diagnosis. This is important for the diagnostic strategy.

Pain Analysis. A complete pain analysis always includes the following four *cardinal questions*:
- Where?
- How?
- When?
- Why?

Localization and Radiation. Conclusions can frequently be drawn from the localization and type of pain. Pain due to organic conditions (e. g., ulcers, cholelithiasis, pancreatitis) is generally circumscribed, unlike pain due to functional disorders. Radiation of the pain to the shoulder indicates cholelithiasis, to the inguinal and genital region nephrolithiasis, to the back, pancreatic diseases, aortic aneurysm, or ulcer penetration).

Position and Movement Dependence. Increased pain while lying down occurs with reflux disease and pancreas diseases. More intense pain while standing occurs with hernias. Increased pain with movement indicates abdominal wall processes (such as trauma), vertebrogenic pain (such as discopathy), or reflux disease.

Nutrition Dependence and Periodic Occurrence. Accentuated pain after eating is typical for cholelithiasis, pancreatitis, abdominal angina, IBS, and gastrointestinal stenoses. The typical periodicity of the most frequent causes of pain is summarized in Fig. 7.**13**.

Diurnal Rhythm. A typical diurnal rhythm can frequently be detected with ulcers and IBS. The following are characteristic for *ulcer pain*:
- occurrence one to two hours postprandial
- never in the morning before eating
- spontaneous pain at midnight
- quick improvement with milk, antacids, or food (food relief).

The following are characteristic for IBS:
- immediately postprandial
- often in the morning on getting up
- never at night
- never during abstention from food.

Pain Originating from the Stomach and Small Intestine

Distribution. Pain originating from the stomach and small intestine can be generally classified as follows:
- ➤ acute and chronic gastritis
- ➤ functional gastric disorders (gastric irritation)
- ➤ ulcerous disease (duodenal ulcer, gastric ulcer)
- ➤ gastric carcinoma
- ➤ rare disorders
- ➤ complaints secondary to general diseases.

Diagnosis. The differential diagnosis is based on the *medical history*, clinical findings, *imaging* (endoscopy, radiologic examination), and biopsy with a histologic analysis.

A detailed medical history is particularly important in gastric diseases. Functional stomach disorders (irritable stomach) are characterized by their relatively indefinite character. They generally occur irregularly and have no periodicity (see Fig. 7.**13**). The pain is frequently accentuated immediately after eating.

Endoscopy is most important for diagnosis of obscure epigastric pain, dysphagia, heartburn, and gastrointestinal bleeding. Another indication is an unclear iron deficiency anemia. *Radiologic examinations* are helpful, particularly in cases of paraesophageal hiatus hernia, motility disorders, Zenker diverticulitis, external compression, or stenoses that cannot be detected endoscopically. Endosonography can be used to detect intramural processes, especially the extent and depth of infiltration of neoplasms, as well as lymph node metastases.

Acute Gastritis

Clinical Features. The clinical picture with acute gastritis is characterized by a diffuse pressure that can increase to intense pain in the stomach region. Eating intensifies the pain. Vomiting often brings relief. The complaints resolve over a few hours to days. The stomach symptoms are frequently accompanied by intestinal manifestations (meteorism, diarrhea).

Erosive gastritis is an important cause of hematemesis (Fig. 7.**14**).

Causes. Apart from infections (primarily *Helicobacter pylori*, very rarely other bacterial [phlegmonous, mycobacterial, luetic gastritis], viral [herpes simplex virus, cytomegalovirus; particularly with AIDS], parasitic or fungal causes), the causes of acute gastritis are: food poisoning (*Staphylococcus aureus* toxin), alcohol, stress (surgery, serious trauma, shock) and in particular drugs, primarily nonsteroidal antirheumatics (e. g., salicylates,

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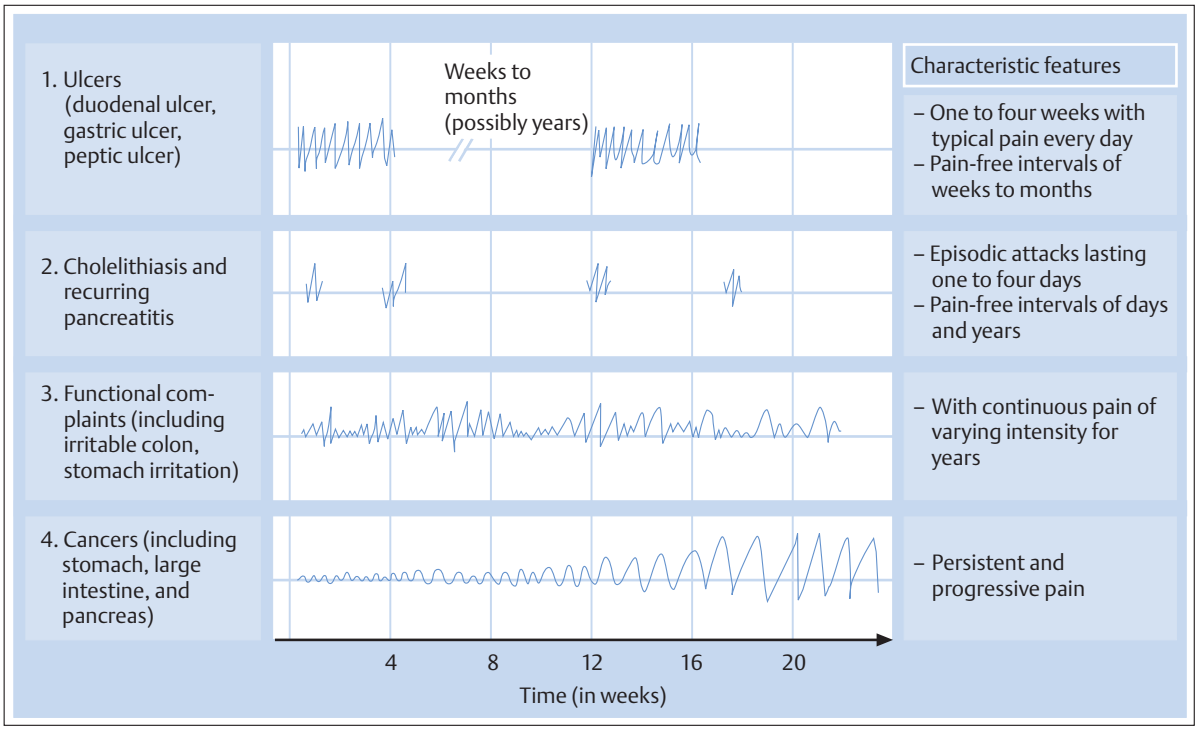

Fig. 7.**13** Typical period of the most common causes of chronic (recurring) upper abdominal pain.

phenylbutazone, indomethacin), corticosteroids, and cytostatic drugs.

Differential Diagnosis. Gastritis is often interpreted as primary, although it is frequently an expression of a more *general disease*. The following diseases present with gastric complaints and must always be considered in differential diagnosis:

- Any serious general disease can show symptoms indicating a stomach disease, such as nausea, belching, loss of appetite, and possibly vomiting.
- These symptoms are particularly frequent in chronic uremia.
- Acute or chronic liver diseases (e. g., due to chronic alcohol abuse) are frequently accompanied by gastric complaints.
- Congestive gastritis, as a manifestation of cardiac insufficiency or portal hypertension, must be considered in patients with cardiac or hepatic disease.
- Among drugs, "digitalis gastritis" in cardiac patients disappears a few days after stopping therapy.
- Allergic gastritis, as a consequence of hypersensitive reactions to food, particularly milk, chocolate, yeast, nuts, citrus fruit, strawberries, shellfish, etc., occurs primarily as part of a generalized gastrointestinal reaction with diarrhea and pain, in some cases combined with systemic symptoms (e. g., tachycardia, drop in blood pressure, asthma, headache, urticaria).

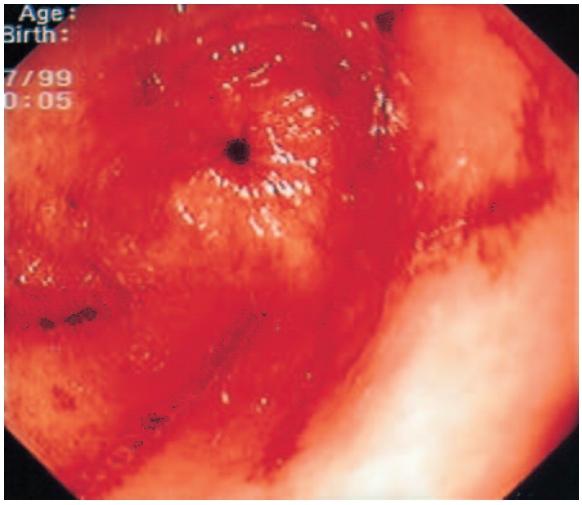

Fig. 7.**14** Marked gastritis with erosion of the pylorus.

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Chronic Gastritis

Type A, B and C gastritis must be distinguished.

Type A Gastritis. Type A gastritis (autoimmune gastritis) primarily affects the gastric body and fundus. It is caused by autoimmune processes. It is typically associated with pernicious anemia. Autoantibodies against parietal cells and intrinsic factor are typical. Gastrin is increased. The risk of development of a gastric carcinoma is significantly increased in chronic-atrophic type A gastritis. Endoscopic surveillance is therefore indicated.

Type B Gastritis. Type B gastritis (bacterial gastritis) is primarily localized in the gastric antrum and is typically caused by *Helicobacter pylori* (Hp). It is more common than type A gastritis and is associated with gastric ulcers, duodenal ulcer, and mucosa-associated lymphoid tissue (MALT) lymphoma.

Type C Gastritis. Type C gastritis (chemical gastritis) is caused by chemical irritation, i. e., reflux of bile (bile gastritis) or duodenal contents (reflux gastritis) and most importantly drugs, in particular use of NSAIDs (NSAID gastropathy).

Rare Cases of Gastritis. Rare, chronic forms of gastritis are lymphocytic, eosinophilic, and granulomatous gastritis.

Diagnosis. Chronic gastritis can only be confirmed by histology. There is no clear relationship to typical clinical symptoms. The majority of patients with histologically demonstrated chronic gastritis are asymptomatic.

Irritable Stomach (Functional Dyspepsia)

Continuous epigastric pain, loss of appetite, nausea, and frequent vomiting are the main symptoms. Eating tends to exacerbate the symptoms and there is generally no periodicity or diurnal rhythm. This information from the medical history generally distinguishes this complaint from an ulcer. The lack of the typical endoscopic changes with irritable stomach is decisive for differential diagnosis.

Ménétrier Disease

Ménétrier disease (giant hypertrophic gastritis) is characterized by bulging rigid stomach folds (similar in appearance to the brain). It is caused by a massive foveolar hyperplasia. Secondary inflammatory changes also frequently occur. Clinically, patients complain of epigastric pain and vomiting. Frequently, a protein loss occurs (exudative enteropathy) resulting in hypoproteinemic edema. The cause of the disease is unknown. It may be difficult to differentiate it from intramural solid tumors (Fig. 7.**15**).

Fig. 7.**15** Ménétrier disease in a 31-year-old woman. The large, rigid abdominal folds imitate an infiltrative abdominal wall process.

Ulcers

The central feature of ulcers is infection with *Helicobacter pylori* (Hp). There has been a radical change in the understanding of ulcers. The eradication of the Hp infection in patients with ulcers not only heals the acute lesion but generally prevents recurrence and complications of ulcers. Only about 10 % of patients infected with Hp in industrialized countries develop an ulcer, but 95 % of patients with a duodenal ulcer are infected with Hp.

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This indicates that Hp infection alone is not sufficient to cause an ulcer. Hp generates conditions that, together with additional risk factors, cause an ulcer: stress, smoking, and a genetic predisposition.

***Helicobacter pylori* Detection.** The presence of Hp can be confirmed

- *histologically* by Giemsa or Warthin–Starry staining of gastric antrum biopsies
- by *urease activity* either with a fast urease test in the biopsy specimen or an exhalation test with ^{13}C or ^{14}C-labeled urea
- by *culture* from gastric antrum biopsies
- by *serology:* serology is, however, not generally useful, because Hp colonizes approximately 10% of persons under 30 and approximately 60% of persons of 60 years, while only 10% of infected persons develop an ulcer.

Clinical Features and Differential Diagnosis. Strongly *localized pain* is characteristic for ulcers, as compared to irritable stomach and acute gastritis. In acute gastritis a diffuse pain upon palpation is generally present in the epigastric region. Many patients with ulcers can point to the exact location of the spontaneous pain and the pain upon palpation. The maximum pain is to the left of the abdominal mid-line with gastric ulcers and to the right with duodenal ulcers.

The character of the pain is important in differential diagnosis versus biliary colic (period and diurnal rhythm of the pain; see Fig. 7.**13**). The pain characteristics and the diurnal rhythm typical for ulcers are particularly important. A biliary colic lasts for one to three days, ulcer pain for three to five weeks. Ulcer pain generally disappears after eating within a few minutes while biliary pain does not. Ulcer pain is virtually never accompanied by nausea while nausea is very frequent with biliary diseases. Appetite is not affected, unlike with gastritis and carcinoma. If the character of the pain is not typical in spite of other signs of an ulcer, the possibility of complications must be considered:

- with continuous and back pain: penetration
- with nausea and vomiting: stenosis.

An ulcer episode, like acute gastritis, can be triggered by stress situations (surgery, serious trauma), alcohol abuse, or drugs (including NSAIDs).

Ulcers occur at all ages, particularly after puberty. Carcinoma incidence increases with age but can also be observed in 20- to 30-year-olds.

Diagnosis. The mainstay of ulcer diagnosis is *endoscopy* (Fig. 7.**16**). Multiple biopsies from and around the ulcer are key for differentiating benign from malignant stomach ulcers.

Radiologic diagnosis is no longer common, but when performed, an *ulcer niche*, may be visible under tangential setting as a contrast agent bulge in the region of the gastric curvature (Fig. 7.**17**). The ulcer niche is visible as a persistent contrast spot in the direct frontal view.

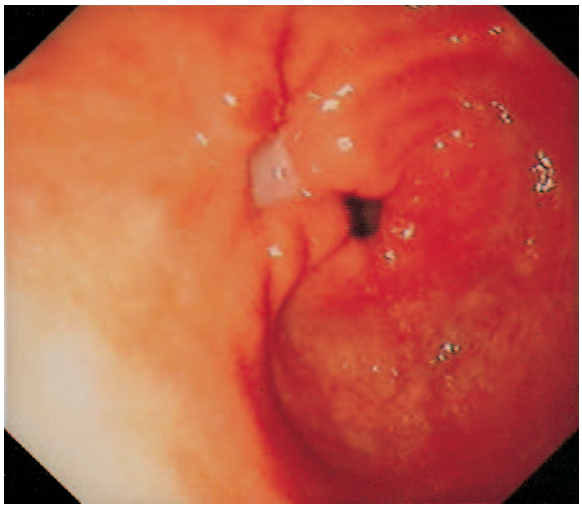

Fig. 7.**16** Prepyloric ventricular ulcer with clear delimitation and reddened edge and marked rugosity in the surroundings.

About 85% of ulcer niches are on the minor curvature of the stomach. The remaining 15% occur at the major curvature, the dorsal wall (back pain), and in the pyloric region. Gastric carcinomas can also form niches. *Indirect ulcer signs* are *spastic retractions* on the wall opposite the ulcer, referred to as ulcer fingers. They are not specific for ulcers, because they are also observed with various tumors. After healing an *hourglass stomach* may develop, which results from shrinkage of the minor curvature by scar tissue and spastic retraction of the major curvature (Fig. 7.**18**).

Duodenal Ulcer

More than 95% of duodenal ulcers occur in the duodenal bulb (pars I; Fig. 7.**19**). Untreated they are characterized by spontaneous healing and recurrence. 60% of untreated cases recur within one year and 80–90% within two years. 95–100% are associated with Hp infection. The main symptom is pain, that typically occurs 90 minutes to three hours postprandial and is relieved by eating (food relief). Asymptomatic ulcers are common. Complications are penetration, particularly into the pancreas (constant pain in the back), stomach outlet obstruction (pain increased postprandially, vomiting), perforation, and hemorrhage.

Postbulbar ulcers are rare. The clinical symptoms correspond to the classical duodenal ulcer, but postbulbar ulcers bleed more frequently.

Gastric Ulcer

The peak incidence of gastric ulcers is in the sixth decade of life and thus about 10 years later than with duodenal ulcers. Men are affected more frequently than

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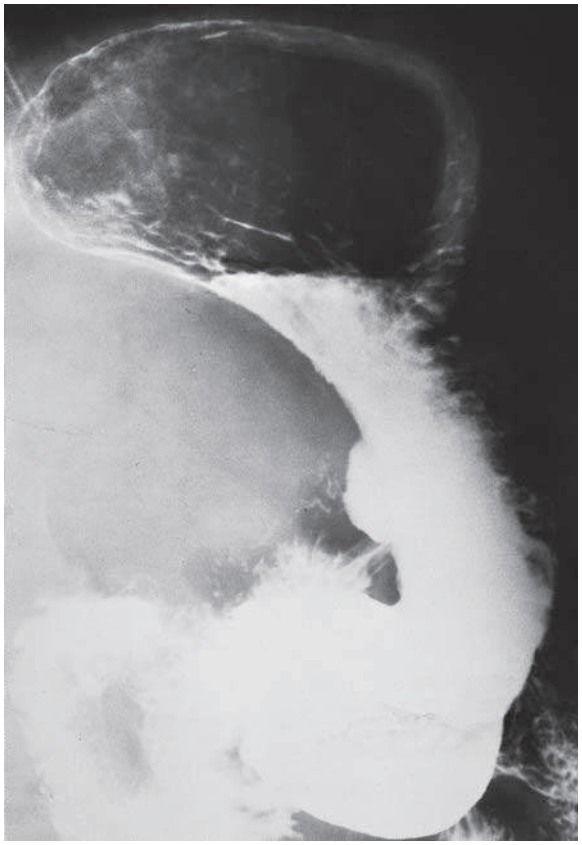


◁ Fig. 7.**17** Large ulcer niche of the minor curvature in a 62-year-old man with gastric ulcer.

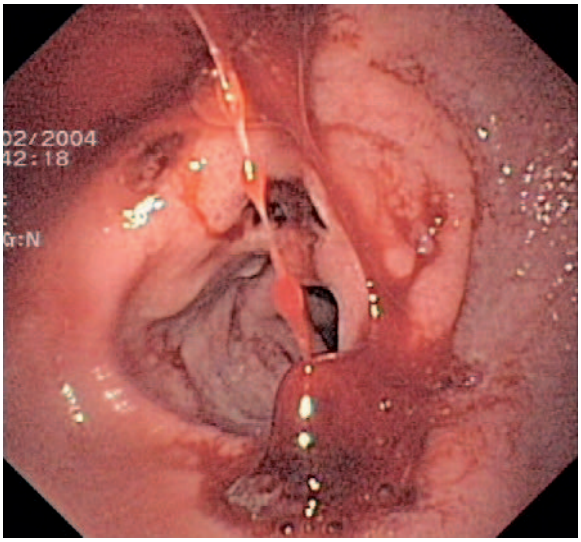
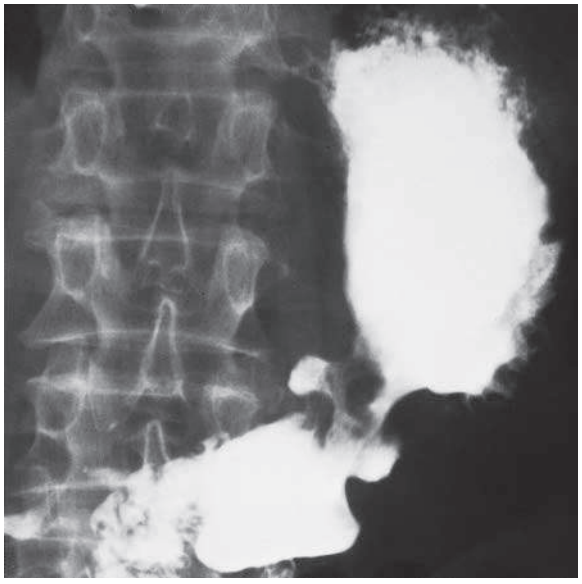


Fig. 7.**19** Multiple duodenal ulcers with active hemorrhage in a 54-year-old woman with *Helicobacter pylori* infection.



a

b

Fig. 7.**18** Gastric ulcer
a Double ulcer in the angulus region (81-year-old man).
b Hourglass stomach after healed gastric ulcer in the same patient, 4 years later.

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women. Benign gastric ulcers are most commonly localized adjacent to the corpus–antrum border. Gastric erosions and ulcers are often caused by NSAIDs. Gastric ulcers not associated with NSAIDs are generally caused by Hp infection. The pain is less typical than in duodenal ulcers and increases after eating. Nausea and vomiting occur even without gastric outlet obstruction, in contrast to the duodenal ulcer. Asymptomatic courses are common.

It is important to note that gastric ulcers, much more commonly than duodenal ulcers, can be caused by carcinoma. Histologic diagnosis is therefore mandatory and the healing must be monitored endoscopically.

Ulcer Associated with Other Diseases

Peptic Ulcer. A peptic ulcer, particularly a duodenal ulcer, is frequently observed in patients with:

- cirrhosis of the liver
- chronic obstructive jaundice
- chronic pancreatitis
- chronic lung disease, especially emphysema
- chronic renal insufficiency
- general arteriosclerosis
- polycythemia vera
- hyperparathyroidism
- systemic mastocytosis.

Peptic ulcers, including gastric ulcers, are frequently observed:

- with NSAID use
- in smokers
- after chemotherapy.

Use of aspirin and other NSAIDs causes gastric ulcers much more frequently than duodenal ulcers. Ulcers and strictures of the small and large intestine also occur.

Stress-induced Erosions. Stress-induced erosions and ulcers are often multiple and frequently occur in areas of the stomach with high activity, after shock, massive burns (Curling ulcer), sepsis, and after serious trauma. Hemorrhage is frequent, particularly in patients on respirators and with coagulation disorders.

Cushing Ulcer. Gastric ulcers frequently occur after brain trauma, brain surgery, or in patients with elevated brain pressure (Cushing ulcer).

Zollinger–Ellison Syndrome. Ulcers are a complication of Zollinger–Ellison syndrome. Gastrinomas (most frequently originating from non-β-pancreatic islet cells or duodenal G cells), through overproduction of gastrin, increase secretion of gastric acid and are thus responsible for the formation of ulcers. Zollinger–Ellison syndrome should be considered in the following situations:

- peptic ulcers with atypical localization (esophagus, postbulbus, jejunal), multiple occurrence (approximately 10%), and resistance to treatment.
- aqueous diarrhea, with or without steatorrhea, with or without hypokalemia and its consequences.
- gastric hypersecretion and increased serum gastrin levels.
- prominent gastric mucosa folds, as with Ménétrier disease
- 25% of cases are associated with multiple endocrine adenomatosis type I (Wermer syndrome). Zollinger–Ellison syndrome must be considered in patients with signs of hyperparathyroidism or hypophyseal tumor. The family medical history is particularly important in view of the inheritance.
- Fasting serum gastrin levels are elevated. Massive hyperchlorhydria and hypergastrinemia (> 1000 pg/mL) are diagnostic. Increased serum gastrin levels are also found in achlorhydria (e. g., pernicious anemia, after vagotomy, stomach resection). In Zollinger–Ellison syndrome serum gastrin levels increase significantly in response to calcium infusion or after secretin administration. These provocation tests are useful for identification of Zollinger–Ellison syndrome in patients with borderline serum gastrin levels (200–1000 pg/mL).

Late Complications of Ulcer Disease

Pyloric Stenosis. Pyloric stenosis is a late complication of chronic recurring ulcers. The character of ulcer pain is changed and loss of appetite occurs. Feelings of fullness and discomfort after meals, which are not present in uncomplicated ulcers indicate stenosis. A stenosis is very likely with vomiting that relieves or cures late pain and with vomiting of food from the previous day. If endoscopic examination identifies empty stomach secretion and food 12 hours after eating, this supports the diagnosis. Food and liquid retention can often be detected by sonography. The diagnosis is confirmed radiologically by slow pyloric passage, dilatation of the stomach, and marked dilution of the contrast agent by stomach secretion and food residues. The nature of the pyloric stenosis (benign or malignant) can generally be defined by endoscopy and histology.

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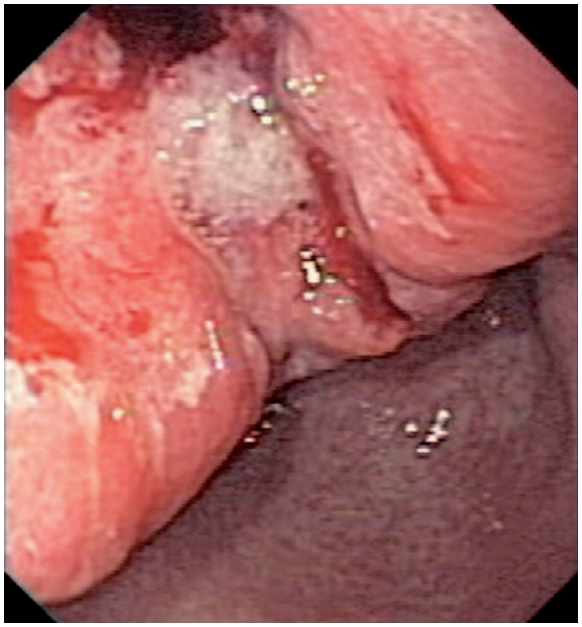

Fig. 7.**20** Exophytically growing ulcerated carcinoma in the prepyloric antrum (moderately differentiated adenocarcinoma).

Gastric Carcinoma

Epidemiology and Risk Factors. 85% of malignant tumors in the stomach are adenocarcinomas. They can grow as space-filling processes or diffusely infiltrate the stomach wall (linitis plastica). Non-Hodgkin lymphoma and leiomyosarcoma are malignant gastric tumors. Nitrates in food, which are converted to carcinogenic nitrites by bacteria, play an important role in the development of the gastric carcinoma. Hp infection also seems to play a significant role. Patients with chronic atrophic type A gastritis are at particular risk for carcinoma. Gastric carcinomas are more frequent in patients with blood group A.

Clinical Features. In contrast to ulcers, the symptoms of gastric carcinoma are less typical. They start slowly, are uncharacteristic, and are not periodic. There is generally no history of stomach complaints. Typical features are the persistence or progression of the complaints and the appearance of general symptoms, particularly weakness (anemia) and weight loss. Iron-deficiency anemia frequently precedes the local symptoms by weeks or months. In contrast to ulcer symptoms, carcinoma pain is not relieved by antacids and is not periodic (see Fig. 7.**13**). In about one-quarter of cases there is no pain, but rather unspecific complaints (feeling of fullness, discomfort, belching, nausea). In other cases the complaints are more diffuse, e. g., loss of appetite and weight loss. Vomiting is typical for tumors in the antrum or cardia. Cardiac carcinoma extending to the esophagus typically causes dysphagia.

Diagnosis. The carcinoma is generally *palpable* only in advanced cases. The early cases are either not sensitive to palpation or present with diffuse pain. A Virchow gland above the left clavicle is typical for advanced gastric carcinoma.

Endoscopy and *histology* are usually diagnostic (Fig. 7.**20**). If endoscopy suggests gastric carcinoma, a negative biopsy does not rule out a carcinoma. Close endoscopic–histologic monitoring is necessary for early detection of gastric carcinoma. Failure of an ulcer to heal after four to eight weeks of medical therapy or early recurrence are indications for a malignant or complicated ulcer.

Detection of early cancer by endoscopy improves prognosis. Early cancer, defined as carcinoma restricted to mucosa and submucosa, is generally cured by surgery.

Hematemesis

Causes. Hematemesis indicates a bleeding mucosal lesion proximal to the duodenojejunal flexure. The main causes of acute upper gastrointestinal bleeding are:

- peptic ulcers
- erosive gastritis
- Mallory–Weiss syndrome
- esophageal varices.

In 80–90% of all cases one of these four diseases is present.

Mallory–Weiss syndrome is caused by tears in the mucosa in the cardia region at the gastroesophageal junction, that generally occur during massive, cramplike vomiting.

Other uncommon causes of hematemesis are:

- esophagitis
- tumors of the gastroduodenal region
- hemorrhagic diathesis
- hemobilia
- hemosuccus pancreaticus
- hemangioma
- Osler disease
- aortointestinal fistula
- mesenteric arterial occlusion
- pseudoxanthoma elasticum.

Hemobilia must be suspected in hematemesis in association with biliary colic or jaundice. The main cause is an abdominal trauma with central or subcapsular liver rupture. In some cases hemobilia may occur months after the trauma. Liver abscess, echinococcus infection, vascular anomalies, liver tumors, and gallstone penetration are other causes of hemobilia.

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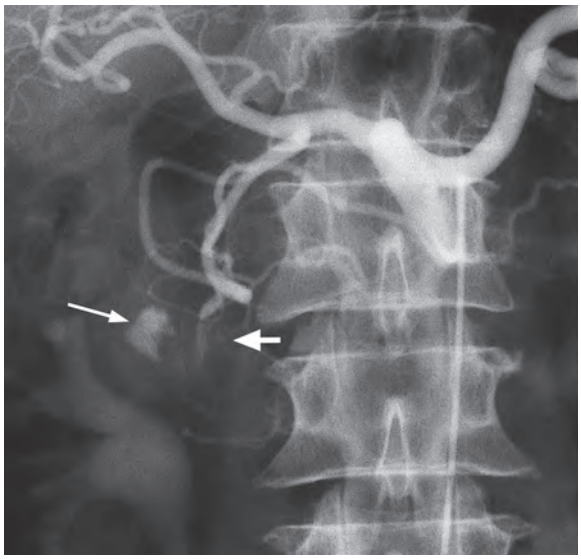

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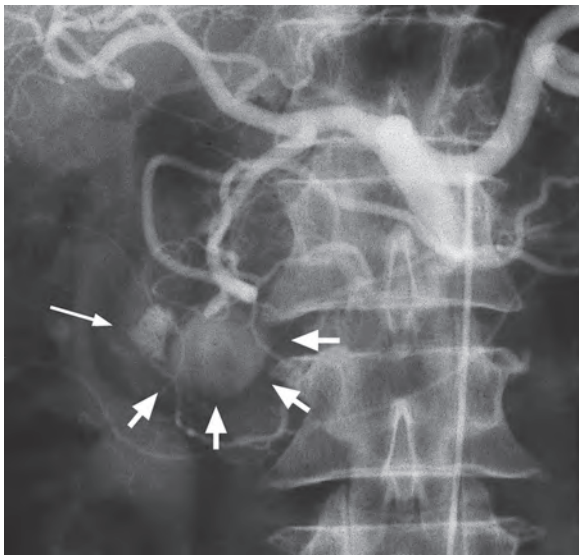

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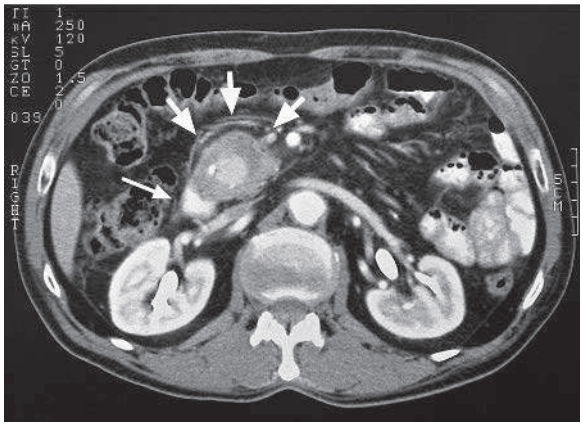

c

Fig. 7.**21** Hemosuccus pancreaticus in a 63-year-old man with chronic pancreatitis.

a, **b** Hemorrhage from the superior anterior pancreatoduodenal artery into a pseudocyst in the head of the pancreas (pseudoaneurysm).

c CT view of the pseudocyst in the head of the pancreas filled with contrast agent. The thin arrow points to a calcification, the thick arrows point to the pseudoaneurysm.

Melena

Causes. Massive tarry stools generally have the same causes as hematemesis.

These are mainly:

- peptic ulcers
- erosive gastritis and Mallory–Weiss syndrome
- esophageal varices
- tumors.

Hematemesis concurring with melena indicates that the source of the bleeding must be proximal to the jejunum. Hematemesis may also be absent in bleeding from the upper gastrointestinal tract. Among others, NSAID therapy must be considered as the cause of hemorrhage. Stress ulcers (particularly after surgical procedures, burns) and hemorrhage due to anticoagulant therapy must be considered.

If melena and no hematemesis are present, all rare sources of bleeding distal from the jejunum must be included in the differential diagnosis.

Various factors affect the occurrence of melena: volume of blood (> 50 mL), intestinal transition time (> 8 h), and effect of hydrochloric acid and intestinal flora on hemoglobin. Rectal bleeding with bright red blood indicates hemorrhage from the colon or distal small intestine (e. g., tumors, diverticula, Crohn disease, ulcerative colitis, angiodysplasia). A massive hemorrhage in the upper gastrointestinal tract may also be associated with bright red rectal bleeding in cases of accelerated intestinal passage. Tarry stools are observed in some cases with hemorrhage from the proximal colon, particularly in case of slow intestinal passage. Any hemorrhagic diathesis, mesenteric arterial and venous thrombosis, or other vascular diseases (e. g., aneurysms, cavernoma, hemangioma) may cause intestinal bleeding.

The effects of specific drugs, particularly *iron formulation*, charcoal preparations, or certain foods in large quantities (e. g., red beets, blueberries) may imitate melena.

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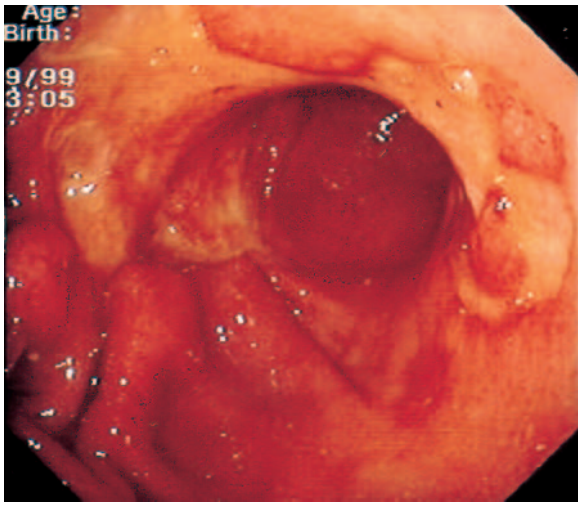

Fig. 7.**22** Non-Hodgkin lymphoma of the stomach. Extensive ulceration in the gastric antrum and body; 70-year-old woman.

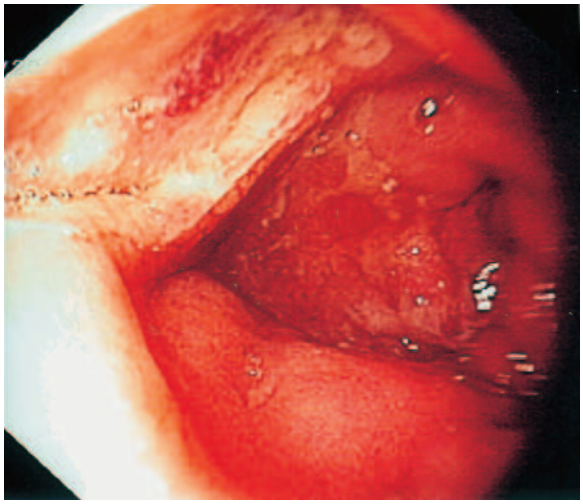

Fig. 7.**23** Extensive ulcer in the duodenal bulbus due to non-Hodgkin lymphoma of the T-cell type; 61-year-old woman.

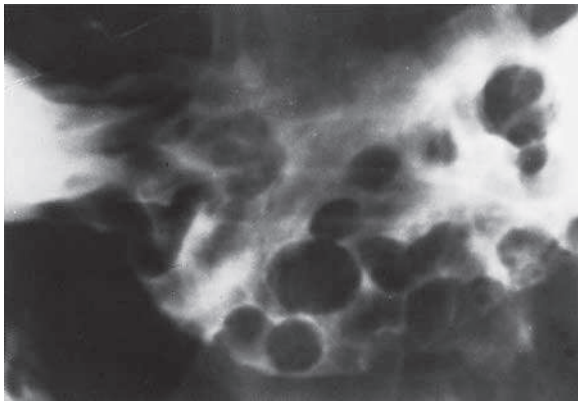

Fig. 7.**24** Intestinal polyposis

Diagnosis. Endoscopy is the method of choice for detection and, if necessary, therapy. An esophago–gastroduodenoscopy followed by, if necessary, a colonoscopy is generally indicated. Angiography for the detection of abdominal hemorrhage is restricted to cases with continuous blood loss of 0.5–2.0 mL/min.

Small intestinal lesions, particularly tumors of the small intestine, are difficult to detect. In cases of intestinal bleeding with negative endoscopic results, tumors of the small intestine should be considered (e. g., schwannoma, leiomyoma, malignant lymphoma, carcinoma). Capsule endoscopy and double balloon enteroscopy are becoming increasingly important in addition to radiologic small intestine imaging, CT and MRI.

Uncommonly recurring blood loss from the pancreas, particularly from a pancreatic pseudocyst in chronic pancreatitis, can be a diagnostic challenge (*hemosuccus pancreaticus*; Fig. 7.**21**).

Rare Gastric Diseases

Malignant Lymphoma. Malignant lymphoma is similar to gastric carcinoma. Primary gastric lymphoma is rare. However, the stomach is the most common extranodal localization of a non-Hodgkin lymphoma (Fig. 7.**22**). The prognosis of malignant lymphoma is significantly better than that of gastric carcinoma. Infection with Hp is associated with the development of gastric lymphoma, particularly the MALT lymphoma. The eradication of the Hp infection causes a regression of the MALT lymphoma in about 50 % of patients.

Lymphoma of the small intestine can also be a complication of sprue (Fig. 7.**23**).

Leiomyoma. This tumor is rare (approximately 1 % of all tumors). The most important clinical symptom is hemorrhage. Endoscopy and radiography show a semispherical, well-circumscribed tumor with central ulceration.

Gastrointestinal Stroma Tumors (GIST). GIST are mesenchymal tumors of the gastrointestinal tract, 60–70 % of which are localized in the stomach. They were until recently frequently classified as leiomyomas or leiomyosarcomas, but have a specific cellular origin and a specific pathogenesis. GIST are identified by mutations of the *cKIT* protooncogene and activation of the KIT receptor tyrosine kinase, and like chronic lymphatic leukemia, respond to treatment with the specific tyrosine kinase inhibitor imatinib mesylate.

Intestinal Polyposis. In contrast to Ménétrier disease, gastric mucosa with intestinal polyposis shows a predominantly normal, smooth aspect with diffusely distributed individual polyps at endoscopy (Fig. 7.**24**). Gastric polyps

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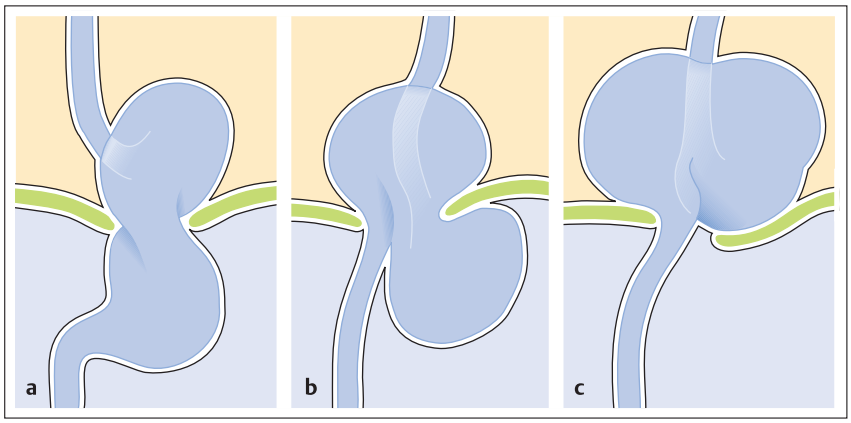

Fig. 7.**25** Paraesophageal hernia with the typical rotation of the major curvature and
a a proximal gastric volvulus
b a distal gastric volvulus
c a total gastric volvulus.

are more frequent in patients with chronic atrophic gastritis, particularly in pernicious anemia. The complaints are uncharacteristic. Depending on the extent and location of the tumors, the polyps may be asymptomatic, may present as gastritis, or result in sudden stenosis. The tumors often bleed, resulting in anemia that may dominate the clinical picture. The diagnosis must be histologically confirmed.

Hamartomatous polyps occur in the colon and the small intestine in *Peutz–Jeghers syndrome* and *juvenile polyposis*. Malignancy is rare compared to familiar adenomatous polyposis, Gardner and Turcot syndromes, and hereditary nonpolyposis colorectal carcinoma.

Very Rare Gastric Diseases. Syphilis, tuberculosis, sarcoidosis, Crohn disease, eosinophilic gastritis, or phlegmonous gastritis are extremely rare causes of gastric complaints. Endoscopy and biopsy are generally diagnostic. With many diseases the diagnosis can only be confirmed if organs other than the stomach are affected (e. g., sarcoidosis, Crohn disease, tuberculosis).

Duodenal Diverticulitis. Duodenal diverticulitis is generally harmless. Sometimes, however, it may cause complaints similar to duodenal ulcers. Annular pancreas must be considered in the differential diagnosis. Periampullar or intraduodenal diverticula originating from the common bile duct may be a rare cause of pancreatitis or cholangitis.

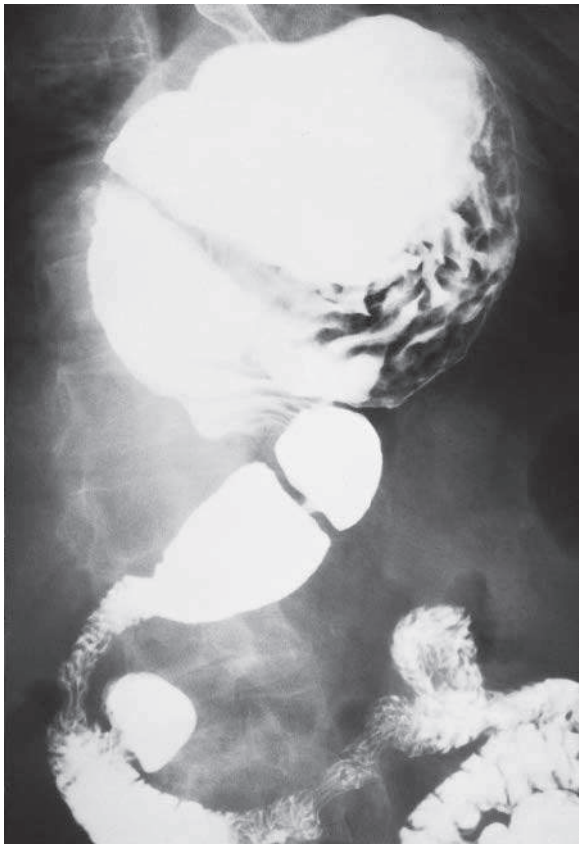

Fig. 7.**26** Large paraesophageal hiatal hernia with "upside-down stomach" in an 83-year-old woman. The radiologic examination shows a total gastric volvulus (see Fig. 7.**25c**).

Hiatal Hernia

Hernia of the viscera through the diaphragm may occur at various sites, particularly in esophageal hernias or congenital or posttraumatic hiatus in the diaphragm. Most common are *paraesophageal* hernias sliding through the esophageal hiatus. A major part of the stomach may be translocated into the chest through the diaphragm. The translocation is usually combined with a chronic gastric volvulus (Fig. 7.**25**). In contrast to a sliding hernia, the paraesophageal hernia may lead to serious complications, particularly strangulation or hemorrhagic anemia. About 30–50 % of patients have no symptoms (Fig. 7.**26**).

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Reflux Esophagitis

See Chapter 26.

Complaints after Gastric Surgery

The following diseases may be encountered in patients after stomach resection:

Preexisting Disease. The preexisting disease was not detected and continues to cause problems after surgery (e. g., IBS, porphyria).

Jejunal Peptic Ulcer. After stomach resection ulcers recur mostly at the anastomosis or immediately distal in the small intestine. The complaints depend on food intake (mostly late pain) and show a periodic course. The pain is primarily localized to the left and is only poorly relieved by antacids. Continuous pain as a result of penetration or hemorrhage is a frequent complication.

Carcinoma of the Gastric Stump. Increased occurrence of cancers can be expected 15–20 years after gastric resection.

Dumping Syndrome. Fast evacuation of the stomach and hypertonic nutrition cause *early dumping syndrome*. The accumulation of hypertonic solutions (particularly sugar) in the jejunum leads to inflow of fluids from the extracellular space into the jejunum and to reduced plasma volume. The distension of the jejunum triggers autonomic reflexes and causes dumping syndrome. The signs start during or immediately after a meal with discomfort and signs of hypovolemia, i. e., sudden onset of weakness, dizziness, sweating, tachycardia, shaking, and paleness. Distribution of food intake over several small meals, reduction of fluid intake while eating, avoiding hypertonic food, and, in some cases, lying down immediately after meals, can generally prevent symptoms. Dumping syndrome is diagnosed primarily from the medical history. It is only observed after surgery for duodenal ulcers with pyloric resection (i. e., not after proximal selective vagotomy without pylorus surgery).

Late dumping syndrome presents similarly, but occurs 1.5–3.0 hours after meals and is caused by reactive hypoglycemia. Sudden evacuation causes postprandial hyperglycemia followed by reactive hypoglycemia. In contrast to early dumping syndrome the symptoms are relieved by eating, particularly sugar.

Leading Loop Syndrome. Recurring pain in the epigastric region combined with vomiting (bile with or without food) is observed with this rare postoperative complication, particularly after Billroth II operation. A feeling of fullness occurs 20–60 minutes postprandial and is often followed by nausea and vomiting. *Blind loop syndrome*, which includes stasis and bacterial colonization in the region of the blind loop of the small intestine, also belongs to this group of disorders.

Bile Acid Reflux Gastropathy (Alkaline Reflux Gastropathy). This is associated with an early feeling of fullness, abdominal pain, and vomiting.

Postvagotomy Diarrhea. This occurs particularly after truncal vagotomy.

Deficiency Symptoms (Including Agastric Syndrome). The symptoms are: protein deficiency, iron deficiency (common), pernicious anemia (rare), and general symptoms of vitamin deficiency (osteomalacia, particularly after gastrojejunostomy or Billroth II operation).

Pain Originating from the Colon

See Chapter 27 for chronic inflammatory intestinal diseases and cancer of the colon.

Irritable Bowel Syndrome (IBS)

Definition. More than 50% of patients with chronic recurring abdominal pain suffer from an irritable colon. This disorder is not restricted to the colon and is better named irritable bowel syndrome (IBS). IBS is a syndrome of unexplained etiology, characterized by disordered motility and secretion, primarily in the colon, and by the lack of a detectable organic cause. There are a number of older and newer terms for the varied symptoms of chronic abdominal pain with no organic cause (e. g., dyspepsia, nonulcerous dyspepsia, gastritis, functional dyspepsia, hyperacidity complaints), which, depending on the main symptoms, can be termed irritable stomach or IBS.

Clinical Features. Intermittent abdominal pain of variable intensity and changing location, combined with stool problems (diarrhea, constipation, or both alter-

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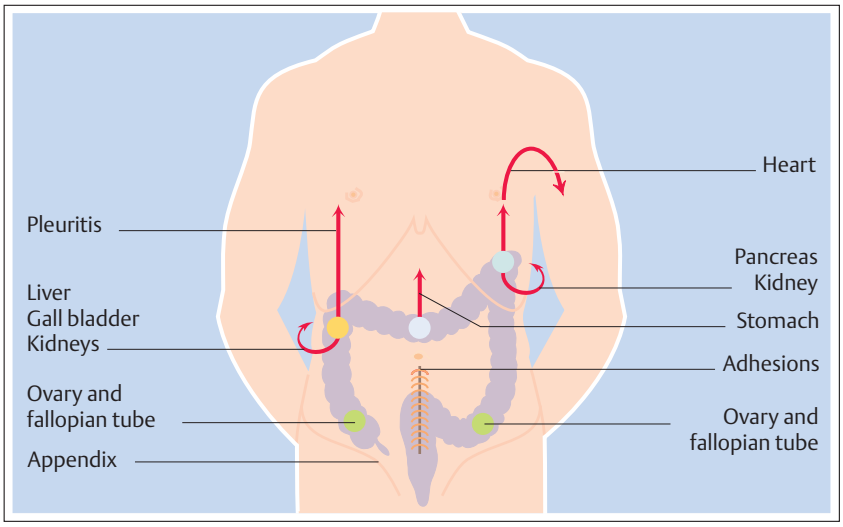

Fig. 7.**27** Misinterpretation of pain in irritable bowel syndrome

nating), are clinically detectable. Chronic constipation or diarrhea without organic cause may be variations of IBS. They differ from IBS by the absence of pain.

Patients with IBS often consult the physician because of an acute exacerbation of the complaints. A detailed medical history of similar earlier episodes is important for the correct interpretation of the acute event. Important information from the medical history could be an appendectomy due to "chronic appendicitis" (i. e., surgery after 1 or 2 weeks of pain).

The pain with IBS varies from an unpleasant feeling of pressure and bloating to severe abdominal colic. The localization of the pain is highly variable, ranging from the hypogastric and midabdominal regions to the left and right, or diffusely throughout the entire abdomen, and thus imitates diseases of the abdomen and the chest (Fig. 7.**27**). A long history with similar episodes of pain and no periodic pain (see Fig. 7.**13**) is an important characteristic. The pain can sometimes mimic an acute abdomen.

Dyspeptic complaints (e. g., nausea, feeling of fullness, primarily postprandial, bloating, flatulence) are frequent accompanying symptoms. The majority of patients suffer simultaneously from multiple other functional disorders. Laxative use is common.

Subgroups of These Symptoms. Abnormal mucous content in the stool or isolated evacuation of sausage-skin-like membranes combined with abdominal colic are typical for *mucous colitis*, which is a subcategory of IBS.

Proctalgia fugax is also a subcategory of IBS. It is a syndrome characterized by episodes of very severe cramplike pain in the rectum and perineal region, that last from a few minutes to an hour and usually occur during the day (DD: coccygodynia). The cause here is also unclear and no organic cause can be found (tentative therapy: nitrates or calcium antagonists).

Diagnosis. Clinical examinations are typically normal in IBS. The physical condition is good with stable weight. Laboratory tests are normal. No occult blood and no parasites can be found in the stool (repeated checks). The colon can often be palpated in the left hypogastric region as a contracted structure (cordon iliaque).

Sometimes endoscopic examination shows a slightly reddened mucosa covered with mucous. Endoscopy often triggers spasms. Endoscopy and radiography are typically normal.

Differential Diagnosis. IBS is a *diagnosis by exclusion* (e. g., carcinoma, ulcer, diverticulitis, cholelithiasis, nephrolithiasis, gynecologic conditions, Crohn disease, sprue, lactose intolerance, collagen colitis, parasites [giardiasis], depression, etc.). The individual diagnostic steps are primarily based on clinical experience. The shorter the history and the older the patient the less likely is IBS. On the other hand a young patient, long history, good physical condition, and constant body weight are suggestive of IBS. IBS and duodenal ulcer or cholelithiasis may possibly coexist. Diverticulitis must always be considered in older patients.

Pneumatosis cystoides intestinalis is characterized by subserous or submucosal gas-filled cysts in the gastrointestinal tract, that can be visualized by plain radiography (Fig. 7.**28**). All sections of the intestine can be affected. In 85 % of cases the pneumatosis is associated with other gastrointestinal diseases (pyloric stenosis, appendicitis, regional enteritis, colitis, anal fistula). The clinical symptoms are uncharacteristic. Hemorrhage is rare.

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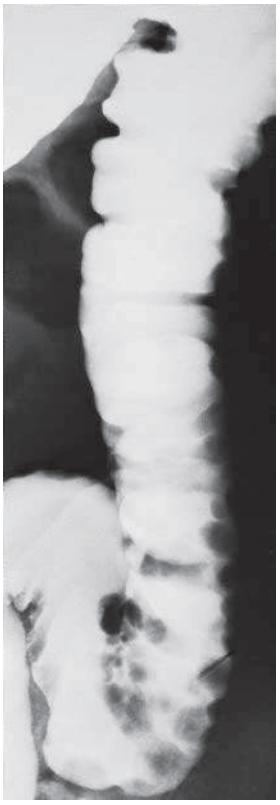

Fig. 7.**28** Pneumatosis cystoides intestinalis

Pain Originating from Bile Ducts and Liver

In differential diagnosis of pain in the epigastrium complaints originating from the bile ducts must always be considered.

The most important symptoms that indicate a biliary disease are: episodic pain in the epigastric region with or without radiation to the right shoulder, acute exacerbation of the pain over 1–3 days, nausea, vomiting, and occasional jaundice, with pain-free intervals often lasting weeks to months.

Cholelithiasis

Clinical Features. So-called gallstone colic is generally triggered by food intake. After a few minutes the pain reaches its peak and can be extremely intense. It is generally clearly different from the pain associated with duodenal ulcers, which increases slowly and is rarely as severe. The term "colic" is not always accurate, because it is generally a severe continuous pain, lasting for several hours. The *pain* is not always circumscribed, is most intense below the right ribs but can also be localized along the mid-line. Radiation to right back and the right shoulder is typical. Nausea is an almost obligatory accompanying symptom. Fat intolerance is very common. Fat intolerance alone, however, without painful colic, is very common and unspecific.

Examination during the pain episode usually reveals an intensive, sometimes only low-grade, sensitivity to palpation in the gall bladder region and a low-grade defense in the right epigastric region.

Epidemiology. Cholelithiasis affects women about twice as often as men. Predisposing factors are pregnancy, obesity, diabetes, and increasing age. The majority of patients with gallstones show no or atypical symptoms, particularly symptoms of IBS.

In Europe and America gallstones are mostly *cholesterol stones* (two-thirds not radio-opaque, about one-third with calcification).

Pigmented gallstones are more frequent in Japan, whereas in the West they are found mostly in patients with hemolytic anemia, particularly with congenital spherocytosis and sickle cell anemia. Patients with cirrhosis of the liver also have an increased incidence of pigmented stones for unknown reasons.

Differential Diagnosis. In general, gallstone colic is so typical that it is easily diagnosed. The following must be excluded in differential diagnosis: right-sided kidney colic, thromboses of mesenteric veins or arteries, acute

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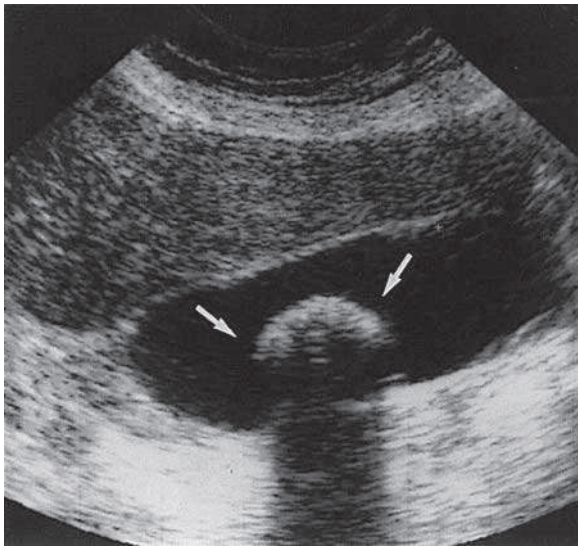

Fig. 7.**29** Typical ultrasound image of cholecystolithiasis with round–oval stone (arrows) and echo shadow.

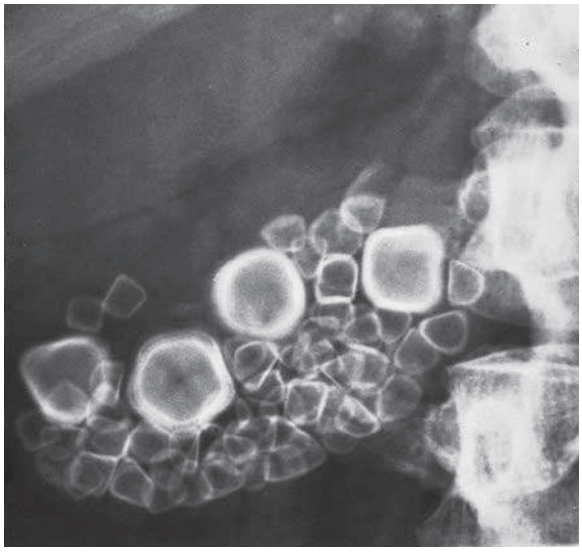

Fig. 7.**30** Gallstones in plain radiograph.

inflammation of a dorsally and cranially placed appendix, duodenal ulcer, hepatitis, and pancreatitis, which is often caused by biliary obstruction. Epigastric and umbilical hernias are also rare causes of pain. Myocardial infarction and right-sided heart failure with acute congestion of the liver are two diseases of organs outside of the abdomen that may mimic gallstone colic.

An acute perihepatitis, which is mostly observed in young women, can easily be misinterpreted as cholelithiasis.

Diagnosis. Sonography is the method of choice to confirm cholecystolithiasis (Fig. 7.**29**). Stones are a frequent finding at sonography of patients with atypical or no biliary symptoms.

Calcium-containing stones are detected by plain radiography (Fig. 7.**30**). Choledochus stones can be detected by ERCP (Fig. 7.**31**). It is assumed that 10% of patients with gallbladder stones also have choledochus stones. The symptoms vary. Typical is either an intermittent obstructive jaundice, mostly in connection with a pain attack, pancreatitis, or cholangitis. However, many patients have no or only minor symptoms. In contrast to cholecystolithiasis, biliary colic with choledocholithiasis is often associated with vomiting. About three-quarters of all patients with choledocholithiasis have pain, which is virtually indistinguishable from that of cholecystolithiasis with respect to localization, severity, and radiation.

Acute cholecystitis can be diagnosed by sonography, MRI and CT.

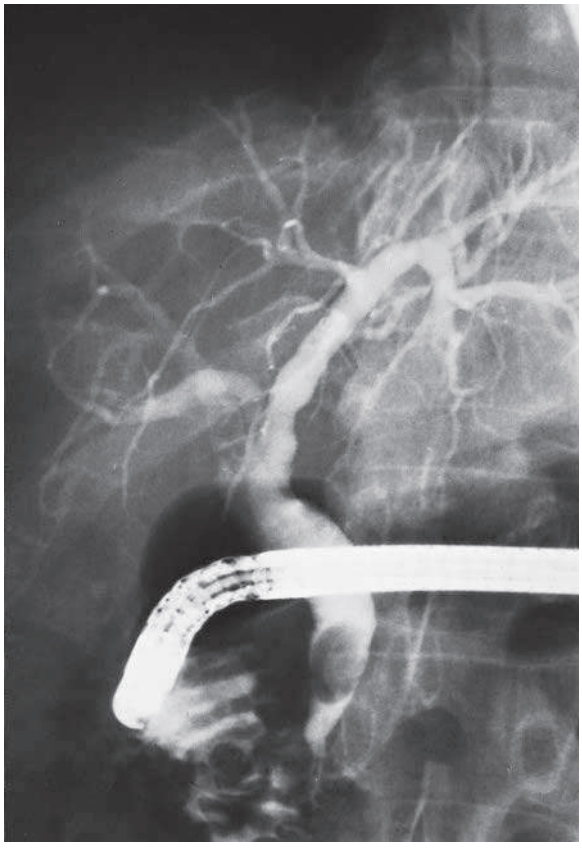

Fig. 7.**31** Distal choledocholithiasis (longitudinal oval contrast-sparing structure) and status after cholecystectomy (ERCP).

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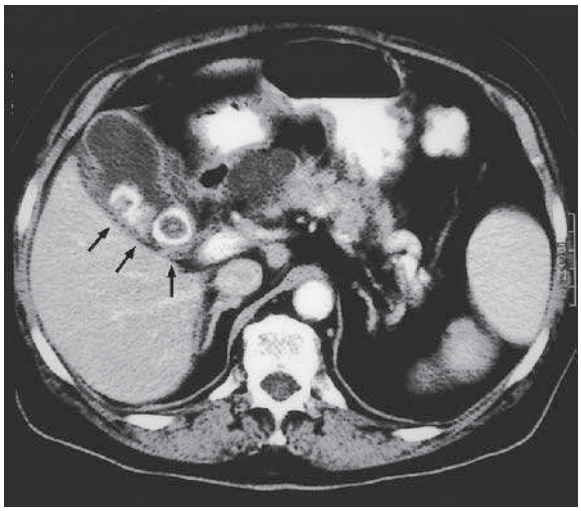

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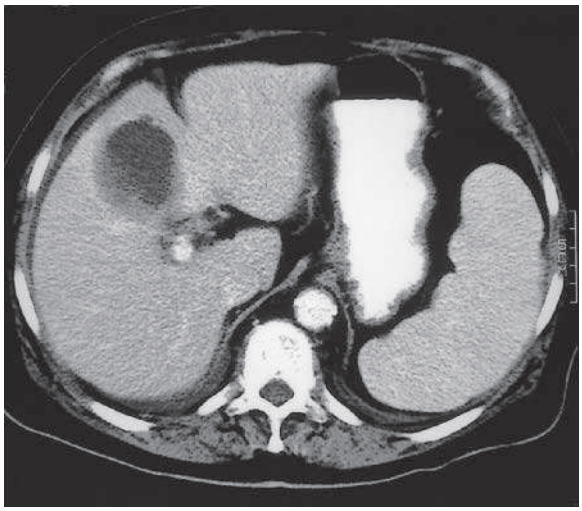

b

Fig. 7.**32** Acute cholecystitis with
a Covered gall bladder perforation and
b Liver abscess formation in a 70-year-old woman. The arrows indicate multiple gall bladder stones.

Liver Diseases Associated with Cholelithiasis

Several liver diseases are secondary to cholelithiasis, particularly choledocholithiasis. In late stages of these liver diseases cholelithiasis may not be symptomatic and must be searched for specifically. Typical liver diseases secondary to cholelithiasis/choledocholithiasis are:

- cholangitis (see Chapter 25)
- liver abscess (see Chapter 25, Fig. 7.**32**)
- secondary biliary cirrhosis (see Chapter 25).

Complaints after Cholecystectomy

If symptoms continue or recur after cholecystectomy, which occurs in 10–15% cases, the following three possibilities must be considered:

- *extrabiliary causes of the complaints*, which were present beforehand and were not corrected by the cholecystectomy
- symptoms originating from the *bile ducts*, which were overlooked during the surgery (e. g., choledocholithiasis)
- *surgical complications in extrahepatic bile ducts* (e. g., postoperative strictures, fistulas, ligation or transsection of the bile duct).

Symptoms persisting after cholecystectomy, particularly after removal of a stone-free gall bladder, frequently indicate an underlying extrabiliary problem (e. g., pancreatitis, ulcer, carcinoma, IBS, etc).

Choledochus Stones and Papillary Stenoses. Choledochus stones or papillary stenoses are the two most common causes of persistent symptoms after cholecystectomy.

Diagnosis is based on the biochemical confirmation of intermittent obstruction (increase of alkaline phosphatase with normal bilirubin), best done immediately after a pain attack. Often a transient hyperamylasemia can be detected. The diagnostic method of choice is ERCP. In choledocholithiasis an endoscopic papillotomy is frequently required to remove the stones. If obstruction of the common bile duct by a process in the head of the pancreas exists (pancreatitis, carcinoma) additional studies are required: sonography, endosonography, CT and cholangio-MRI.

A long cystic stump after cholecystectomy rarely causes clinical symptoms, unless new gallstones are formed.

Liver Swelling. Liver swelling can cause epigastric pain by capsule tension. The first consideration here should be alcohol-induced hepatitis (see Chapter 25), acute venous congestion of the liver, and Budd–Chiari syndrome (see Chapter 25). The liver is enlarged, and painful upon palpation. An acute liver inflammation (e. g., hepatitis, cholangitis, abscess, echinococcus) may also cause pain. Intensive pain at a more circumscribed location with a palpable resistance often indicates a malignant process (see Chapter 25). The diagnosis is made by sonography, CT, MRT, and if applicable laparoscopy.

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Differential Diagnosis of Pain in the Right Hypogastric and Midabdominal Region

Biliary and Extrabiliary Causes. Differential diagnosis must include, in addition to biliary causes, duodenal ulcers, pancreatitis, hepatopathies (alcohol-induced hepatitis, congestion of the liver, space occupying processes), parasites (e. g., *Fasciola hepatica*), acute perihepatitis, renal affections, neoplasm of liver, bile ducts, pancreas, duodenum, kidneys, colon, and a radicular pain syndrome from the back. Metabolic diseases, collagenosis, and pain from vascular causes must also be considered. Indistinct pressure sensations occasionally occur with the rare Chilaiditi syndrome, which is characterized by the interposition of the colon in the right hypochondriac region between the liver and the diaphragm (Fig. 7.**33**). This syndrome must not be misinterpreted as free intraabdominal air.

Anomalies of Localization and Shape of the Gallbladder. Anomalies in the localization and shape of the gall bladder (e. g., septum formation, Phrygian cap, diverticula) can be identified by sonography. In most cases these findings are coincidental without clinical correlation. Therefore, cholecystectomy rarely resolves all complaints. Adenomyomatosis of the gall bladder, which may be associated with cholelithiasislike pain is rare and can be cured by cholecystectomy.

Functional Complaints. Differentiation between bile duct dyskinesia (functional motility disorders) and physical obstruction (primarily adenomyomatosis in the cervical region of the gall bladder) is not possible by clinical examination. Dyskinesia is probable when other functional complaints are present.

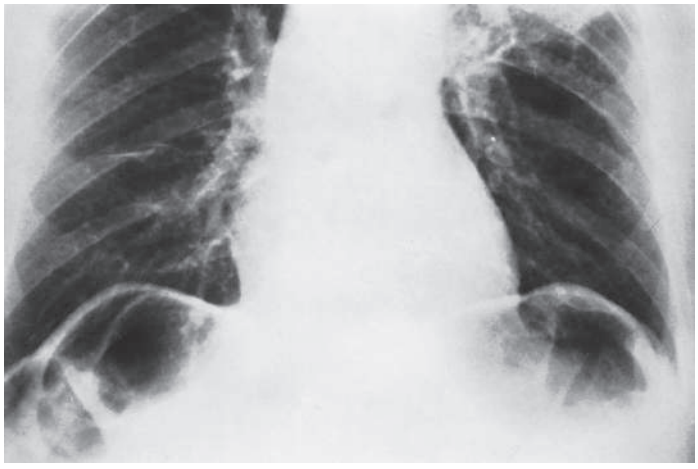

Fig. 7.**33** Chilaiditi syndrome. The haustrae are clearly visible; 65-year-old man.

Diseases of the Pancreas

Clinical Features. The main clinical symptoms that indicate disease of the pancreas are:

- pain
- cholestasis
- weight loss
- diabetes mellitus
- diarrhea/steatorrhea (Fig. 7.**34**).

Acute and chronic pancreatitis and pancreatic carcinoma are the most important diseases. Acute and chronic pancreatitis in the early stages generally have an identical clinical picture, characterized by one or more acute episodes of pancreatitis. The main difference is the long term course. In contrast to chronic (progressive) pancreatitis, *acute* (reversible) pancreatitis is cured

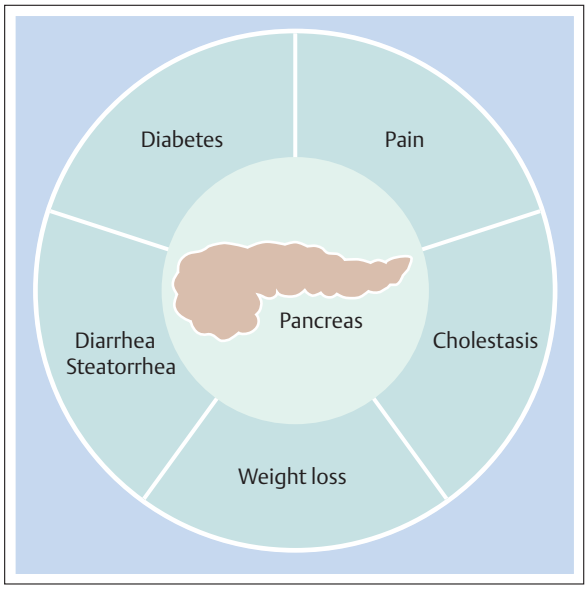

Fig. 7.**34** Main clinical symptoms that may indicate a disease of the pancreas.

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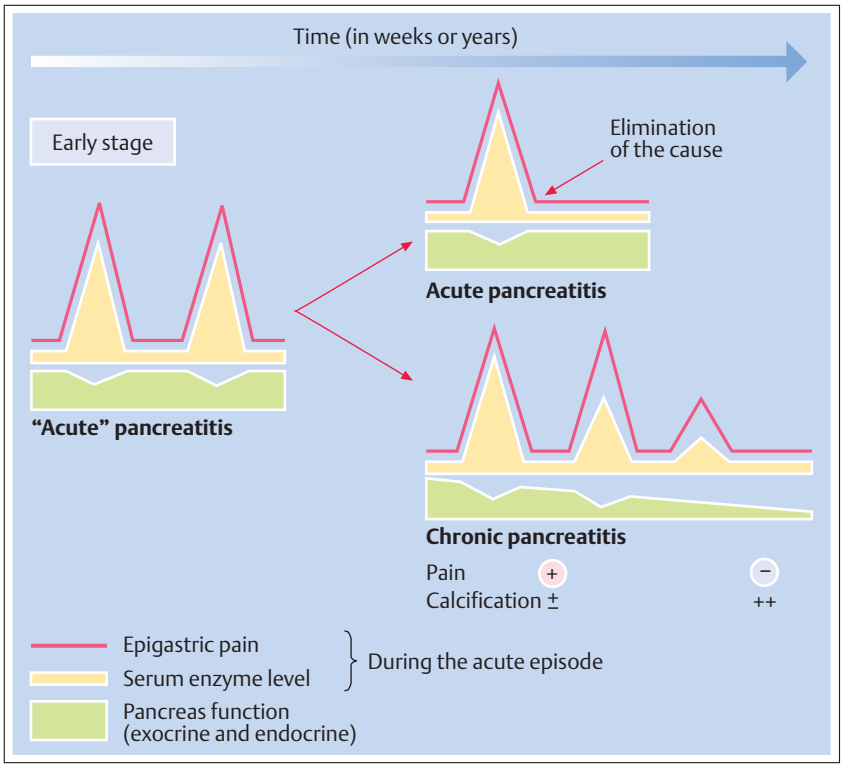

Fig. 7.**35** Natural course of acute and chronic pancreatitis.

after causal therapy (primarily cholelithiasis). Morphologically, scars and pseudocysts may persist after severe acute pancreatitis. Typical signs of *chronic* pancreatitis are irreversible exocrine and/or endocrine insufficiency, often combined with pancreatic calcifications, which on average occurs 5–6 years after onset of the disease (Fig. 7.**35**). Approximately 50% of cases of nonalcoholic chronic pancreatitis are primarily painless and become symptomatic in general with weight loss due to diabetes mellitus or diarrhea/steatorrhea. The etiology is important for the prognosis. Biliary pancreatitis virtually never becomes chronic, while in alcohol uses chronic pancreatitis is common.

Diagnosis of Diseases of the Pancreas

The diagnosis of diseases of the pancreas is based on medical history, clinical findings, imaging (abdominal radiograph, sonography, endosonography, CT, cholangio-MRI, ERCP), and laboratory tests, including various tests for evaluation of the exocrine pancreatic function (Tab. 7.**8**). Tab. 7.**9** shows typical laboratory results for the three most important diseases of the pancreas. Unlike the parameters for hepatobiliary diseases (see Chapter 25), tests for diseases of the pancreas are much less informative for differential diagnosis. However, in most cases it is possible to interpret the laboratory results correctly in the context of the clinical and imaging findings.

Amylase. Elevated amylase levels in blood and urine indicate acute pancreatitis. An increase in enzyme activity to four or five times above normal with subsequent normalization is characteristic of acute pancreatitis. Elevated levels persist longer in urine (7–10 days) than in serum (1–5 days). Numerous extrapancreatic diseases may cause an increase in serum and urine amylase levels and must be considered in the differential diagnosis (Tab. 7.**10**).

In macroamylasemia the amylase circulates as a macromolecular aggregate or as a complex with immunoglobulins, which are too large for renal excretion. This is usually a chance finding. The diagnosis is made chromatographically.

Determination of lipase, trypsin, or pancreas isoamylase can increase diagnostic accuracy in selected cases.

Low amylase and lipase values are found in acute pancreatitis if hypertriglyceridemia is present.

Exocrine Pancreatic Function. Chymotrypsin or elastase in the stool best reflects the exocrine function of the pancreas.

The tests listed in Tab. 7.**8**, most of which are more complex and in some cases invasive, are only used in selected cases. The pancreozymin–secretin test has the greatest specificity and sensitivity. The test requires intubation of the duodenum and a radiologic confirmation of the posi-

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tion of the probe. After stimulation of the exocrine pancreas with *pancreozymin* and *secretin* the enzyme secretion and the secretion volume are measured. The test yields pathologic results if ≥ 50 % of the glandular tissue is lost.

The noninvasive, probeless pancreatic function tests, the *N-benzoyl-L-tyrosyl-p-aminobenzoic acid* (*NBT-PABA*) test and the pancreolauryl test are used to estimate the intestinal pancreas-specific digestion capacity. Both tests are based on the detection of degradation products that are released by pancreas-specific enzymes after oral application of the test substance, and are resorbed from the intestine and excreted in the urine.

Serum enzyme tests for trypsin, lipase, and pancreas isoamylase show pathologically low values in severe pancreatic insufficiency.

Disorders of fat digestion (steatorrhea) only occur with advanced exocrine pancreatic insufficiency and are characterized by a fat content of the stool > 7 g/24 h.

Endocrine Pancreas Function. A *pathologic glucose tolerance* is found in many pancreatic diseases. It is either transient (e. g., acute pancreatitis) or progresses slowly (chronic pancreatitis, pancreatic carcinoma).

Pancreas Insufficiency. Pancreatic insufficiency is not the same as chronic pancreatitis. Pancreatic insufficiency can be reversible (e. g., after acute pancreatitis, alcoholic pancreas damage) or it can progress as is typical for chronic pancreatitis. A normal pancreas function does not exclude a pancreatic disease. A normal pancreozymin–secretin test, for example, may be expected after a distal 50 % pancreas resection or with circumscribed lesions of the distal half of the pancreas.

Table 7.**8** Laboratory analyses in diseases of the pancreas

Serum enzymes
– amylase (also of diagnostic significance in urine)
– lipase
– (trypsin)
– (pancreas isoamylase)
Exocrine function tests
– secretion capacity
– pancreozymin (CCK) secretion test
– Lundh test
– chymotrypsin or elastase in stool
– digestion capacity
– NBT-PABA test
– pancreolauryl test
– quantitative stool fat determination
– acinar atrophy
– trypsin, lipase, pancreas isoamylase
Endocrine function tests
– blood glucose
– oral glucose tolerance test
– HbA_{1c}, fructosamine

Table 7.**9** Laboratory findings in diseases of the pancreas

	Serum (and urine) enzymes	Exocrine pancreas insufficiency	Endocrine pancreas insufficiency
Acute Pancreatitis	++ (2–3 days)	± (1–3 weeks, possibly longer)	± (approx. 1 week)
Chronic pancreatitis			
– early stage			
– episodic	++	± (often transient)	± (often transient)
– late stage			
– episodic	+	++	++
– in interval	–	++	++
Pancreatic carcinoma	±	+ (including carcinoma of the head of the pancreas)	+ (in 30–50 %)

Acute Pancreatitis

Clinical Features. Acute pancreatitis is generally a severe clinical disease, frequently with peritonitislike symptoms and various local and systemic complications, up to and including shock and multiple organ failure. A leading symptom is severe continuous epigastric pain, which can often be felt in the right epigastric region in biliary pancreatitis. Belt-shaped radiation of the pain along the ribs on both sides and to the back is typical. Ulcers, intestinal perforation, acute cholecystitis, and myocardial infarction must be considered in the differential diagnosis.

In comparison to a perforation, the abdomen is generally less tense. It is rarely board-hard, although there is almost always a severe diffuse sensitivity to palpation of the bloated abdomen with rebound tenderness in later stages. Initially the abdomen may be soft without rebound tenderness. The discrepancy between the severity of the symptoms and the discrete physical findings is typical for this stage. In this stage a circumscribed pain upon palpation is found. The patient's face

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Table 7.**10** Extrapancreatic causes of hyperamylasemia and hyperamylasuria

With abdominal pain
- ulcer perforation
- acute cholecystitis
- ileus and peritonitis
- mesenteric arterial occlusion
- ruptured extrauterine gravidity
- aorta aneurysm/rupture
- appendicitis

With or without atypical abdominal pain
- parotitis and other diseases of the salivary glands
- renal insufficiency
- macroamylasemia
- medications (opiates)
- diabetic ketoacidosis
- chronic alcoholism
- paraneoplastic
- burns
- myocardial infarction
- anorexia nervosa

No hyperamylasuria with macroamylasemia; increased serum lipase even with ulcer perforation, acute cholecystitis, ileus, and peritonitis, mesenteric infarction, aorta aneurysm/rupture, and after opiate administration; serum lipase and trypsin are also increased with renal insufficiency.

Table 7.**11** Causes of acute pancreatitis

- Biliary (primarily cholelithiasis)
- Alcoholic
- Metabolic (hypertriglyceridemia, hypercalcemia [hyperparathyroidism], renal insufficiency)
- Drugs (azathioprine, 6-mercaptopurine, antiretroviral nucleoside analogs, particularly didanosin [DDI], pentamidine, thiazide, furosemid, sulfonamides, oral contraceptives, tetracycline, valproic acid, metronidazole, ranitidin, sulindac, salicylates etc.)
- Infectious (mumps, viral hepatitis, other viral infections [coxsackie, ECHO, cytomegalovirus, HIV], mycoplasma, *Mycobacterium avium* complex, *Campylobacter jejuni*, etc.)
- Traumatic (primarily blunt abdominal trauma)
- Postoperative (after abdominal and nonabdominal surgery, relatively frequent after kidney transplants)
- Vascular (ischemic [e. g., after cardiac surgery], embolic, during vasculitis [e. g., with systemic lupus erythematodes, panarteritis nodosa, or thrombotic thrombocytopenic purpura])
- Endoscopic retrograde cholangiopancreaticography (ERCP)
- Papillary obstruction (e. g., papillary stenosis, papillary or pancreatic carcinoma, parasites [ascariasis], duodenal diverticulitis, Crohn disease)
- Duct anomalies (e. g., pancreas divisum)
- Hereditary
- Idiopathic

is pale and sunken with a perforation, but often reddened with pancreatitis. Leukocytosis is almost always present. In contrast to myocardial infarction, the diagnosis may be difficult because similar electrocardiographic findings are obtained in acute pancreatitis and posterior myocardial infarction. Skin signs are common with severe pancreatitis: brownish-green coloring of the navel region (Cullen sign) or the flank region (Grey–Turner sign).

Diagnosis. Typical clinical signs of acute pancreatitis are confirmed by *increased serum (and urine) amylase* and exclusion of extrapancreatic hyperamylasemia (see Tab. 7.**10**). The serum levels increase four to five times above normal within the first 12 hours and then normalize over one to five days. The lipase generally remains higher for a longer time (seven to 14 days).

A *transient blood glucose increase* is not always encountered but, if present, indicates acute disease of the pancreas. Jaundice rarely occurs, but a short-term hyperbilirubinemia combined with cholestasis can frequently be demonstrated biochemically, in some cases after normalization of the amylase values. *Hypocalcemia* is an indication of a severe acute pancreatitis. The calcium level, with other parameters (including leukocytes, fasting blood glucose, urea, arterial oxygen concentration, LDH) are included in the prognostic score to differentiate mild from severe forms. In clinical practice contrast-enhanced CT and measurement of C-reactive protein are the most important investigations. Values $>$ 120–150 mg/dL indicate severe pancreatitis.

Imaging is used primarily to detect gallstones and local complications, particularly necroses, infected necroses, or abscesses and pseudocysts (see below). Pancreatic edema and exudate are signs of acute pancreatitis and can be detected by CT and often by sonography in the early phase. CT is ideal for detecting necroses in the pancreas. Abscesses that may require surgery can be detected at an early stage by sonography or CT. In acute biliary pancreatitis, ERCP with stone extraction is diagnostically and therapeutically most important.

Causes. The most frequent cause of acute pancreatitis is cholelithiasis (about 40–70 % of cases). Alcohol use can be clinically identical but this is generally an acute episode of chronic pancreatitis. Other causes of acute pancreatitis are listed in Tab. 7.**11**. No cause can be detected in 10–20 % of cases; 30–50 % of pancreatitis cases recur episodically.

Complications of Acute Pancreatitis. Local and systemic complications of acute pancreatitis are listed in Tab. 7.**12**.

A typical local complication is an inflammatory tumor, in general associated with pseudocysts. Main symptoms are persistence of active pancreatitis for more than 10 days and/or affection of neighboring organs by pancreatic edema. The clinical situation is variable and typically presents with cholestasis, stenosis, vomiting, and gastrointestinal hemorrhage (Fig. 7.**36**).

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Table 7.**12** Complications of acute pancreatitis

Local
– necrosis (sterile, infected)
– pseudocysts
– abscess formation
– obstruction or fistula to colon
– gastrointestinal hemorrhage (ulcer, varices with splenic vein thrombosis, ruptured pseudoaneurysm)
– right-sided hydronephrosis
– rupture or hematoma of the spleen
Systemic
– shock
– coagulation disorders
– respiratory failure
– acute renal failure
– hyperglycemia
– hypocalcemia
– panniculitis nodularis
– retinopathy
– psychosis

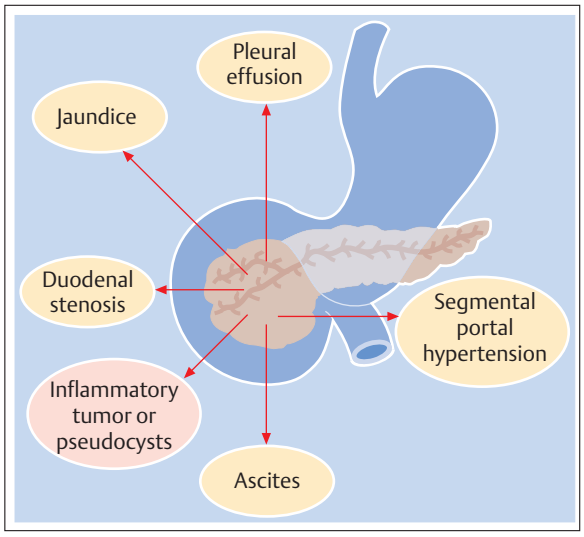

Fig. 7.**36** Typical local complications of pancreatitis.

Differential Diagnosis versus Chronic Pancreatitis. The clinical differentiation between acute and chronic pancreatitis is very difficult, particularly in the early stages. Common to both are clinically and biochemically similar episodes of pancreatitis and increased incidence of local complications, particularly *pseudocysts*. The decisive difference is the progressive exocrine and endocrine pancreatic insufficiency, which occurs 5–6 years after the beginning of the disease in chronic pancreatitis only. Chronic pancreatitis occurs more often in men than in women, particularly after 45 years of age, and is frequently related to alcohol use.

Acute pancreatitis, in contrast, occurs in men and women with equal frequency, generally from 45 years of age and is most commonly caused by cholelithiasis.

Chronic Pancreatitis

Causes. Chronic pancreatitis is characterized initially by recurring episodes of pancreatitis and later by exocrine and endocrine pancreatic insufficiency. The primary cause of chronic pancreatitis in more than 60% of cases is alcohol use. Other cases have no clear cause or the causes are rare (e. g., pancreatic duct obstruction, hyperparathyroidism, hyperlipidemia, trauma, analgesic use, or hereditary). Mutations of the gene for cationic trypsinogen can cause the rare *hereditary pancreatitis*. Mutation of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR), also without any clinical signs of a cystic fibrosis, or of the serine protease inhibitors Kazal type 1 (SPINK1) are associated with some cases of chronic pancreatitis that were formerly classified as idiopathic. Cholelithiasis rarely causes chronic pancreatitis.

Epidemiology. Men are affected approximately seven times more often than women.

Clinical Features. Approximately 10–20% of patients with chronic pancreatitis have no pain, particularly in nonalcoholic chronic pancreatitis (idiopathic-senile form, hyperparathyroidism, analgesic use). Diabetes mellitus or steatorrhea is generally the first clinical manifestation. Local complications (e. g., obstructive jaundice) are rarely caused by chronic pancreatitis.

Chronic pancreatitis in the *early stage* presents typically with episodic attacks of epigastric pain followed by weeks or months without pain. Continuous pain over weeks, particularly postprandial or recurring at short intervals, indicates local complications, particularly pseudocysts. Elevated pressure in dilated pancreatic ducts often causes continuous pain. Local complications can be diagnosed by sonography, endosonography, CT, MRT, or ERCP. A pancreatic carcinoma must always be considered. In older patients with continuous pain for less than 18 months, weight loss, and no history of pancreatitis, a pancreatic carcinoma is more probable than chronic pancreatitis.

The *pain episode* in chronic pancreatitis is clinically and biochemically virtually identical to acute pancreatitis. Spontaneously occurring, continuous pain in the epigastrium, persisting for hours to a few days and often associated with vomiting and subileus, is characteristic. The intensity of the pain is very variable and ranges from mild stomach discomfort to very severe pain with the feeling of dying.

Weight loss of 5–10 kg or more is almost always associated with chronic pancreatitis and generally occurs in the early stages of the disease, before diabetes mellitus or steatorrhea develop.

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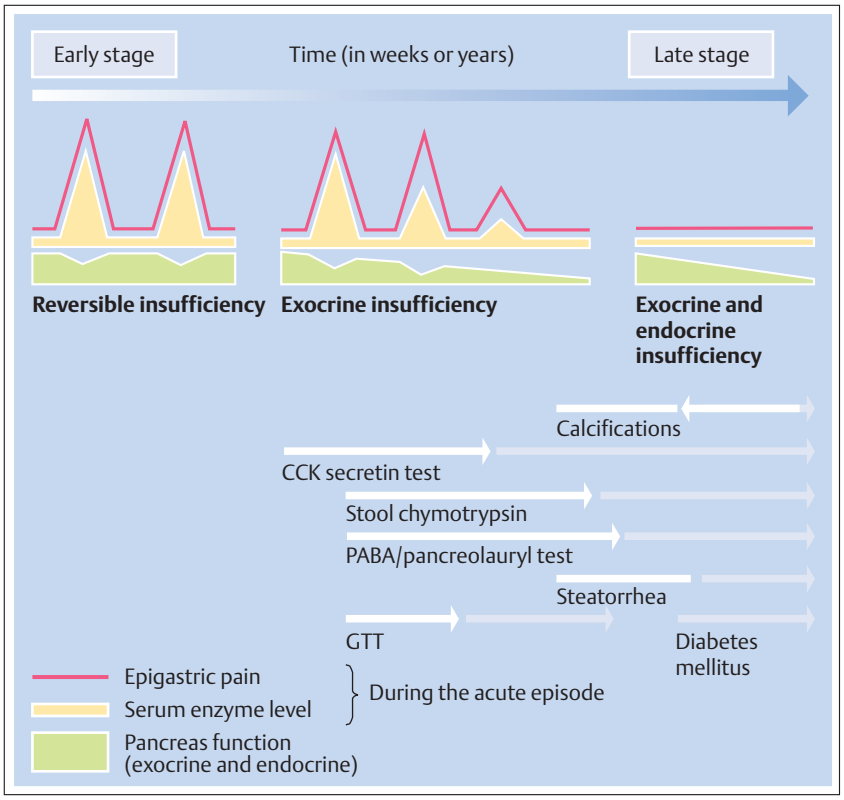

Fig. 7.**37** Natural course of chronic pancreatitis.

Chronic pancreatitis always leads to *diabetes mellitus*, generally within three to five years, and can be diagnosed by an oral glucose tolerance test (Fig. 7.**37**). Pancreatogenic diabetes must be suspected especially in younger, non-obese patients without family history and with a history of recurring abdominal pain or alcohol use.

Persistent meteorism may indicate chronic pancreatitis. Diarrhea and steatorrhea generally develop later. Fatty stools, not occuring otherwise, are pathognomonic for pancreatogenic steatorrhea. Steatorrhea is a later complication. With the development of pancreatic calcifications, diabetes, and severe exocrine pancreatic insufficiency the pain generally disappears spontaneously unless there are local complications (burnt-out pancreatitis).

Diagnosis. Early exocrine pancreas insufficiency can only be detected by relatively complex function tests. Pancreatic calcifications can be detected in $>60\%$ of patients by plain radiography (Fig. 7.**38**). Stones are formed primarily in the pancreatic duct system and are detected by sonography, endoscopy, CT or ERCP.

Various imaging procedures are used for the assessment of pancreatic diseases. Sonography, as well as endosonography and CT, are very useful for diagnosis and monitoring of acute pancreatitis, for detection of pseudocysts, cholelithiasis, pancreatic carcinoma, and in cholestasis/jaundice. ERCP and magnetic resonance cholangiopancreaticography (MRCP) are primarily used in etiologically unclear, recurring pancreatitis and local complications of pancreatitis. In early chronic pancreatitis imaging procedures are of limited value, in particular in differentiating acute pancreatitis.

Complications. Local complications of chronic pancreatitis are common: pseudocysts, pancreatogenic ascites, cholestasis with or without jaundice, thrombosis of the splenic veins, duodenal stenosis, gastrointestinal hemorrhage, and stenoses or fistula formation in the colon. Many of these local complications also occur with acute pancreatitis.

Differential Diagnosis of Pancreatic Carcinoma. Differential diagnosis of chronic pancreatitis versus carcinoma of the head of the pancreas can be very difficult. Positron emission tomography (PET) may be helpful. Nevertheless, it is often not possible, even during surgery, to decide whether a small pancreatic carcinoma with accompanying pancreatitis or chronic pancreatitis only is present. With the exception of papillary carcinoma, which causes obstructive jaundice very early and has a good prognosis with radical surgery, the prognosis for pancreatic carcinoma is very poor.

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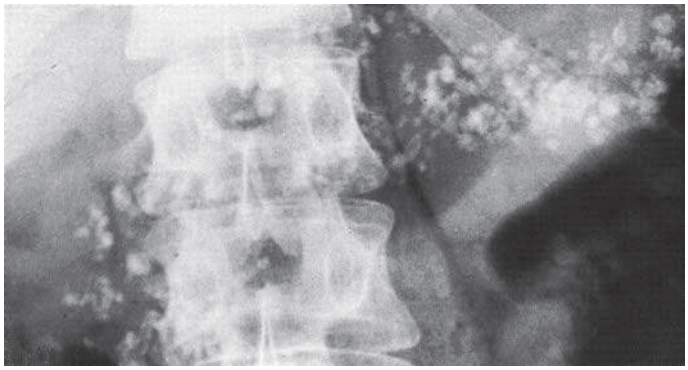

Fig. 7.**38** Plain radiograph demonstrating diffuse calcifications in chronic pancreatitis.

Space-Occupying Lesions in the Pancreatic Region

Epigastric pain, generally continuous combined with back pain is frequent in pancreatitis or pancreatic carcinoma. Tumor expansion can cause obstructive jaundice or duodenal stenosis.

Occasionally, a round, firm, elastic, sharply delineated tumor can be palpated in the epigastric region, particularly in patients with pseudocysts.

The most important examinations are sonography, endosonography, CT or MRCP, and, in some cases, percutaneous or endoluminal biopsy.

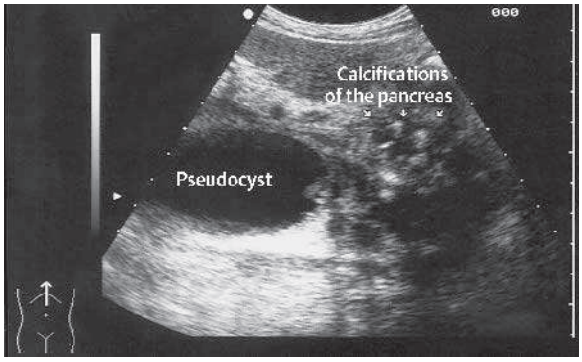

Fig. 7.**39** Ultrasound image of chronic pancreatitis with large pseudocyst and multiple calcifications (note the typical echo shadow).

Pancreatic Cysts

Pancreatic cysts are classified as:

- congenital pancreatic cysts, occasionally associated with kidney and liver cysts
- cystadenoma
- retention cysts (expansion of the pancreatic duct system as a result of obstruction)
- pseudocysts (resulting from pancreas necrosis and without epithelium).

Clinical Features. Cysts and pseudocysts are common complications of acute and chronic pancreatitis, that may occasionally be asymptomatic. Pseudocysts develop in about 15% of patients with acute pancreatitis, typically within one to four weeks. Amylase/lipase elevation for 10 days or more, often with signs of inflammation (e. g., fever, leukocytosis, and increased ESR), is common in pseudocysts.

Pseudocysts can be complicated by abscess formation, hemorrhage, possibly with hemosuccus pancreaticus, penetration into neighboring organs with gastrointestinal hemorrhage, obstructive jaundice, duodenal stenosis, or thrombosis of the splenic vein.

If ascites or a pleural effusion with high protein and amylase content develop in pancreatitis, a pseudocyst is likely.

Rarely, pseudocysts may extend to the chest (e. g., via mediastinum into the supraclavicular region), manifested by clinical and radiologic findings (mediastinal, cardiac and pulmonary changes, effusions).

Diagnosis. Larger pseudocysts can be palpated as firm, elastic tumors. Sonography can be used to detect cysts > 1–2 cm in diameter. If a cyst grows or persists, it usually must be surgically removed. Alternatively, endoscopic and sometimes percutaneous drainage can be performed. Cysts can also spontaneously regress. Endoscopic retrograde pancreaticography (ERP) can show even smaller cysts before surgery if they communicate with the pancreatic duct system (Fig. 7.**40**). However, this examination carries the risk of aggravating inflammation.

Pancreatic Carcinoma

Epidemiology and Localization. The symptoms of pancreatic carcinoma are unspecific. This diagnosis must always be considered in older patients with abdominal pain without evidence of gastric or hepatic disease (average age 55 years, men affected twice as often as women). Risk factors for pancreatic carcinoma are

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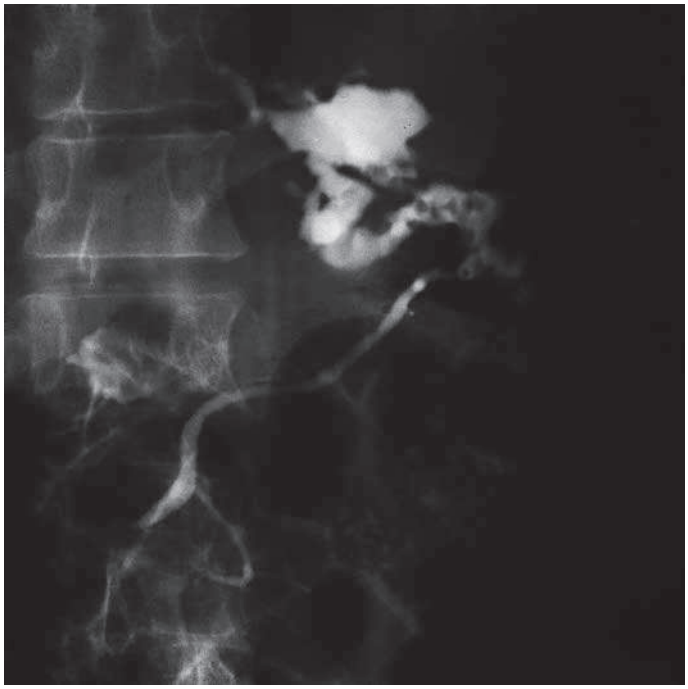

Fig. 7.**40** Pseudocysts in the tail of pancreas (endoscopic retrograde pancreaticography, ERP).

poorly defined. Heavy smokers seem to be affected more often than nonsmokers.

More than 90% of pancreatic carcinomas are ductal adenocarcinomas. Islet cell carcinomas represent only a small proportion. Pancreatic carcinoma occurs in the head of the pancreas in about 70% of cases, in the body in 20%, and rarely in the tail. The clinical symptoms vary depending on the size and localization of the tumor.

Clinical Features and Diagnosis. *Carcinoma of the pancreas head* is primarily characterized by *periampullar localization* with the triad of *pain*, *weight loss*, and *progressive obstructive jaundice* with dark urine, acholic stool, and pruritis. An enlarged, palpable gall bladder (*Courvoisier sign*, ≤50% of cases) indicates distal choledochus obstruction. Painless obstructive jaundice is found in about 25% of patients. Dilated bile ducts can usually be visualized by sonography. Diagnosis generally requires ERCP and/or biopsy guided by sonography, endosonography or CT. Percutaneous biopsy should be avoided in resectable tumors because of the risk of needle tract metastases. Positron emission tomography (PET) can be useful here to differentiate between inflammatory and neoplastic processes.

Pain and *weight loss without jaundice* are initial symptoms for *nonpapillary carcinomas*. The pain, initially intermittent, later continuous, is localized in the epigastric region, primarily to the left and typically radiates to the back. Increased pain when lying down, and improvement when standing and bending forward, is typical, similar to chronic pancreatitis. Pancreatitis episodes resulting from duct obstruction may be the first manifestation of a pancreatic carcinoma. Signs of poor assimilation, particularly diarrhea, steatorrhea, and weight loss, may precede other manifestations of the tumor by months.

Thrombophlebitis migrans is present in < 10% of cases. A pancreatic carcinoma or an acute pancreatitis is rarely the cause of *panniculitis nodularis* (*Pfeifer–Weber–Christian syndrome*).

Amylase and lipase are almost always in the normal range. The oral glucose tolerance is pathologic in 30–50% of cases. Exocrine pancreatic insufficiency can generally be detected with carcinoma of the pancreatic head. CEA and CA19–9 are frequently elevated, with the latter being relatively specific for pancreatic carcinoma.

Other Tumors of the Pancreas. The rare *cystadenoma* and *cystadenocarcinoma* occur mainly in middle-aged women. The cardinal symptom is a palpable tumor in the epigastric region.

Neuroendocrine tumors of the pancreas are discussed in Chapter 27.

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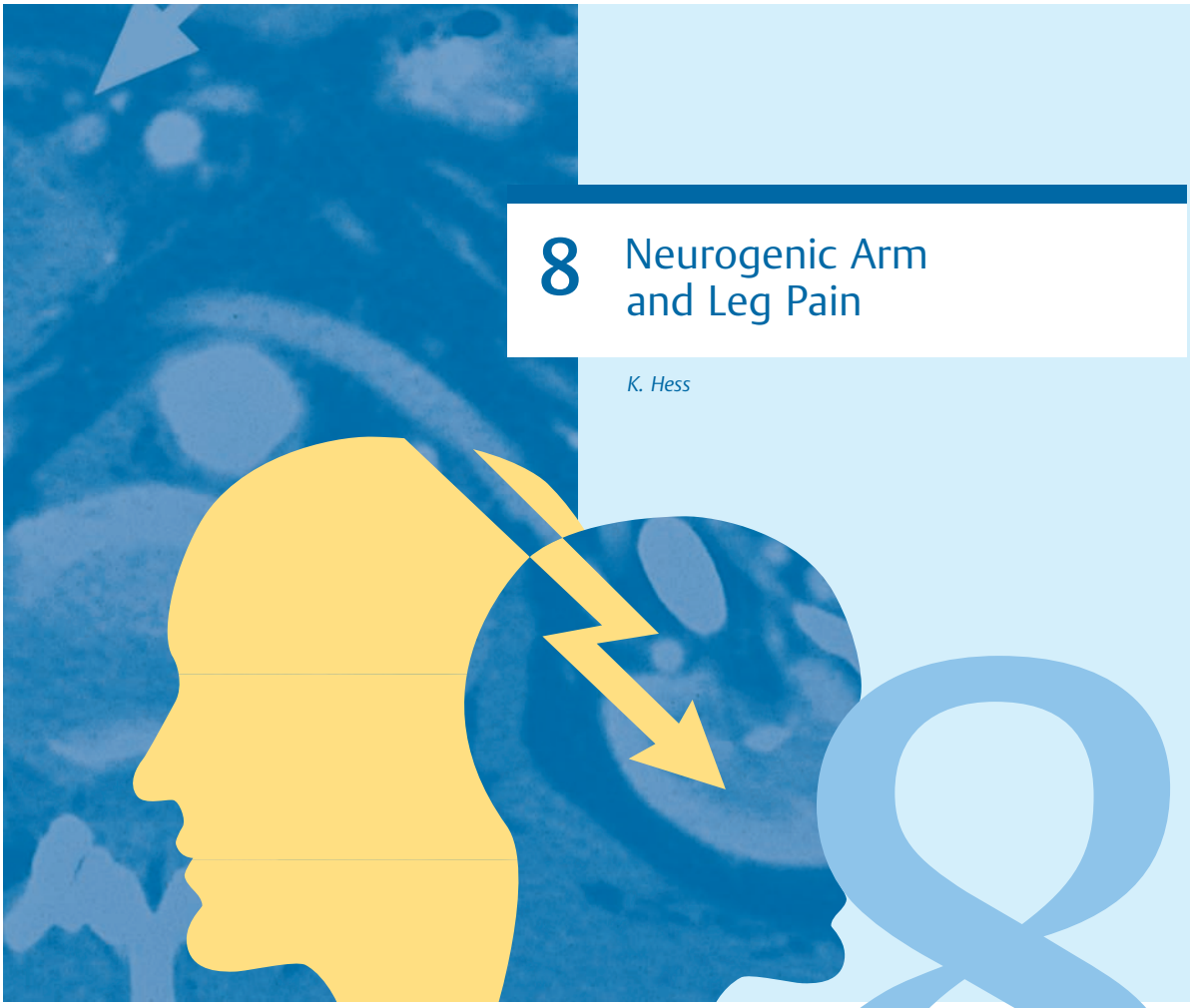

8 Neurogenic Arm and Leg Pain

K. Hess

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8.1 Introduction and Definitions

The differential diagnosis of the cardinal symptoms of neurogenic pain includes neurological diseases and syndromes with prodromal or predominating, accompanying neurogenic pain. Included are internal medical, rheumatological, as well as a few gynecological, urological, and dermatological pain syndromes with similar pain character, localization, and evolution. The differential diagnosis of neurogenic pain should help to quickly obtain a diagnosis. Symptoms and signs of neurological diseases and syndromes are discussed if they are relevant for the differential diagnosis. More detailed descriptions can be found in the dedicated literature.

Definition and Clinical Findings of Neurogenic Pain

Definition. Unpleasant, bearable to unbearable body sensations are generally termed painful, with the exception of some special forms (itching, burning, tingling). Neurogenic pain is that which arises from a primary disorder, trauma, or dysfunction of neural afferent structures or their accompanying structures. Here, root pain (radicular pouch pain? neural pain?) is included in the term "neurogenic," although its pathogenesis is controversial. This is justified by the fact that root pain cannot be distinguished from other neurogenic pains based on its symptomatology.

Characteristics of Pain. In general, neurogenic pain can be clearly distinguished from other sources of pain (Tab. 8.**1**).

- Frequently, neurogenic pain is particularly disagreeable and of a *neuralgiform* (i. e., cutting, burning, or electrifying) character that is, astonishingly enough, independent of whether the lesion/dysfunction is within the central or peripheral nervous system. In addition, this form of pain is often largely *resistant to conventional nonsteroidal analgesics* or opiates, and causes an enormous amount of suffering.
- Neurogenic pain typically occurs within the area of *innervation of a nerve or central afferent system* (dorsal root of the spinal nerves, spinoreticularthalamic projections, posterior fasciculus, thalamus, corona radiate). Correspondingly, the particular somatotopical location of neurogenic pain is diagnostically very important. Central pain often presents itself in the arm or leg as a hemi-pattern, quadrant-pattern or para-pattern; rarely is it monomelic or tetramelic (e. g., high paraplegia). Radix, plexus, or mononeuropathy pains are monomelic and rarely quadrantic. Polyneuropathy pains are mostly distal and paramelic or tetramelic.
- Often *dysesthesia*, such as tingling/stabbing or a sensation of being constricted (shell/girdle/swelling), as well as *neurological signs are found within the area of pain*. Various dysfunctions may exist in pain of central origin. Loss of graphesthesia, positional and vibration senses are linked to functional disturbances of the posterior column. Disturbances of the anterior column result in sensory deficits of a central dissociated type (absence of pain perception and temperature perception but normal sensibility to touch). With radicular or peripheral nerve pain, hypesthesia and fluctuating hypalgesia are found, and tactile dysesthesia, allodynia or hyperalgesia are also common (Tab. 8.**2**).
- *Provocation tests* (see Tab. 8.**1**) are important diagnostic tools in lesions of the peripheral nervous system. With respect to the site of the lesion, however, they should be interpreted carefully. Lasègue sign, femoral stretch pain, and pain when the arm is pulled by the examiner are primarily considered radicular provocation maneuvers although they may be positive in distal nerve lesions as well. Likewise, the abnormal Tinel sign of the distal nerves may be positive in proximal lesions (Valleix point!). Except for the positive Lasègue sign in myelopathies, there are no similar tests in central pain syndromes.
- *Autonomous disturbances* within the area of pain in lesions of the peripheral nerves are associated with hypofunctions (anhidrosis, absence of piloerection) or dysfunctions (dyshidrosis, vasodysregulation, see Algodystrophy Syndromes, section 8.5) but typically do not occur in radicular syndromes. Central lesions rarely may cause autonomous disturbances, in particular anhidrosis, in the arms or legs.

Neuralgia. As a good rule of thumb one should keep in mind these associations:

- rheumatologic pains with local inflammatory signs or pain upon pressure
- continuous vascular pains with circulation disorders
- dermatologic pains with skin changes
- neurogenic pains with sensory disturbances, as described above.

However, neuralgiform pain often long precedes any local signs. In addition such signs may be absent entirely, or either barely detectable clinically or only through further investigations. Diseases that manifest themselves exclusively, or mainly, with neurogenic pain are termed *neuralgias*.

Deafferentation Pain. The theory of deafferentation pain stems from the experience that pain emerging from structural lesions of the peripheral nervous system may become detached from its origin, i. e., it cannot or can

Table 8.**1** Neuralgiform pain: clinical criteria

- Pain character (duration/paroxysmal pain; often burning) and resistance to analgesics
- Pain areas (neurological projection areas)
- Neurological signs (sensory disturbance)
- Provocation tests
  - cervical spine provocation maneuvers, pulling the arm, Lasègue sign, femoral nerve stretch pain
  - costoclavicular compression, Valleix pressure points
  - Tinel sign (abnormal mechanical sensitivity of the nerves)

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only moderately be altered by blockades and other manipulations at the site of the lesion. Causative factors such as the critical extent of the lesion, the timing, and preceding manipulations are not yet fully understood. However, it must be a lesion of a large nerve (ulnar, median, sciatic, plexus, radix; Tab. 8.**3**), and the condition is often preceded by an algodystrophy syndrome (see section 8.5).

Differential Diagnosis. Myalgia, cramps, tetanus, painful spasms, and dystonia, as well as neuromyotonia are not neurogenic pains according to the definitions as outlined above. They are easily recognized by their additional signs and are only listed here as part of a comprehensive differential diagnosis.

Table 8.**2** Sensory disturbances and pain: somatology and terminology

Medical history and symptoms
- Numbness
- Disturbance of sensation
  - spontaneous = paresthesia e. g., burning, tingling, constricted
  - by touching = dysesthesia e. g., electrifying, burning, sandlike
- Neuralgiform pain
  - continuous pain, often boring, dull, or cutting, e. g., radicular pain
  - lancinating pain (paroxysmal), e. g., trigeminal neuralgia, diabetes mellitus, Fabry syndrome, tabes dorsalis
  - causalgia (burning, often fluctuating)

Clinical findings
- Hypesthesia–hypalgesia–thermhypesthesia: raised threshold, normal perception of the sensory modality
- Hyperesthesia–hyperalgesia: lowered threshold, normal perception of the sensory modality
- Dysesthesia = sensory disturbance of the senses touch or pain, i. e., abnormally perceived sensory modality, different from pain
- Allodynia = sensation of pain for tactile stimuli, i. e., abnormally perceived sensory modality e. g., in postherpetic neuralgia
- Hyperpathia = abnormally, intense (mostly burning) pain, of abnormal duration and extension despite raised threshold
- Causalgia = burning pain in residual (severe) lesions of a nerve, associated with autonomic disturbances, i. e., algodystrophy syndrome (complex regional pain syndrome type II)
- Pallanesthesia/pallhypesthesia = loss of vibration sense

Table 8.**3** Clinical syndromes with deafferentation pain

- Avulsion of a spinal root, tearing or amputation of a plexus
- Postherpetic
- Plexus lesion after radiotherapy
- Extended lesion of the median, ulnar, or sciatic nerve (e. g., postoperative or traumatic scarring)

8.2 Central Pain Syndromes (Brain, Spinal Cord)

Neurogenic pain of central origin is rarely seen in the everyday neurological practice. However, there are a number of prominent syndromes of differential diagnostic relevance with the cardinal symptom pain, which are caused by lesions in central, afferent projection systems. Usually, they are easily diagnosed in the neurological context.

Déjerine–Roussy Syndrome. Continuous, intense, and therapeutically unresponsive pain, together with hemianesthesia of all modalities, may develop as the result of lesions in the posterolateral thalamus, mostly caused by vascular infarcts; it is often pronounced in the arm and accompanied by hemiataxia, choreoathetosis (hand, feet), and anomalous postures ("thalamic hand"). The neurological examination determines the diagnosis. Rarely, parietal (sub-)cortical infarcts or tumors cause similar sensory disturbances (pseudothalamic syndrome). In parietal lesions a rare, so-called pain asymbolia may be observed in which the patient perceives pain yet remains indifferent.

Wallenberg Syndrome. Intense unilateral facial or arm pain, or hemilateral pain may herald or initially accompany a lateral medullary infarction. The diagnosis is made from the neurological examination findings of Horner syndrome, crossed dissociated sensory disturbance, and deficits of caudal cranial nerves (dysphagia, hoarseness, rhinolalia). Other deficits, in particular vestibulo-cerebellar dysfunctions, are sometimes also associated with the syndrome. Carotid dissection with Horner syndrome is obvious in the differential diagno-

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sis. The dissociated sensory disturbance and other findings are decisive (see Chapter 5, Facial Pain).

Anterior Spinal Artery Syndrome. Acute, mostly intense, back pain and particularly bilateral leg pain, occurring hours before the onset of pareses, often herald and dominate the syndrome, together with burning or stabbing sensations and disturbed temperature sensation in the areas which later will be hypesthetic. A *dissecting aneurysm of the abdominal aorta* can also begin with these signs and symptoms, but does not necessarily develop into the typical neurological syndrome with paraparesis, sphincter paresis, and dissociated sensory disturbance with a para-pattern or quadrant pattern. Rarely, a spinal *subarachnoid hemorrhage* and an *epidural abscess/hematoma* can have a similar onset. However, meningism, local vertebral findings, and inflammatory signs will lead to the correct diagnosis. *Hematomyelia*, traumatic or in connection with a spinovascular malformation, can be reliably delineated from the anterior spinal artery syndrome only by magnetic resonance imaging.

Syringomyelia. Unilateral or bilateral longstanding insidious weakness in the arm, together with loss of pain and temperature sensation, numerous burn scars, and poorly healing wounds indicates this diagnosis in patients with ill-defined, often fluctuating, yet persistent pains in the arm(s). The pain frequently has a para-pattern or quadrant pattern. The neurological syndrome with atrophic hand or arm paresis, dissociated sensory deficit, often spastic ataxic gait disturbance, and loss of posterior column functions render the diagnosis likely. Reliable delineation from an *astrocytoma* or *ependymoma of the spinal cord* is accomplished by magnetic resonance imaging.

Funicular Myelosis. Acral tingling, including the nose, chin, and ears, is almost always the cardinal symptom. Rarely, the disorder begins with searing leg and/or arm pains. The neurological examination reveals a polyneuropathy syndrome and the diagnosis can be made quickly with the help of further diagnostic investigations.

Tabes Dorsalis. Sharp, so called "lancinating" pain, occurring repeatedly at the same location is the trademark of this currently rare tertiary syphilis. Pain localizations can vary and are mainly in the legs or the trunk. Pathogenetically, it is assumed that discharges in the posterior root play an important role. The classic neurological syndrome with Argyll Robertson pupil, posterior root syndrome, and posterior column syndrome, with areflexia and ataxia, as well as "trophic" arthropathies and ulcers is unmistakable.

Disseminated Encephalomyelitis. With the exception of trigeminal neuralgia (see Chapter 5), pain is not a relevant differential diagnostic cardinal symptom in multiple sclerosis. Dull or sharp, continuous pain in the arms or legs, as well as lancinating pseudoradicular limb pain resulting from posterior column lesions, can be found in patients with a long-established diagnosis and chronic deficits. However, the most common pain in these patients, as in traumatic spinal cord lesions, is of a spastic nature.

Posterior Cervical Contusion. Intense bilateral arm pain radiating into all fingers after a trauma of the cervical vertebrae can last for days to weeks. It is often accompanied by tingling and/or numbness in some of the pain areas. Pathogenetically, microlesions in parts of the posterior columns (substantia gelatinosa) are thought to be responsible for this condition. Bilateral radicular irritation syndromes can be delineated in a differential diagnosis by cervical provocation maneuvers, better defined areas of pain and sensory disturbances as well as the presence of additional reflex and motor deficits.

8.3 Radiculopathy

Radicular pains as a sign of a radiculopathy (Fig. 8.**1**) are, together with headaches, the most frequent "neurological" pains.

> With every pain of neurogenic nature in the arms or legs a radicular affection should always be considered.

Independent of etiology, the clinical manifestations can encompass a radicular irritation and deficit syndrome and local findings (vertebrogenic syndrome). *Radicular irritation syndrome* is defined by a history of radicular pain and positive radicular provocation maneuvers, and indicates the presence of a current radicular compression or other acute lesion (e. g., radiculitis).

Clinical Findings. By definition, radicular pain follows its *dermatome* (Figs. 8.**2**, 8.**7**), although only partial areas may be "occupied" (e. g., only the lateral border of the foot in S1, only the instep in L5, only the inside of the lower leg in L4). The dependence of radicular pain on body position and movement as well as the fact that it can be provoked by certain maneuvers is notable (see Tab. 8.**2**). Each patient knows which head movements will make the arm pain better or worse, or which resting position will make the leg pain come or go. Standing up, walking around, or moving the arm or leg usually im-

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proves the pain, whereas resting or lying down often worsens it. Nights may be agonizing, whereas the day is much better.

Differential Diagnosis. Nocturnal pain of similar nature characterizes osteogenic sarcoma, osteomyelitis, severe obstructive vascular disease, and compartment syndrome, all of which are important differential diagnoses that can be excluded by local findings.

Lower back, back, or neck pains in rheumatologic syndromes can be accompanied by spondylogenic (tendomyopathic, pseudoradicular) radiations in the arms or legs, which often are difficult to distinguish from radicular pains. *Spondylogenic pains* radiate along the motion segments and not along dermatomes and, in contrast to radicular pains, are accompanied by pressure pain but not sensory deficits in the area of the pain. In addition, they are exacerbated during daytime by work and motion, whereas rest and nighttime ease the pain. The pain during coughing, sneezing, pressure maneuvers, or laughter is located in the neck and back in rheumatic patients and shoots along the segment into the arms and legs in "radicular patients."

Pain in central lesions, or in lesions of the plexus or peripheral nerves, is usually uniform and, moreover, is hardly affected by radicular provocation maneuvers.

Diagnostic Tests. *Radicular provocation maneuvers* for cervical roots consist of pulling the arm and cervical spine maneuvers (cervical spine reclination, ipsilateral cervical spine rotation/abduction, each for at least 30 seconds, Fig. 8.**3**). For upper lumbar roots they consist of the femoral stretch maneuver and for lower lumbar roots and S1, the Lasègue sign (Fig. 8.**4**) and sitting with extended legs, also the Valleix pressure points. The maneuvers are not specific for individual roots since they may be positive in lesions of the plexus or large nerves as well. A corresponding radicular deficit syndrome is not obligatory, yet is commonly present.

Radicular deficit syndrome encompasses the motor, sensory, and reflex deficits resulting from a radicular lesion. The deficit may be absent or only negligible. In particular, in monoradicular deficits, often only a band of hypalgesia (with otherwise normal sensibility) and a variance in reflexes, without apparent paresis, are detectable, due to the strong overlap with neighboring segments.

> The often biphasic time course of radicular (compression) syndromes, i. e., first radicular pain, then a deficit syndrome is of note.

Compressive radicular syndromes and *radiculitis* are the two main etiologic groups of radiculopathies (Tab. 8.**4**). The neurological manifestations are similar and determined by the affected root. Etiologic evidence is gained only after clarification of the local findings.

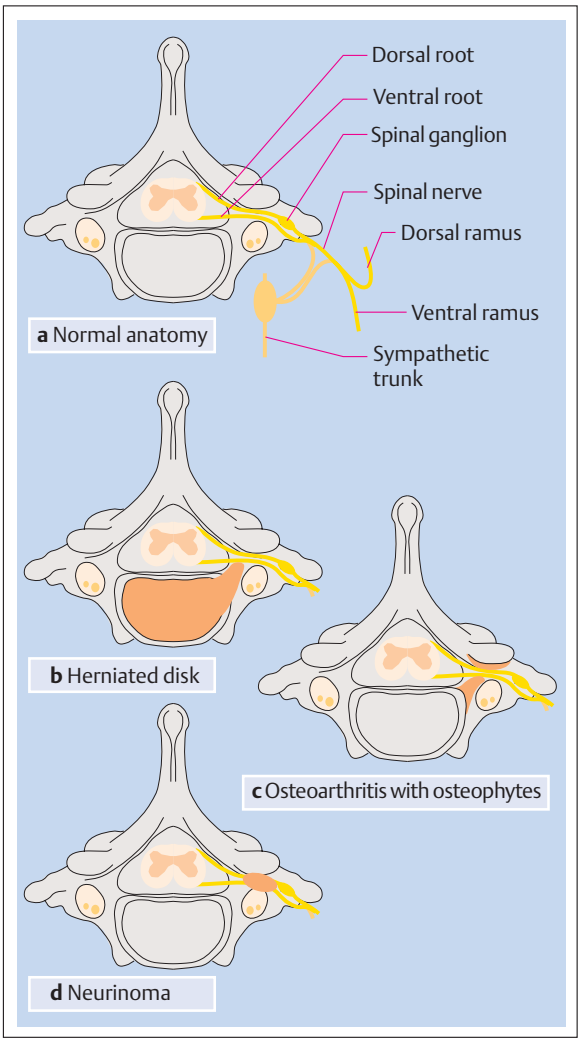

Fig. 8.**1** Spinal cord segment
a Schematic diagram of the thoracic level. Important: the cervical (except spinal nerve C8) and lumbar segments do not have their own sympathetic efferences, but rather receive them from the sympathetic trunk.
b herniated disk
c arthrosis with osteophytes
d neurinoma.

Table 8.**4** Causes of radicular syndromes

Compression by the musculoskeletal system
– Herniated disk
– Osteochondrous, spondylotic stenosis of the foramina
– Narrow lateral recess
Tumor
– Metastasis
– Neurinoma, meningioma
Radiculitis
– Herpes zoster
– Borreliosis
– Sarcoidosis (Boeck disease)
– Behçet disease

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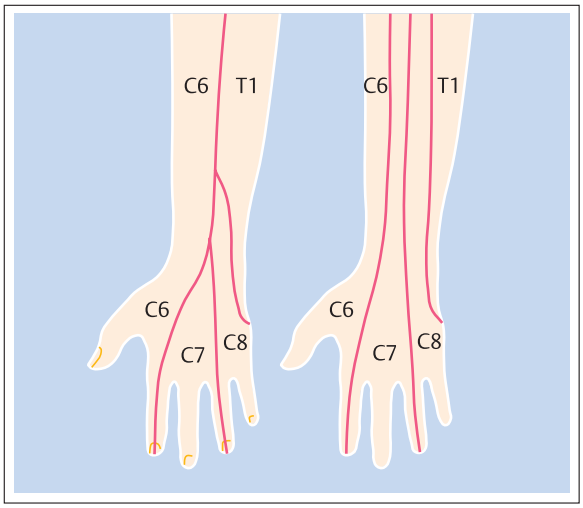


Fig. 8.**2** Dermatomes C6/C7/C8 in the forearm and hand. Radicular irritation causes radiation of pain into and/or tingling in the respective segment. C6 = thumb, C7 = middle finger, C8 = little finger. Index and ring finger vary.

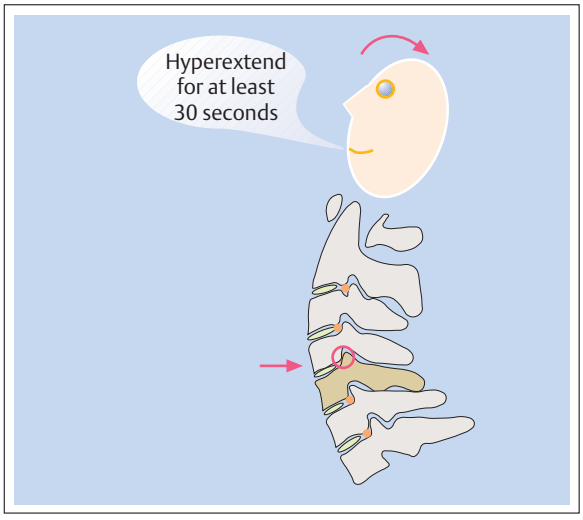


Fig. 8.**3** Provocation maneuver to test for signs of cervical radicular irritation: hyperextension of the cervical spine. Irritation symptom: tingling and/or pain in the affected dermatome. Combined rotation/abduction of the cervical spine may cause (ipsilateral) radicular irritation symptoms.

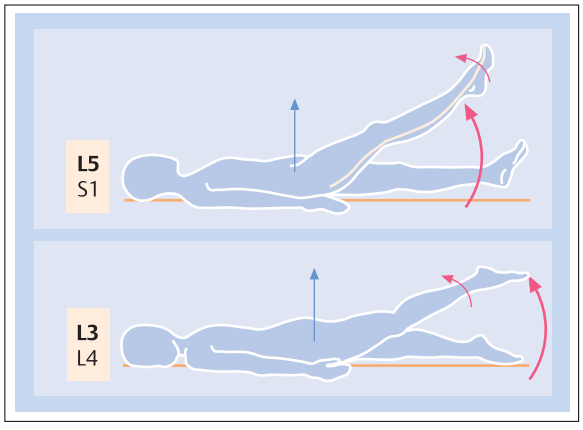
Radicular Compression Syndromes:

- A herniated disk often occurs acutely with/after a "lifting trauma" and is typical in young adults.
- Compression syndromes in *degenerative obstructions of foramina* or *lateral recesses* are common in long-term back patients, and often the onset is poorly defined. Multiradicular syndromes are frequent and confusing. With a refractory course one must consider at an early stage space-occupying processes such as a neurinoma, a meningioma, or a metastasis.
- *Neurinoma of the root* is prototypical for strangulating compression of a root over many months to years. Fluctuating, yet increasingly persistent, radicular pain dominates. Sensory or motor monoradicular deficits are insidious and remain inconspicuous for a long time. In these cases, neuroimaging results are also decisive.
- Similar courses are observed in *meningioma* and in slower progressing, solitary *bone metastases* (above all breast, kidney, and thyroid carcinomas). Multiple bone metastases, multiple myeloma, and malignant lymphoma in the spinal region attack massively with quickly intensifying bone and radicular pain, multiradicular deficits, and early compression of the spinal cord and cauda.

Radiculitis. Shingles (herpes zoster) is the prototype of a radiculitis. The radicular pain sometimes precedes the exanthematous delineation of the dermatome by days. The persistent, wearing, postherpetic pains are almost always accompanied by skin changes in the affected dermatome.

Borrelia radiculitis can begin and remain monoradicular. The pain, however, is often bilateral–zonal or saltatory–pluriradicular and ends without a skin rash in a radicular deficit syndrome.

Rare etiologies are granulomatous processes like tuberculosis, sarcoidosis, and Behçet syndrome.



◁ Fig. 8.**4** Provocation maneuvers to test for signs of lumbar radicular irritation.

a Lasègue sign (L5, S1). Lancinating pain in the affected dermatome, together with blocked movement in the hip joint and involuntary pelvic tilt (blue arrow) are the criteria for judgment. The extension of the foot (*Bragard sign*) aggravates the pain. Additional or isolated tingling may ensue in the affected dermatome if the leg is continuously lifted.

b Femoral stretch pain (L3, L4!). The femoral stretch pain (*reversed Lasègue sign*) is aggravated by simultaneous, gentle flexion of the knee. Note: provoked back pain or tearing/pulling in the thigh are not radicular signs (*pseudo-Lasègue sign*).

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8.4 Plexus Lesions, Polyneuropathy, and Mononeuropathy

Clinical Findings. In contrast to most painful radicular affections, acute *focal lesions of the plexus of peripheral nerves often proceed painlessly*. This is mainly due to the high number of motor fibers and the different anatomical structures which make compression less likely compared to the anatomically restricted spinal ganglia. In addition, a circumscribed lesion of sensory fibers does not primarily cause pain, but instead, sensory loss or distortion (paresthesias, dysesthesias) in the sensory area. For example, compressive ulnar or radial pareses or a traumatic upper plexus paresis are generally painless. Even a neoplastic plexus compression may manifest as a painless leg or arm paresis with numb areas. *Long lesions* of mixed or sensory nerves, on the other hand, tend to cause neuralgiform pain, which must be delineated from radicular syndromes. Typical examples are the perioperative stretching of the sciatic nerve. Moreover, massive lesions of parts of a plexus or peripheral nerve with a large sensory volume (median or sciatic nerve) may cause deafferentation pain as observed after avulsion of a root.

Diagnostic Tests. Besides the diagnostically decisive neurological deficit syndrome, the abnormal Tinel sensitivity of the impaired sensory nerve is the most important diagnostic sign (see provocation maneuvers, Tab. 8.**1**). With respect to the Tinel phenomenon, it must be kept in mind that even a healthy nerve can be stimulated mechanically (danger of false-positive signs if not tested on both sides) and that the positive Tinel sign and localization of the lesion must not necessarily correspond. For example, the Valleix pressure point, which represents abnormal Tinel sensitivity of the sciatic nerve at the buttock, is positive in the case of an S1 radicular compression as well as that of a sciatic lesion at the thigh.

Etiology. As is true with radicular syndromes, the signs and symptoms may not, or only to a limited extent, allow one to determine the etiology. The etiologic clarification (Tab. 8.**5**) entails two steps: first, localization of the lesion, then determination of its etiology.

In the arms and legs, entrapment and compression neuropathies as well as traumatic lesions are etiologically predominant, and all other causes are comparatively rare.

Table 8.**5** Causes of plexus lesions and mononeuropathies

- Traumatic lesion with/without neuroma, causalgia
- Entrapment neuropathy/compression neuropathy
- Neurinoma
- Vasculitis
- Plexitis/neuritis
- Postradiation lesions

8.5 Algodystrophy Syndromes

Mild autonomous dysfunctions, which extend over the area of a lesioned peripheral nerve, are common and are identifiable by their sudomotor, sympathetic response. However, after a severe local trauma, more widespread and severe autonomous reactions may develop, which are almost always associated with a permanent pain in the affected area. These pain syndromes, which are pathogenetically only partially understood and grouped as algodystrophy syndromes, are distributed and sustained, but not directly caused, by dysfunctions of the autonomous system. Many different names complicate the nomenclature:

- *Sudeck syndrome* (algodystrophy syndrome) is a focal variant.
- *Complex regional pain syndrome* (CRPS), formerly referred to as posttraumatic reflex sympathetic dystrophy or causalgia if the pain was of a burning character, is topographically more widely distributed.
- The so-called *quadrant syndrome* (see below) is the most extended variant, with involvement of the entire associated quadrant of the body, according to the functional anatomy of the autonomous system.

Etiology. Triggers are often mild traumas, as well as severe limb traumas, such as fractures or traumas of the nerves of varying severity. Spontaneous onset without a clear external cause has also been reported.

Clinical Findings. In the area of fluctuating, burning or dull, persistent pain or dysesthesia, signs of autonomous dysfunctions such as varying redness, hyperhidrosis, and swelling of the hand or foot should, at least temporarily, be detectable. Neurological findings include an impairment of superficial sensory functions, sometimes a hypalgesia, tactile dysesthesias, allodynia, or hyperpathy.

The following indicators restrict the differential diagnoses of algodystrophy syndromes to mainly nonneurological diseases: osteomyelitis, osteogenic sarcoma, painful pseudoarthrosis, inflammatory skin and joint diseases.

Pain, dysesthesia, and sensory and autonomous disturbances can spread across an entire quadrant of the body (*quadrant syndrome*). In the majority of patients, a sympathetic blockage, either by conduction anesthesia or guanethidine, alleviates the pain. Quadrant syndrome can also be caused by a lesion of the sympathetic trunk, whereby upper quadrant syndrome is often accompanied by signs of sympathetic deficit, such as Horner syndrome and anhidrosis. Pancoast syndrome

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frequently manifests in this way, including radicular arm pain (malignant infiltration of the nerve roots) that occurs sooner or later in the course of the disease.

Differential Diagnosis. Focal algodystrophy syndromes must mainly be delineated from local inflammatory processes like osteomyelitis. Quadrant syndrome must be differentiated from central, mainly spinal, pain syndromes such as those resulting from syringomyelia or astrocytoma. Crossed neurological findings are usually easy to clarify.

8.6 Differential Diagnosis of Unilateral Neurogenic Arm Pains

Topical Neurological Syndromes:

- central pain syndromes of the arms
- radicular syndromes
- lesions of the plexus
  - Pancoast syndrome
  - plexitis, including neuralgic shoulder amyotrophy
  - familial plexopathies (hereditary neuralgic amyotrophy, relapsing familial plexopathies)
  - radiation-induced plexus pareses
- thoracic outlet syndrome (TOS) (scalenus anterior syndrome, scalenus anticus syndrome, Naffziger syndrome)
- pronator teres syndrome
- carpal tunnel syndrome
- neuropathy of the cutaneous antebrachial posterior and medial nerves, as well as the posterior branch of the ulnar nerve
- cheiralgia paresthetica
- digitalgia paresthetica.

Clinical Features and Differential Diagnosis

Central Syndromes. Unilateral arm pain of central origin is generally unmistakable due to the accompanying neurologic findings. Acute initial pain in the arm (and face) is typical for Wallenberg syndrome. Gradually increasing pain in the arm after a stroke is typical for Déjerine–Roussy syndrome. Arm pains due to syringomyelia or an astrocytoma in the cervical spinal cord, rarely due to multiple sclerosis, are insidious, dull, and tearing, with a tendency to become bilateral. Accompanying neurologic signs and corresponding neuroimaging findings easily confirm the diagnosis. Diffusely localized, tearing shoulder or arm pain, particularly while working with the arms, can signal a latent dystonia and herald the onset of Parkinson syndrome or a torticollis.

Radicular Syndromes. In extensive neuralgiform arm pain, the three most common cervical radicular syndromes C6, C7, and C8 must be evaluated (see Radiculopathy, p. 302). It should be kept in mind that the dermatomes (see Fig. 8.**2**), often only partially, and predominantly distally, show evidence of pain and/or sensory loss. This may result in misleading overlaps with areas of the peripheral nerves.

- *C6 syndrome* with painful areas in the lateral upper arm, the medial forearm, and the thumb (and index finger) can be easily distinguished clinically from carpal tunnel syndrome, in which nocturnal pain and rare tingling sensations may extend beyond the area of the median nerve in the hand, but the clinically observable sensory loss never does (see below).
- *C7 syndrome* with painful areas in the anterior upper arm, anterior forearm, as well as the index and middle finger should also be distinguished from carpal tunnel syndrome.
- *C8 syndrome* with painful areas at the inner side of the upper arm and forearm, the medial side of the hand, as well as the ring and little fingers may occasionally be difficult to distinguish from scalenus anterior syndrome (Naffziger syndrome with lower plexus paresis, see above) or from a painful ulnar nerve lesion, if the area of the pain is only partial. Radicular provocation maneuvers, the local findings on the cervical spine, upper thoracic aperture, and ulnar nerve, and the distinct neurologic signs are definitive. C8 syndrome may be an essential part of Pancoast syndrome (see below).
- The rare upper cervical radicular pain *syndromes C3 and C4* are characterized by pain in the neck, cervical triangle, or the shoulder, and are easily recognized only if discernable deficits are found, e. g., sensory loss in the respective dermatomes and/or paresis of the diaphragm.
- *C5 radicular syndrome* can also cause refractory pain in the scapula. Radicular provocation maneuvers or sensory loss in the dermatome are helpful if accompanying shoulder or upper arm pain is absent.

The term *neuralgic shoulder amyotrophy* encompasses many acute painful arm pareses with the typical course of pain followed by paresis of predominantly one or more shoulder muscles. Radicular compression syndromes and radiculitis are most often causative, less frequently plexus neuritis (see below). If the pain is mostly in the shoulder and upper arm, the C4 or C5 nerve roots and possible sensory disturbances in areas at the deltoid and the neck must be evaluated.

Plexus Lesions. *Pancoast syndrome*, typically caused by adenocarcinoma or squamous cell carcinoma of the

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lung, denotes the characteristic disease of the cervical plexus and radicular infiltration by a malignant process. The carcinomatous penetration of the pleural cupula causes shoulder pain, which quickly evolves into a quadrant syndrome. An often dominating arm pain, which mainly radiates into the ulnar region, is the sign of the infiltration of the plexus and the C8 and T1 roots. In contrast to radicular processes, infiltration of the sympathetic trunk causes autonomic dysfunctions with ipsilateral Horner syndrome and quadrantic anhidrosis, which may long precede the motor and sensory losses of a combined C8/T1 lesion.

Painful plexus lesions may be difficult to differentiate from multiradicular deficit syndromes because, for instance, cervical radicular provocation maneuvers can yield false positives. The most important features are a striking onset with dominating shoulder or arm pain, excessive Tinel phenomena, and frequent pain to pressure in the supraclavicular soft tissue, as well as distinct neurologic findings (spared muscles of proximal nerves). The history must be scrutinized for previous vaccinations (tetanus!), serum sickness, cytomegalovirus or Epstein–Barr virus infections, injections of contaminated heroin or cocaine, and a positive familial history (hereditary neuralgic amyotrophy). Moreover, systemic necrotizing vasculitis in polyarthritis nodosa, Churg–Strauss syndrome, Wegener granulomatosis, or allergic angiitis can begin with plexus neuritis. Often, however, the disease is idiopathic.

Radiation-induced plexus injuries with initial, neuralgiform arm pain are easily identifiable in view of the case history and typical skin changes. A traumatic plexus laceration (frequently together with avulsions of the roots) is dominated by paresis and sensory loss, and the deafferentation pain follows later.

Thoracic Outlet Syndrome. Differentiation of *neurogenic shoulder girdle syndrome* from the collection of the so-called thoracic outlet syndromes (TOS) is often very difficult. The best defined and most frequent TOS is cervical rib syndrome, caused by a taut ligament that spans from an abnormal C7 transverse process or from the stump of a cervical rib to the first rib, thereby compressing the medial trunk from below. Fatigue, pain, and tingling in the arm, provoked or aggravated by working with or lifting of the arm, are all hallmarks, albeit unspecific. Sensory loss on the ulnar side of the forearm, later in the ulnar side of the hand, is typical. Pareses and atrophies of the muscles of the hand may be absent for a long time. Atrophy of the thenar muscle, which later becomes conspicuous, often leads to the misdiagnosis of carpal tunnel syndrome. The brachial plexus is often Tinel sensitive in the supraclavicular area, and the costoclavicular compression maneuver (Fig. 8.**5**) usually evokes prompt tingling in the forearm and hand. Coracoid, angulated transverse C7 processes, cervical, or stump ribs (Fig. 8.**6**) effectively confirm the diagnosis. Neurogenic shoulder girdle compression syndromes without these radiological findings are very rare. Although such rib anomalies are found in approximately 0.5 % of the healthy population, they have no pathological significance alone.

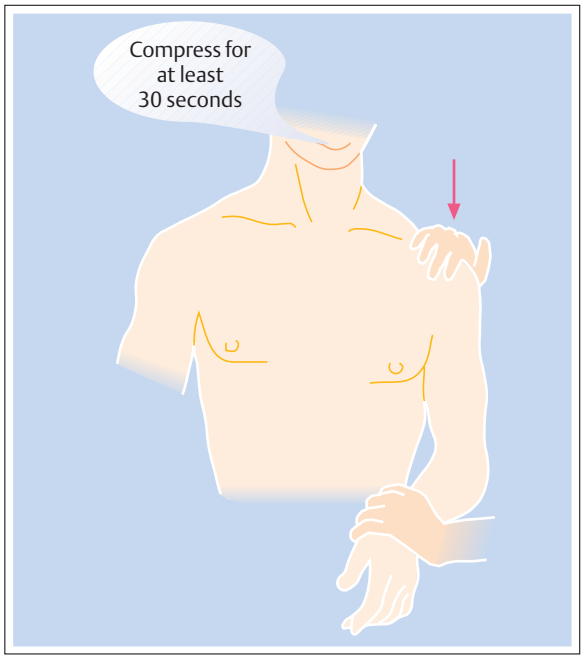

Fig. 8.**5** Costoclavicular compression maneuver. While the patient keeps his upper body relaxed in a slightly forward position, the shoulder is strongly pressed downward by the examiner (red arrow). In neurogenic, *thoracic outlet syndrome*, segmental tingling and numbness are provoked. Note: only a unilateral, positive maneuver on the side of the symptoms can be assessed.

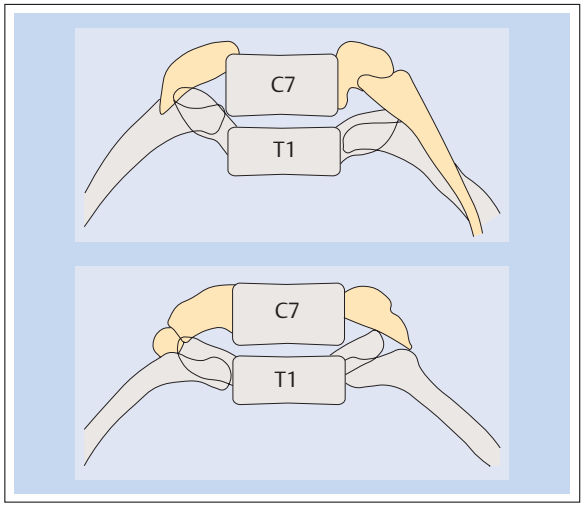

Fig. 8.**6** Anomaly of the C7 transverse process. Deformed C7 transverse process and cervical rib or rib stump in 2 patients with neurogenic *thoracic outlet syndrome*, redrawn from the radiographs. The side with the coracoid, angulated, transverse processes is symptomatic. Note: 0.5 % of healthy people have similar, yet asymptomatic anomalies.

Carpal Tunnel Syndrome. Carpal tunnel syndrome, a "nocturnal troublemaker" like the radicular pain

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syndromes, is rightfully called "*brachialgia paresthetica nocturna*." Typically, it starts with a tearing pain in the hand or arm, always with numbness or tingling, at night or early in the morning. Shaking or massage quickly alleviates the pain. During daytime, tingling or numbness occurs in one or in all fingers that are innervated by the median nerve; initially only after work, later permanently. Numbness in the fingertips, reduced fine motor coordination, and, often late in the course, atrophy of the thenar muscle, are indicative. The Phalen test and electrodiagnostic tests confirm the diagnosis. Difficult to distinguish in a differential diagnosis are the C6 radicular syndrome (tingling in the thumb and index finger) and C7 (index and middle finger). The segmental sensory disturbance of the radicular syndrome with the inclusion of the dorsal hand area and the forearm, reflex differences, and most importantly cervical radicular provocation maneuvers and radiographic studies of the cervical spine in four planes, clarify the diagnosis.

Pronator Teres Syndrome. This is a rare compression neuropathy of the median nerve in the elbow, which is heralded by tingling in the hand and pain in the forearm, e. g., after hours of using a screwdriver. Abnormal Tinel sensitivity of the median nerve in the elbow and sensory loss in its area, including the palmar branch, are important indicators for a correct diagnosis. Electrodiagnostic tests clarify the tentative diagnosis. As is true for cervical rib syndrome with similar onset (see above), a careless diagnosis, even from the specialist, often leads first to the ineffective decompression of the median nerve at the wrist.

Sulcus–Ulnaris Syndrome. The sulcus–ulnaris syndrome is usually painless, but frequently accompanied by an annoying epicondylitis at the elbow with exercise-dependent pain radiating into the wrist and typical local pain to pressure.

Sensory Neuropathies. *Mononeuropathy* of purely sensory nerve branches is rare in the arms. Most often it becomes apparent with numbness and/or tingling in the affected area, sometimes also with burning and painful sensitivity to touch. Localized sensory disturbances and the Tinel sign are diagnostic. Etiologically, scars from long-forgotten accidents or operations and neuromas must be looked for in the first instance. In addition, compression or entrapment neuropathy, neurinoma, glomus tumor (Tinel sign with palpatory findings!), as well as diabetes and vasculitis (in particular, periarthritis nodosa) with a multiplex type of mononeuritis, are further possibilities. Polyneuropathy may begin as a mononeuropathy. Hereditary neuropathy with liability to pressure palsies (HNNP) with its erratically changing pareses caused by pressure is an example of this type of progression.

Cheiralgia paresthetica, i. e., neuropathy of the superficial branch of the radial nerve, is a typical sensory mononeuropathy. At a minimum, the area of the anatomical snuffbox is affected. The condition is most often due to pressure by a watchband or a tool. Analogously, there are neuropathies of the medial antebrachial cutaneous nerve and of the dorsal branch of the ulnar nerve (side of the hand). The *digitalgia paresthetica* of single digital branches is most often the result of a pressure lesion as well. Particularly in neuropathies of the fingers with a localized pain to pressure, glomus tumors must be taken into consideration. These are not always located under the fingernail, but cannot be missed upon thorough inspection.

8.7 Differential Diagnosis of Unilateral Neurogenic Leg Pains

Topical Neurological Syndromes:

- central pain syndromes of the legs
  - anterior spinal artery syndrome, Parkinson syndrome, dystonia syndromes
  - multiple sclerosis
- radicular syndromes
  - special form: lumbar spinal stenosis with neurogenic claudication
- lesions of the plexus
  - malignant processes, radiation lesions, plexitis
  - retroperitoneal hematoma
- syringe injuries
- proximal asymmetric diabetic neuropathy
- mononeuropathies
  - piriform muscle syndrome
  - ilioinguinal and genitofemoral nerve neuropathies (spermatic neuralgia)
  - paresthetic meralgia
  - paresthetic gonalgia
  - tarsal tunnel syndrome
  - Morton neuralgia
  - digitalgia paresthetica.

Signs and Differential Diagnosis

Central Syndromes. Unilateral leg pain of central origin is rare. Diseases with bilateral leg pain (see below), which may begin unilaterally as an exception, e. g., anterior spinal artery syndrome, must be taken into consideration. Déjerine–Roussy syndrome (see above) is easily identified clinically. Parkinson syndrome may be heralded by wrenching leg pains, which are aggravated by exercise, as a sign of an associated dystonia. Finally, infiltrating or excavating processes in the distal spinal cord, as well as multiple sclerosis, may cause chronic, dull, or tearing

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unilateral or bilateral pain in the leg; accompanying sphincter dysfunction, and/or dissociated sensory disturbances are pertinent to localization and diagnosis.

Radicular Syndromes. In neuralgiform leg pain, the presence of the three most frequent radicular syndromes (L4, L5, and S1; Fig. 8.**7**) should first be investigated according to the criteria outlined in the section on radiculopathies:

- *L4 syndrome* with painful areas in the anterior thigh and medial lower leg has a differential diagnostic overlap only with meralgia (see below), and lesions of the saphenous nerve (paresthetic gonalgia) if the area of the pain is only partial.
- *L5 syndrome* with painful areas in the posterolateral thigh, shin, instep, and big toe can hardly be mistaken if osteomyelitis and compartment syndromes are excluded.
- *S1 syndrome* with painful areas in the posterior thigh, lower leg, lateral border of the foot, and little toe must also primarily be differentiated from nonneurological pain.
- The rare *L3 associated pain syndrome* like the L4 syndrome must be differentiated from meralgia (see below). Likewise, the rare *L1* and *L2* pain *syndromes* must be differentiated from neuropathies of the iliohypogastric, ilioinguinal, and genitofemoral nerves (see below). In radicular pain syndromes of unknown origin, plexus lesions must be considered in a differential diagnosis.

Neurogenic claudication goes against the rule, since rest aggravates radicular pain. The leg pains are of the radicular type, yet they are initiated by walking or standing, and are almost always accompanied by tingling in the feet or a sense of heaviness in the legs. Causes are a lumbar lordosis formation in combination with degenerative narrowing of the foramina or spondylolisthesis. One or more roots may be affected. Bending over or lying down frequently alleviates the pain quickly. The differential diagnosis of peripheral, vascular claudication is easy, given the radiation pattern of the pain and tingling and findings after palpation of the pulses. (The very rare neurogenic claudication in vascular or compressive spinal cord diseases with marginal perfusion, which deteriorates with exercise, causes little or no pain.)

Plexus Lesions. As with the arms, painful plexus pareses of the lower limbs may be difficult to differentiate from (multi-)radicular lumbar irritation or sensory loss syndromes. The neuralgiform pains are described as "sciatica" and are frequently localized in one dermatome (monoradicular), e. g., only in the lower leg. There are no direct plexus provocation maneuvers (pressure to the hypogastric region sometimes causes lancinating pain), but the Lasègue sign may be positive as with a radicular irritation. Further neurological exploration (involvement of the paraspinal muscles, pattern of sensory disturbance) and local abdominal and neuroradiologic findings confirm the diagnosis.

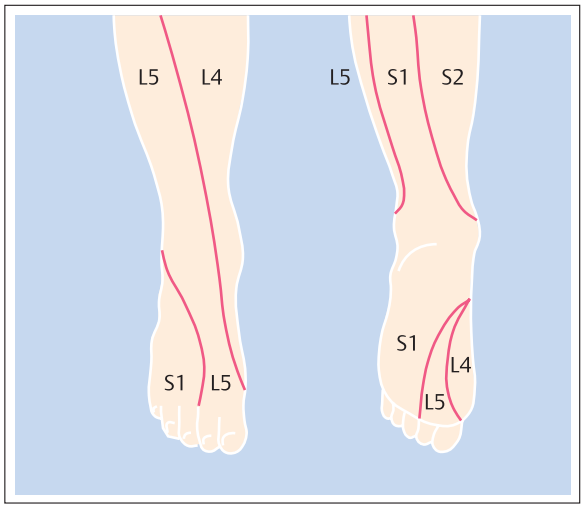

Fig. 8.**7** Dermatomes L4/L5/S1 in the lower leg and foot. Radicular irritation causes radiation of pain into, and/or tingling in, the respective segments. L5 = big toe, S1 = little toe.

Retroperitoneal hematoma most often begins acutely, is rarely insidious, with pain in the inguinal region and anterior thighs, and is followed by pareses and sensory disturbances of the femoral nerve with hematoma of the iliacus muscle and/or of the obturator nerve with a psoas muscle hematoma. Femoral traction pain is positive as with an L3 or L4 syndrome, but the lumbovertebral pain syndrome is absent, and the medical history reveals a coagulopathy (hemophilia), elevated INR (low Quick value), or the unholy alliance of anticoagulation and anti-aggregation (ask about nonsteroidal antirheumatic drugs!).

The rare *lumbosacral plexitis*, with the same etiology as the arm plexus neuritis (see above), also begins acutely. Mainly parts of the lumbar (femoral nerve) or sacral (sciatic nerve) plexus are affected and similarly, the pain precedes the paresis by hours or days.

With an insidious onset, *malignant infiltrating/compressive processes* must be evaluated. In these cases the pain may long precede neurological or local findings. Where there is a history of radiotherapy with a field in the region of a plexus, a radiation-induced plexus lesion must be considered, even after many years.

An *iatrogenic plexus or sciatic nerve lesion* caused by intra-arterial injections (inferior gluteal artery) or deposition of toxic substances, usually manifests itself immediately after the injection, rarely with a latency of several hours, with "sciatica," leg paresis, and sensory disturbances. Agonizing neuralgiform leg pains, often with little functional loss, may occur after overextension of the sciatic nerve in hip replacement surgery. Other intraoperative, traumatic (fracture of the pelvis), and perinatal plexus lesions are self-evident and frequently less painful.

Diabetic Neuropathies. The pathogenetically complex, proximal diabetic asymmetric neuropathy affects predominantly, and also acutely, the femoral nerve (more rarely, also other proximal nerves of the legs) and poses

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a differential diagnostic brainteaser especially in latent diabetes mellitus. Radicular syndromes in particular, but also plexus processes can often hardly be distinguished clinically from a diabetic neuropathy.

Mononeuropathies:

- The *piriform muscle syndrome* is a rare, almost exclusively posttraumatic, entrapment neuropathy of the sciatic nerve in the sciatic foramen after a fall on the buttocks, typically without sciatica, but with local pain to pressure and abnormal Tinel sensitivity of the sciatic nerve. The likewise rare catamenial "sciatica" denotes a compression neuropathy at the same location due to patches of endometriosis. It reveals itself by correlation with the menstrual cycle.
- *Inguinal compression neuropathies* of the iliohypogastric, ilioinguinal, and/or genitofemoral nerve are extreme "troublemakers." Almost always as a long-term consequence of an operation in the inguinal region, and rarely without obvious cause, tearing, torturing, and persistent pain develops unilaterally in the groin, often radiating into the genitals ("spermatic neuralgia"), with little relief when lying down. Sensory disturbances in the overlapping areas often cannot be documented and conduction anesthesia is diagnostic. The differential diagnosis includes *high lumbar radicular pain* (see above) and the so-called pudendal neuralgia, also most often an entrapment neuropathy with pain centered on the midline and the genitalia.
- *Paresthetic meralgia* is more common. It is a compression or entrapment neuropathy of the lateral femoral cutaneous nerve at its passage through the inguinal ligament or in the minor pelvis. Often there is only a slightly annoying, numb oval patch in the lateral thigh. Sometimes, however, tearing or burning pain, even at night, and extremely painful hyperesthesia in the lateral thigh dominate. The differential diagnosis versus the L3 radicular irritation and sensory loss syndrome is often treacherous and a neuroradiologic examination may be necessary in case of doubt. Clinical help in reaching a decision may be via an abnormal Tinel sensitivity at the inguinal passage, normal motor and reflex findings, and the extent of the affected area. It never reaches across the midline of the thigh medially. Frequently, however, it extends to the iliac crest and sometimes slightly distal to the knee. Sometimes, exploratory conduction anesthesia of the nerve also interrupts radicular pain. Femoral stretch pain may also be positive in meralgia. If a ligamentous entrapment neuropathy is doubtful (e. g., no pendant belly, no abnormal Tinel sensitivity at the inguinal passage, no exposition to pressure) retroperitoneal and abdominal examinations for compressing processes should be conducted.
- Analogous syndromes are known for the main branch of the *obturator nerve* (medial and distal area of the thigh), the infrapatellar branch of the saphenous nerve (paresthetic gonalgia, lateral infrapatellar area), the saphenous nerve (distal medial area of the lower leg), and the sural nerve (area of the lateral cutaneous branch: lateral border of the foot), as well as from calcaneal branches.
- Besides the rare *digitalgia paresthetica* with a corresponding sensory disturbance, there is a distinct disease of the plantar nerves of the toes, i. e., *Morton neuralgia* (distention neuropathy with neuromalike formations). Lancinating pain into the forefoot/little toe during walking, the Tinel sign, and the immediate relief obtained from local infiltration with procaine (approach from the dorsum of the foot) confirm the diagnosis.
- *Tarsal tunnel syndrome* is also characterized by dysesthesia at the medial border of the sole of the foot during walking, sometimes even spontaneous dysesthesia at night. Findings are rare in this chronic entrapment neuropathy of the tibial nerve in the bony–fibrous tarsal tunnel at the internal malleolus. However, conduction block at this site and electrodiagnostic tests (decreased nerve conduction velocity in the canal) are diagnostic.

8.8 Differential Diagnosis of Bilateral Neurogenic Arm and/or Leg Pains

Topical Neurological Syndromes:

- central pain syndromes (anterior spinal artery syndrome, syringomyelia, tabes dorsalis)
- affections of the cauda equina
- polyradiculitis (Bannwarth syndrome, Guillain–Barré syndrome, HIV, and others)
- bilateral radicular syndromes of various origins
- polyneuropathy (diabetes, alcohol, HIV, and others)
- painful legs and moving toes syndrome
- hereditary neuralgic amyotrophy.

Signs and Differential Diagnosis

Central Syndromes. The dramatic onset of *anterior spinal artery syndrome* with devastating, lancinating leg (rarely arm) pains leaves little doubt and few differential diagnostic possibilities (see Central Pain, p. 301). In

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chronic bilateral neuralgiform arm pain with central signs, syringomyelia or cervical spinal cord astrocytoma must be considered.

Stereotypical, often well localized, lancinating pains, predominantly in the legs, but also in the arms or the trunk, are easily diagnosed as tabes dorsalis with the accompanying neurological findings (see Central Pain, above).

Involvement of the Cauda Equina. Severe leg pain is typical in *cauda equina radiculitis* (and arachnoiditis), ankylosing spondylarthritis, as well as cytomegalovirus associated caudal radiculitis (in AIDS), which can be distinguished clinically from the HIV polyneuritis to a greater or lesser degree by the dominating sphincter dysfunctions and severe leg pareses. Inflammatory caudal syndromes can be painless, for instance in herpes simplex type II infections (Elsberg syndrome). Similarly, space-occupying processes with compression of the cauda equina cause lower back pain rather than leg pain, although there are exceptions, e. g., in ependymoma filling the entire spinal canal or neurofibromas of the filum terminale.

Polyradiculitis. The onset of a polyradiculitis is acute or rapid, often with distal tingling/numbness or weakness. It has a determined course from weeks to months and is initially often accompanied for days by tearing pain in the leg (and arm). This is typical for *Bannwarth syndrome* (Lyme borreliosis) as well as for the various forms of *Guillain–Barré polyradiculitis*. In contrast to the polyneuropathies, the cerebrospinal fluid (CSF) is pathologic (high protein contents and/or pleocytosis).

Bilateral Radicular Syndromes. In bilateral (multi-)radicular irritation and loss syndromes, the differential diagnosis must take into consideration an epidural hematoma, an epidural abscess, a spinal subarachnoid hemorrhage, as well as bone metastases, with lumbar localizations predominantly found in prostate carcinoma. Radicular provocation maneuvers, clinical and radiological local findings, as well as the CSF (tumor cells), are differential diagnostic criteria. Radicular pain behaves inversely in neurogenic claudication (see Differential Diagnosis of Unilateral Neurogenic Leg Pains, p. 308) in that movement aggravates and rest alleviates the pain.

Polyneuropathies. Bilateral neuralgiform pain in the lower leg and/or foot with insidious onset and a chronic course indicate a small-fiber polyneuropathy. Tingling/numbness in the toes may occur with the pain from the onset or come later. Pain/burning/tingling in fingers and hands occur much later but may be the first manifestations, e. g., when provoked by exposure to cold or heat (Fabry disease!). The neurological findings may be subtle for a long time and the "glove and stocking" pattern of sensory loss, plantar anhidrosis, and hyporeflexia are predominant signs to look for. The differential diagnoses include *polyradiculitis* (in particular chronic inflammatory demyelinating polyradiculopathy), diseases of the cauda equina, or other *bilateral radicular lesions*, all of which do not cause anhidrosis. Common etiologies are noxa, which predominantly affect small fibers, diabetes mellitus, alcohol, disulfiram, treatment with gold and avitaminosis (painful feet). In addition, several *paraprotein-associated neuropathies* (amyloidosis, essential mixed cryoglobulinemia, neuropathies with monoclonal gammopathy of undetermined significance [MGUS]), as well as *angiokeratoma corporis diffusum Fabry*, begin predominantly, and sometimes acutely, with dull, burning, or lancinating pains in the feet or hands. The wrenching leg pains in HIV polyneuropathies are probably of mixed neuropathic, as well as radiculopathic and myelitic derivation.

Painful Legs and Restless Legs. Painful legs and moving toes syndrome describes a peculiar writhing, continuous, and, most often, bilateral restlessness of the toes, together with tearing or dull pains in the feet or legs. Without other neurological findings it is considered an independent entity (of central origin?). On the other hand, restlessness of the toes may be the result of various forms of pain and is therefore nonspecific, e. g., in diabetic polyneuropathy or in a spinal root disease.

Restless legs syndrome includes diffuse dysesthesia rather than pain per se in the legs with restlessness, which is manifested either by walking around or by involuntary movements. The complaints typically begin or culminate in the evening or at bedtime and are dissipated by voluntary movements. Transitions are fluid to "painful legs and moving toes syndrome" and idiopathic, as well as symptomatic, forms exist.

Analogous to the legs, *painful hands and moving fingers syndrome*, as well as *restless arms syndrome*, are described. Bilateral neurogenic arm or hand pain without relevant participation of the legs is altogether rare. The differential diagnosis comprises mainly acute or chronic, bilateral cervical radicular syndromes. Bilateral carpal tunnel syndrome may manifest itself in a strikingly similar manner. With an acute onset, an exceptional bilateral plexitis, or neuralgic shoulder amyotrophy (see above) may be possible, i. e., the rare hereditary autosomal-dominant neuralgic amyotrophy (family history).

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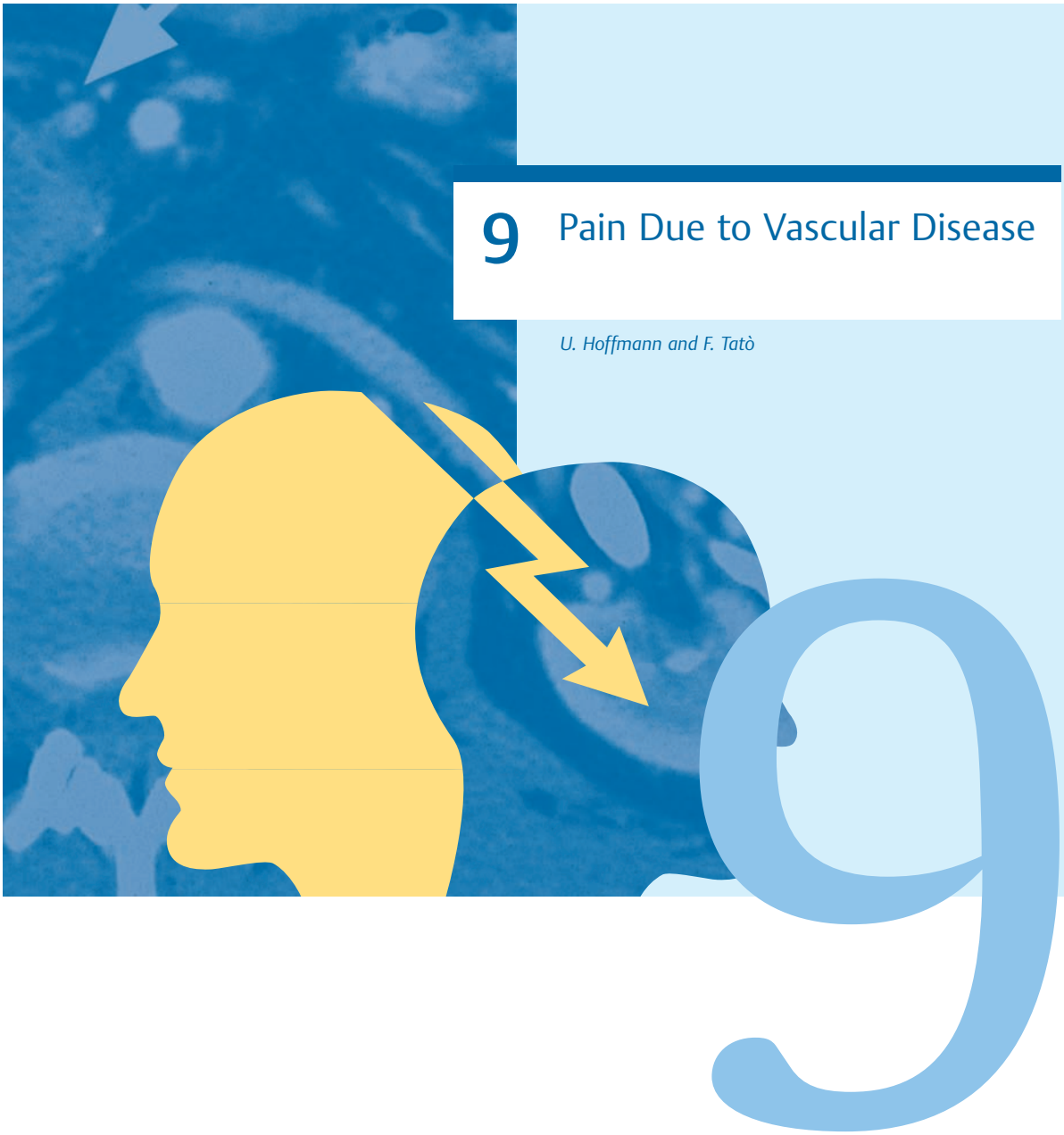

9 Pain Due to Vascular Disease

U. Hoffmann and F. Tatò

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9.1 Arterial Disorders

Arterial Occlusive Disease

Definition and Classification. The term arterial occlusive disease encompasses etiologically heterogeneous disorders leading to the obstruction of the arterial circulation. Arterial occlusive disease can be classified according to the affected anatomic site:

- aorta, upper and lower limbs (peripheral arterial disease)
- cerebral arteries (cerebrovascular disease)
- coronary arteries (coronary heart disease)
- visceral arteries (renovascular disease and mesenteric occlusive disease).

This chapter will focus on the differential diagnosis of peripheral arterial disease (PAD).

Epidemiology. PAD is common. Impaired arterial circulation of the lower limbs is found in 2% of working men 35–45 years old. The frequency of PAD increases with age and reaches approximately 18% in the age group over 65.

> However, up to two-thirds of patients with objective signs of PAD are asymptomatic.

Symptoms

Intermittent Claudication

Pain Characteristics. Patients complain of reproducible, strictly exercise-dependent pain in the affected limb, most frequently in the calf. Intensity and timing of the pain correlate with the degree of exertion (uphill walking worse than on flat ground) and the symptoms disappear within seconds to a few minutes after resting. The pain-free walking distance may vary according to the time of the day. Some patients with well collateralized arterial obstructions experience a decrease in pain while continuing walking at constant or slightly reduced pace (*walking-through phenomenon*).

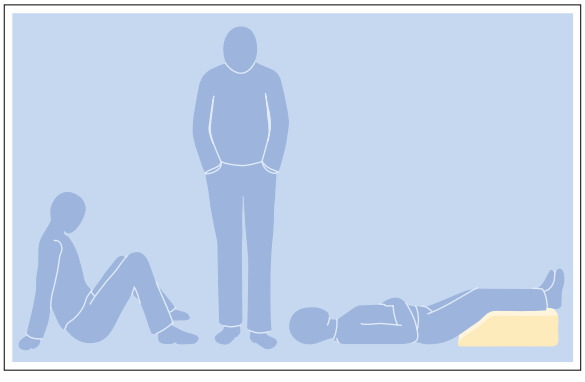

Fig. 9.**1** Typical posture needed for optimal resolution of claudication pain. Left: compression of the cauda equina. Center: arterial claudication. Right: venous claudication.

Localization of Pain. Ischemic pain upon exertion typically occurs below the arterial obstruction. The most common and best recognized site is claudication of the calf, resulting from stenosis or occlusion of the superficial femoral or popliteal arteries. Obstructions of the aorta and iliac arteries may lead to claudication of the hips, buttocks, and thigh. Obstructions of crural and pedal arteries result in isolated claudication of the foot, which is frequently combined with exercise-induced numbness of the toes. PAD affecting the subclavian artery may cause arm claudication, usually in the forearm. Typical claudication with the above-mentioned characteristics has a high specificity for PAD.

> Atypically localized claudication of the gluteal region, thigh, or foot is frequently misinterpreted as an orthopedic problem, thus delaying the diagnosis of PAD. Some patients experience gluteal and thigh claudication simply as muscular fatigue upon exertion.

Differential Diagnosis. Arterial claudication must be distinguished from the neurogenic form. Intermittent claudication of the cauda equina or *spinal claudication* causes neurological symptoms after a pain-free walking distance, particularly when walking downhill. Usually both legs are involved. The typical appearance is a pseudoradicular syndrome combined with weakness of the legs and lower back pain. Contrary to arterial claudication, standing is not sufficient for complete relief. Symptoms are improved by kyphosis of the spine, although they usually do not resolve completely (Fig. 9.**1**). Lordosis, however, increases the underlying stenosis of the spinal canal. Besides the narrow spinal canal, additional compression may result from increased perfusion of spinal structures during exercise. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the spine confirms the diagnosis.

A further differential diagnosis of exercise-induced leg pain is *venous claudication*. This rare syndrome is particularly seen in young, physically active patients after extensive deep vein thrombosis with persistent occlusion of the pelvic veins. Intensive physical activity leads to a decompensation of the impaired venous out-

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flow from the leg. Plethysmography during walking documents a continuous increase of the volume of the affected leg up to the onset of pain. The increasing, painful tension of the leg forces the patient to stop walking and is best relieved by elevation of the leg.

Particularly in elderly patients, arterial claudication has to be differentiated from pain due to frequent *musculoskeletal* or *neurological co-morbidities*. A precise history, combined with a skilled physical examination, and simple, noninvasive technical examinations (see p. 317) usually allows the correct allocation of the symptoms.

Ischemic Rest Pain and Skin Lesions

Ischemic Rest Pain. Unlike in intermittent claudication, patients with ischemic rest pain have a severely impaired arterial perfusion when at rest, which is insufficient to meet the basal nutritive requirements of the tissues. The pain occurs particularly while supine and improves when sitting (grandfather sleeping in his chair). Ischemic rest pain affects almost exclusively the most distal part of the limb (toes and foot, rarely fingers). Rest pain localized in the calf or thigh is usually not caused by ischemia but is probably caused by cramp, muscular overexertion, neuropathies, venous disorders, or skeletal disease. Impaired active and passive movement of the limb indicates an arthrogenic cause of the pain. History (previous intermittent claudication?) and physical examination usually lead to the correct diagnosis.

Necrosis. When untreated, severe limb ischemia at rest will proceed to necrotic lesions (Fig. 9.**2**). Depending on the presence or absence of infection, these lesions are classified as wet or dry gangrene. Spontaneous ischemic lesions typically occur at the most distal location (toes, heel), where perfusion is most severely impaired.

Stages of Peripheral Arterial Disease

Tab. 9.**1** shows the most commonly used classification of PAD (modified Fontaine classification).

Perfusion of the limb is compensated in stages I and II, whereas it is decompensated in stages III and IV, indicating threatened viability of the extremity (*critical limb ischemia*). Patients with a nonischemic skin lesion (e. g., posttraumatic, venous, or neuropathic) in a limb with impaired but compensated perfusion are classified as complicated stage II.

The more detailed Rutherford classification of PAD includes in the definition of the stages hemodynamic parameters assessed by noninvasive technical tests (see below).

Fig. 9.**2** Initial gangrene of the left hallux in a 32-year-old woman with thromboangiitis obliterans (multiple occlusions of the crural arteries).

Table 9.**1** Modified Fontaine stages of peripheral artery disease

Stage	Definition
I	Objective signs of PAD without symptoms
II a	Intermittent claudication, pain-free walking distance > 200 m
II b	Intermittent claudication, pain-free walking distance < 200 m
III	Rest pain
IV	Necrotic lesion, gangrene

Diagnostic Approach

Physical Examination:

- Accurate *palpation of peripheral pulses* is in many cases sufficient to confirm the presence of PAD and allows an approximate localization of the arterial obstruction. However, it is important to stress that palpable pulses do not rule out PAD. Particularly in arterial stenosis without total occlusion all peripheral pulses may remain palpable.
- Stenosis of arteries can accurately be detected by *auscultation*. Turbulence occurring at the location of arterial narrowing produces systolic and rarely systolic–diastolic murmurs that can be heard with a stethoscope (Fig. 9.**3**). Sites routinely auscultated in PAD patients are the lateral neck (carotid artery), the supra- and infraclavicular fossa (subclavian and axillary artery), the upper and middle abdomen (aorta, intestinal, and renal arteries), the lateral lower abdomen and groin (iliac arteries and femoral bifurcation), the inside of the thigh (femoral arteries) and the popliteal fossa (popliteal artery). A bruit already audible at rest is a reliable sign of arterial stenosis.

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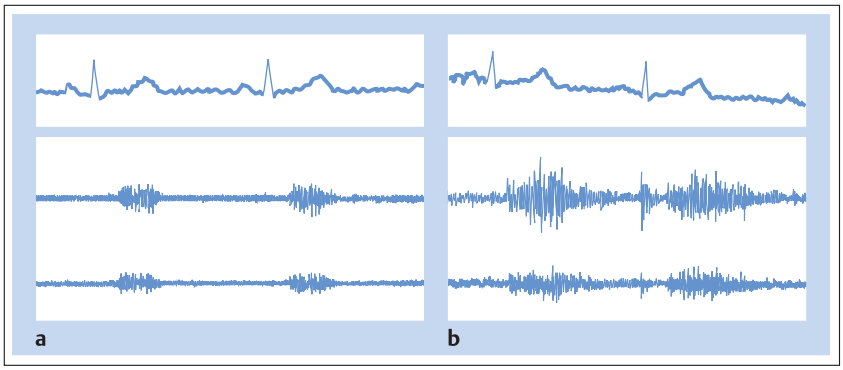

Fig. 9.**3** Phonoangiogram of an arterial stenosis.
a Short bruit at rest.
b Louder and longer bruit after exercise.

Fig. 9.**4** Ratschow positioning test in predominantly right-sided PAD.
a A few seconds after stopping rotational exercise of the feet and lowering of the legs to a hanging postion, reactive hyperemia and venous filling is evident in the left foot, while the right foot remains pale and without venous filling.
b After 30 seconds, reactive hyperemia and venous filling is evident in both feet.

Some murmurs become audible only after exertion (e. g., five to ten knee bends). A short postexertional systolic murmur in the groin is physiological. Physical exertion leads to an increase in the volume, length, and tone frequency of murmurs caused by arterial stenoses. These bruits must be distinguished from spontaneous arterial tones in patients with increased blood pressure amplitude (aortic valve regurgitation).

Systematic arterial auscultation is a simple but very valuable tool, which allows the detection of early stages of arterial occlusive disease (in many cases before the onset of symptoms).

Functional Tests. Severity of lower limb ischemia can be assessed semiquantitatively by the Ratschow position-

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ing test and the walking test. The Allen test is used for ischemic syndromes of the arm and hand.

- In the *Ratschow positioning test* the supine patient is asked to rotate the feet with 90° elevated legs until the onset of fatigue or claudication. In this phase, paleness of the affected foot may be noticed. After sitting up and lowering the legs to a hanging position redness of the skin due to reactive hyperemia and venous filling normally occur within five to ten seconds. Onset of reactive hyperemia after 30 seconds indicates severe circulatory impairment; onset after more than 45 seconds is a sign of very severe ischemia (Fig. 9.**4**).
- In the *walking test* the patient's pain-free and maximal walking distance is assessed during supervised walking at a pace of two steps per second on level ground.
- The *Allen test* can be used to estimate severity of arm ischemia due to proximal arterial obstruction. The patient is asked to open and close the fist with the arm elevated and while the radial and ulnar arteries are manually compressed at the wrist. When complete paleness of the hand is present, the arm is lowered and the wrist arteries are released. Visible reperfusion of the hand normally occurs within seconds, and the degree of delay correlates with the severity of ischemia. This test is also very valuable for the diagnosis of distal arterial occlusions of the hand and fingers. The pattern of reperfusion of the hand after selective release of the radial and ulnar artery allows accurate identification of occluded digital arteries and demonstrates the patency of the palmar arches.

Hemodynamic Measurement and Vascular Imaging. In more than 90% of patients PAD can be diagnosed by accurate history, palpation of pulses, and auscultation. Simple technical tests such as pulse volume recordings by segmental plethysmography and measurement of the systolic ankle artery pressures confirm the diagnosis and allow objective quantification of the severity of ischemia. In addition, segmental plethysmography identifies the approximate level of arterial obstruction. The indication for vascular imaging by duplex ultrasound or angiographic techniques should be based on the results of clinical examination and these simple noninvasive tests.

Technical Tests for the Evaluation of Hemodynamically Significant PAD

Segmental pulse volume recordings (plethysmography) are performed with pressure cuffs at the level of the thighs, calves, and feet. Pulse volume recordings of the fingers and toes are assessed by acral plethysmography. Characteristic changes of the pulse curve with reduced amplitude, broadening, and delayed peak time are seen distal to arterial obstructions (Fig. 9.**5**). The degree of pulse volume abnormality correlates accurately with the severity of ischemia. A flat pulse volume recording with missing or barely visible pulsation indicates critical limb ischemia. The level at which the pulse volume recordings become abnormal indicates the localization of arterial obstruction. Unlike in ankle pressure measurements, the results of segmental plethysmography are not affected by medial calcinosis, making this tool particularly valuable for the evaluation of PAD in diabetes.

Measurement of systolic ankle pressures is easily performed with a regular blood pressure cuff and a simple continuous wave Doppler ultrasonograph device. Pressure measurements at the toes or fingers may be useful in selected patients. These measurements require special pressure cuffs and registration of pulse curves either by plethysmography or a laser Doppler device. The systolic ankle pressures, measured at rest in the supine position, should be equal or higher than the systemic pressure at the arm. A lower ankle pressure confirms the presence of arterial obstruction. Resting systolic ankle pressures of 50 mmHg or less indicate critical limb ischemia.
The recording of ankle pressures after exercise is a valuable test for the objective assessment of severity of PAD. Treadmill testing allows exercise testing under standardized conditions. Ankle pressures drop only marginally after exercise in healthy subjects. However, exercise induces a marked and prolonged drop in ankle pressure in PAD patients. The degree and duration of this drop correlate with the severity of ischemia. Exercise testing is very useful for the differentiation between arterial claudication and nonvascular causes of leg pain in PAD patients with co-morbidities. A drop of the ankle pressures below 50 mmHg after exercising up to the onset of pain confirms the diagnosis of arterial claudication.

Duplex sonography (duplex scan) is a combination of B-mode ultrasound with pulsed wave Doppler analysis. This noninvasive technique allows precise localization and morphological characterization of arterial obstructions, combined with the simultaneous assessment of the hemodynamic relevance (Fig. 9.**7**). Color coding of the Doppler signal facilitates the localization of blood vessels and the detection of hemodynamically significant obstructions (Fig. 9.**6**). For most vascular regions a duplex scan is the first-line noninvasive imaging technique and it has replaced invasive diagnostic angiography in many clinical settings. The decision to perform percutaneous revascularization can be made based on the results of noninvasive clinical tests and duplex scan in most PAD patients.

Microvascular diagnostic techniques such as capillary microscopy (with or without fluorescent dyes), laser–Doppler, and measurement of transcutaneous oxygen tension ($TcPo_2$) provide prognostically relevant information on cutaneous microcirculation distal to arterial obstructions. In addition, capillary microscopy is a valuable tool for the differential diagnosis of the Raynaud phenomenon, showing typical capillary changes in collagen vascular diseases.

Arterial angiography achieves the highest resolution imaging of the topography of arterial stenoses and obstructions (Fig. 9.**8**). Angiography provides a complete

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overview of the arterial circulation of the examined region and is the basis for surgical and percutaneous revascularization procedures. In medically treated patients without indication for invasive revascularization, angiography is usually not required. The angiographic study of the vascular morphology may provide important information about the etiology of arterial occlusive disease (e. g., characteristic, convex delimitation of the proximal thrombus in embolic arterial occlusions).

Magnetic resonance angiography (MRA) performed with or without intravenous application of ferromagnetic contrast media is an increasingly common, noninvasive alternative to conventional angiography. Spatial resolution of MRA has continuously improved during the past years due to rapid and ongoing progress in MR technology. Excellent image quality is already possible with current high-end technology, and MRA is likely to replace conventional angiography in most clinical applications in the near future.

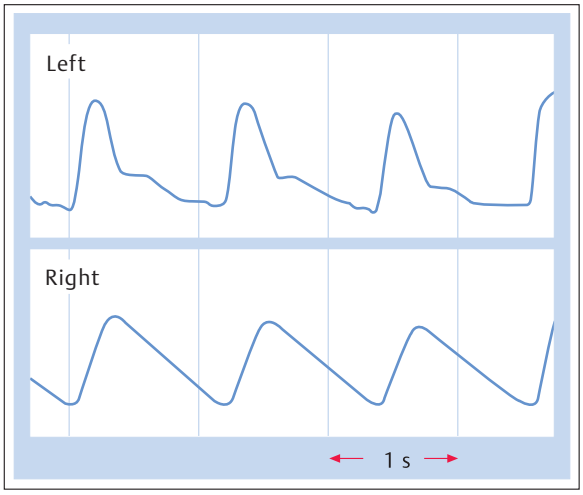

Fig. 9.**5** Acral, electronically amplified plethysmography with simultaneous registration of both halluces. Upper: normal pulse curve with dicrotic wave. Lower: flat poststenotic pulse curve with delayed peak time (distal to occlusion of the superficial femoral artery).

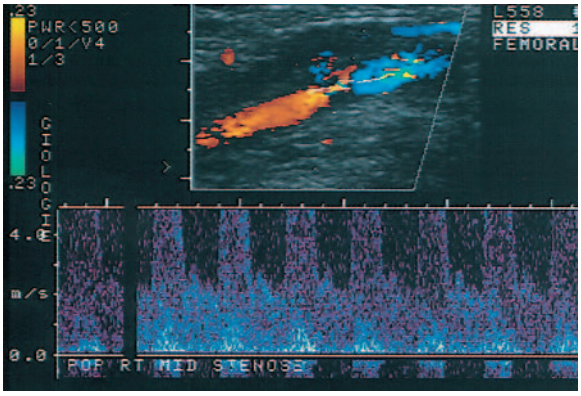

Fig. 9.**6** Color-coded duplex ultrasound of a stenosis in the popliteal artery. Blood flow is coded red in the prestenotic segment and blue in the poststenotic segment (turbulence with partly reversed flow). The sample volume of the pulsed Doppler is located in the stenosis (two small white lines). Doppler signals (below) are characterized by a high systolic and diastolic velocity and marked spectral broadening.

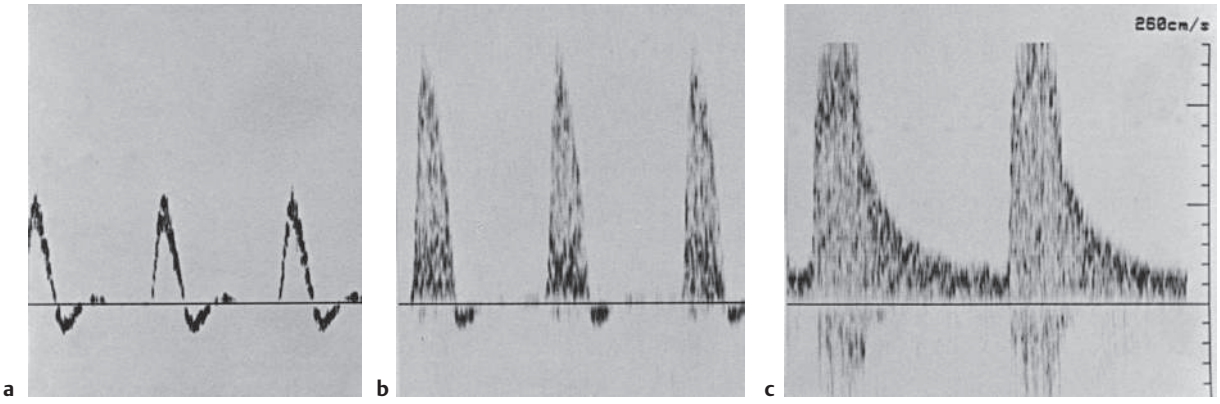

Fig. 9.**7** Pulsed Doppler signals with simultaneous frequency analysis from arteries of the leg.

a Normal curve: narrow spectral band ("clear systolic window") and late systolic retrograde flow.

b Stenosis < 50 %: spectral broadening (loss of systolic window), slightly elevated peak systolic velocity, and conserved late-systolic retrograde flow.

c Stenosis > 50 %: marked spectral broadening, extremely elevated peak systolic and diastolic velocity with lack of retrograde flow.

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Table 9.**2** Causes of peripheral artery disease

- Obliterating arteriosclerosis
- Thromboangiitis obliterans
- Connective tissue disease
  - polyarteritis nodosa
  - systemic lupus erythematosus
  - systemic sclerosis
  - rheumatoid arthritis
- Giant cell arteritis (temporal arteritis, polymyalgia rheumatica)
- Takayasu arteritis
- Amyloidosis
- Thrombocytosis (essential or secondary)
- Cryoglobulinemia
- Cold agglutinin disease
- Trauma (also blunt)
- Iatrogenic
- Drug abuse
- Fibromuscular dysplasia
- Cystic adventitial disease
- Popliteal entrapment syndrome
- Pseudoxanthoma elasticum
- Endothelial tumors
- Congenital (e. g., stenosis of the subclavian artery in isthmic aortic stenosis)

Obliterating Arteriosclerosis

Pathogenesis. The etiology of occlusive arterial disease is heterogeneous (Tab. 9.**2**). The leading cause of PAD is obliterating arteriosclerosis. The arterial occlusion usually occurs in two phases. A phase of slowly progressive luminal narrowing due to increasing plaque burden is followed by sudden, thrombotic occlusion.

> Onset of clinical symptoms usually requires at least 50 % narrowing of arterial diameter.

Endothelial damage is a central factor in the initiation of atherogenesis. Very early in the development of arteriosclerosis, cardiovascular risk factors like smoking, diabetes, hypercholesterolemia, and hypertension lead to functional impairment of endothelial cells (endothelial dysfunction). This stage is followed by increased deposition of lipids, migration of monocytes, and proliferation of smooth muscle cells in the subendothelial vascular wall. These processes are induced by inflammatory cytokines and growth factors produced by activated monocytes, lymphocytes, and platelets. The degree of inflammation within the arterial wall determines the growth and structure of the arteriosclerotic plaque. High inflammatory activity leads to degradation of fibrous plaque components and to the formation of unstable plaques, prone to rupture. Plaque rupture is frequently followed by arterial thrombosis leading to total vascular occlusion and sudden ischemic events. Inflammatory activity of arteriosclerosis is reflected by slightly elevated levels of plasma C-reactive protein (CRP). Elevated CRP is increasingly recognized as a marker of cardiovascular risk.

Fig. 9.**8** Intra-arterial digital subtraction angiography showing high-grade stenosis of the right common iliac artery and stenosis of the left internal iliac artery. Multiple plaques are also present.

Risk Factors. The management of patients with PAD due to obliterating arteriosclerosis must include the evaluation and treatment of risk factors. Smoking, diabetes, hypercholesterolemia, and hypertension are the classical cardiovascular risk factors. Well established, additional risk factors for PAD are low HDL cholesterol, elevated lipoprotein (a), and hyperhomocysteinemia. Young patients with arteriosclerotic vascular disease should be evaluated for the presence of familial hypercholesterolemia and rare causes of premature arteriosclerosis (pseudoxanthoma elasticum, Werner syndrome).

> Arteriosclerosis is always a generalized disorder. Therefore, diagnosis of arteriosclerosis should prompt the search for manifestations of the disease in other vascular regions.

Nonarteriosclerotic causes of arterial occlusive disease include a wide range of differential diagnoses (Tab. 9.**2**).

Thromboangiitis Obliterans (Buerger Disease)

This disorder typically occurs in young adults with excessive tobacco use. Men are preferentially affected, but an increasing incidence has been reported in women.

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Diagnosis of thromboangiitis obliterans is based on the presence of the following three clinical criteria:

- disease onset before the age of 40
- selective involvement of distal arteries (calf, hand, and foot)
- presence of migratory thrombophlebitis (see Fig. 9.**23**, histology: chronic panphlebitis).

In cases with incomplete manifestation (migratory thrombophlebitis is present only in approximately 40 % of the patients), or with an atypical distribution (involvement of large arteries), diagnosis can only be suspected. The etiology of Buerger disease is unknown. Some findings suggest an autoimmune mechanism (reduced levels of complement C4, elevated anti-elastin and anti-endothelial cell antibodies), but markers of systemic inflammation such as CRP and erythrocyte sedimentation rate (ESR) are only marginally elevated. Life expectancy is usually normal, due to the fact that coronary and cerebrovascular involvement is very rare. However, the disease has an unfavorable prognosis with regard to limb salvage, particularly if patients continue smoking.

Collagen Vascular Disease

Inflammation and thrombotic occlusion of small arteries is also a typical feature of vascular involvement in connective tissue disease. Small vessel occlusions with acral ulceration and gangrene of the fingers and toes are a frequent finding in systemic sclerosis and systemic lupus erythematosus. Polyarteriitis nodosa can cause multiple aneurysms as well as occlusions of small and medium-sized muscular arteries. Diagnosis is supported by the detection of typical autoantibodies (ANA, ENA, ANCA). Patients with polyarteriits nodosa frequently have positive serologic tests for hepatitis B.

Giant Cell Arteritis

This panarteritis of medium and large-sized arteries typically involves one or more branches of the carotid artery, most frequently the temporal artery (*temporal arteritis*). *Polymyalgia rheumatica* is a frequent manifestation of this disease, which can occur with or without vascular involvement. In some patients, giant cell arteritis may affect also extracranial arteries. Peripheral involvement is seen most frequently in the axillary artery. Typical laboratory findings are highly elevated markers of systemic inflammation (ESR, CRP) and negative tests for autoantibodies. The disease occurs almost exclusively in patients older than 55 years (see Chapter 4).

Takayasu Arteritis

Clinical Findings. Takayasu arteritis is a rare, large-vessel vasculitis affecting predominantly the aortic arch and its proximal branches in young women. The disorder is more common in Asia, whereas arteriosclerotic obstructions of the aortic arch predominate in central Europe. Involvement of the carotid arteries and proximal subclavian arteries may lead to intermittent cerebrovascular ischemia or even to permanent cerebral defects. Less frequently, patients experience intermittent claudication of the arms (e. g., when cleaning windows). Diminished or absent carotid and arm pulses, and arterial bruits over the neck and clavicular region are the leading clinical findings. Pulses of the lower limb are usually normal and ankle pressures are normal or elevated.

Diagnosis. Involvement of the abdominal aorta and its branches may lead to renovascular disease and mesenteric occlusive disease. Aortic aneurysms are a typical complication in the late course of the disease. The ESR is markedly elevated, particularly during bouts of inflammatory activity, which may last months and are frequently accompanied by generalized symptoms. Tests for autoantibodies are negative. The course of the disease is chronic in most patients.

Differential Diagnosis. The possibility of subclavian steal syndrome should be considered in patients with stenosis or occlusion of the subclavian artery. Severe subclavian obstructions proximal to the verterbral artery lead to inversion of blood flow in the vertebral artery, thus allowing collateral blood supply to the arm via the vertebrobasilar circulation. These patients may suffer from symptoms of cerebral hypoperfusion during arm exercise (see Chapter 31). Proximal obstruction of the subclavian artery with subclavian steal syndrome is usually arteriosclerotic. Large-vessel vasculitides more frequently involve the distal part of the subclavian artery (distal to the vertebral artery) and the axillary artery.

Iatrogenic Arterial Disease

Inadvertent intra-arterial injection of drugs (e. g., barbiturates, dicloxacillin, heroin) may cause severe limb ischemia and result in amputation. Angiitis with occlusion of small and larger arteries is rarely seen after penicillin treatment. Arterial punctures either with or without insertion of a catheter may lead to dissection of an intimal flap with arterial thrombosis in the resulting pocket. Arterial narrowing and occlusion is also seen after radiation treatment for malignant disease, frequently after a latency of months to several years.

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Popliteal Entrapment Syndrome

Aberrant fibrous or muscular structures in the popliteal fossa may lead to compression of the popliteal artery. The most frequent form is caused by abnormal insertion of the medial head of the gastrocnemius muscle at the lateral femur condyle. Walking and jumping causes repeated trauma to the popliteal artery in these patients. Damage to the arterial wall may result in an aneurysm and is frequently complicated by thrombosis and peripheral embolism. The disorder affects primarily young, physically very active individuals, typically occurring with an acute or subacute ischemic syndrome.

Distinction from thromboangiitis obliterans may sometimes cause problems (bilateral involvement). Arterial occlusions due to arterial compression in the adductor canal rarely occur in athletes (adductor canal syndrome).

Cystic Adventitial Disease

This disorder, characterized by cysts in the arterial wall, usually affects the popliteal artery (Fig. 9.**9**). A variable degree of luminal narrowing is seen, depending on the volume state of the cyst. Typically, this results in intermittent ischemic symptoms.

Fig. 9.**9** Angiogram showing high-grade stenosis of the popliteal artery due to an adventitial cyst.

Fibromuscular Dysplasia

Fibromuscular dysplasia may involve not only the renal arteries but also the carotid, mesenterial, and iliac arteries. Angiography shows characteristic sequential stenoses and aneurysms (“string of beads”).

Essential Thrombocytosis

Essential thrombocytosis and thrombocytosis in polycythemia may be complicated by occlusions of larger and particularly of smaller arteries. Typically, these patients complain of persistent acral pain, which responds promptly to the first dose of aspirin. Vasculopathies of unknown origin are sometimes unexpectedly solved by performing a platelet count.

Medial Calcinosis

Medial calcinosis (Mönckeberg medial sclerosis) has to be distinguished from arteriosclerosis, which primarily affects the intima. Plain radiography demonstrates tubular calcification of the arterial wall (Fig. 9.**10**). Medial calcinosis is seen most frequently in diabetes and

Fig. 9.**10** Medial calcinosis of the popliteal artery (plain radiography).

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chronic renal failure. Usually, no luminal narrowing occurs, as long as the intima is not affected. In marked medial calcinosis, arteries become stiff and resist compression by blood pressure cuffs. This causes the measurement of erroneously high blood pressure values. This pseudohypertension is particularly relevant for the measurement of ankle pressures (see above). Rarely, medial calcinosis may also prevent correct measurement of arterial blood pressure in the arm. In these cases, arterial blood pressure can only be assessed by an invasive, intra-arterial measurement.

Embolic Occlusions

Definition. Arterial embolism leads to sudden occlusion of the lumen (Fig. 9.**11**). Embolic material typically clings to the arterial wall at the site of bifurcations, where the luminal diameter narrows (femoral bifurcation, calf trifurcation).

Fig. 9.**11** Angiogram showing embolic occlusion of the popliteal artery with curved delimitation of the embolus.

Clinical Findings. The patient reports the sudden onset of severe pain in the affected limb, and usually remembers the exact time when symptoms began. Pain is immediately followed by other symptoms of ischemia. Depending on the localization of the embolus, these may reflect acute critical limb ischemia (paleness, coldness, numbness, and loss of function) or the sudden onset of intermittent claudication.

Source of Embolism. Emboli originate most frequently from the heart:

- Atrial fibrillation and myocardial infarction are common causes of embolism due to the formation of parietal thrombi.
- Bacterial endocarditis is the cause of septic embolism.
- Rare atrial myxoma may be complicated by embolization of part of the myxoma.
- Arterio-arterial embolism is caused by thrombi originating from aneurysms or ruptured plaques of large arteries.
- In lower limb embolization, palpation can reveal an abdominal or peripheral aneurysm as the source of the embolus.
- Rarely, arterial embolism is caused by paradoxical embolism originating from deep vein thrombosis (patent foramen ovale).
- In cholesterol embolism, small arteries are occluded by cholesterol crystals that usually originate from ruptured aortic plaques. Involvement of the renal circulation causes acute renal failure. The skin shows a characteristic bluish mottling (livedo reticularis). Acral lesions of the toes are very painful and healing is typically slow. Eosinophilia is a common laboratory finding.

Aneurysms of Peripheral Arteries

Fusiform and Saccular Aneurysms

These types of aneurysms typically involve the following peripheral arteries (in descending order of frequency):

- popliteal artery
- common femoral artery
- iliac artery (Fig. 9.**12**)
- subclavian artery.

Frequently, involvement is bilateral or multilfocal (e. g., a combination of abdominal aortic aneurysm and politeal aneurysm). Dilatating arteriosclerosis (dilatative arteriopathy) frequently leads to aneurysmatic dilatation of long arterial segments.

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Clinical Findings. The leading clinical finding is a palpable, pulsating mass. Frequently medical attention is only sought when complications of the aneurysm have occurred.

> Unlike in aortic aneurysms, rupture is a rare event in peripheral arteries.

Recurrent embolization of thrombi from the aneurysm represents a serious threat to the limb. Compression of the adjacent vein may cause acute venous stasis and suggest deep vein thrombosis.

Diagnostic Approach. Aneurysms may easily be missed by angiography when the aneurysmal cavity is filled by mural clots. The calcified outline usually visible in abdominal aneurysms is frequently absent in peripheral arteries. Ultrasound allows assessment of the diameter of the aneurysm as well as detection of mural clots (Fig. 9.**13**). CT or MRI provide precise information on the relationship to adjacent anatomic structures and are the basis for planning surgical treatment.

Pathogenesis. Fusiform and saccular aneurysms are mostly arteriosclerotic. Additional etiologies are congenital (basal cerebral arteries), traumatic, mycotic (in bacterial endocarditis), and poststenotic. Dissecting aneurysms are very rare in peripheral arteries (mostly thoracic aorta). Compression syndromes may cause aneurysms due to chronic traumatic damage to the arterial wall. These syndromes should be particularly considered in young patients with aneurysm of the popliteal artery (popliteal entrapment) or of the subclavian artery (thoracic-outlet syndrome, TOS).

False Aneurysms (Pseudoaneurysms)

Unlike true aneurysms, pseudoaneurysms are not surrounded by arterial wall. They represent an extraluminal collection of blood connected with the arterial lumen.

> A false aneurysm may develop as a complication of arterial puncture.

False aneurysms also occur at the anastomoses of synthetic bypass grafts or venous transplants (graft aneurysms).

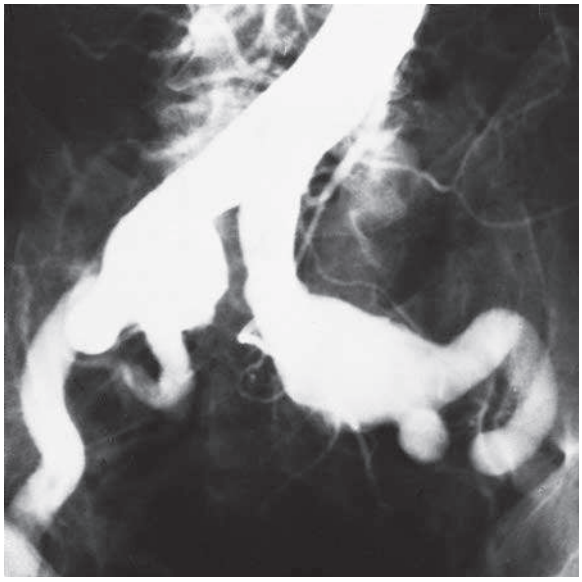

Fig. 9.**12** Angiogram showing bilateral aneurysms of the common iliac arteries with elongation of pelvic arteries.

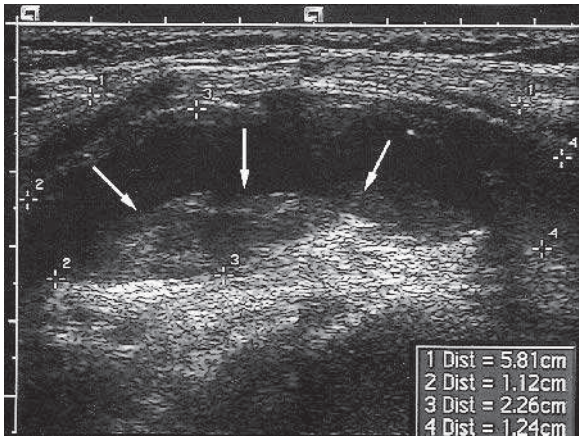

Fig. 9.**13** Sonographic longitudinal section of a popliteal aneurysm with a mural clot. The maximal diameter of the aneurysm is 2.3 cm with a length of approximately 6 cm. The arrows indicate the mural clot.

Arteriovenous Fistula

Solitary Arteriovenous Fistula. The principal clinical finding in solitary arteriovenous fistula is a continuous systolic–diastolic murmur, frequently with a palpable whir. Increased arterial pulsation and pulsating veins may be an additional sign. These fistulas are usually acquired, mostly posttraumatic. Typical complications of high-volume arteriovenous shunts are high-output heart failure due to chronic volume overload and chronic venous insufficiency in the affected limb due to increased peripheral venous pressure.

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Congenital Angiodysplasia. Unlike solitary large-volume arteriovenous fistula, multiple small-volume arteriovenous fistulas are due mostly to a congenital angiodysplasia (naevus flammeus, limb hypertrophy, atypical varicose veins). Sometimes these fistulas fuse to a pulsating angioma. Usually, no bruits are audible. These fistulas can be detected by Doppler ultrasound or by comparative measurements of perfusion in symmetric segments of the limb (venous occlusion plethysmography, duplex ultrasound). MRI provides imaging of the arterial and venous anatomy and of the extension of arteriovenous angiodysplasia in the soft tissue. Angiography allows precise detection of the arteriovenous shunts (Fig. 9.**14**).

◁ Fig. 9.**14** Convoluted small-volume arteriovenous fistula of the left upper arm of a young woman with congenital angiodysplasia. Aneurysmatic enlargement of the feeding artery.

Functional Vascular Disease

a b

These disorders are caused either by a pathologically increased tendency to vasospasm or rarely by an abnormal vasodilatation (erythromelalgia).

Vasospasm of Large Muscular Arteries (Ergotism)

The main muscular arteries of the upper arm and the thigh are the typical location of vasospasm in ergotism. These vasospasms cause high-grade, smooth narrowing of long arterial segments and result in intermittent claudication or even gangrene (Fig. 9.**15a**). The history is crucial to correct diagnosis. The disease usually affects young patients taking *ergotamine tartrate preparations* for the treatment of migraine (particularly suppositories). Nonhydrogenated ergotamine alkaloids induce vasospasm only when applied parenterally (thrombo-

◁ Fig. 9.**15** Ergotism
a High-grade, smooth stenosis of the femoropopliteal arteries in a woman with ergotism (abuse of suppositories).
b Follow-up angiography after one month: complete resolution.

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Fig. 9.**16** Vasospastic attack in a 38-year-old woman with primary Raynaud phenomenon. Acral paleness is evident in both middle fingers and the right forefinger.

Fig. 9.**17** Hand angiography in a 32-year-old man showing multiple occlusions of carpal and digital arteries. Ulcereation was present at the tip of the middle finger.

embolic prophylaxis with dihydroergotamine heparin). The high-grade arterial stenoses are reversible within days after discontinuation of the drug (Fig. 9.**15b**). In the Middle Ages, gangrenous ergotism (St. Anthony fire) was a feared disease caused by the contamination of grain with *Claviceps purpurea*. In rare cases, reversible vasospastic arterial stenoses are seen without exposure to ergotamine.

Raynaud Phenomenon

Definition. Vasospastic or primary Raynaud phenomenon is characterized by recurrent, symmetric attacks of white or bluish discoloration of the fingers (with exception of the thumb), usually triggered by cold, or less frequently by emotional stress (Fig. 9.**16**). An underlying disease is not detectable. Secondary Raynaud phenomenon is caused by the occlusion of digital arteries and/or an organic angiopathy. Only this form may lead to trophic skin ulcers (rat-bite necrosis).

Clinical Findings. Primary Raynaud phenomenon affects primarily young women. Symptoms usually start after puberty or in early adulthood. Combination with arterial hypotension and migraine is frequent, rarely also with Prinzmetal angina. Vasospastic Raynaud syndrome debilitates particularly patients with occupational or recreational cold exposure (career choice is important).

Unlike primary vasospastic phenomenon, secondary Raynad phenomenen is characterized by a pathological Allen test and abnormal acral plethysmography. Angiography demonstrates arterial occlusions (Fig. 9.**17**). Vasospastic attacks may precede arterial occlusions by years in patients with connective tissue disease. In other etiologies, symptoms of acral ischemia begin suddenly and are initially limited to isolated fingers, including the thumb.

Causes. In secondary Raynaud phenomenon the following causes should be considered: arteriosclerosis, thromboangiitis obliterans, collagen vascular disease, thrombocytosis, occupational trauma (vibration syndrome in workers using pneumatic drills, hypothenar hammer syndrome caused by repeated use of the palm as a hammer), embolism in costoclavicular compression syndromes, exposure to polyvinylchloride, chemotherapy with bleomycin, cryoglobulinemia, and cold agglutinin disease.

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Acrocyanosis and Erythrocyanosis

These functional disorders primarily affecting young women are caused by vasospastic changes in the microcirculation. Acrocynosis is characterized by persistent, more or less cold-dependent bluish discoloration of the fingers, occasionally also of the nose and ears. Capillary microscopy shows generalized dilation of nailfold capillaries without relevant morphological changes. Erythrocyanosis appears as a red-bluish discoloration of the skin, which involves predominantly the region of the ankles. In most cases these symptoms resolve spontaneously later in life.

Erythromelalgia

This disorder consists of usually symmetric attacks of erythema and burning pain of the extremities. The attacks are triggered by heating of the skin above a "critical" temperature (e. g., hot bath). The idiopathic form with unknown etiology should be distinguished from secondary erythromelagia, which is frequently associated with a myeloproliferative syndrome (essential thrombocytosis, polycythemia vera).

9.2 Microvascular Disease

Diabetic Microangiopathy

Diabetic microangiopathy is a typical late complication of diabetes particularly affecting the retina, kidneys (Kimmelstiel–Wilson glomerulosclerosis), and feet. Debilitating consequences are blindness, end-stage renal failure, and amputation. Neuropathy, microangiopathy, and macroangiopathy regularly coexist in the diabetic foot and may be difficult to distinguish. Acral ulcerations are a sign of angiopathy, while plantar ulceration at pressure spots (malum perforans) indicate predominance of neuropathy (Fig. 9.**18**). The course of the disease is frequently complicated by a marked tendency to infection. Fistula and osteomyelitis of the toes and midfoot is a common finding. Increased permeability of capillaries is demonstrated with radiolabeled or fluorescent tracers, and may explain the well known tendency to edema formation (Fig. 9.**19**). Incorporation of abnormal proteins in the arteriolar wall reduces the contractivity of resistance vessels. Histology shows thickening of the capillary basal membrane, endothelial proliferation, and microaneurysms, which are directly visible at funduscopy. Blood flow characteristics are also negatively affected.

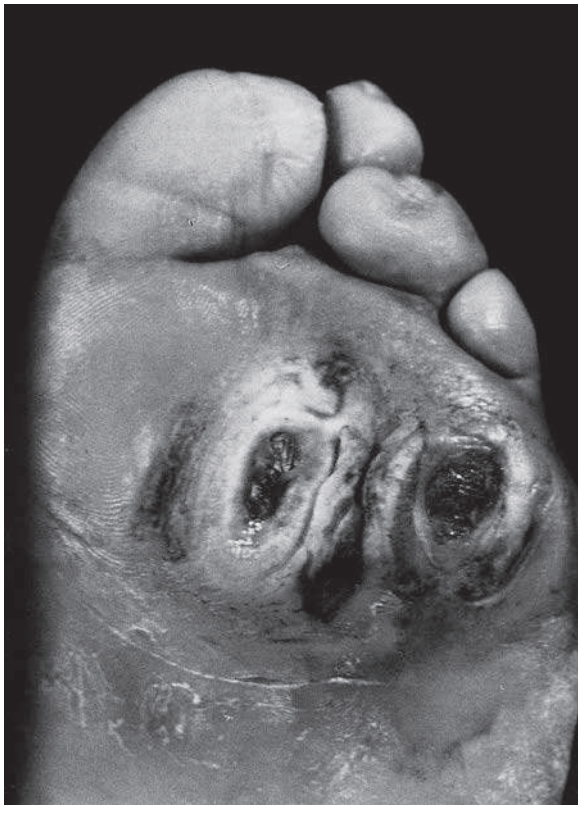

Fig. 9.**18** Ulcerations in diabetic angiopathy and neuropathy, partly as malum perforans; in a 60-year-old woman.

Microangiopathy in Connective Tissue Disease

Microangiopathy develops particularly in systemic sclerosis, mixed connective tissue disease, and dermatomyositis. The combination of microangiopathy and occlusion of small arteries results in acral ischemia and the clinical picture of secondary Raynaud phenomenon. Capillary microscopy shows giant capillaries, rarification of capillaries, increased transcapillary diffusion of Na–fluorescein, and capillary aneurysms (Fig. 9.**20**). Advanced cases develop avascular fields with tendency to ulceration.

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a

b

Fig. 9.**19** Nailfold capillaries one minute after the appearance of Na–fluorescein.
a Restriction of fluorescence to the pericapillary halo in a healthy individual.
b Diffuse extravasation of the dye into the interstitial space in a woman with long-lasting diabetes, i. e., ground glass opalescence.

Livedo Reticularis and Livedo Racemosa

Livedo reticularis indicates patchy cyanosis with annular configuration around a pale center caused by functional vasospasm. The term "livedo racemosa" is used when the symptom is caused by organic abnormalities of the small vessels. The organic form (also called lividoid vasculitis) is frequently accompanied by micro-ulcerations of the lower extremities and less frequently of the upper extremities. Some of these patients test positive for antiphospholipid antibodies. Involvement of the central nervous system with small cerebral infarcts is possible (Sneddon syndrome).

Fig. 9.**20** Imaging of dilated nailfold capillaries with the infrared fluorescent dye indocyanine green. The tip of the right capillary carries a microaneurysm as is typically seen in systemic sclerosis and mixed connective tissue disease.

Paroxysmal Finger Hematoma

Paroxysmal finger (or hand) hematoma is a harmless, (but for the patient alarming), condition due to localized rupture of a small blood vessel (probably a venole). Middle-aged women are preferentially affected. The hematoma develops either spontaneously or after mechanical irritation (carrying of bags, etc.) in one finger or the palm of the hand following a sudden sharp pain (Fig. 9.**21**). Resolution of the hematoma usually takes one or two weeks. This condition is unrelated to bleeding disorders and is comparable with the better known spontaneous subconjunctival hemorrhage.

Fig. 9.**21** Paroxysmal finger hematoma.

Tibialis Anterior Syndrome

Tibialis anterior syndrome is diagnosed when acute occlusion of the anterior tibial artery results in ischemic muscle necrosis of the anterolateral calf (erythema, swelling, pain). Peroneal paralysis with foot drop is a typical symptom. The syndrome may also be seen with patent circulation (normal dorsalis pedis arterial pulse). Physical overexertion (e. g., prolonged hiking) is the

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typical trigger, particularly in young men. The syndrome developed in a patient who presented to our clinic after having ice skated the whole afternoon on a frozen lake. These cases are caused by transcapillary filtration of fluid into the tibialis anterior compartment. Since this compartment is tightly enclosed by fascia, this results in a continuous increase in tissue pressure, until capillaries collapse.

9.3 Diseases of the Veins

Superficial Thrombophlebitis

Superficial thrombophlebitis has to be distinguished from deep vein thrombosis with regard to prognosis as well as treatment.

Varicophlebitis (Fig. 9.**22**) is characterized by erythema, swelling, and pain at the site of a pre-existing varicose vein. Frequently the disease is preceded by minor trauma. Ascending varicophlebitis of the greater saphenous vein is of particular relevance, since it can lead to symptomatic pulmonary embolism or spread into the deep venous system.

Superficial thrombophlebitis, particularly in the case of migrating thrombophlebitis or phlebitis saltans, may involve previously normal veins without varicosis (Fig. 9.**23**). Unlike varicophlebitis, which lacks inflammatory infiltrates (in spite of the clinical signs of inflammation), migrating thrombophlebitis is histologically characterized by a chronic panphlebitis. This segmental, inflammatory phlebopathy is seen most frequently in thromboangiitis obliterans and in paraneoplastic syndromes associated with carcinoma, rarely in connective tissue disease and Behçet syndrome. Migrating thrombophlebitis may also be an isolated entity. A special form of migrating phlebitis is Mondor disease, which typically involves the superficial veins of the lateral chest and may spread to the veins of the arm.

Fig. 9.**22** Varicophlebitis of the greater saphenous vein.

Fig. 9.**23** Migrating thrombophlebitis in a 38-year-old man with thromboangiitis obliterans.

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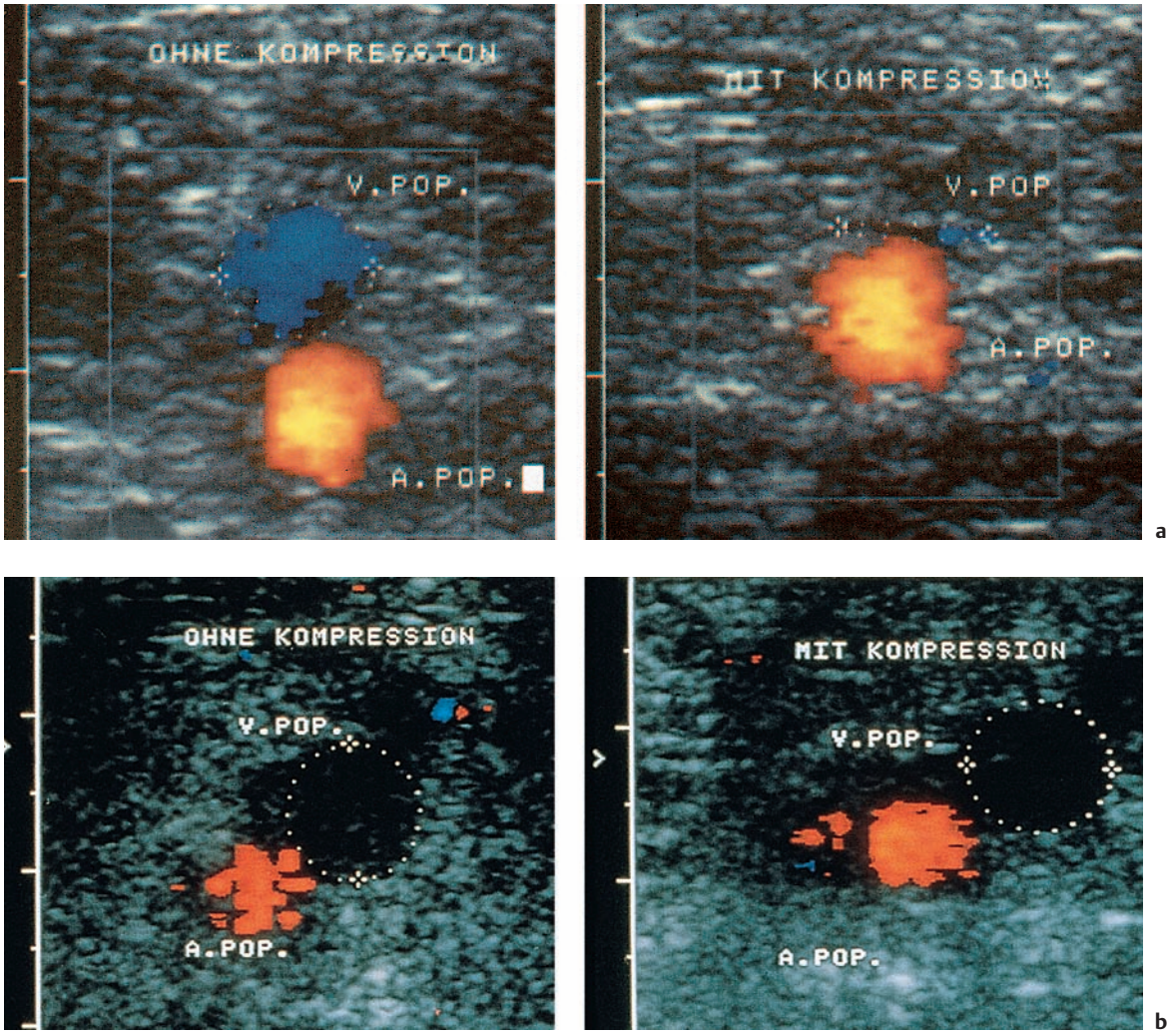

Fig. 9.**24** Color-coded duplex ultrasound of the popliteal vessels (cross section).

a Normal presentation of the vein (blue) and the artery (red) in a healthy person (without compression). Pressure with the probe leads to complete compression of the vein (with compression).

b Patient with deep vein thrombosis. The vein has no flow and is not compressible with the ultrasound probe.

Deep Vein Thrombosis of the Pelvis and Legs

Clinical Findings. The clinical picture of deep vein thrombosis (DVT) stretches between the extremes of *phlegmasia coerulea dolens* and *totally asymptomatic* disease. In the former, massive thrombosis of the complete venous cross section results in acral gangrene due to a rise in tissue pressure above capillary pressure. Between these extremes lies the typical DVT, quite easily recognizable on the basis of edema, livid discoloration, petechiae (which may rarely progress to extensive subcutaneous hemorrhages), and calf tenderness. General symptoms are not usually prominent, as long as pulmonary embolism has not occurred. Subfebrile temperature, moderately elevated ESR, and leukocytosis may be present.

Diagnostic Approach. Early diagnosis may be difficult. Large surveys show that only 50–60% of cases are correctly diagnosed based on *physical examination*. Comparative palpation of the calves (subfascial edema), inspection of the standing patient (unilateral livid discoloration of the foot, bulging veins on the back of the foot), and prominent subcutaneous collateral veins may indicate the diagnosis.

Clinical suspicion always requires *additional diagnostic tests* in order to confirm or rule out the diagnosis of DVT. Currently, direct visualization of the thrombosis is achieved primarily by B-mode ultrasound (compression ultrasound) or color-coded duplex ultrasound (Fig. 9.**24**), which have an accuracy of approximately

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Fig. 9.**25** Acute iliofemoral deep vein thrombosis in a 20-year-old woman. The contrast medium flows through the greater saphenous vein and pudendal veins to the opposite side (antegrade phlebography from the back of the foot).

Table 9.**3** Causes of deep vein thrombosis

Trigger of thrombosis	Predisposing factors
– surgery – trauma – pregnancy and delivery – immobilization – prolonged sitting – venous compression (May–Thurner syndrome, tumor, aneurysm, hematoma)	– age – previous thrombosis – varicose veins – heart failure (diuretics) – obesity – malignant disease – oral contraceptives – thrombophilia

95%. Simpler technical procedures like Doppler ultrasound and plethysmographic techniques have become of minor significance for the diagnosis of DVT. Plethysmography is an indirect method, which detects abnormalities in venous outflow caused by the thrombosis. A negative D-dimer test rules out DVT with high probability. Phlebography is used predominantly in uncertain cases to achieve a definitive diagnosis (Fig. 9.**25**). Phlebography is mandatory before aggressive treatments like surgical thrombectomy or fibrinolysis.

Types of lower limb DVT. Calf vein thrombosis is the most common form and at the same time the most difficult to diagnose, since its course is frequently bland. Involvement of the veins of the thigh (ascending form) not only increases the risk of pulmonary embolism, but also of future development of severe chronic venous insufficiency. Thrombosis of the pelvic veins and multilevel thrombosis usually causes unequivocal symptoms, except when the thrombus occludes the venous lumen only partially.

Causes. Tab. 9.**3** summarizes the most important factors predisposing to DVT. Compression of the left common iliac vein by the right common iliac artery is probably the reason why DVT is more common in the left than in the right leg. An actual fibrous stenosis is occasionally seen at this site of compression (May–Thurner syndrome). DVT is still regularly seen after surgery and trauma, although its frequency has been reduced by pharmacological thromboembolic prophylaxis. Hip replacement surgery is one of the most common causes. However, it is important to stress that several medical conditions like heart failure, myocardial infarction, stroke, and malignant neoplasias also have a high risk of DVT. Differential diagnosis of venous stasis should include causes of localized venous compression (tumors, aneurysms, Baker cyst, or large, subfascial hematoma), and paresis with failure of the muscle pump (e.g., residual state after poliomyelitis).

Extended coagulation tests are warranted particularly when thrombosis affects young patients without a history of an overt cause, in recurrent thrombosis, or in thrombosis with unusual localization (cerebral, visceral). These laboratory tests are discussed in Chapter 15. Underlying malignant disease is not rare and may be discovered in approximately 8% of patients over 50 years of age either at the time of or following the diagnosis of DVT.

Arm Vein Thrombosis (Thrombose Par Effort)

Onset of pain, edema, and livid discoloration of the arm after arm exertion (tennis, bowling, long driving, etc.) indicates acute arm vein thrombosis. Collateral veins are usually visible on the shoulder at an early stage. Occlusion of the subclavian or axillary vein can be demonstrated by phlebography (Fig. 9.**26**). These veins pass through the bottleneck between the clavicle and the first rib and between the tendon of the pectoralis minor muscle and the coracoid process. Frequently arm vein thrombosis has therefore to be interpreted as a complication of neurovascular thoracic outlet compression syndrome (Paget–Schrötter syndrome). Impeded venous runoff due to compression by an intrathoracic

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mass should be excluded, particularly if phlebography shows an atypical localization of the occlusion (radiological imaging studies of the mediastinum).

Arm vein thrombosis occurs as a complication of venous catheters, but only rarely in the setting of internal diseases.

Primary Varicosis

Definition and Epidemiology. Primary varicosis indicates a tubular or saccular dilatation of superficial and perforating veins, which is remarkably common in industrialized countries. The Basel study revealed clinically relevant varicose veins in 4% of 30-year-old and 23% of 60-year-old employees. Varicose veins representing only a cosmetic problem are far more common. Occurrence is facilitated by a sedentary lifestyle and prolonged standing, as well as hereditary and hormonal factors.

Classification. Optimal treatment requires an exact classification of varicose veins. General terms like "varicose syndrome" or "varicose complex" are insufficient:

- Truncular varicosis of the greater and lesser saphenous veins can be distinguished from side-branch varicosis by inspection and palpation.
- Small caliber varicose veins, which usually are only of cosmetic relevance, are classified as reticular varices and teleangiectasias.
- Valvular incompetence of the greater saphenous vein trunk, including the uppermost valve in the groin, results in flow reversal during coughing and pressing, which can produce a palpated impact over the vein in the standing patient. A venous sound can be heard with a stethoscope in cases with marked turbulence of the regurgitating blood. This finding helps in distinguishing an inguinal hernia from the dilatated orifice of the greater saphenous vein. The Trendelenburg test is also used to diagnose valvular incompetence of the greater sahenous vein trunk. Doppler sonography is the technical procedure most widely used to detect valvular incompetence in both saphenous veins.
- Incompetent perforating veins result in palpable, frequently painful fascial gaps. Induration frequently develops in the surrounding skin (hypodermitis) and can mimic thrombophlebitis. Compression or contraction of the calf produces an outward flow, which can be documented by Doppler ultrasound. Duplex ultrasound is the best technique for the detection of incompetent perforating veins.

Fig. 9.**26** Thrombotic occlusion of the left subclavian vein in a woman with costoclavicular compression syndrome (phlebography of the arm).

Chronic Venous Insufficiency

Definition. Chronic venous insufficiency designates a chronic impairment of venous backflow, which affects approximately 20–25% of the working population.

Clinical Findings. Characteristic findings are heaviness and pain in the legs, particularly while standing, as well as more or less pronounced edema of the ankles and calves. Symptoms diminish with elevation of the legs. Nocturnal cramps in the calves are frequent. Inspection, which is best performed with the patient standing, reveals livid discoloration of the feet and prominent, bulging veins. A typical finding is so-called corona phlebectatica paraplantaris, a crown of congested veins stretching from the medial to the lateral side of the foot. Brown hyperpigmentation, depigmentated areas of capillary rarefication (atrophie blanche), induration, and eventual ulceration preferentially of the medial ankle (area of the Cockett perforating veins) complete the clinical picture (Figs. 9.**27**, 9.**28**).

Pathogenesis. Chronic venous insufficiency may be caused by one or more of the following factors:

- mechanical obstruction of venous backflow (venous occlusion, partial recanalization, etc.)
- valvular incompetence of the deep venous system
- valvular incompetence of the perforating veins
- valvular incompetence of the superficial venous system

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Fig. 9.**27** Typical chronic venous insufficiency with edema, hyperpigmentation, atrophie blanche, livid discoloration, and corona phlebectatica paraplantaris.

Fig. 9.**28** Large venous ulcer at the typical location (medial calf and ankle).

Fig. 9.**29** Secondary varicosis in a young man after a left-sided deep vein thrombosis of the pelvis and thigh.

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- incompetence of the muscle pump due to paresis or impaired joint mobility.

> Isolated abnormality of the superficial venous system without involvement of perforating veins usually does not lead to the symptoms of chronic venous insufficiency.

The degree of impairment of venous backflow depends on the severity of these conditions and on the number of involved factors.

Chronic venous insufficiency may be caused by primary varicosis with incompetent perforating veins or by *postthrombotic damage* to the deep veins. Deep veins usually recanalize spontaneously after thrombotic occlusion. However, the valves of these veins are permanently damaged. Insufficiency of the deep veins dominates the clinical presentation. It can be diagnosed by Doppler studies during pressing maneuvers or by retrograde press phlebography. These procedures can detect also persistent occlusions and stenoses.

Secondary varicose veins develop frequently as a consequence of the postthrombotic syndrome (Fig. 9.**29**). These dilated collaterals form in the groin and genital region after pelvic vein thrombosis and in the drainage area of the greater saphenous vein after deep vein thrombosis of the thigh. Notably, postthrombotic syndrome follows acute DVT after an asymptomatic lag phase. Progressive impairment of venous backflow may develop several years later.

The aforementioned five causes of chronic venous insufficiency lead to constant venous hypertension while standing. The elevated pressure is transmitted to the microvasculature where it damages the capillary circulation. Enlarged and tortuous capillaries can be detected through intact skin by in vivo microscopy. Thrombosis of capillary tufts leads to a decrease in the number of capillaries and eventually to the development of so-called atrophie blanche, discolored skin areas lacking capillaries in the center (see Fig. 9.**27**).

Capillary rarefication causes a marked drop in transcutaneous oxygen pressure. This microvascular ischemia plays a major role in the development of venous ulceration. Microangiopathy in severe chronic venous insufficiency involves not only blood capillaries but also lymphatic vessels (fluorescence microlymphography, indirect lymphography with Iotasul). The typical indurated plaques seen in these cases are partly due to lymphatic congestion.

Onset of chronic venous insufficiency at school age or in adolescence suggests congenital valvular aplasia as a possible cause. Other forms of angiodysplasia characterized by nevus flammeus, limb hypertrophy, and atypical varicose veins should also be considered. These disorders may be associated with arteriovenous fistulas, venous aneurysms, aplasia of deep veins, and hypoplastic lymphatic vessels, thus requiring extensive diagnostic imaging (MRI, angiography) and hemodynamic evaluation before active treatment can be considered.

9.4 Disorders of the Lymphatic Vessels

Acute lymphangitis is an easily recognizable cause of pain, when characteristic red stripes extend from a peripheral skin lesion (which may be small and difficult to detect) to proximal swollen lymph nodes (lymphadenitis).

Edema is the leading symptom in *chronic lymphatic disorders*. Pain usually occurs only during bouts of erysipelas, which frequently complicate the disease. The differential diagnosis is discussed in Chapter 12.

9.5 Thoracic Outlet Syndrome (TOS)

Thoracic outlet syndrome (TOS) is a combination between an organic and a functional disorder. The disease is due to an anatomical bottleneck. However, this organic abnormality becomes functionally relevant only at specific positions of the arm (compression of the neurovascular structures). The main symptoms are pain, paraesthesia, and sensation of "falling asleep" of the affected upper extremity. The symptoms are triggered or increased by certain positions of the arms (sleeping with bended arm, elevation of the arm while holding an umbrella).

Diagnostic Approach. The diagnosis is based on the reproducibility of symptoms, the loss of pulses, and the onset of vascular bruits in the supraclavicular fossa (arterial stenosis) during mechanical provocation tests. Disappearance of pulses can be documented by acral pulse recording during the test (elevation of the 90° bended arm with and without turning the head to the opposite side). Symptoms that occur only in extreme and nonphysiological positions are common also in normal individuals and have little diagnostic value.

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Causes. Compression of the neurovascular structures can occur at three anatomical sites:

- scalene gap
- costoclavicular space
- insertion of the tendon of the pectoralis minor muscle.

Costoclavicular compression between the clavicle and the first rib is by far the most frequent form. Resection of the first rib (as opposed to scalenotomy) is the treatment of choice in these cases. Cervical ribs lead to narrowing, particularly of the scalene gap. However, it should be stressed that cervical ribs do not necessarily produce symptoms. Compression due to the tendon of the pectoralis minor muscle is a rare finding, which is best documented by angiography during provocation tests.

Differential Diagnosis. Disorders of the cervical spine have to be considered. Tension of the paravertebral muscles can cause impaired motility of the shoulders and neck and result in a secondary neurovascular syndrome.

Complications. Severe cases can lead to neurological and vascular complications: paresis and sensory deficits, occlusions of the subclavian artery or vein, and poststenotic aneurysms, which may cause recurrent embolization into peripheral arteries of the arm.

9.6 Restless Legs

Restless legs are a common symptom, which predominately affects nervous individuals and is unrelated to vascular disorders. The patients complain of unpleasant sensations and pain as soon as the legs come to a resting position. The symptoms are relieved by movement. Sometimes the syndrome may be caused by an underlying neurological disorder or iron deficiency. However, no abnormal findings can be found in the majority of cases. This phenomenon is highly relevant in general practice (see also Chapter 8).

9.7 Sudeck Disease

Sudeck disease is a disorder of unknown etiology, which usually occurs after traumatic injury of an extremity. The early stages are characterized by a warm, pitting edema of the acral extremity with continuous pain. Local hyperthermia is followed by hypothermia (due to vasospasm) during the later course of the disease (Stage II). The edema turns pale or slightly cyanotic. The pain is particularly pronounced during exercise (danger of disablement). Radiography shows a characteristic unilateral patchy demineralization.

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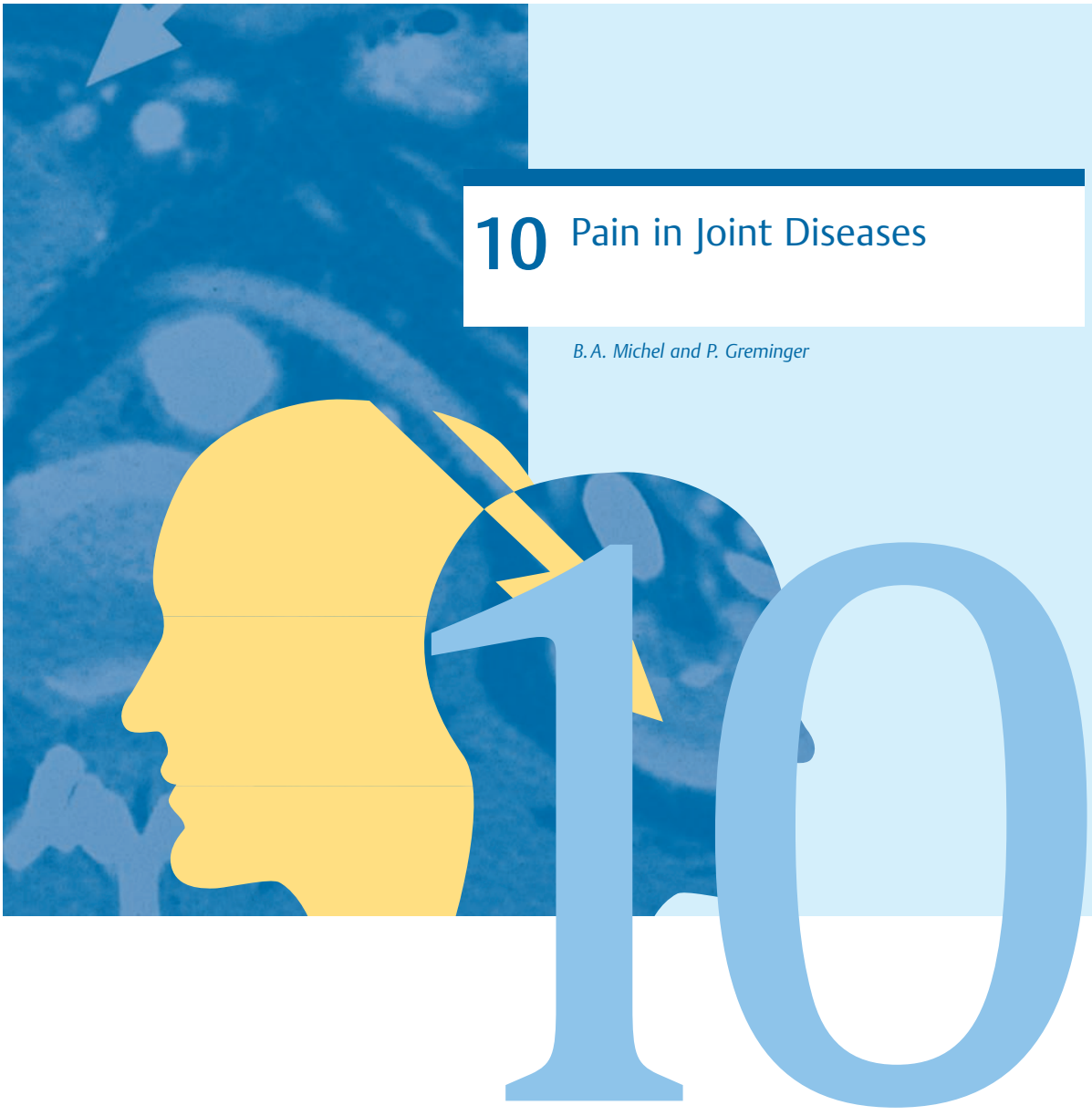

10 Pain in Joint Diseases

B. A. Michel and P. Greminger

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General Differential Considerations in Joint Pain

The symptom "joint pain" has to be clinically substantiated. In not all cases does the joint itself represent the origin of the disorder. Affections of soft tissue may also give rise to joint symptoms. Joint disorders usually are associated with the following symptoms:

- swelling (sometimes with effusion)
- warmth
- pain upon pressure
- functional deficit.

Acute monoarthritis needs immediate evaluation: an infectious disorder must be considered. Other forms of acute joint inflammation include arthritis in gout and pseudogout (calcium pyrophosphate arthropathy). These affections are often associated with severe redness of the skin and tenderness. Other joint disorders usually take a chronic course from the very beginning, such as rheumatoid arthritis, connective tissue diseases, and osteoarthritis. Joint disorders of the spondylarthropathy group usually show intermittent acute to chronic courses.

10.1 Inflammatory Rheumatic Joint Disorders

Rheumatoid Arthritis

Epidemiology. Rheumatoid arthritis is the most frequent inflammatory rheumatic joint disease. Women are affected about three times more often than men.

Clinical Findings. *Symmetric distribution of the joint disorder* is characteristic. In the early phase of the disease hand, metacarpophalangeal and interphalangeal joints (Fig. 10.**1**), as well as knee and metatarsophalangeal joints, are affected. Involvement of the distal interphalangeal joints is rare and points to differential diagnoses, such as psoriatic arthritis or reactive arthritis. Usual symptoms of rheumatoid arthritis include joint pain and swelling, often associated with severe and long-standing morning stiffness, as well as loss of strength, particularly in the hands. Fatigue and general malaise, and at times slightly elevated temperatures, are often the first indications of the *ongoing disease process*. Without effective medication, rheumatoid arthritis is characterized by functional deficit due to progressive joint destruction. Late stages are characterized by deformities, rheumatic nodules, as well as postinflammatory changes of bones, joints, and soft tissue.

In later stages of the disease *extra-articular manifestations* may occur. This includes pleuropericarditis, rheumatic nodules, eye involvement, and more rarely, vasculitis with sensorimotor disturbances or amyloidosis.

Diagnosis. Already in the early course of the disease *radiologic changes* may be detected in the hands and feet. In the early stage changes include periarticular soft tissue swelling and demineralization of the periarticular bones. In later stages they include joint space narrowing along with erosions and subluxations (Fig. 10.**2**). It is rare for ankylosis to be a feature. Involvement of the cervical

Fig. 10.**1** Rheumatoid arthritis with joint swelling and moderate ulnar deviation of the fingers.

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spine however is frequent. Rheumatoid arthritis may lead to spondylarthritis, instability, or rarely ankylosis, but also to destruction of the atlantal dentate ligaments through inflammatory pannus resulting in atlantoaxial subluxation or even compression of the spinal cord.

Laboratory examination often reveals elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), normochromic and normocytic anemia, thrombocytosis, and low serum iron. Rheumatoid factors tend to be positive at later stages.

The diagnosis of rheumatoid arthritis is based on the history, typical clinical findings (pattern of joint involvement), as well as radiographic and laboratory findings.

Differential Diagnosis. In the differential diagnosis the following disorders have to be considered:

- connective tissue diseases (particularly systemic lupus erythematosus and systemic sclerosis)
- polymyalgia rheumatica (patients over 60 years of age)
- *Parvovirus*-induced arthritis (usually self-healing)
- osteoarthritis of the fingers.

Rarely, difficulties in the delineation of reactive arthritis are encountered. Most often this disorder shows asymmetric oligoarticular joint involvement along with enthesiopathies.

Felty Syndrome

Felty syndrome is a rare, systemic manifestation of *rheumatoid arthritis*. Its hallmarks are hepatosplenomegaly, leukopenia, and frequently treatment resistant skin ulceration of the lower extremities. The majority of patients show rheumatoid nodules, lymphadenopathy, high titer rheumatoid factors, as well as antinuclear antibodies. A genetic disposition is characterized by the association with HLA-DR4, which is encountered in over 90% of patients.

Adult Still Disease

Clinical Findings. Still disease is a *rare form of rheumatoid arthritis*. Men and women less than 40 years of age are equally effected. Acute episodes of this inflammatory disorder are characterized by high fever spikes (usually over 39 °C). Arthralgias or even oligoarthritis (especially wrists), phalangitis, weight loss, and transient, salmon-colored exanthema of the trunk and the proximal extremities are characteristic manifestations.

Further findings include hepatosplenomegaly, lymphadenopathy, elevated ESR, marked leukocytosis, and very high values for serum ferritin. Rheumatoid factors and antinuclear antibodies are negative.

Fig. 10.**2** Rheumatoid arthritis: considerable erosions, joint space narrowing, and periarticular osteopenia.

Differential Diagnosis. Other causes of fevers such as infections and inflammatory intestinal disorders, including Crohn disease and colitis ulcerosa, have to be considered in a differential diagnosis.

Sjögren Syndrome

Definition and Epidemiology. Sjögren syndrome is characterized by inflammatory involvement of tear, salivary, and, mucosal glands (in the intestinal and the pulmonary airways) resulting in *sicca symptoms*. The syndrome may evolve as a primary syndrome or as an accompanying disorder in association with rheumatoid arthritis or another connective tissue disease (Tab. 10.**1**). Women over 50 years of age constitute more than 90% of patients.

Table 10.**1** Sjögren syndrome

Sicca complex	and connective tissue disease
Xerophthalmia Xerostomia	Rheumatoid arthritis Systemic sclerosis Systemic lupus erythematosus Periarteritis nodosa Dermatomyositis

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Fig. 10.**3** Dry, cracked tongue in Sjögren syndrome. 79-year-old woman.

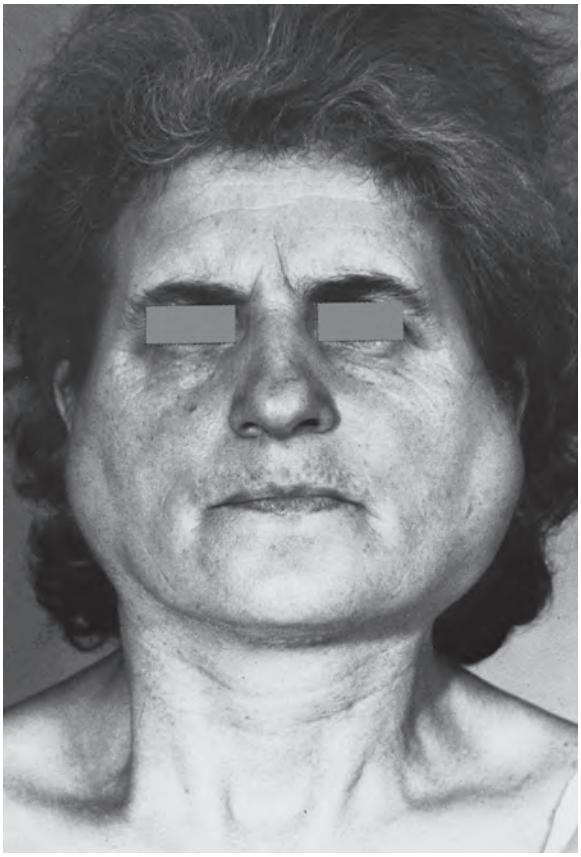

Fig. 10.**4** Swelling of both parotid glands in Sjögren syndrome. 50-year-old woman. ▷

Clinical Findings. Dryness leads to the characteristic manifestations, which are:

- xerophthalmia (keratoconjunctivitis sicca with sensation of foreign bodies, burning, and redness)
- xerostomia (Fig. 10.**3**) with impaired swallowing, hoarseness, coughing, and development of severe caries.

Characteristic are recurrent, symmetrical, painful, enlarged salivary glands, particularly the parotid glands (Fig. 10.**4**). Further symptoms include fatigue, fever, arthritis similar to rheumatoid or pillar arthralgias, lymphadenopathy, vasculitic ulcerations, particularly of the legs, as well as neuropathies. Renal involvement is more rare (interstitial nephritis, tubular acidosis). Transitions to malignant lymphomas may occur.

Diagnosis. ESR is often highly elevated. Further typical findings include hypergammaglobulinemia, rheumatoid factors, and anti-SS-A (Ro), as well as anti-SS-B (La) antibodies.

Differential Diagnosis. Treatment with antidepressants (dry mouth), sarcoidosis, and HIV infection have to be considered in the differential diagnosis. The diagnosis of Sjögren syndrome is strongly supported with the positive Schirmer test (measurement of tear flow), as well as biopsy of the lips.

Juvenile Chronic Arthritis

Classification. Juvenile chronic arthritis (JCA) is classified according to its presentation at the onset of disease. There are three forms:

- The *systemic form* (Still disease) is characterized by episodes of fever with salmon-colored rash, hepatosplenomegaly, and lymphadenopathy. Often arthritic complaints will follow.
- In the *polyarticular form*, distal finger joints are often involved, in contrast to rheumatoid arthritis in adults. In this form, rheumatoid factor usually is negative.
- The *oligoarticular form* shows two special aspects: under the age of four years destructive iridocyclitis may occur; children with positive antinuclear antibodies should undergo regular ophthalmologic examination since iridocyclitis may be asymptomatic. Oligoarthritis after the age of eight years usually displays features similar to ankylosing spondylitis.

Differential Diagnosis. The following disorders have to be considered: acute rheumatic fever, bacterial polyarthritis, tuberculosis, and sarcoidosis. In the differential diagnosis puncture or synovial biopsy of the involved joint are helpful.

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Spondylarthropathies

Common Features. Tab. 10.**2** lists all disorders within the family of spondylarthropathies. These inflammatory, mostly chronic, musculoskeletal diseases share clinical, radiologic, histopathologic, and genetic features:

- peripheral, usually oligoarticular arthritis involvement of the spine and sacroiliacal joints
- involvement of tendons and tendon insertions (enthesiopathy)
- extra-articular features (eyes, skin, mucosa, more rarely heart and lungs)
- familiar aggregation and association with HLA-B27.

Often these diseases are called *seronegative* due to the fact that rheumatoid factors and autoantibodies are usually not found.

Ankylosing Spondylitis (Bekhterev Disease)

Clinical Findings. Ankylosing spondylitis represents the classical spondylarthropathy. This chronic inflammatory disorder affects sacroiliacal, costovertebral, and facet joints leading to progressive ankylosis. Hips and shoulders are most commonly affected whereas other joints are less often involved. Systemic manifestations are rare (uveitis anterior, aortitis with aortic insufficiency, pulmonary fibrosis).

Men are affected more often and more severely than women. First symptoms usually develop between the ages of 20–40. Typical symptoms include low back and buttock pain at night, radiating towards the dorsal aspects of the knees. Motion is followed by decreased pain. Stressing the sacroiliacal joints is painful due to inflammation (Mennel or Patrick sign). Axial involvement often leads to early ankylosis with typical deformities: hyperkyphosis of the thoracic spine, flattening of the lower spine (Fig. 10.**5**). Plantar and achilles enthesiopathies are frequent origins of heel pain. Hip involvement leads to a tendency towards contracture.

Diagnosis. Although elevated ESR is typical, it may also be normal. Typical changes of the sacroliacal joints in radiographs show narrowing of the joint space along with sclerosing and erosive features (Fig. 10.**6**), finally leading to ankylosis. Involvement of the spine is characterized by ossification of the ligaments (Fig. 10.**7**).

Table 10.**2** Frequency of HLA-B27 and sacroiliitis in spondylarthropathies

	HLA-B27 (%)	Sacroiliitis (%)
Ankylosing spondylitis	95	100
Reactive arthritis (Reiter syndrome)	70	30
Psoriatic arthropathy	50	20
Enterocolitic arthropathy	50	20
SAPHO syndrome	40	30
Undifferentiated spondylarthropathy	50	20

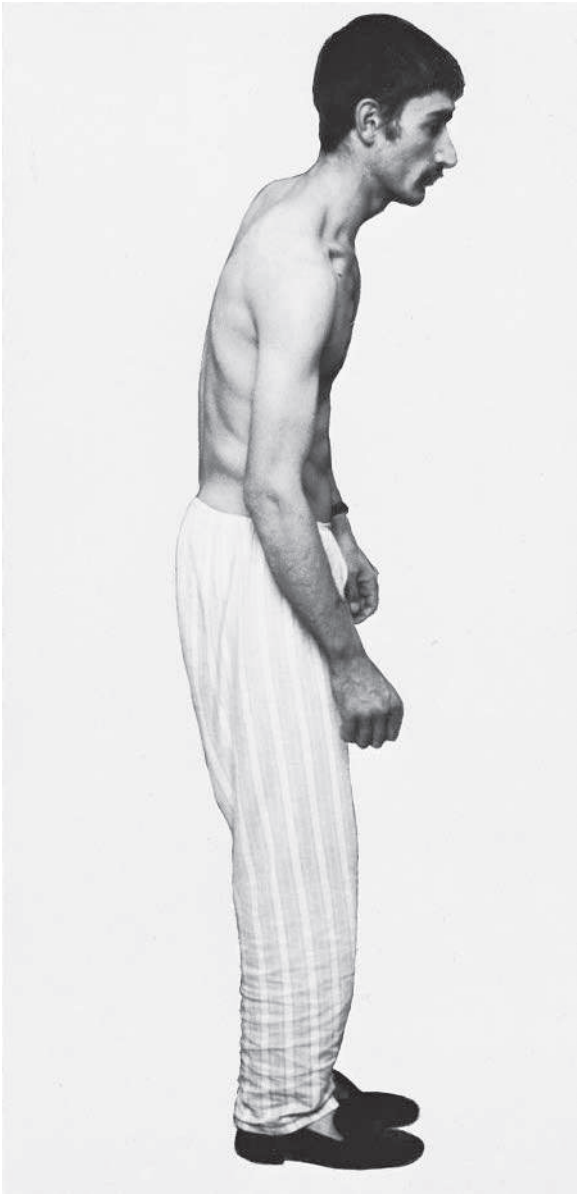

Fig. 10.**5** Typical positioning of a patient with Bekhterev disease.

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Fig. 10.**6** Sacroiliac joints in Bekhterev disease.

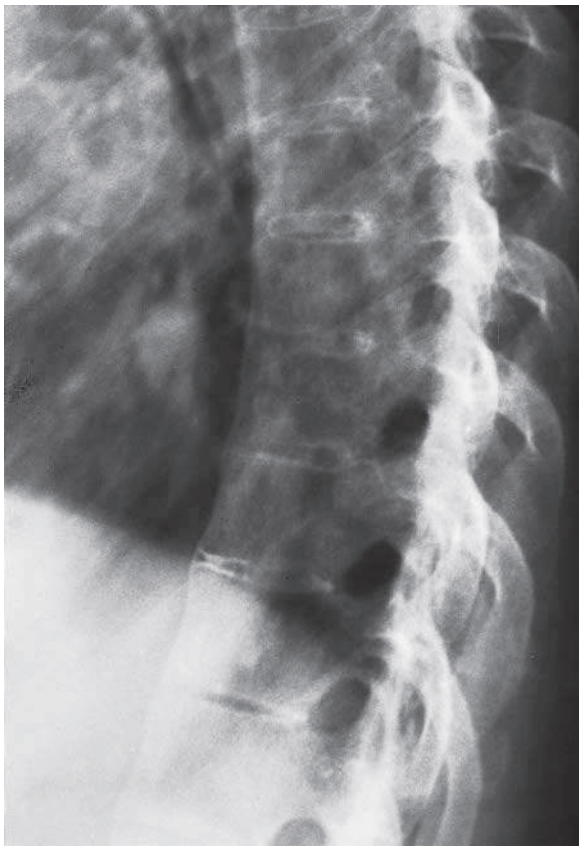

Fig. 10.**7** Ossified ligaments along the spine in Bekhterev disease. ▷

Fig. 10.**8** Psoriatic arthritis

Hallmarks for diagnosis are the classical history of pain, clinical features, and radiographic examination. Determination of HLA-B27 usually is not necessary.

Psoriatic Arthritis

Clinical Findings. The typical pattern of joint involvement in psoriatic arthritis is either characterized by arthritis of all finger joints (DIP, PIP, and MCP joints) resulting in a so-called dactylitis or sausage finger, as well as a transverse involvement of the DIP joints. In contrast to rheumatoid arthritis, the joint swelling is rather tight and the skin often shows a red livid coloration. Arthritis may appear after skin involvement, which is especially the case in children. Radiographically, the hallmark findings consist in both ankylosing ossification and destructive processes at the same time. Given this typical feature, diagnosis is often possible without skin involvement (Fig. 10.**8**). Nails may show so-called oil spots or onycholysis, particularly when distal joints of fingers or toes are affected. The typical course of psoriatic arthritis is characterized by episodes of highly acute disease and long-standing remissions. Involvement of the spine and the sacroiliac joints (mostly asymmetrical) is less frequent, as compared to ankylosing spondylitis.

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Differential Diagnosis. Similarities exist with rheumatoid arthritis (symmetrical pattern of joint involvement without affecting the DIP joints), osteoarthritis of the fingers (joint involvement preferentially of DIP and PIP joints), reactive arthritis (manifestation after intestinal or urogenital infection), as well as crystal arthropathies (joint fluid examination).

Reactive Arthritis (Reiter syndrome)

Definition. Reactive arthritis in its full form is called Reiter syndrome. The syndrome is characterized by arthritis, urethritis, and conjunctivitis, occasionally associated with mucocutaneous lesions. Men between 20 and 40 years of age are most often affected.

Causes. Reactive arthritis affects women and men equally after intestinal infections. After urogenital infections most patients are men. Triggering microorganisms includes *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Brucella*, as well as *Chlamydia* and *Ureaplasma*. In contrast to septic arthritis, these microorganisms can not be cultivated from joint tissue or fluid.

Clinical Findings. The first symptoms of a reactive arthritis may evolve only a few weeks after intestinal or urogenital infection. Along with fatigue and occasional fever, several manifestations may occur. Usually, acute asymmetrical oligoarthritis of larger joints of the lower extremities is the first manifestation. Other manifestations include involvement of a single finger or toe with livid skin coloration (so-called dactylitis or sausage finger), spondylarthropathy with lower back pain in the early morning and stiffness of the spine, frequently along with asymmetric involvement of the sacroiliac joints and inflammatory changes in tendon sheaths, tendons, and ligaments. Extra-articular symptoms are found in the skin and mucosa (keratoderma blennorrhagicum of palms and soles, erythema nodosa, oral ulceration), eyes (often conjunctivitis), and urogenital tract (sterile urethritis, balanitis and cystitis), as well as in the gastrointestinal tract (enteritis). Only very occasionally, nail changes may occur similar to the ones encountered in psoriasis.

Diagnosis. The culture of the feces, as well as PCR examination of the serum may detect the enteral infectious agents, as well as *Chlamydia* in the urine in the early stages of the disease. Determination of HLA-B27 does not really contribute to confirming the diagnosis, although 70 % of the cases are positive. In the differential diagnosis gonococcal urethritis with septic arthritis should be considered.

Rheumatic Fever

The typical example of a reactive arthritis is rheumatic fever. Currently, this disorder is very rarely encountered in Europe. After infection with beta-hemolytic streptococci group A, fever and polyarthritis, predominantly of the larger joints, carditis, and later chorea minor, transient erythema anulare marginatum of the trunk and thighs, as well as subcutaneous rheumatic nodules, may evolve.

> Anti-streptolysin titers should always be considered in association with the history and clinical findings, since this titer is not specific for rheumatic fever.

Arthropathies Associated with Enterocolitis

Colitis ulcerosa and Crohn disease may be associated with inflammatory changes of the spine and peripheral joints in about 10 %–20 % of patients. More rare causes of enterocolitic arthropathies are Whipple disease, arthritis after gastrointestinal bypass operation, as well as gluten-induced enteropathy.

Clinical Findings. In *colitis ulcerosa* the arthropathy most often evolves after the enteric symptoms. In contrast, joint involvement is not really a primary manifestation in *Crohn disease*, although inflammatory changes in the gastrointestinal tract may be detected endoscopically in the early stages.

Axial involvement as well as sacroiliitis may precede intestinal symptoms by years. Clinical and radiographic findings often can not be distinguished from classical ankylosing spondylitis. This activity in the peripheral joints often reflects the general intestinal inflammatory activity. Spinal inflammation however appears to take place independently. In contrast to ankylosing spondylitis, arthritis in enterocolitis disorders lasts only from a few days to a few weeks and may change location frequently. Sacroiliitis associated with gastrointestinal diseases often remains asymptomatic and is frequently detected by chance in radiographic examinations.

Systemic manifestations include anterior uveitis (up to 10 %, most often along with axial involvement), painful stomatitis ulcerosa, erythema nodosa, and pyoderma gangrenosum.

In *Whipple disease* arthralgias or transient nondestructive arthritis of small and larger joints may precede abdominal manifestations by years. Involvement of the spine and sacroiliac joints, as well as spondylarthritis is rare. Men between 40 and 60 years of age should be examined for *Tropheryma whipplei* if any arthritic condition of unclear origin occurs. The leading clinical symptoms for Whipple disease are abdominal discomfort with diarrhea and weight loss, slightly elevated

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Fig. 10.**9** SAPHO syndrome with swelling of the clavicular-costosternal area on the right side.

temperatures, lymphadenopathy, uveitis, and more rarely eye muscle paresis and encephalopathy.

Behçet Disease

Behçet disease belongs to the vasculitides. Most patients are originally from the eastern Mediterranean regions and the Orient. The main rheumatological complaints include chronic synovitis of larger and smaller joints. The diagnosis is based on two main symptoms plus one minor symptom.

Clinical Findings.
Main symptoms are:
- mucosal ulcerations in the mouth and/or intestinal tract
- genital ulcerations (vulva, penis, scrotum)
- ocular manifestations (uveitis anterior, hypopyon, retinal vasculitis).

Minor symptoms are:
- skin disease (erythema nodosa, folliculitis)
- arthritis (predominantly knee or ankle joints)
- neurologic symptoms (meningitis, involvement of cranial nerves)
- vessel disease (venous thrombosis, arterial aneurysms).

SAPHO Syndrome

Definition. SAPHO describes the most frequent manifestations of the syndrome: **s**ynovitis, **a**cne, **p**ustulosis, **h**yperostosis, and **o**steomyelitis. Men and women are equally affected and the disorder may evolve in patients of any age.

Clinical Findings. A hallmark finding of this disorder of unclear origin is an often asymmetrical, painful swelling in the clavicular-costosternal area (Fig. 10.**9**). The following features are frequent:
- sternoclavicular hyperostosis
- palmoplantar pustulosis
- inflammatory axial involvement
- peripheral oligoarthritis, particularly of large joints.

Manifestations often evolve sequentially; skin and bone symptoms may be found many years apart. Low back pain, axial stiffness, and painful joint swellings are, as with other spondylarthropathies, typical. Palmoplantar pustulosis is characterized by well delineated vesicles or pustules, as well as superficial scaling of the palms and soles. Differentiation from psoriatic skin disease is often not possible. As a complication of clavicular-costal hyperostosis, thrombosis of the subclavian vein or the superior vena cava may occur as a consequence of compression.

Diagnosis. Imaging of the strong increase in activity in bones and joints is best done by skeletal scintigraphy. At times, bone changes may simulate infectious osteomyelitis or tumors in radiographs. Such features therefore need more intensive examination.

Undifferentiated Spondylarthropathy

In about 30% of all patients with spondylarthropathies no specific diagnosis is possible. Many manifestations of spondylarthropathies may occur without fulfilling clear criteria for a specific disease, such as isolated peritendinitis of the achilles tendon or severe low back pain in the early morning in a young man. Such, mostly early, forms of spondylarthopathies are classified as undifferentiated.

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Arthropathies Associated with Metabolic Diseases

Arthritis Urica (Gout)

Epidemiology and Causes. *Primary gout* in men occurs about 10 times more often than in women. In men, gout develops most frequently between the ages of 40 and 50 years, but in women usually only after the age of 60 years. Triggering factors include rich meals with high purine intake and/or alcohol consumption.

Clinical Findings. *Classical acute gout* is always very painful, it occurs during the night, and patients may not be able to walk on the inflamed joints. Typically, the involved joint is red, swollen, and extremely painful. Slightly raised temperatures, elevated ESR, and leucocytosis are the rule. Without treatment the acute attack will subside in about a week, leaving the involved joint slightly painful for longer periods. The first metatarsophalangeal joint is most often involved, however, gout may occur in any joint. In such cases the differential diagnosis of acute septic arthritis or reactive arthritis, as well as psoriatic arthritis has to be considered. Acute onset in rheumatoid arthritis is also possible. In elderly people, pseudogout (chondrocalcinosis) has to be differentiated from gout.

In *later stages of the disease* deposition of urate occurs in tendons, bursa, and joints, which is known as chronic tophaceous gout (Fig. 10.**10**). Tophi are located most often in the neighborhood of the involved joints, but may be found at the external ear as well (Fig. 10.**11**).

Diagnosis. In radiographs, well-delineated erosions at the end of bones are characteristic for gout (Fig. 10.**12**). The diagnosis of gout is supported by increased serum uric acid levels and proven by the positive finding of uric acid crystals in the joint fluid.

Pathogenesis. The cause of primary gout is multifactorial. About 20 % of cases show enzyme defects leading to the overproduction of uric acid. In all other patients uric acid is not excreted sufficiently, probably based on an epithelial insufficiency.

> Acute attacks of gout with normal or only slightly increased serum uric acid may occur. This is especially true when uricosuric agents have been taken before the attack.

In elderly patients pseudogout (see Chondrocalcinosis, below) always has to be considered. Serum uric acid levels do not parallel clinical symptoms. However, most patients with increased serum uric acid of over 600 μmol/L will sooner or later be symptomatic.

Complications. The most important complication of gout is the so-called *gout kidney*. Impairment of the kidney is a consequence of hyperuricemia and increased excretion of uric acid. On histological examination, inflammatory interstitial infiltrates as a consequence of deposition with uric acid are found along with an eventual pyelonephritis caused by lithiasis, as well as vascular changes (nephrosclerosis). Many patients with gout develop hypertension. Therefore it may be difficult to differentiate between secondary consequences of hypertension or gout when interpreting renal insufficiency. Gout nephropathy itself may lead to hypertension.

Hyperuricemia and gout are often associated with diabetes mellitus, hyperlipoproteinemia, and hypertension; therefore gout is considered a risk indicator. Whether gout alone or only in combination with other risk factors may lead to coronary sclerosis is controversial.

Secondary Gout. Features of gout may evolve in all diseases associated with increased cell death (e. g., myelo- and lymphoproliferative diseases) or by any treatment leading to decreased excretion of uric acid, such as diuretics. In addition, secondary hyperuricemia may be found in ketosis (fasting, decompensated diabetes mellitus, fat-rich meals), acromegaly, hypo- and hyperparathyroidism, CO intoxication, lead intoxication, myxedema, and with the intravenous application of fructose.

Chondrocalcinosis (Pseudogout)

Deposition of calcium pyrophosphate crystals may lead to joint inflammation. The acute attack may not be differentiated clinically from a gout joint attack. Most often larger joints are involved. Differentiation of crystals is possible by the examination of joint fluid. Radiographically, typical calcifications may be found in

Fig. 10.**10** Chronic tophaceous gout of the index finger.

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Fig. 10.**11** Auricular tophus. 72-year-old man.

Fig. 10.**12** Cystic defects in the bone in a patient with gout.

meniscae and superficial layers of the joint cartilage (Fig. 10.**13**).

Chondrocalcinosis has a preference for middle aged and elderly persons, but may occur at any age. Often chondrocalcinosis will be found as an accompanying disorder in damaged joints (osteoarthritis, posttraumatic arthritis) or in metabolic diseases (hyperparathyroidism, hematochromatosis, Wilson disease, gout, ochronosis).

Axial involvement is rare and may show calcifications of the intervertebral disks. The course of axial disease is clinically silent with the diagnosis most often resulting from a chance finding in a radiograph of the vertebrae.

Fig. 10.**13** Chondrocalcinosis with calcifications of meniscus and cartilage.

Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Axial hyperostosis is often detected in radiographs by chance. This disorder is characterized by overshooting ossifications with osseous bridge building between single vertebrae without narrowing of the intervertebral spaces. It is based on ossification of the longitudinal ligaments of the spine. The right side of the thoracic spine is preferentially involved, however, ossifications may develop at any site including peripheral joints.

Usually hyperostosis is followed by clinical ankylosis, whereas occurrence of pain is rare. In the shoulder area, severe symptoms may be due to hyperostosis at the inferior aspect of the acromion leading to irritation of the subacromial area (impingement). In the pathogenesis,

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metabolic disturbances are thought to be the possible cause of the hyperostosis, since metabolic disorders are associated with this disorder, such as impaired glucose tolerance, hyperlipidemia, and hyperuricemia.

Ochronosis (Alkaptonuria)

Definition and Pathogenesis. Ochronosis is a congenital disorder of metabolism characterized by a deficiency of homogentisic acid oxidase leading to an incomplete metabolism of phenylalanine. This may all take a symptom-free course for years while it is only recognizable in the urine: homogentisic acid is excreted at higher levels and when oxidized the urine will change color to a dark blue.

Clinical Findings. Black spots may evolve in many areas and are often recognized as first symptoms of the disease. Homogentisic acid is deposited in cartilage, tendons, and sclerae leading to a darker brown to black discoloration which is called ochronosis (Fig. 10.**14**). Only many years later does cartilage destruction occur. In this stage, changes in the spine, ossifications of tendon insertion, especially at the pelvis and hips, leading to osteoarthritis of the hips and knees, as well as the elbows occurs. The changes of the spine include severe sclerosis of the horizontal plates of the vertebrae as well as osteophytoselike changes along with severe degeneration of the intervertebral disks. The radiographic hallmarks at the spine are horizontal calcifications of the disks (Fig. 10.**15**).

Fig. 10.**14** Dark discoloration of the external ear in ochronosis.

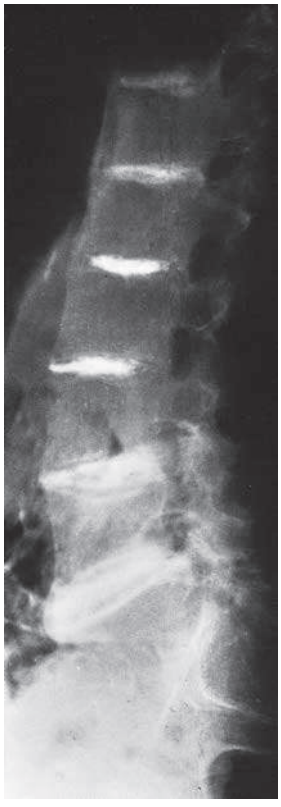

Fig. 10.**15** Bands of calcification of the intervertebral disks in ochronosis.

Primary Amyloidosis

Primary amyloidosis may give rise to amyloid deposits in synovial tissue and hyaline cartilage resulting in pain, stiffness, swelling, and occasionally impaired mobility of the involved joints. In the differential diagnosis, rheumatoid arthritis and other arthritis, which in turn may lead to secondary amyloidosis, must be considered.

Hemochromatosis

The first symptoms of the arthropathy in hemochromatosis occur in the inflammatory stage of the disease. In about 20% of all patients, joint symptoms are the first sign of the disease. In later stages of disease about 90% of all patients will have some joint symptoms.

The most characteristic feature of the arthropathy is the involvement of the MCP joints II and III, most often in a symmetrical pattern. In active disease, periarticular tissue swelling with redness and warmth may be found. Cysts, loss of cartilage, and larger osteophytes towards the radial aspects of the finger

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are typical radiologic changes. The laboratory diagnostic investigations are described in Chapter 25 (including findings in liver biopsy and determination of mutations in the *HFE* gene).

Wilson Disease

Diffuse osteoporosis is most often found in Wilson disease (hepatolenticular degeneration). Degenerative changes, particularly in the knee joints, periarticular classification, as well as osteochondritis dissecans may be observed.

Other Arthropathies

Hematologic Disorders

Severe joint destruction may be found in *coagulopathies*. Hemolytic anemias (thalassemia, sickle cell disease), acute leukemia, and malignant lymphoma may be associated with arthritides as well (see Chapters 13, 14, and 15).

Arthrititis Associated with Neoplasms

Hypertrophic Osteoarthropathy. The hallmark disorder of paraneoplastic arthritides is the so-called hypertrophic osteoarthropathy often preceding the manifestation of a tumor by a long period of time. This disorder is characterized by:

- clubbed fingers and hourglass nails
- arthralgias and arthritides of hands, elbows, ankles, knees, and MCP joints
- periostial proliferations in radiographs in the area of the diaphyses of long bones
- neurovegetative symptoms (hyperhydrosis, hyperthermia, peripheral vasodilatation)
- possibly gynecomastia.

The full picture of hyperthrophic osteoarthropathy is most often found in bronchial carcinoma. However, it may be found in many intrathoracic and extrathoracic disorders as well (see Chapter 3).

Arthropathies in Endocrine Disorders

Endocrine disorders such as acromegaly, hyperparathyroidism, and hyperthyroidism/hypothyroidism may be associated with arthropathies. Long-standing cortisone intake may be followed by osteonecrosis of the femur head. Such complications may evolve in systemic lupus erythematosus and progressive sclerosis as well.

Arthropathies in Neurologic Disorders

The so-called *neuropathic joint disorders* result in an impressive diffuse destruction of the joints, which usually is pain-free. Such changes may occur with disturbances of deep and superficial sensitivity, whereas repeated microtraumas and overuse of joint tissue may lead to extensive destruction of the joints. Similar joint disorders may be observed in *tabes dorsalis* and in *syringomyelia*.

About 10% of patients who have *diabetic polyneuropathy* will develop neuropathic arthropathy with special preference for tarsal and MTP joints, and more rarely of the finger joints.

Cartilage Disorders

Polychondritis (relapsing polychondritis) belongs to the connective tissue diseases and is characterized by inflammation and partial destruction of the cartilage, especially of the nose, ears, trachea, and larynx. Asymmetrical arthropathy of large and small joints is characteristic. The eyes may be also affected (episcleritis, uveitis). Further findings may include alterations of the heart valves (aortic insufficiency) or renal involvement. This rare disease may develop as a primary disease or in association with systemic lupus erythematosus, rheumatoid arthritis, or multiple myeloma.

Osteochondritis dissecans is a disorder based on mechanical traumatic damage of the superficial joint cartilage which may lead to arthropathy. Most often involved are the knee and hip, more rarely the elbow.

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10.2 Degenerative Joint Disorders

Osteoarthritis

Epidemiology. Osteoarthritis is the most common joint disorder, which tends to appear between 50–60 years of age. Prevalence is strongly dependent up on age. With the exception of the hips, all other joint localizations are more often found in women. Knees, finger joints, hips (Fig. 10.**16**), and the small intervertebral joints are most often affected.

Clinical Findings. Only a small group of patients showing radiologically osteoarthritis develops symptoms. In early stages disease of the pain during first steps of walking, when getting tired, and upon weight bearing are typical. Later on even night pain and persistent pain may develop, particularly in active disease. Irritation of the joint is most often associated with excessive joint fluid and stiffness. The erosive form of osteoarthritis of the fingers may mimic rheumatoid arthritis (Tab. 10.**3**).

In clinical examination, the joint capsule is thickened, the swelling appears to be tight and even bony. In activated disease stages the joint is painful upon palpation and flexion (pain on end-phase joint flexion). Limitations correspond to the severity of osteoarthritis. Instability and deviations may give rise to more destructive disease. Bony protuberances are frequently encountered in osteoarthritis of the fingers already at early stages and are named according to their localization (Heberden nodes for the DIP joints, Bouchard nodes for the PIP joints, and so-called Rhiz osteoarthritis for the metacarpal joint) (Fig. 10.**17**). Crepitus results from a rough superficial area of the joint, however, this is not proven per se for osteoarthritis.

Often osteoarthritis is associated with secondary periarthropathic changes in the soft tissues and may involve painful changes in tendons, ligaments, and muscles. Such soft tissue is especially painful upon palpation.

Diagnosis. Joint narrowing, loss of cartilage, osteophytes, subchondral sclerosis, and cysts may be found. Laboratory findings are normal.

Late Consequences. Osteoarthritis of the fingers is only rarely followed by severe limitations of function. Such is

Table 10.**3** Differential diagnosis of rheumatoid arthritis and erosive osteoarthritis of the fingers

	Rheumatoid arthritis	Osteoarthritis
Age	40–60 years	50–70 years
Sex	M : F = 1 : 3	M : F = 1 : 10
Inheritance	(+)	++
Sites of occurrence	Wrist, metacarpophalangeal and proximal interphalangeal joints of the fingers	Proximal and distal interphalangeal joints of the fingers, carpometacarpal joint of the thumb
Joint swelling	Soft and gelatinous, no erythema	Firm to hard, frequent erythema
Morning stiffness	> 30 min	< 30 min
Radiographic findings	Bandlike osteopenia diffuse joint space narrowing, erosions at capsular attachment	No osteopenia, focal joint space narrowing, osteophytes, rare subchondral erosions
Laboratory findings	Signs of inflammation (elevated ESR, anemia, thrombocytosis); rheumatoid factors may be positive	No abnormalities

Fig. 10.**16** Severe osteoarthritis of both hips.

Fig. 10.**17** Typical deformities in osteoarthritis of the distal and, to a lesser degree, of the proximal interphalangeal joints.

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the case especially in osteoarthritis of knee and hips. Hip osteoarthritis is characterized by early limitation of the internal rotation, and only later of the external rotation, of the joint. At later stages all functions are impaired. In addition, contraction of the psoas and adductor muscles may lead to pain of the lumbar spine. Inflammatory disease of the hips (coxitis) is characterized by early pain upon flexion, in contrast to osteoarthritis. In rapid progressive disease and unusual localization of osteoarthritis, such as in the shoulder and wrist, calcium pyrophosphate arthropathy (calcinosis) must be excluded.

Secondary Osteoarthritis. Secondary osteoarthritis may develop after mechanical trauma, disconfigurations of joints (such as osteonecrosis or dysplasia), or in metabolic diseases, including gout and hemochromatosis.

Degenerative Disease of the Spine (Ostearthritis of the Intervertebral Joints, Spondylosis Deformans)

The most frequent localization of osteoarthritis is found in the joints of the spine. Most often involved are the cervical and lumbar spine. Degenerative disease of the disks leads to narrowing of the intervertebral spaces, followed by secondary degenerative changes of the vertebral bodies (spondylosis) and the intervertebral joints (osteoarthritis of the spine).

Osteoarthritis of the Cervical Spine. Severe degenerative changes of the cervical spine are always followed by a limited motion (Fig. 10.**18**). Neck pain, often radiating to the occipital aspects of the head and pain radiating to the arms (brachialgia), with or without radicular deficits may develop. Vertigo (dizziness) and tinnitus may occur. Severe degenerative changes may lead to narrowing of the spinal canal or even cervical myelopathy, more often to segmental radicular deficits. Numbness of hands and arms is common and not always clearly delineated. Acute cervical pain may develop due to acute disk herniation, often along with blockade and stiff positioning of the head, radiation of pain, and radicular deficits. Degenerative diseases may be best demonstrated in the lateral view radiograph of the cervical spine. However, if radicular deficits are found, the respective causes must be clarified by MRI or CT.

Fig. 10.**18** Spondylosis cervicalis

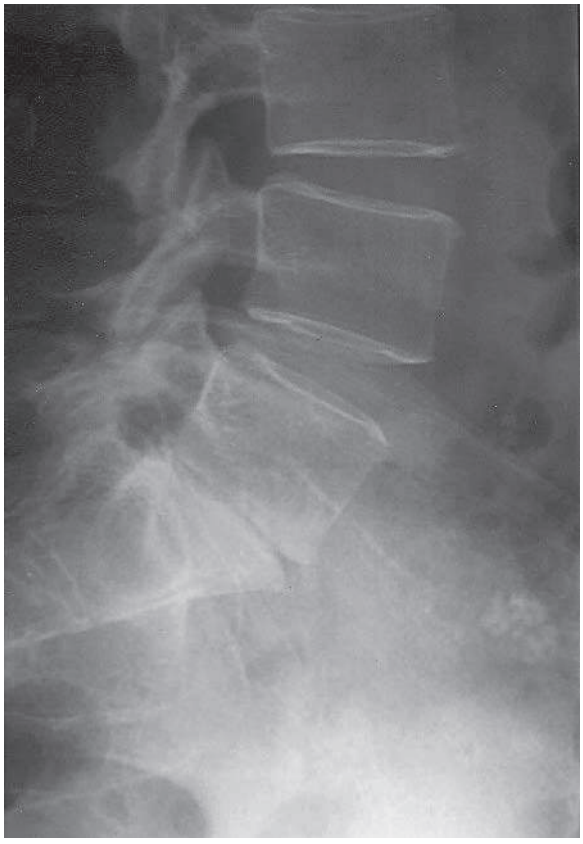

Fig. 10.**19** Lumbar osteochondrosis

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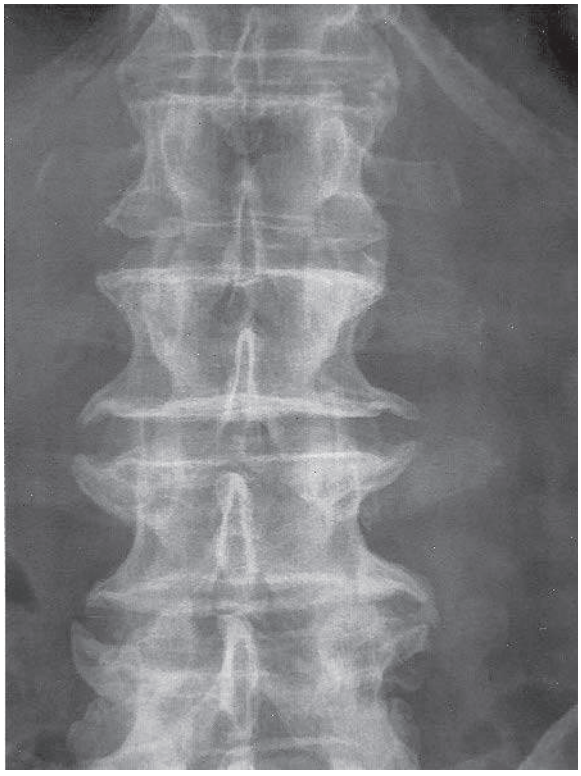
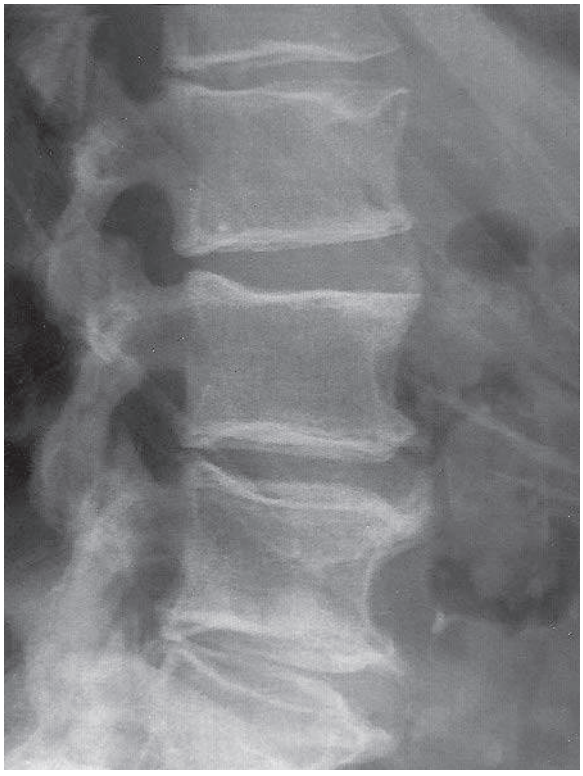


a



b

Fig. 10.**20** Hyperostosis of the lumbar spine.
a Antero-posterior view
b Lateral view

Osteoarthritis of the Lumbar Spine. Degenerative diseases of the lumbar spine often give rise to typical osteoarthritic pain during first motion after longer periods of rest (after sitting, standing, getting up in the morning) and after strenuous exercise (carrying weight in flexed position).

Complications. Along with degenerative changes, the mobility of the spine is impaired and the paravertebral musculature tightened. *Disk herniations* and bony changes may lead to radicular or pseudoradicular pain syndromes. After the age of 60, narrowing of the spinal canal as a consequence of degenerative changes is frequent. Clinically indicative is diffuse radiating pain in the legs, along with weakness forcing the patient to stop when walking (claudicatio spinalis).

Lumbar disk herniation may be followed by acute or chronic recurrent severe pain in the lumbar spine radiating to one or both legs and blockade of the lumbar spine, often associated with a visible scoliosis. Pain upon coughing and sneezing is typical. Positive leg stretch (Lasègue sign) points to a radicular syndrome with deficits in sensibility, motor action, and reflexes. Most frequent are disk herniations of the 4th and 5th lumbar disks.

Diagnosis. Degenerative changes can clearly be seen in the radiograph (Fig. 10.**19**). However, osteoarthritis of the intervertebral joints is best seen in computed tomography (CT). This imaging method may detect narrowing of the spinal canal or disk herniations as well. MRI allows an overview of the entire lumbar spine.

Differential Diagnosis. Axial hyperostosis has to be considered in the differential diagnosis of spondylosis. This disorder is associated with obesity, hyperuricemia, glucose-intolerance, and hyperlipedemia (Fig. 10.**20**). Ossification is much broader than in degenerative spondylosis. Hyperostosis typically can be seen in the thoracic spine, often in an isolated area with prevalence on the right side. In early stages of hyperostosis, narrowing of the intervertebral spaces is not found, in contrast to degenerative disease.

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10.3 Soft Tissue Rheumatism

Fibromyalgia

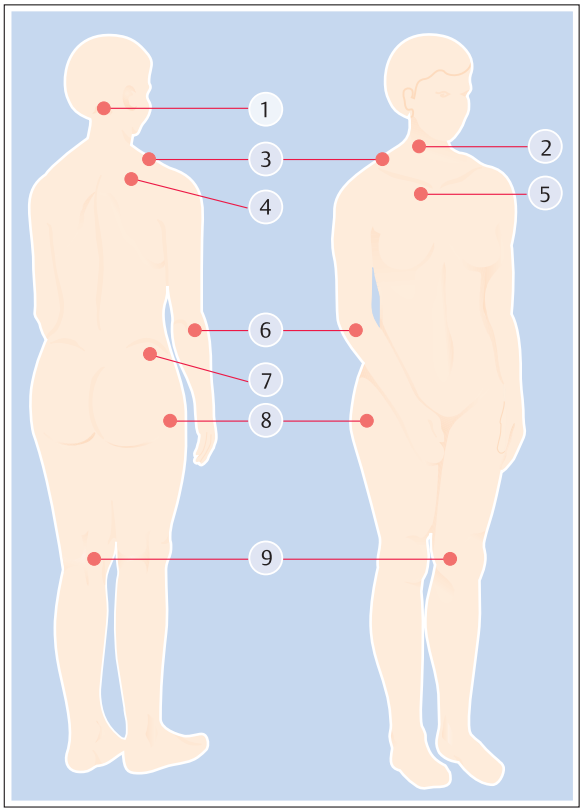

Fig. 10.**21** Characteristic trigger points in fibromyalgia.
1 *Occiput:* bilateral, at the suboccipital muscle insertions
2 *Low cervical:* bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
3 *Trapezius:* bilateral, at the midpoint of the upper border
4 *Supraspinatus:* bilateral, at origins, above the scapula spine near the medial border
5 *Second rib:* bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
6 *Lateral epicondyle:* bilateral, 2 cm distal to the epicondyles
7 *Gluteal:* bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
8 *Greater trochanter:* bilateral, posterior to the trochanteric prominence
9 *Knee:* bilateral, at the medial fat pad proximal to the jont line

Definition. The generalized form of soft tissue rheumatism is called fibromyalgia. Women are more affected than men, with a prevalence between the ages of 30 and 50.

Clinical Findings. This frequently encountered *tendomyalgia* is characterized by widespread, symmetrical, diffuse pains along with vegetative symptoms and characteristic tender points of muscles and muscle insertions (Fig. 10.**21**). Accompanying symptoms include fatigue, sleep disturbances, morning stiffness, an irritable colon, headache, and depression.

Disturbed sensitivity to pain is thought to represent a hallmark of the disease although the exact mechanism is unknown. Psychogenic factors appear to be important as well. Laboratory and radiologic findings are normal.

The *tender points* usually are clearly delineated in a symmetrical manner. Other points examined for comparison are less, or not, tender (for example other muscles, clavicula). These control points are important in the delineation of general pain syndromes and other expressions of pain. In a differential diagnosis, polymyalgia rheumatica, disorders of the spine, myopathies, and connective tissue diseases must be considered. Equally important are disorders of the subcutaneous connective tissue such as panniculosis (multiple small painful hardened areas) or panniculitis in pancreatic diseases or sarcoidosis.

Periarthropathies

Periarticular tender changes of the soft tissue may be found in ligaments, tendon insertions, muscles, and bursa. Such periarthropathies are especially common around larger joints such as the shoulders, hips, and knees. Such changes of the soft tissue may be associated with primary joint disease or degenerative, as well as inflammatory, processes in the soft tissue itself.

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Periarthropathia Humeroscapularis

This periathropathy is a frequent cause of complaints. The rotator cuff plays an important role, whereby most often single muscles or a combination of muscles are involved. Subacromial narrowing by hyperostosis, degenerative changes, calcifications (Fig. 10.**22**), or instability may lead to pain upon motion.

Diagnosis. The clinical examination is mostly characteristic. Affections of the diverse involved structures can be delineated: painful abduction for the supraspinatus muscle, external rotation for the infraspinatus muscle, and internal rotation for the subscapularis muscle. Pain and weakness are indicators of inflammation or even partial rupture of involved structures. Pseudoparesis may be seen in complete rupture of the rotator cuff, i. e., abduction of the arm is only possible to around 30°. Adhesive capsulitis leads to so-called frozen shoulder often leading to complete blockade of the shoulder joint.

Radiologic and dynamic ultrasound examination are useful diagnostic tools.

Fig. 10.**22** Periarthropathia humeroscapilaris (calcification of the supraspinatus tendon).

Differential Diagnosis. In the differential diagnosis of periarthropathy, septic arthritis, crystal arthropathy, but also extra-articular causes such as pneumothorax and tumor infiltration have to be considered. Somewhat more difficult is the delineation of cervicobrachialgias due to degenerative diseases of the cervical spine or neuralgic shoulder amyotrophy, where pareses should be sought.

Other Localized Periarthropathies

Other localized soft tissue syndromes involve the elbow (epicondylopathia humeri radialis or so-called tennis elbow; epicondylopathia humeri ulnaris or so-called golfer elbow), tenosynovitis (most often as a consequence of mechanical overuse, but also a potential first manifestation of systemic rheumatic disorders), or affections of the bursa. The latter are often very painful and tender upon palpation. Swelling and redness may also be found. Fluid aspiration will help the diagnosis. Tumors, ganglions, abscess, gout, or rheumatic nodules must be considered in the differential diagnosis.

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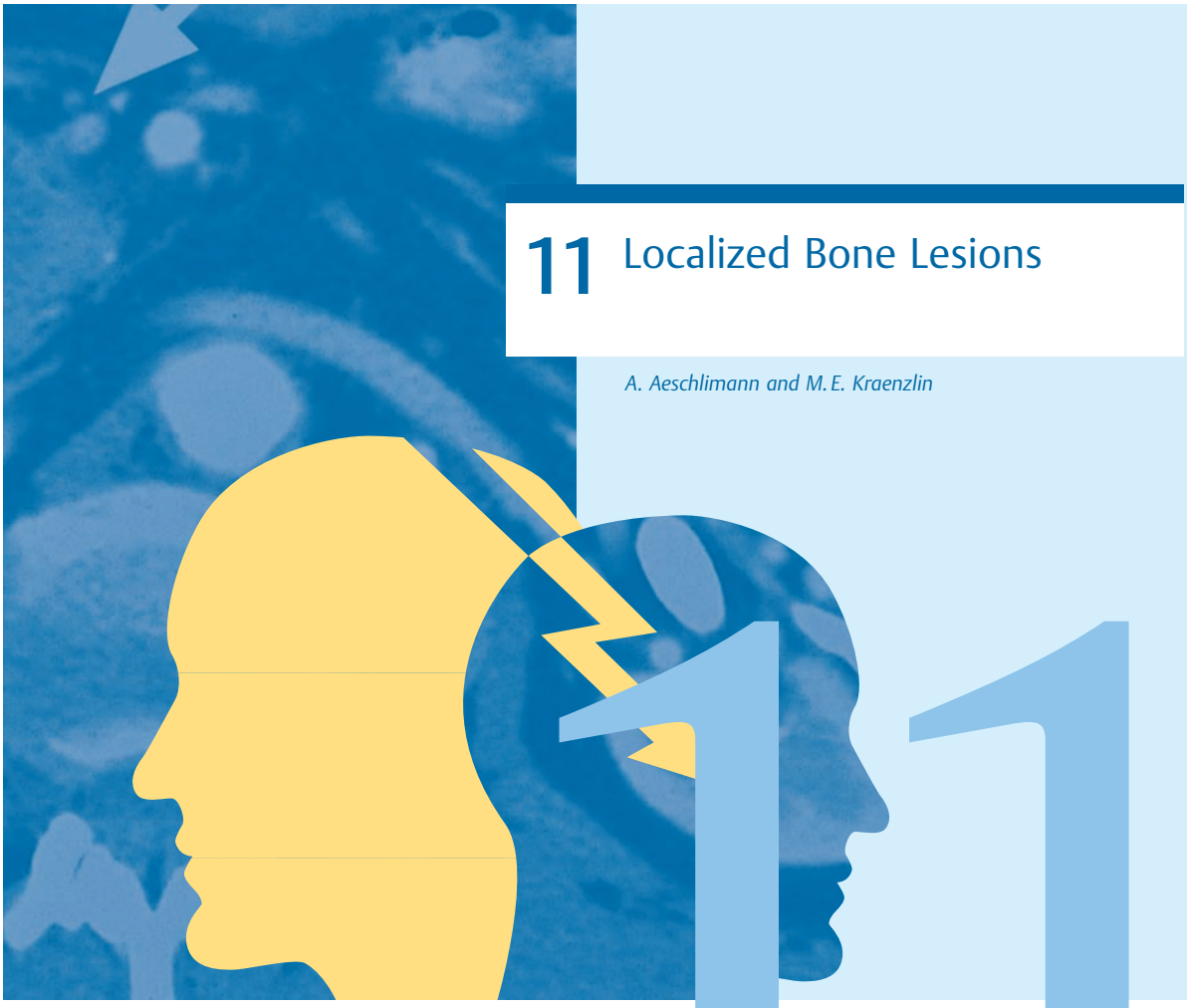

11 Localized Bone Lesions

A. Aeschlimann and M. E. Kraenzlin

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The Diagnostic Assessment of Bone Pain

The Characteristics of Bone Pain. In general medical practice, bone pain may be hard to distinguish from other types of pain on the basis of history and physical examination alone, because pain arising from bone tends to resemble pain arising from the surrounding tissues. Bone pain can be acute or chronic, exercise-induced or present at rest, and it may, or may not, be accompanied by other symptoms. Acute pain is typical of primary or secondary fractures, e. g., in osteoporosis or pathological fractures. Chronic pain, often of a dull quality, is typical of many bone diseases including osteoporosis, osteomalacia, Paget disease, and multiple myeloma. Stress fractures produce exercise-induced pain, while certain types of tumor, e. g., osteoid osteoma, produce pain at rest. Yet some localized or systemic diseases of bone can remain asymptomatic for long periods, as is often the case in osteoporosis. The clinical history should include any accompanying symptoms, such as a decline in general health, weight loss, fever, or diaphoresis.

Laboratory Tests. Expert opinions differ about the most useful tests to obtain when evaluating bone pain. In general medical practice, one should measure the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, blood urea nitrogen (BUN), creatinine, and liver enzymes, obtain a urinalysis, and determine the serum levels of calcium, phosphate, and alkaline phosphatase (AP) as indices of bone metabolism. Hypercalcemia usually indicates hyperparathyroidism or metastatic disease, while the AP level reflects osteoblastic activity and is therefore elevated in association with metastases, fractures, or Paget disease. Bone AP can be differentiated from hepatic AP by measurement of the bone isozyme of AP, or by simultaneous measurement of leucine aminopeptidase.

Imaging studies are of central importance in the differential diagnosis of bone disease. Plain radiographs often provide initial clues to the diagnosis, but frequently appear normal. Modern complementary techniques, such as magnetic resonance (MR) imaging, computed tomography (CT), and scintigraphy (i. e., bone scanning), are almost always necessary. Scintigraphy permits a reliable assessment of the extent of bone involvement in metastatic disease, although it can be negative in certain types of tumor, e. g., multiple myeloma. Osteodensitometry has recently gained wide acceptance for the assessment of osteoporosis, despite certain difficulties in the interpretation of the findings. Important information for the differential diagnosis of all bone tumors is the age of the patient and the site of the tumor (epiphysis, metaphysis, or diaphysis?). Finally, if the diagnosis remains unclear after a thorough noninvasive workup, a tissue biopsy may be necessary.

11.1 Localized Bone Changes

Bone Tumors

Bone tumors are classified according to histological characteristics. The cell structure and the additional characteristics of the tumor tissue are taken into account in the nomenclature (Tab. 11.**1**). From a clinical point of view (disease staging), it is not always easy to differentiate between benign and malignant forms because tumors can display very different growth patterns. Metastases from tumors (Fig. 11.**1**) are very frequent secondary forms of tumor and must always be considered in a differential diagnosis, especially of ostalgia, as must the tumors of the hematopoietic system (lymphoma, leukemia, multiple myeloma).

Bone Tumors Derived from Cartilage

Chondroma. Chondromas are benign neoplasms of which more than half of all cases are found in the hands and feet. *Enchondroma* describes a chondroma that is localized in the intramedullary cavity; *periosteal (juxtacortical) chondroma* describes a chondroma that is located in the periosteal region of the bone. These tumors are generally asymptomatic and are discovered as an incidental finding on standard radiographs (Fig. 11.**2**). A small osteolytic lesion is usually seen with typical central calcifications. Slight pain and/or swelling are possible or a pathological fracture may occur.

At diagnosis, chondroma must be differentiated, in particular, from an epidermoid cyst (usually located at a distal phalanx), a bone cyst, and chondromyxoid fi-

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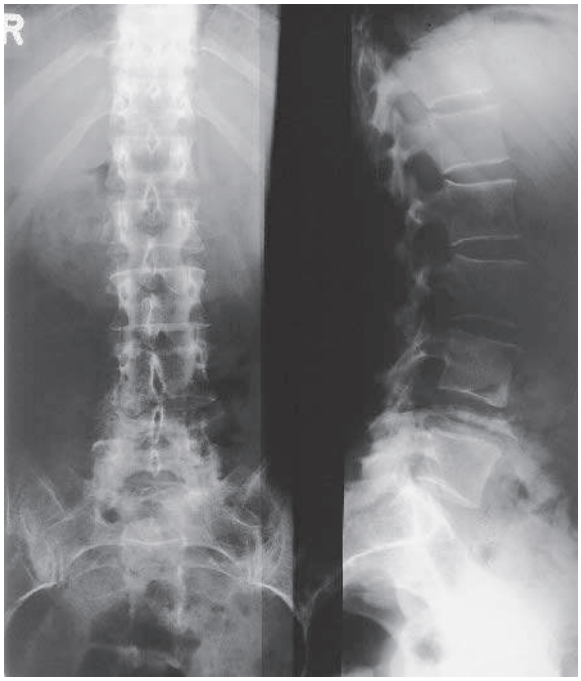

Fig. 11.**1** Osteolytic metastasis with pathological fracture of the vertebral body L4 in the presence of breast carcinoma.

Fig. 11.**2** Enchondroma of the proximal femur. ▷

broma. If there is rapid growth *malignant transformation* must always be considered, especially in the region of the anterior chest wall. Here it is often difficult to differentiate between chondroma and so-called low-grade osteosarcoma. Malignant transformation is also frequently observed in the familial form of enchondromatosis (Ollier disease) and in patients with Maffucci syndrome (multiple enchondroma and hemangioma).

Chondroblastoma. Chondroblastoma is a tumor that occurs predominantly in the epiphysis and is associated with slow, progressive growth in the second decade of life. Local, aggressive growth and occasionally metastasis (with a preference for the lungs) is possible. Chondroblastoma may cause local pain, joint effusion, and permanent muscular contraction. Radiographically, the lesion is osteolytic with well-defined margins, some calcifications and a periosteal reaction may be visible.

The *differential diagnosis* of a lytic lesion in the epiphysis in patients between 10 and 30 years of age includes not only chondroblastoma but also aneurysmal bone cyst, giant cell tumor, Brodie abscess, chondrosarcoma, and histiocytic tumors.

Condromyxoid Fibroma. This very rare tumor (< 1% of all bone tumors), with a preferred location in the lower extremities, usually develops into an eccentric osteolysis in the metaphysis. Histological typing is not always easy. Chondromyxoid fibroma must be differentiated from chondroma, giant cell tumor, and unicameral bone cyst.

Osteochondroma. Osteochondroma (Fig. 11.**3**), also known as osteocartilaginous exostosis, is a bone projection that may be solitary or multiple. Continued growth after skeletal maturity, or an exceptionally thick cartilaginous cap, always suggests malignant transformation. Solitary osteochondroma is usually asymptomatic but may be perceived as a swelling or, if it is close to the joint, may lead to restriction of movement.

Multiple exostosis frequently affects several members of the same family. It appears predominantly in the long bones, is not uncommonly bilateral and symmetric, and may consist of as many as 50 osteochondromas. Local complications due to compression, *malignant degeneration* (chondrosarcoma), and disturbed growth have been described. Therefore, regular clinical and radiological assessments are indicated, especially in the growth years.

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Fig. 11.**3** Osteochondroma of the toe.

Table 11.**1** Nomenclature of bone tumors

*Benign tumors	Malignant tumors
Cartilogenic tumors	
Chondroma, enchondroma	Chondrosarcoma
Chondromyxoid fibroma	
Chondroblastoma	
Osteochondroma	
Osteogenic tumors	
Osteoma	Osteosarcoma
Osteoid osteoma	
Osteoblastoma	
Fibrous tissue (fibrogenic) tumors	
Nonossifying fibroma	Fibrosarcoma
Ossifying fibroma	Malignant fibrous histiocytoma
Myelogenic tumors	
	Reticulum cell sarcoma
	Lymphosarcoma
	Myeloma
Tumors of unclear etiology	
	Giant cell tumor
	Ewing sarcoma
	Adamantinoma
Vascular tumors	
Hemangioma	Hemangioendothelioma
Lymphangioma	Hemangiopericytoma
	Hemangiosarcoma
Other tumors	
Chordoma	
Neurilemoma (schwannoma, neurinoma)	
Langerhans cell histiocytosis (eosinophilic granuloma)	
Lesions resembling tumors	
Solitary bone cyst	
Bone infarction	
Aneurysmal bone cyst	
Gorham osteolysis	
Fibrous dysplasia	

* Even so-called "benign" tumors can grow slowly and aggressively in some cases (see text). In these cases, the possibility of malignant transformation must be considered.

Chondrosarcoma. Chondrosarcoma is the second most frequent tumor after osteosarcoma and is a malignant tumor primarily affecting the pelvis and shoulder girdle. In the region of the anterior chest wall (costochondral and sternum), chondrosarcoma is the most frequently occurring malignant tumor. As with other malignant tumors, metastasis is possible. In the early phase, it is often difficult to distinguish chondrosarcoma from benign chondroma. The lytic lesions tend to have poorly defined margins, extend into the soft tissues, and may present calcifications. Chondrosarcoma may occur as a primary or secondary tumor (malignant degeneration of osteochondroma, multiple exostosis, fibrous dysplasia, or after radiation).

Osteogenic Tumors

Osteoma. Osteomas are hematomas with a preference for the cranial skeleton or the paranasal sinuses. Extracranial locations are extremely rare and have to be differentiated from periosteal osteosarcoma, especially in the tibia. Osteoma is generally asymptomatic, voluminous, and may lead to headache, symptoms similar to sinusitis, and signs of compression.

Osteoid Osteoma. Benign osteoid osteoma may affect any part of the skeleton, but has a preference for the

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long bones of the lower extremities where it is located in the diaphysis and metaphysis, and occasionally the epiphysis. Young patients report intense pain in the night that reacts well to salicylate or nonsteroidal antirheumatic medication. However, this clinical sign is nonspecific.

Radiologically, a radiolucent center of usually less than 1.5 cm diameter, possibly with calcifications (the so-called nidus) and peripheral reactive sclerosis is indicative (Fig. 11.**4**). The diagnosis can be confirmed by skeletal scintigraphy or, better still, by CT (delineation of the nidus).

Diagnosis must *differentiate* osteoid osteoma from osteoblastoma, in particular, and from Brodie abscess, intracortical angioma, mucoid and aneurysmal cysts.

Osteoblastoma. Osteoblastoma is much rarer than osteoid osteoma. It is found predominantly in the metaphysis of the long bones (especially of the femur), in the joint of the vertebral arch, and the spinal processes and in the foot. Clinically, osteoblastoma may be asymptomatic or cause progressive pain, a restriction of joint movement, or joint effusion.

Radiologically, bubblelike structures are seen (generally >20 mm) with slightly sclerotic margins (Fig. 11.**5**). Central calcifications can often be identified. It is not uncommon for aneurysmal bone cysts to occur as secondary lesions.

These generally benign tumors (although malignant transformations have been described) must be differentiated histologically from osteosarcoma.

Osteosarcoma. Osteosarcoma is the most frequent malignant bone tumor and can occur at any skeletal location with a predilection for the metaphyses of the long bones. Osteosarcoma may occur as a primary or secondary lesion, e. g., in the context of Paget disease or after radiation. Rapidly increasing pain, local tumorous swelling, and increased AP levels are often the first clinical signs. The radiological picture may vary depending on growth. The osseous structures are indistinctly delineated with periosteal reaction as a sign of aggressiveness.

Connective Tissue Tumors

Nonossifying Fibroma. Asymptomatic nonossifying fibroma is almost always discovered as an incidental finding. The radiologic picture shows a well-circumscribed osteolytic central lucency predominantly in the metaphysis and diaphysis of the long bones with a special peripheral preference for the distal tibia (Fig. 11.**6**). Nonossifying fibroma is found mostly in children and adolescents in the growth phase. If there are multiloculated lesions, neurofibromatosis must be considered. Large tumors may be the cause of pathological fractures.

Fig. 11.**4** Osteoid osteoma with typical central nidus in the coronoid process of the elbow.

Fig. 11.**5** Osteoblastoma in the region of the articular process of C5.

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Fig. 11.**6** Nonossifying fibroma in the metaphysis of the distal tibia.

Ossifying Fibroma. This is a rare tumor whose relationship to osteofibrous dysplasia and adamantinoma is the subject of controversy.

Fibrosarcoma. Fibrosarcoma is a rare tumor that affects men in particular and may occur as a primary or secondary lesion after radiation or due to Paget disease. The clinical and radiologic picture of this tumor, which mainly affects the long bones, is similar to that of osteosarcoma and can only be differentiated from it by histologic examination.

Malignant Fibrous Histiocytoma. Malignant fibrous histiocytoma was previously regarded as a relative of osteosarcoma and/or fibrosarcoma, whereas it is currently seen as a clinical and pathological entity. It is a rare, malignant, osteolytic bone lesion that is seen to differ histologically from fibrosarcoma because of the predominance of histiocytic structures.

Myelogenic Tumors

These tumors and multiple myeloma and malignant lymphoma will be discussed extensively in Chapter 14.

Vascular Tumors

Hemangioma. Hemangioma is typically located in the vertebral bodies but is also found in the calvaria and in the long bones. It may be asymptomatic or cause localized, and sometimes radiating, pain. If the spine is affected by compression, neurologic deficits, such as peripheral dysesthesias, diminished vibratory perception, pyramidal signs, dysfunctional sphincter control, or signs of paralysis, may be observed.

The typical thickened trabecular structures are highly characteristic of the *radiological appearance* of asymptomatic hemangiomas. The appearance can however be atypical, so that other tumorous diseases such as plasmocytoma, metastases, lymphoma, or giant cell tumor have to be excluded.

Lymphangioma. Lymphangiomas are benign and generally occur as multiple osteolytic bone lesions.

Hemangioendothelioma, hemangioendosarcoma, hemangiopericytoma. These tumors are very rare (< 1% of all malignant bone tumors).

Histiocytic Tumors

Langerhans Cell Histiocytosis. Langerhans cell histiocytosis is the histiocytosis found most frequently in children. It may occur in adults as an isolated lesion of the axial skeleton. This spheroidal tumor is also known as eosinophilic granuloma and is found predominantly in boys between five and 15 years of age. If there are multiple lesions (*Letterer–Siwe syndrome*), systemic manifestations such as hepatosplenomegaly, lymphadenopathy, leucopenia, thrombocytopenia, and anemia may occur.

Another form, the *Hand–Schüller–Christian syndrome*, manifests with multiple bone lesions, and exophthalmos and diabetes insipidus may be present.

The skeletal manifestations occur predominantly in the flat and long bones. Painful swelling causes the patient to seek medical advice. The radiological appearance is single, or multiple, irregularly distributed osteolytic alterations that, depending on their location, lead to various complications such as mastoiditis, collapse of the vertebral bodies, etc.

Other Tumors

Chordoma. Potentially malignant chordoma arises from notochord remnants and has a preference for the base of the skull or the sacrococcygeal region.

Tumors of Unknown Etiology

Giant Cell Tumor. Giant cell tumors occur more frequently in women between the 20th and 40th years of life. Its preferred locations are the metaphyses with projections into the epiphyses at the knee and distal radius (Fig. 11.**7**). Disease status is difficult to assess. There may be metastasis to the lungs in 1–2% of cases.

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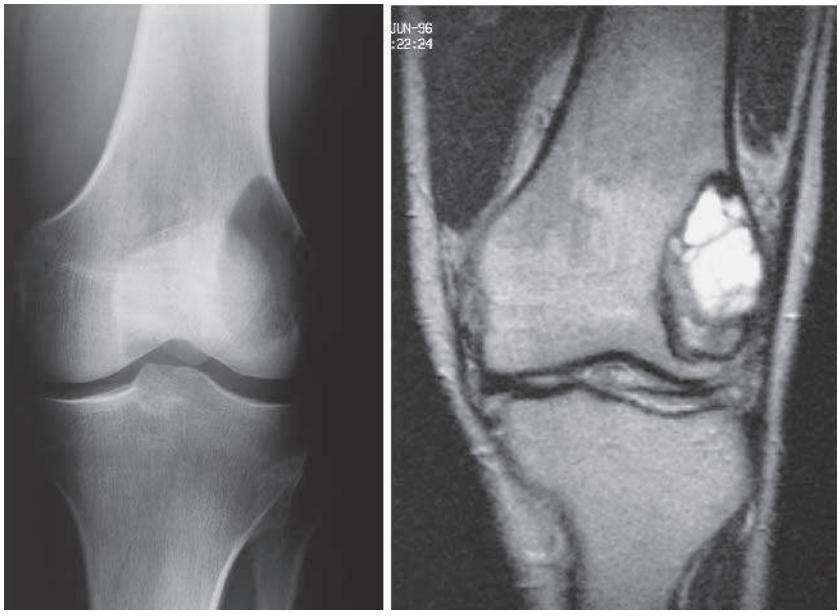

a b

Fig. 11.**7** Giant cell tumor of the distal metaphysis and epiphysis of the femur.
a Radiograph
b MR image

◁ Fig. 11.**8** Ewing sarcoma in the region of the fibula.

Ewing Sarcoma. Ewing sarcoma is, after osteosarcoma and chondrosarcoma, the third most frequent primary malignant bone tumor. It generally occurs between the 10th and 25th years of life. The first clinical sign is pain, soon followed by swelling and general symptoms of illness. Metastasis to the lungs is often already present at the time of diagnosis.

The *radiological appearance* may vary. Typically, a moth-eaten destruction of margins is seen adjacent to irregularly distributed osteolytic foci with periosteal reactions (Fig. 11.**8**). The symptoms may sometimes be similar to those of osteomyelitis.

Adamantinoma. Adamantinoma is the rarest of the primary malignant bone tumors. It is mainly found in the diaphysis of the tibia. Adamantinoma (ameloblastoma) of the mandible is likewise extremely rare.

Lesions Resembling Tumors

Solitary Bone Cyst. Solitary bone cyst is generally an incidental finding in adolescents and has a preference for the metaphysis of the femur and humerus (Fig. 11.**9**). As a rule, bone cysts do not cause any symptoms, but may lead to pathological fractures and, consequently, be identified.

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Fig. 11.**9** Juvenile bone cyst with a pathological fracture of the humerus.

Fig. 11.**11** Fibrous dysplasia of the left proximal femur and the iliac wing.

◁ Fig. 11.**10** Medullary bone infarction in the metadiaphyseal region of the proximal humerus.

Bone Infarction. Asymptomatic bone infarction is generally found radiologically in the center of the metaphysis (in the lower extremities) and typically has a 2 × 3 cm diameter bizarre matrix ("bone in bone") (Fig. 11.**10**). It may occur as an isolated, symmetric, or bilateral lesion. If its occurrence is associated with osteonecrosis in the epiphyses, the differential diagnosis must include dyslipidemia, pregnancy, ethyl abuse, collagenosis, drug-induced hypercorticism, hemoglobinopathy, and Gaucher disease.

Aneurysmal Bone Cyst. Aneurysmal bone cyst is a benign tumor of the bone that is most commonly diagnosed in young persons (five to 25 years). It is usually asymptomatic, but may cause pain and local swelling in some cases. The case history will often reveal trauma.

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Radiologically, aneurysmal bone cysts appear as multicameral osteolytic zones, not infrequently with multiple fluid–fluid levels on the MRI/CT images.

In its *secondary form* (approximately 30% of cases), aneurysmal bone cyst is associated with another generally benign tumor (giant cell tumor, osteoblastoma, chondroblastoma, fibrous dysplasia, etc.).

If there is cortical destruction of the delineating osseous rim and projection into the soft tissues, the possibility of *malignant degeneration* must be considered.

Gorham Osteolysis. Gorham osteolysis is a rare bone disease whose etiology is unknown. Approximately 200 cases have been described so far. *Radiologically*, a local, diffuse, and irregular osteolysis without periosteal reaction is seen. Pain may occur and laboratory findings may be nonspecific.

Fibrous Dysplasia. Fibrous dysplasia may occur as a monostotic or polyostotic lesion and may be asymptomatic or cause local pain and pathological fracture. Men and women are equally affected.

Radiologically, there are cystic bone lucencies with displacement of the cortex and destruction of the bone architecture (Fig. 11.**11**). If the disorder is extensive, AP levels may be increased. Fibrous dysplasia progresses slowly until it arrests in adulthood.

Fibrous dysplasia may be associated with *extraskeletal manifestations*, the most frequent being café-au-lait spots and hyperactivity of endocrine organs (precocious puberty, hyperthyroidism, hypersomatotropism, hypercortisolism [Cushing disease], and renal tubulopathy with hypophosphatemia [McCune–Albright disease]).

Gaucher Disease

Gaucher disease is an autosomal recessive familial sphingolipidosis in which an enzymal deficiency of glucocerebrosidase leads to the deposition of glucocerebrosidase in the phagocytic cells of the reticuloendothelial system.

In *type I*, which has been observed with particular frequency in Ashkenazi Jews, the liver, spleen, bone, and bone marrow are mainly affected. The skeletal manifestations are diverse and include, above all, nonspecific bone and joint pain, joint contractures, osteonecrosis, pathological fractures, pseudo-osteomyelitis, and spinal deformity.

In the much rarer *type II* (infantile form, rapidly progressive, often fatal in the first two years of life) and in *type III*, additional, sometimes severe, neurological manifestations are found.

Mastocytosis

In mastocytosis diffuse infiltration of the mast cells into various organs occurs, especially in the skin and the skeleton (see Chapter 3). In the skin (in rare cases, there are no skin manifestations), mastocytosis may lead to urticaria pigmentosa. In the bone, there may be localized lytic and sclerotic lesions and generalized osteoporosis.

Diseases with Hyperostosis

Hyperostosis may occur in the context of various diseases (e. g., Paget disease, renal osteodystrophy), many of which have already been discussed in this chapter.

Toxic Hyperostosis. This may be caused by fluoride, phosphorus, beryllium, arsenic, bismuth, and strontium intoxication.

Osteopetrosis (Albers–Schönberg Disease). Osteopetrosis is a rare hereditary disease of the bone. There are two types, namely, the autosomal recessive form (severe form) and the autosomal dominant form (milder form).

Osteopetrosis (marble bone disease) derives from an osteoclast insufficiency, so that the bone matrix cannot be resorbed at all or only inadequately and, at the same time, the function of the osteoblasts is unaffected. Thus, there is excessive bone regeneration and an increase in bone mass. Despite obvious osteosclerosis, fracture may occur due to the formation of biomechanically "inferior" bone.

The more frequent *osteopetrosis tarda* is generally asymptomatic and is discovered radiologically as an incidental finding. The symptoms may include anemia, increased susceptibility to caries, and sometimes fractures. The rarer *congenital* or malignant form begins in the uterus and manifests itself postpartum as hepatosplenomegaly, pancytopenia, cranial nerve dysfunction, or hydrocephalus.

Hypertrophic Osteoarthropathy. Hypertrophic osteoarthropathy Marie–Bamberger is associated with ossifying periostitis of the long bones (tibia, fibula, humerus), joint pain, clubbed finger, and hourglass nails. This syndrome is most frequently observed in the presence of a

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malignant tumor of the lung (usually bronchial carcinoma and mesothelioma).

Pachydermoperiostosis is an autosomal dominant hereditary disorder (also known as Touraine–Solente–Golé syndrome) in which clubbed fingers and toes, skin disorders, and thickening of the soft tissue, as well as periosteal bone regeneration, most frequently at the radius, ulna, and tibia are seen.

Hyperostosis Frontalis Interna. Hyperostosis frontalis interna represents a standard variant and is, thus, benign. It is characterized by nodular thickening of the inner aspect of the frontal bone and occurs almost exclusively in women. Since it is associated with virilism, diabetes mellitus, hypertonia, and obesity, an endocrine/metabolic etiology is assumed (*Morgagni syndrome*). A similar radiologic picture may be seen in the context of acromegaly or Paget disease.

Osteonecrosis

Definition. Osteonecrosis is a more or less circumscribed loss of cells and tissue in bone and bone marrow.

Pathogenesis. Osteonecrosis has many causes (fracture, vascular disease, metabolic disturbance, medications, etc.; Tab. 11.**2**). The most important pathogenetic factor is a compromised blood supply due to abnormalities of the microcirculation and macrocirculation. A major contributing factor is the accompanying edema, which elevates the intraosseous pressure and leads to compression of smaller blood vessels and capillaries. Osteonecrosis can, in principle, affect any bone and any segment of a bone, though it tends to arise in the epiphyses.

Clinical Features. The symptoms and signs are variable and nonspecific, ranging from asymptomatic disease (osteonecrosis is often an incidental radiologic finding), through pain only with mechanical stress, to continuous pain rendering the patient unable to walk. The diagnosis is made from plain radiographs. If these reveal the classic findings of osteonecrosis, further studies are unnecessary.

Radiologic Findings. *Plain radiographs* reveal no abnormality in the initial stage of this disorder. In the more advanced stage, they reveal areas of lucency juxtaposed with areas of sclerosis, one or more subchondral fractures, and fragmentation (Fig. 11.**12**).

Bone scintigraphy (bone scan) reflects the state of bone perfusion and remodeling; it is therefore useful for the early detection of perfusion abnormalities. In early osteonecrosis, scintigraphy reveals diminished radionuclide uptake. Subsequently, when reparative bone formation is in progress, revascularization of the surrounding bone tissue causes an increase in radionuclide uptake.

MRI, of all the imaging techniques, displays bone marrow changes with the greatest sensitivity and specificity and permits the most precise localization of the area of necrosis and determination of its extent. The images reveal a central area of necrosis with a reactive peripheral zone where it borders on the surrounding, normal bone tissue. It is not known how long after the onset of symptoms that MRI changes begin to appear, but the available evidence suggests a latency interval of four to six weeks.

a

◁ Fig. 11.**12** Osteonecrosis of the medial femoral condyle.
a Plain radiograph, patient standing on one leg.
Fig. 11.**12 b** ▷

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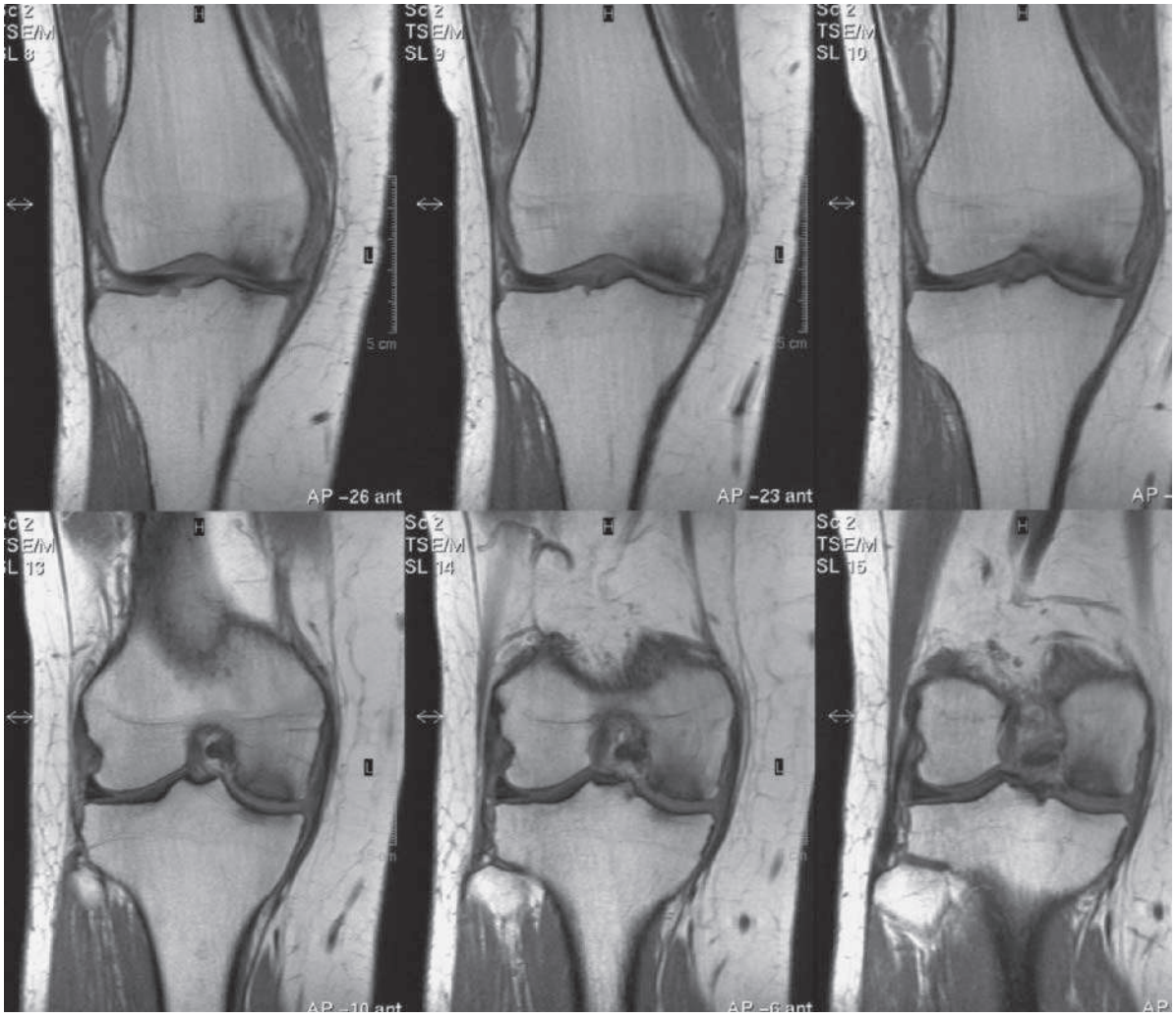

b

Fig. 11.**12** Osteonecrosis of the medial femoral condyle. **b** MRI.

There are a number of different types of osteonecrosis, which will be described in the following paragraphs.

Avascular Necrosis in Childhood and Adolescence

Perthes Disease (also called Perthes–Calvé–Legg–Waldenström disease) consists of osteonecrosis of the femoral head in children, usually between two and 10 years of age. Bilateral involvement a few months apart is not uncommon. The etiology is unknown; genetic factors seem to be important, and a role for trauma has also been proposed.

Köhler Disease. This manifests itself as osteonecrosis of the scaphoid bone and the sesamoid bones of the great toe (Köhler I) or, alternatively, of the second metatarsal head (Köhler II). The first type is rare. The second type mainly affects young girls. In the active phase, it causes local swelling and pain.

Osgood–Schlatter Disease. In this disease, aseptic necrosis of the tibial tuberosity arises during the growth years, causing local swelling and pain. Spontaneous healing usually follows, leaving no permanent defect.

Kümmel–Verneuille Disease. This consists of aseptic necrosis of a vertebral body, leading to rapid collapse. Radiographs reveal a bandlike lucency in the center of the vertebral body (so-called vacuum phenomenon).

Scheuermann Disease. It remains unclear at present whether this disorder is due to circumscribed osteonecrosis of the upper and lower endplates, or to another cause (Fig. 11.**13**). It sometimes produces a fixed abnormal posture (kyphosis), but the radiologic changes of Scheuermann disease are also found in asymptomatic persons.

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Fig. 11.**13** Scheuermann disease with typical Schmorl nodes.

Table 11.**2** Diseases and other factors in the pathogenesis of osteonecrosis

Trauma – fractures – burns – sprains – vascular injuries – arthroscopic procedures	**Iatrogenic** – glucocorticoid therapy – radiation – hemodialysis – organ transplantation
Hematologic – hemoglobinopathies (sickle cell anemia, thalassemia) – coagulopathies (thrombocytopenia) – polycythemia – anemia	**Vascular/rheumatologic** – systemic lupus erythematosus – polymyositis – rheumatoid arthritis – Raynaud disease – giant cell arteritis
Metabolic – hyperlipidemia – hypercortisolism – pregnancy – Gaucher disease	**Gastrointestinal** – pancreatitis – inflammatory bowel diseases
Infectious – osteomyelitis – viral infections – HIV	**Other** – alcoholism – smoking – caisson disease (decompression sickness)

Osteonecrosis in Adulthood

Avascular (Aseptic) Necrosis of the Femoral Head. The etiology cannot be determined in every case, but common causes of this problem include high-dose glucocorticoid therapy, alcohol abuse, hepatic and pancreatic diseases, metabolic disorders, such as hyperlipidemia, Gaucher disease, renal osteopathy, and hyperuricemia, rheumatoid arthritis and other collagenoses, coagulopathies, hemoglobinopathies (sickle cell anemia), and decompression trauma (in professional and sport divers).

Radiologic signs include subchondral flattening of the femoral head, subchondral radiolucency, and fragmentation. The differential diagnosis of avascular necrosis of the femoral head in adults includes monoarthritis, bone destruction by tumor, transient osteoporosis of the femoral head, and infection.

Osteonecrosis of the Knee Joint (Ahlbäck Disease). This disorder consists of spontaneous, idiopathic osteonecrosis of the knee joint, usually arising between the ages of 40 and 60 and affecting women three times more often than men. Pain in the knee joint usually begins acutely. Physical examination typically reveals tenderness to pressure on the affected femoral or tibial condyle. There may be an accompanying synovitis with joint effusion.

Osteonecrosis can also arise in the aftermath of an arthroscopic procedure or any other type of knee trauma. Patients with persistent discomfort after arthroscopy should therefore undergo an MRI study of the knee to rule out incipient or established osteonecrosis.

The *differential diagnosis* of Ahlbäck disease includes osteochondritis dissecans, an activated arthrosis, meniscus lesions, stress fractures, and transient osteoporosis. Osteochondritis dissecans and activated arthrosis usually cause pain of gradually increasing severity. The clinical differentiation of a meniscus lesion from osteonecrosis may be more difficult, but MRI often helps in such cases. Transient regional osteoporosis can also cause pain of acute onset.

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Paget Disease of Bone

Definition. Paget disease is a focal, monoostotic or polyostotic disease characterized by increased bone remodeling, bone hypertrophy, and abnormal bone structure, causing pain and bone deformities in symptomatic patients. Its complications affect the bones (fractures and neoplastic transformation), joints (secondary arthrosis), and nervous system (neural compression).

Pathogenesis and Epidemiology. The process of locally increased bone remodeling is initiated by an increase in bone resorption by osteoclasts, which is then followed by a compensatory increase in bone formation by osteoblasts. The result is a disorganized mosaic pattern of woven and lamellar bone in the affected portion of the skeleton. These structural changes cause the bone to be larger in size, less compact, more heavily vascularized, and more prone to deformation and fractures than normal bone.

The *etiology* of Paget disease has not yet been definitively identified. There appears to be a genetic component (15–30% of patients have a family history of Paget disease). There is also a high degree of ethnic and geographical variability in the prevalence of the disease. It is most common in Europe, North America, and New Zealand. There is a north–south gradient: the disease affects 6–8% of the population above age 55 in England (ranging from the lower to the higher figure depending on the region of the country), but only 0.5% of the same age group in Italy and Greece. On the other hand, some studies point to a viral infection as the cause of the disease.

Paget disease affects persons of both sexes, men slightly more often than women. It is rarely seen in persons below age 25 and is thought to arise mainly from age 40 onward.

Clinical Findings and Complications. The signs and symptoms of Paget disease are highly variable, depending both on the affected portion of the skeleton and on the degree of activity of bone remodeling. Most patients with the disease are thought to be asymptomatic, but a considerable number suffer from bone pain, secondary arthrosis, bone deformities, and neurological complications (e. g., neural compression in the vicinity of the affected bone). The complications of Paget disease are listed in Tab. 11.**3**.

The disease usually affects the skeleton asymmetrically, most commonly involving the pelvis, femur, vertebral column, skull, and tibia. Clinical experience suggests that the areas involved at the time of diagnosis remain the only ones involved over the further course of the disease. Involvement of new areas years after the diagnosis is made is a very rare event. Malignant transformation to osteosarcoma is also rare.

Diagnostic Evaluation. Paget disease is most frequently discovered because of an elevated AP concentration, or as an incidental finding on a radiograph performed to examine another medical problem. The diagnosis is made on the basis of the clinical findings and confirmed by the characteristic radiological picture. The degree of activity of bone remodeling is determined by laboratory tests (the main indices are an elevated serum AP concentration and the bone-resorption parameters pyridinolines and telopeptides). Skeletal scintigraphy is used to identify further, possibly asymptomatic foci.

Radiologic Findings. The cardinal findings are:
- progressive, wedge-shaped osteolysis
- accentuation and coarsening of the trabecular pattern
- thickening of cortical bone with increase of bone volume.

The disease can be separated into three stages on radiological grounds, though it should be kept in mind that these stages do not occur sequentially, but rather simultaneously in adjacent areas of bone (Figs. 11.**14**, 11.**15**):
- *Lytic stage:* a usually sharply circumscribed area of radiolucency, corresponding to osteolysis, with involvement of cortical bone.
- *Combined stage:* osteolytic areas combined with adjacent areas of patchy sclerosis (new formation of lamellar, mosaic bone tissue).
- *Sclerotic stage:* the affected area appears patchy, stringy, and deformed by the increase of volume.

Table 11.**3** Complications of Paget disease

- Pain
- Skeletal deformities
- Secondary arthrosis
- Fractures
- Malignant transformation (rare, in about 0.7–1.0%)
- Neurological complications
- Cardiac complications (only in severe and extensive disease):
  - heart failure
  - valvular stenosis
  - conduction disorders (AV block, left bundle branch block)

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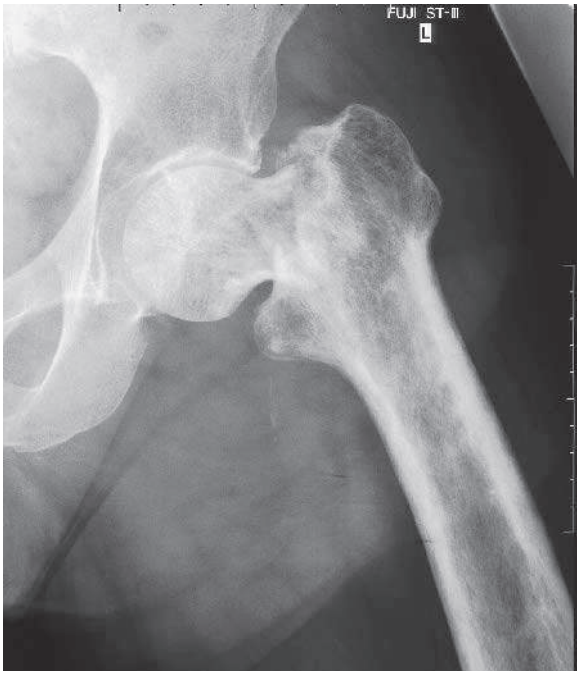

Fig. 11.**15** Paget disease of the iliac wing and pubic rami, with early secondary coxarthrosis.

◁ Fig. 11.**14** Paget disease of the left femur, with a pathological fracture of the femoral neck.

11.2 Generalized Bone Changes

Osteoporosis

Definition. Osteoporosis is a systemic disease of the skeleton in which bone mass is reduced and bone quality is impaired, resulting in diminished resistance to mechanical stress and a higher risk of fracture. Osteoporosis has both primary and secondary forms (Tab. 11.**4**).

Epidemiology and Relevance. The lifetime risk of an osteoporotic fracture is 20–40% in women over age 50 and 15% in men over age 50. The incidence of vertebral fracture is 5.8 per 1000 persons per year in women aged 50–55, and 29 per 1000 persons per year in women over age 75. The corresponding figures for men in these two age groups are 3.3 and 13.6 per 1000 persons per year, respectively. On the other hand, the incidence of non-vertebral fracture is 19 per 1000 per year in women over age 50 and 7.3 per 1000 per year in men over age 50. Osteoporotic fractures are associated with high morbidity (20% of patients require nursing care, and up to 50% cannot live fully independently) as well as high mortality (25% for proximal fractures of the femur).

Pathophysiology. An individual's bone mass at a given age is determined both by the amount of bone laid down in youth and by the amount lost in later life. The major cause of bone loss in women is menopause. Important causes in both sexes include normal aging and various diseases that affect bone metabolism. Maximal bone mass is usually reached shortly after age 20. Its magnitude in both men and women is determined by genetic factors, sex hormones, lifestyle, and mechanical stress (physical activity), as well as by the degree of exposure to certain risk factors (Tab. 11.**5**). Among these determinants of maximal bone mass, genetic factors are clearly the most important.

The main causes of loss of bone substance during and after middle age, in other words, the main causes of osteoporosis, are estrogen deficiency due to menopause (or hypogonadism in men), the aging process, lifestyle and environmental factors, and a number of diseases that lead to increased bone loss (Tab. 11.5). Women are much more likely to suffer from primary osteoporosis due to menopause or aging than from secondary forms of the disorder. However, among men with osteoporosis as many as 50% have a secondary form (see Tab. 11.**4**).

Clinical Features. Osteoporosis remains asymptomatic until it results in a fracture (see next paragraph). The most prominent symptom of an osteoporotic fracture is pain, usually of acute onset. The acute pain of a vertebral fracture is often followed by chronic back pain due to muscle spasm, which is induced by the antalgic and

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other postural changes resulting from the original fracture.

It is unclear at present whether osteoporosis can cause pain in the absence of fracture and, if so, to what extent. Microfractures may conceivably cause small hemorrhages, edema, and pain of periosteal and endosteal origin.

Secondary Osteoporosis

Like primary osteoporosis, secondary osteoporosis is defined as a loss of bone mass, structure, and function associated with fractures. But, unlike primary osteoporosis, it can be causally traced to one or more underlying diseases (e. g., hypercortisolism) or to other factors impairing bone metabolism (e. g., medications). Secondary osteoporosis accounts for 15–20 % of all cases of osteoporosis in women, and for about 50 % of all cases in men.

> Osteoporosis can also be the initial manifestation of an underlying disease, e. g., multiple myeloma.

Secondary Osteoporosis Due to Endocrinopathy. A number of endocrine disorders can cause secondary osteoporosis:

- *Hypogonadism*: the major role played by estrogen deficiency in women in the pathogenesis of osteoporosis is well known, but in men, too, hypogonadism nearly always causes osteoporosis. It is particularly important to note that men who have undergone orchiectomy or are treated with gonadotropin releasing hormone (GnRH) agonists as antiandrogenic therapy for prostatic carcinoma often develop osteoporosis and are at markedly elevated risk for fractures.
- *Hypercortisolism*: endogenous hypercortisolism due to Cushing disease or Cushing syndrome (of whatever cause), as well as the long-term use of exogenous glucocorticoids, markedly elevates the risk of osteoporosis. Excessive circulating glucocorticoid activity interferes with bone metabolism by a number of mechanisms. Osteoblast activity is directly inhibited, while bone degradation is increased through multiple indirect effects, including lowering of sex hormone levels, possibly increased renal loss of calcium, and perhaps a reduced level of physical activity due to the underlying illness.
- *Hyperthyroidism* leads to increased bone remodeling with a net catabolic effect. Long-lasting hyperthyroidism can therefore cause significant loss of bone substance. However, because hyperthyroidism is usually diagnosed early in its course, manifest osteoporosis due to hyperthyroidism is quite rare today. Thyroid hormone treatment may also be a risk factor for osteoporosis, but the data regarding this are not entirely consistent. In general, men and premenopausal women being treated with thyroid

Table 11.**4** Types of osteoporosis

Primary osteoporosis
– idiopathic juvenile osteoporosis
– postmenopausal osteoporosis
– senile osteoporosis
Secondary osteoporosis
– Endocrine origin
– hypogonadism
– hypercortisolism (steroid medication, Cushing syndrome)
– hyperthyroidism
– hyperparathyroidism
– hyperprolactinemia
– diabetes mellitus
– Gastrointestinal diseases
– chronic inflammatory bowel diseases
– malabsorption
– malnutrition
– primary biliary cirrhosis
– lactose intolerance
– Bone marrow diseases
– multiple myeloma (plasmacytoma)
– diffuse bone metastases
– Rheumatological and connective tissue diseases
– rheumatoid arthritis
– osteogenesis imperfecta
– Ehlers–Danlos syndrome
– Marfan syndrome
– homocystinuria
– Other causes
– immobilization
– chronic alcoholism
– organ transplantation
– other

Table 11.**5** Risk factors for osteoporosis

Relative fracture risk (RR) ≥ 2	Relative fracture risk (RR) 1–2
– age > 65 years	– estrogen deficiency
– early menopause (< 45 years)	– endogenous estrogen exposure < 30 years
– hypogonadism (in men)	– calcium intake < 500 mg/day
– prior history of osteoporotic fracture	– primary hyperparathyroidism
– femoral neck fracture in a first degree relative	– rheumatoid arthritis
– corticosteroid therapy	– ankylosing spondylitis
– chronic gastrointestinal disease, e. g., sprue, Crohn disease	– treatment with anticonvulsants
– increased bone destruction	– hyperthyroidism
– anorexia nervosa	– diabetes mellitus
– BMI < 18 kg/m^2	– smoking
– marked physical inactivity	– alcohol abuse
– chronic renal failure	
– organ transplantation	

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The Diagnostic Assessment of Osteoporosis

Conventional Radiographs. If the findings of the history and physical examination arouse suspicion of osteoporosis, and particularly of osteoporotic fracture(s), then conventional radiographs should be obtained. These remain the method of choice for the documentation of fracture-related bone deformities and are also very helpful in differential diagnosis. Plain radiographs may indicate the presence of secondary forms of osteopenia or may reveal the need for additional diagnostic studies such as CT, MRI, or skeletal scintigraphy.

Radiological findings consistent with osteoporosis include increased radiolucency of bone, a "stringy" trabecular system (spongiosa), accentuation of the upper and lower end plates of the vertebral bodies, and reduced cortical density (Fig. 11.**16**). Nonetheless, osteoporosis cannot be diagnosed from a plain radiograph alone in the absence of vertebral fractures. The diagnosis of osteopenia/osteoporosis requires the loss of at least 30 % of initial bone mass.

Densitometry. The determination of the mineral content of bone, usually by means of dual energy X-ray absorptiometry (DEXA), is currently considered the best way to assess the risk of a bone fracture. There is a well-documented correlation between bone mineral content and fracture risk; the lower the mineral content, the higher the risk of fracture. A diminution of mineral content by one standard deviation is associated with an approximately doubled risk of fracture.

Densitometric classification of osteoporosis (valid only for the DEXA method in caucasian postmenopausal women):

- *normal*: bone density within one standard deviation (SD) of the mean value for young adults (in terms of the T score, $T \geq -1$)
- *osteopenia*: bone density below the mean value for young adults by more than one SD, but by less than 2.5 SD (in terms of the T score, $-1 \geq T \geq -2.5$).
- *osteoporosis*: bone density 2.5 SD or more below the mean value for young adults ($T \leq -2.5$).

Laboratory Tests (Tab. 11.**6**) are used mainly to demonstrate or rule out the various causes of secondary osteoporosis, primary osteoporosis being diagnosed by exclusion if none of these are present, and to assess the dynamic state of bone remodeling. Increased bone degradation is a risk factor for fracture. The laboratory parameters are usually normal in primary idiopathic osteoporosis. If the basic battery of laboratory tests suggests the presence of another underlying illness, further specific testing should be performed.

Table 11.**6** Laboratory tests in the evaluation of osteoporosis

General	Special
– erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) – differential blood count – calcium, phosphate – alkaline phosphatase (AP) – serum glutamic-oxaloacetic transaminase (SGOT) – creatinine – total protein	*Serum:* – osteocalcin or bone isoenzyme of AP (when total AP is elevated) – parathormone in hypercalcemia or hypocalcemia – 25-(OH)-vitamin D in hypercalcemia or hypocalcemia – protein electrophoresis when the ESR is elevated – thyroid-stimulating hormone (TSH) – in some cases, tryptase (for the diagnosis or exclusion of mastocytosis) *Urine/serum:* – markers of bone resorption

hormones are not at elevated risk of osteoporosis, but the risk of osteoporosis may indeed be higher in postmenopausal women, perhaps because of the simultaneous presence of other risk factors.

➤ *Hyperprolactinemia* leads to a decline in the gonadal production of sex hormones and thereby to an elevated risk of osteoporosis.

➤ *Diabetes mellitus*: the complex metabolic abnormalities in diabetes mellitus also affect bone. The risk of developing osteoporosis is elevated in type I diabetes but seems not to be so in type II diabetes. The pathogenesis of osteoporosis in diabetes is multifactorial; insulin deficiency, genetic factors, vitamin D deficiency, and osteoblast dysfunction are all thought to be contributing factors.

➤ *Primary hyperparathyroidism*: see p. 375.

Medication-Induced Secondary Osteoporosis. The medications that most commonly induce secondary osteoporosis include the glucocorticoids (see above), high-dose heparin, LHRH analogues, and aromatase inhibitors.

Transplantation Osteopathies. Bone disorders arise after heart, liver, or kidney transplantation through a number of mechanisms. The underlying illness (i. e., the reason for transplantation) and its treatment can affect bone metabolism, while the immunosuppressive agents given after transplantation, often including glucocorticoids, can also lead to increased bone loss.

Immunogenic Secondary Osteoporosis. Osteoporosis can also be promoted by immunological mechanisms, e. g.,

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by the increased cytokine activity that is part of the inflammatory process in rheumatoid arthritis. Osteoporosis accompanying chronic inflammatory bowel diseases is mainly due to the calcium and vitamin D deficiencies that they produce.

Osteoporosis Due to Inherited Diseases of the Supporting Tissue of Bone. *Osteogenesis imperfecta* (OI), an inherited disease characterized by abnormal collagen metabolism, is currently classified into seven different subtypes (numbered I–VII). It is often caused by a mutation in one of the two genes encoding type I collagen, resulting in impaired collagen synthesis and instability of the collagen molecule. The clinical spectrum of OI is extremely broad. Some forms are lethal shortly after birth, while others may be so mild as to escape clinical notice. The main clinical manifestation of OI is bone fracture after very mild trauma (hence the colloquial name "brittle bone disease"). The fractures often occur in a bimodal temporal distribution, with peak incidence shortly before puberty and then again after menopause (in women). Aside from abnormal fragility of bone, other signs of the disease include blue sclerae (in more than 50% of patients), hearing impairment due to otosclerosis, deformed teeth, short stature, and hyperextensibility of the ligaments.

Other inherited diseases than can be accompanied by osteoporosis include homocystinuria, Ehlers–Danlos syndrome, and Marfan syndrome.

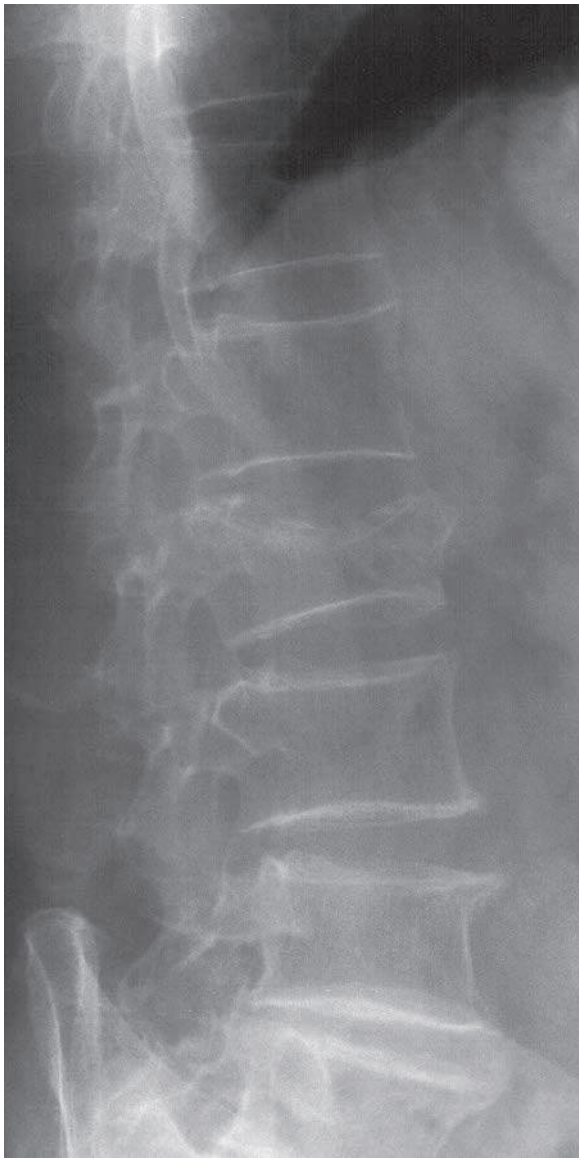

Fig. 11.**16** Osteoporosis: note the accentuation of the upper and lower plates of the vertebrae and the L2 compression fracture.

Osteomalacia

Definition. Osteomalacia is a generalized metabolic disease of bone characterized by diminished mineralization, which, as a consequence of the continuous remodeling of bone, leads to an accumulation of nonmineralized bone matrix (osteoid). Nonmineralized osteoid is less resistant to mechanical stress than adequately mineralized bone.

Pathogenesis. Vitamin D deficiency and abnormalities of vitamin D metabolism are the most common causes of osteomalacia. Other possible causes are summarized in Tab. 11.**7**.

Vitamin D deficiency is due to diminished production of vitamin D in the skin (inadequate exposure to sunlight), inadequate dietary intake of vitamin D, diminished hydroxylation (activation) of vitamin D, or resistance to the biological effect of 1,25-$(OH)_2$-D_3 (Tab. 11.**7** and Fig. 11.**17**).

➤ *Increased loss of vitamin D*: vitamin D deficiency may be due to impaired enteric resorption of vitamin D_3

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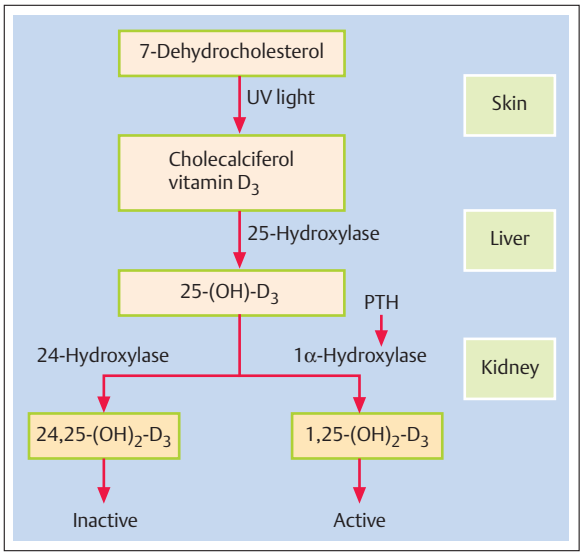

Fig. 11.**17** Vitamin D metabolism. PTH = parathyroid hormone.

Table 11.**7** Causes of osteomalacia

Vitamin D deficiency – diminished vitamin D production in the skin – inadequate dietary intake of vitamin D – malabsorption (gastrointestinal disease such as celiac disease, Crohn disease)
Increased loss of vitamin D – disturbance of the enterohepatic circulation (gastrointestinal disease such as celiac disease, Crohn disease) – increased catabolism of vitamin D (anticonvulsants, phenobarbital, rifampicin, glutethimide)
Diminished 25-hydroxylation of vitamin D – hepatic diseases (primary biliary cirrhosis, chronic active hepatitis, alcoholic cirrhosis) – genetic mutation affecting 25-hydroxylase (?) – isoniazide
Diminished 1α-hydroxylation of vitamin D – renal failure – ketoconazole – vitamin D-dependent rickets, type I (VDDR-I) (mutation of 1α-hydroxylase)
End organ resistance – vitamin D-dependent rickets, type II (VDDR-II) (mutation of vitamin D receptor) – phenytoin
Hypophosphatemia – oncogenic osteomalacia – X-linked hypophosphatemic rickets – autosomal hypophosphatemic rickets – antacids (phosphate binders)
Renal tubulopathies – Fanconi syndrome – renal tubular acidosis
Primary mineralization defects – hypophosphatasia – medications: etidronate, fluoride

because of *gastrointestinal diseases*, e. g., celiac disease. Bowel disease also impairs the reuptake of vitamin D metabolites (enterohepatic circulation of vitamin D) causing continuous loss of vitamin D. Osteomalacia occurs mainly in malabsorptive diseases such as celiac disease, regional enteritis, Crohn disease, idiopathic steatorrhea, partial gastric resection with gastroenterostomy, and small intestine resection. Hepatic and pancreatic diseases can also cause osteomalacia.

➤ *Accelerated vitamin D metabolism* can be caused by treatment with anticonvulsants or tuberculostatic agents (phenobarbital, primidone, phenytoin, rifampicin, and glutethimide).

Diminished hydroxylation of vitamin D in the liver occurs in primary biliary cirrhosis, alcoholic cirrhosis, and chronic active hepatitis. A special form of vitamin D deficiency is seen in *end-stage renal disease*. Phosphate retention, diminished 1α-hydroxylase activity, the retention of mineralization inhibitors, metabolic acidosis, and the generation of an abnormal collagen matrix all contribute to the pathogenesis of so-called renal osteopathy. The most common form of bone involvement in patients with chronic renal failure is osteitis fibrosa cystica, a consequence of secondary hyperparathyroidism. Isolated osteomalacia is less common in renal patients. Often one sees a combination of a mineralization disorder with the effects of secondary hyperparathyroidism. In summary, renal osteopathy is a complex disorder (a mixture of osteomalacia, osteoporosis, and hyperparathyroidism) and is thus considered to be a distinct type of bone disease.

A further, rare cause of osteomalacia is vitamin D-dependent rickets, type I (VDDR-I), also called pseudovitamin D-deficiency rickets.

➤ *End-organ resistance* to 1,25-$(OH)_2$-D_3 is present in vitamin D-dependent rickets, type II (VDDR-II), as a consequence of a diminished number or affinity of vitamin D receptors, or of inadequate binding of the hormone-receptor complex to DNA.

➤ *Hypophosphatemia* is often seen in vitamin D deficiency as a consequence of secondary hyperparathyroidism. There are also types of osteomalacia in which low serum levels of phosphate are the primary defect and the serum calcium concentration remains normal.

The most important types of disease causing hypophosphatemia are inherited disturbances of phosphate metabolism, and the most common of these is X-linked hypophosphatemic rickets (hereditary vitamin D-resistant rickets, phosphate diabetes). The disease is transmitted on the X chromosome. An inactivating mutation of the *PHEX* gene causes a renal tubular defect with severe renal loss of phosphate.

A rare type of hypophosphatemic osteomalacia is oncogenic osteomalacia. Some tumors, mostly of mesenchymal origin, secrete fibroblast growth factor 23 (FGF-23) that apparently has a phosphaturic ef-

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fect. The tumors causing oncogenic osteomalacia are often quite small, and its diagnosis and clinical differentiation from vitamin D-resistant rickets can be difficult.

- *Renal tubulopathies*: renal tubular acidosis often causes osteomalacia. The underlying defect consists of an inability to secrete H^+ ions (protons) and decreased reuptake of bicarbonate. Acidosis per se can influence the mineralization process, and systemic acidosis leads to decreased tubular reuptake of phosphate. At the same time, there may be renal salt loss and, in consequence, secondary hyperaldosteronism.
  Fanconi syndrome is a rare condition associated with various disturbances of the renal tubular transport mechanisms. It is characterized by renal loss of phosphate, bicarbonate, glucose, and amino acids. Fanconi syndrome can be a familial abnormality or arise in the setting of congenital diseases such as cystinosis, hereditary fructose intolerance, galactosemia, glycogen storage diseases, and others. It can also occur in acquired conditions such as immunological diseases, myeloma, and nephropathies of various types. Osteomalacia in Fanconi syndrome is mainly due to phosphate loss and renal tubular acidosis.
- *Hypophosphatasia*: the precise sequence of events in the process of mineralization is not yet understood in full detail. When osteoblasts produce a lower than normal amount of AP, e. g., in the genetic disease called hypophosphatasia, mineralization cannot proceed normally and osteomalacia results. Hypophosphatasia is an autosomal recessive disorder characterized by markedly reduced synthesis of AP in the liver and in bone.

Clinical Findings. The clinical presentation of vitamin D deficiency and osteomalacia is variable, reflecting not only the low serum calcium level, but also diminished bone mineralization and lack of vitamin D_3. There may be muscle weakness, tetany, diffuse bone pain, and fractures. Hypocalcemia produces symptoms and signs of increased neuromuscular excitability, including paresthesia in the perioral area, fingers, and toes, and spontaneous or latent tetany.

Vitamin D deficiency often produces muscle weakness (myopathy), mainly in the proximal segments of the limbs (waddling gait, stiff and small-stepped gait). Elderly patients with vitamin D deficiency are prone to frequent falls.

Vitamin D-dependent rickets, type I (VDDR-I), occurs in childhood as a severe form of rickets with hypocalcemic tetany, myopathy, motor retardation, and delayed growth. Dental enamel hypoplasia is an accompanying manifestation.

Children with *vitamin D-dependent rickets, type II* (VDDR-II), are normal at birth but develop the illness by the age of two years. Two-thirds have marked alopecia.

The clinical picture of *X-linked hypophosphatemic rickets* is highly variable; its major features are hypophosphatemia, osteomalacia, and short stature. Hypophosphatemia is found shortly after birth, but the characteristic deformity of the long bones appears only after the child has begun to bear weight (walk). This is often also the moment at which growth retardation is noted. In contrast to the hypocalcemic varieties of rickets, this condition is not associated with dental enamel hypoplasia or proximal myopathy.

The clinical manifestations of *hypophosphatasia* are also highly variable. The condition sometimes occurs in childhood with skeletal deformities and markedly elevated mortality, but less severe forms of the condition can occur only later in life with bone pain and sometimes fractures.

Laboratory investigations. The laboratory findings in osteomalacia depend on the causes, which are summarized in Tab. 11.**8**. Biochemically, osteomalacia is characterized by calcium and phosphate serum levels that are decreased or in the lower range of normal, with an increased alkaline phosphatase activity. The vitamin D deficiency is proven by measuring the 25-OH-D_3 serum level: determination of the 1,25-$(OH)_2$-D_3 is only necessary in particular situations.

Secondary hyperparathyroidism also leads to a rise in tubular re-absorption of calcium and a lowering of the re-absorption of phosphate. Therefore, the phosphate levels are frequently decreased, because simultaneously there is less gastrointestinal absorption of phosphate. Calcium excretion in the urine is decreased. Bone resorption is stimulated as a result of the secondary hyperparathyroidism, and the bone metabolism parameters may be increased (both resorption and formation parameters).

In gastrointestinal diseases, additional laboratory changes are frequently detected that indicate malabsorption, e. g., iron deficiency with hypochromic microcytic anemia in celiac disease.

> Vitamin D deficiency is demonstrated by measurement of the serum concentration of 25-(OH)-D_3. The serum concentration of 1,25-$(OH)_2$-vitamin D need not be measured, except in special situations.

Radiological Findings. Changes that are specific for osteomalacia include *Looser zones* (pseudofractures); a blurred, milky-glass appearance of the vertebral bodies and, occasionally, signs of secondary hyperparathyroidism (subperiosteal resorption at the phalanges, bone cysts or resorption at the distal ends of the long bones). The mineral structure of the bones appears rarefied, with diminished cortical thickness (Fig. 11.**18**).

In the *vertebral bodies*, the structures under the upper and lower end plates become denser than normal because of excessive callus formation within the cancellous bone (trabecular system). This is the so-called rugger jersey phenomenon. Longstanding osteomalacia leads to softening of bone, causing a concave deformation of the vertebral bodies ("codfish vertebrae"). The intervertebral disks appear thickened and biconvex. In

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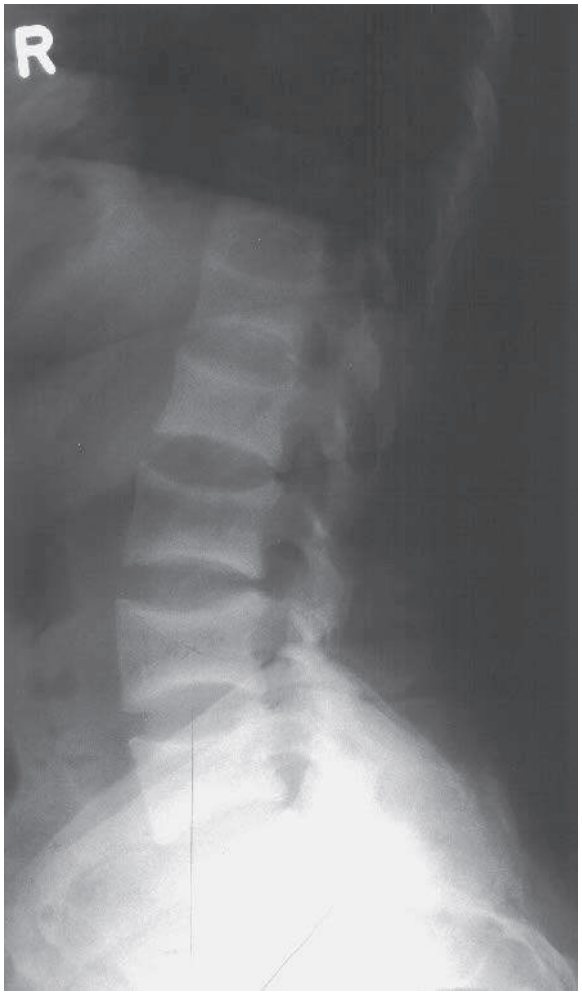
Table 11.**8** Laboratory abnormalities in osteomalacia of various causes

	Ca^{2+}	PO_4	AP	PTH	25-(OH)-D	$1,25\text{-}(OH)_2\text{-}D^*$
– vitamin D deficiency	↓	↓	↑ ↑	↑ – ↑ ↑	↓	N–(↓)
– diminished 25-hydroxylation	↓	↓	↑ ↑	↑ – ↑ ↑	↓	N–(↓)
Diminished 1α-hydroxylation						
– VDDR-I	↓	↓	↑ ↑	↑	N– ↓	↓ ↓
– renal failure	↓	↑	↑ – ↑ ↑	↑ – ↑ ↑	N	↓
End-organ resistance						
– VDDR-II	↓ – ↓ ↓	↓	↑ ↑	↑	N– ↓	↑ –N
Hypophosphatemia						
– X-linked hypophosphatemic rickets	N	↓ ↓	↑ ↑	N	N	(N)– ↓
– oncogenic osteomalacia	N	↓ ↓	↑ ↑	N	N	(N)– ↓
Renal tubulopathies						
– Fanconi syndrome	N	↓ – ↓ ↓	↑	N–(↓)	N	N– ↓
– renal tubular acidosis	N–(↓)	↓ –(N)	↑	N	N	N
– hypophosphatasia	N	N	↓ – ↓ ↓	↓ –(N)	N	N

Symbols: N, within normal range; ↑, increased; ↓, decreased; (↑) or (↓), mildly increased or decreased; ↑ ↑ or ↓ ↓, markedly increased or decreased.

* To be measured only in special situations (e. g., on suspicion of 1α-hydroxylation or a receptor defect).



severe cases, there may be deformation of other bone segments that are subject to heavy mechanical stress (e. g., the femur). There is often also radiological evidence of secondary hyperparathyroidism.

Skeletal scintigraphy (bone scanning) often reveals intense radionuclide uptake by the entire skeleton, with local accentuation at the sites of the pseudofractures. The scintigraphic appearance is not pathognomonic, however, as it can also be produced by metastatic disease.

A search for the (typically small) tumors that produce *oncogenic osteomalacia* generally requires tomographic study of the entire body with MRI or CT. These tumors sometimes also express somatostatin receptors. Thus, ^{111}In-octreotide scintigraphy has recently been used with success to localize them.

◁ Fig. 11.**18** Osteomalacia with blurred, milky-glass structure of the vertebral bodies and increased density of the upper and lower plates.

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Hyperparathyroidism

Primary Hyperparathyroidism

Pathogenesis. Primary hyperparathyroidism and malignant tumors are the most common causes of hypercalcemia. Primary hyperparathyroidism is a relatively common endocrine disorder with peak incidence between the ages of 40 and 80. It affects women more often than men, in a ratio of 3:1. This condition is diagnosed more often, and earlier, at this time than in the past.

The pathophysiological basis of primary hyperparathyroidism is a disturbance of the feedback loop linking the serum parathormone concentration to the extracellular calcium concentration (elevated set point of the calcium-sensing receptor). Eighty percent of cases are due to a solitary parathyroid adenoma, which is usually benign. Parathyroid carcinoma is quite rare (< 1%). About 20% of cases are due to hyperplasia of multiple parathyroid glands.

Primary hyperparathyroidism sometimes appears as a familial disorder of genetic origin, either with or without other accompanying types of endocrine dysfunction. The most common underlying disease in such cases is the autosomal dominant disorder *multiple endocrine neoplasia, type I* (MEN-I), which causes not only primary hyperparathyroidism, but also tumors of the pituitary gland, the endocrine pancreas, and the adrenal gland.

Clinical Findings. The clinical features of primary hyperparathyroidism depend on the severity of hypercalcemia. The symptoms and signs of hypercalcemia include loss of energy, polyuria, polydipsia, loss of appetite, and nausea.

> Despite the above considerations, most patients with primary hyperparathyroidism are asymptomatic.

The neurological and psychiatric manifestations of primary hyperparathyroidism include fatigue, prostration, irritability, and loss of concentration. About 15% of patients develop kidney stones. Nephrocalcinosis (renal parenchymal calcification) is unusual. The classic bone finding of osteitis fibrosa cystica is currently rare. Generalized loss of bone mass (osteoporosis) is much more common and is associated with an elevated risk of fractures.

Diagnostic Evaluation. Primary hyperparathyroidism is diagnosed by the demonstration of hypercalcemia in the presence of a normal or elevated serum concentration of intact parathormone (i.e., an inappropriately high parathormone concentration in the face of hypercalcemia). Humoral hypercalcemia due to a malignant tumor is mediated by parathormone-related peptide (PTHrP). It is associated with a lowering (suppression), rather than elevation, of the serum parathormone level, and current tests for intact parathormone display no cross-reactivity to PTHrP. Hypercalcemia with a normal or elevated parathormone concentration, if it is not due to primary hyperparathyroidism, can only be due to ectopic parathormone production or to treatment with lithium or thiazide diuretics. The last two causes are easily revealed, by the clinical history.

Radiological changes include diffuse demineralization (osteoporosis) as well as subperiosteal resorption of bone, which is particularly evident in the phalanges (Fig. 11.**19**). A pathognomonic radiological sign is loss of the lamina dura of the teeth. Because hypercalcemia and primary hyperparathyroidism are now usually diagnosed early in their course, before any of the specific radiologic signs appear, routine radiographic studies are not indicated unless there is clinical suspicion of a particular bone lesion that must be demonstrated or excluded. Bone densitometry, however, is now part of the routine diagnostic assessment of primary hyperparathyroidism.

Fig. 11.**19** Hyperparathyroidism with subperiosteal resorption of the phalanges.

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Table 11.**9** Differential diagnosis of secondary hyperparathyroidism

Diminished gastrointestinal calcium resorption
– diminished dietary intake of calcium
– lactose intolerance
– diminished absorption of calcium consumed in the diet
– pancreatic diseases (fat malabsorption)
– celiac disease
– vitamin D deficiency
Increased calcium loss or increased need for calcium
– Bone
– in the growing years
– in the aftermath of pregnancy and breastfeeding
– bisphosphonate treatment
– Breastfeeding
– Kidney
– idiopathic hypercalciuria
– loop diuretics
– Soft tissues
– rhabdomyolysis
– sepsis
Diminished parathormone effect
– chronic renal failure
– pseudohypoparathyroidism (G protein deficiency)

Secondary Hyperparathyroidism

Pathogenesis. Secondary hyperparathyroidism arises in response to a fall in the serum calcium level. It reflects the normal reaction of the parathyroid glands to a decline in the extracellular calcium concentration. Its many causes are summarized in Tab. 11.**9**.

A special type of secondary hyperparathyroidism is that which accompanies *renal failure*. The skeleton is involved in more than 75% of patients with chronic renal failure whose glomerular filtration rate (GFR) is below 60 mL/min. Phosphate retention in such patients leads to increased secretion of parathormone, while renal failure simultaneously leads to a decline of 1α-hydrolase activity and therefore to diminished synthesis of 1,25-$(OH)_2$ vitamin D. In addition, metabolic acidosis and, possibly, direct toxic injury to osteocytes, may well be further pathogenetic factors for the development of renal osteodystrophy. Secondary hyperparathyroidism is associated with hypertrophy of all of the parathyroid glands.

The most common finding is bone involvement with increased bone remodeling due to secondary hyperparathyroidism, followed by mixed renal osteodystrophy (secondary hyperparathyroidism and mineralization disorder), so-called adynamic bone disease, and osteomalacia. In addition to renal osteodystrophy, patients with end-stage renal disease can also develop osteoporosis, which is associated with an elevated risk of fracture.

Diagnostic Evaluation. Secondary hyperparathyroidism is diagnosed by the demonstration of a normal or low serum calcium concentration in combination with elevated parathormone levels. It is worth remembering that hypocalcemia due to gastrointestinal diseases such as sprue is often accompanied by hypophosphatemia, but hypocalcemia due to chronic renal failure is accompanied by hyperphosphatemia.

Secondary hyperparathyroidism of long duration, e. g., in chronic renal failure, can lead to autonomy of parathormone secretion, so-called *tertiary hyperparathyroidism*. In this condition, the serum calcium concentration is elevated and the serum concentration of intact parathormone is also elevated.

The *radiological findings* of secondary hyperparathyroidism resemble those of primary hyperparathyroidism. In cases with simultaneous vitamin D deficiency, the findings resemble those of osteomalacia (see above).

Acknowledgement

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Edema

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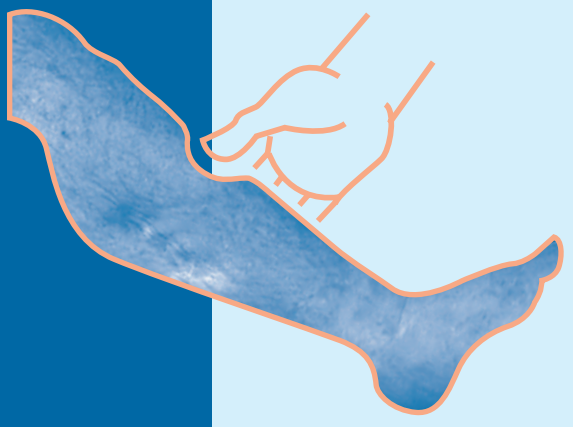
12

12 Generalized and Localized Edema

U. Hoffmann and F. Tató



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12 Generalized and Localized Edema

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Pathophysiology and General Considerations

Definition. Edema is a pathological accumulation of fluid in the interstitial space.

Pathophysiology. Normally there is a balance between the amount of fluid, salts, and proteins that leave the capillary lumen, and the amount of substances that are reabsorbed and transported back. Small molecules are primarily reabsorbed on the venular branch of the capillaries in order to reach the bloodstream again, whereas large protein molecules return preferentially via the lymphatic vessels. The most significant pathophysiological mechanisms that lead to the formation of edema are increased venous and capillary pressure, increased permeability of the capillary wall, and diminished drainage efficiency of the lymphatic system. In certain cases several pathogenetic factors add to edema formation. The interstitium is able to absorb several liters of fluid before clinically apparent edema occurs. Therefore a precondition for the development of edema is renal sodium and water retention.

Localization. When considering the differential diagnosis of edema, localization gives the first indication. Generalized edema leads one to suspect a disorder that affects the whole body. Classic examples are heart failure and hypoproteinemia. In these cases it is important to incorporate the findings in certain organs such as the heart or the kidneys, as they are decisive elements when considering the differential diagnosis. If edema develops locally, which means it only affects a particular part of the body, then one searches primarily for local causes. Phlebedema, lymphedema, and Quincke edema would be prototypes for edema with a local origin.
When assessing edema of the lower limbs, it must be taken into account that minor swelling can be a physiological phenomenon. After standing or sitting quietly for long periods (for example in a car or airplane), many people experience discreet to moderately pronounced symmetrical edema of the lower limbs. The tendency to premenstrual swelling is also well known.

A differential diagnosis can normally be narrowed down considerably by carefully recording the medical history and carrying out a physical examination.

12.1 Generalized Edema

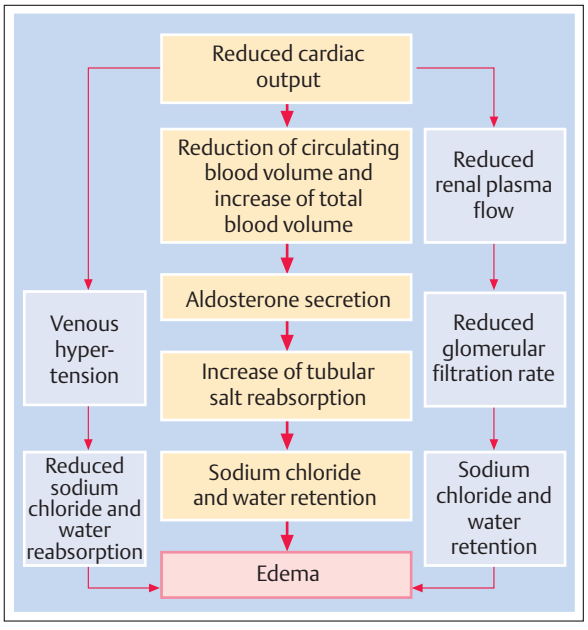

Fig. 12.**1** Pathogenetic factors involved in edema formation related to heart failure.

Edema Related to Heart Failure

Pathophysiology. Heart failure leads to an increase of the left ventricular end-diastolic pressure and ultimately to pulmonary edema. If there is a disturbance of the right ventricular function, central venous pressure increases, which may be clinically recognizable by distention of the jugular vein. The increase in venous pressure may be transferred as far as the venular side of the capillary vessels, so that less insterstitial fluid is reabsorbed. In addition, decreased cardiac output activates humoral and neurohumoral proccesses, which lead to increased water and salt retention by the kidneys and consequently to an increase in the amount of extracellular fluid (Fig. 12.**1**).

Clinical Features. Due to fluid retention, edema develops and usually presents as pitting edema (Fig. 12.**2**). It mainly affects dependent parts of the body. Thus mobile patients may develop edema that presents as symmetrical leg swelling. Bedridden patients, on the other hand, may develop edema of the back and buttocks. Serious biventricular heart failure can cause the edema to affect the genital region and occasionally the upper extremities. In many cases pleural or pericardial effusion is present. Chronic liver congestion may additionally lead to

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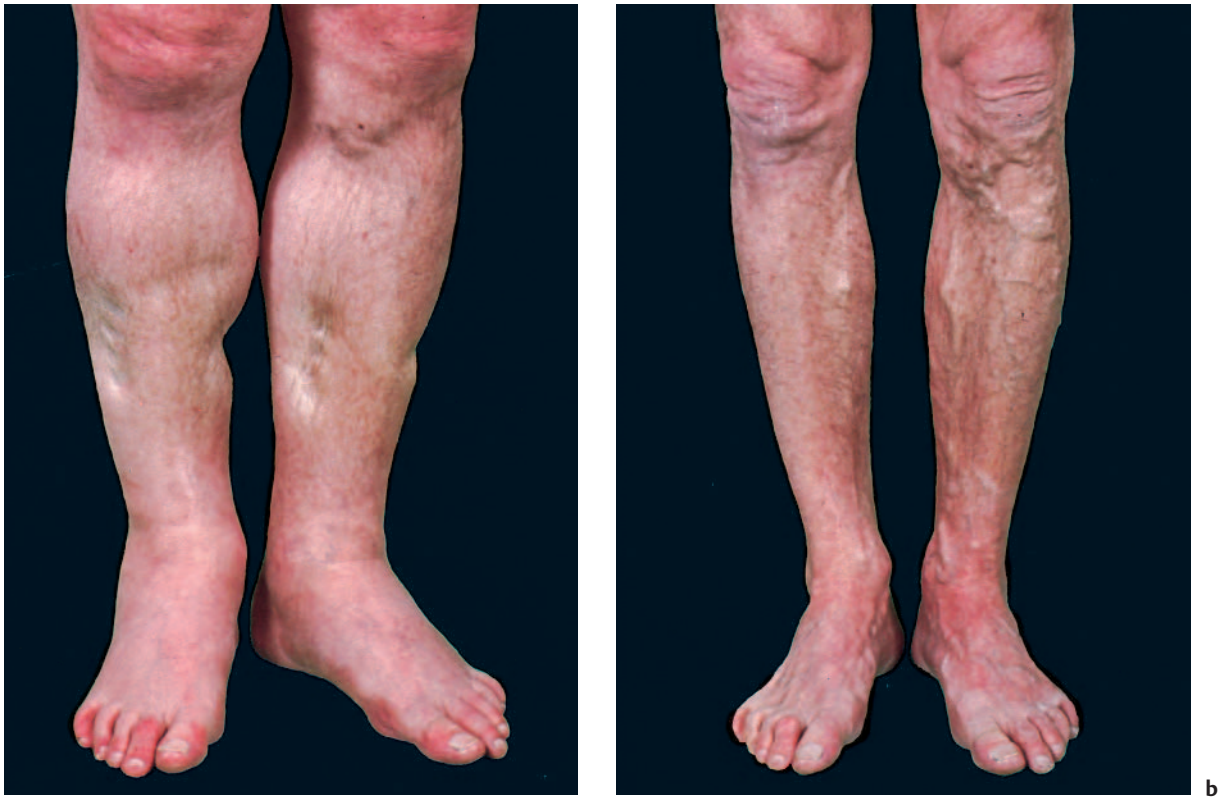

a b

Fig. 12.**2** Marked lower limb edema in a patient with right heart failure.

a Typical appearance of pitting after pressure was applied.
b Disappearance of edema after treatment with diuretics.

hypoproteinemia due to diminished liver function (see below). Additional symptoms that suggest valvular, myocardial, or coronary heart disease support the diagnosis.

Hypoproteinemic Edema

Clinical Features and Diagnosis. In contrast to cardiac edema, hypoproteinemic edema is less dependent on the position of the body. The face, and in particular the eyelids, may be affected. The edema is decidedly soft and pitting. The diagnosis is confirmed by determining total protein plasma level and the protein electrophoresis. Hypoproteinemic edema regularly occurs if the total plasma protein level is less than 5 g/dL (50 g/L) and the plasma albumin content is below 1.5–2.5 g/dL (15–25 g/L). If the albumin level is below 2.0 g/dL (20 g/L) there is a pronounced tendency to thrombosis, as the plasma level of antithrombin III also decreases.

Etiology. Hypoproteinemic edema may be caused by a number of diseases:

➤ *The Nephrotic Syndrome.* The main disease that causes hypoproteinemic edema is nephrotic syndrome. The determining factors for the diagnosis are pronounced proteinuria (> 3.5 g/day) and hypoproteinemia (< 2.0 g/dL). The serum albumin is distinctly reduced while high molecular weight proteins (mainly α2-globulin and β-globulin) decrease moderately. The serum cholesterol level is increased. Apart from hypoproteinemia other factors, such as sodium retention and the disturbance of the capillary permeability, are also involved in the pathogenesis of edema. The possible causes of the nephrotic syndrome as well as its symptoms will be discussed in Chapter 29.

➤ *Serious liver diseases* are usually associated with moderate to pronounced edema formation. Edema due to hypoproteinemia is based on impaired liver protein synthesis (in particular the albumins). Pressure on the intrahepatic part of the inferior vena cava or disturbance of the venous return due to ascites may lead to an increase in venous pressure in the inferior vena cava and thus augments edema formation in the lower limbs. Other symptoms of liver failure (see Chapter 25) lead to the correct diagnosis.

➤ *Exudative Gastroenteropathy.* Hypoproteinemic edema is a main clinical symptom of exudative gastroenteropathy. This disease is characterized by a loss of plasma proteins into the intestinal lumen. Hypoproteinemia results if enteral protein loss is higher than the maximal protein synthesis capacity of the liver. In contrast to nephritis, intestinal protein loss

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Fig. 12.**3** Pretibial myxedema in a patient with hypothyroidism.

affects all protein fractions. The determination of α1-antitrypsin in serum and stool (physiological loss < 2.6 mg/g stool weight) or the more complex quantitative determination of the fecal excretion of radioactively marked macromolecules (e. g., ^{51}Cr-albumin) are important when making the diagnosis. Diseases such as ulcerative colitis, polyposis, hypertrophic gastropathy (Ménétrier syndrome), or idiopathic sprue come into question as causes of exudative gastroenteropathy (see Chapters 27, 28). These diseases can be easily detected endoscopically or radiologically. If intestinal lymph drainage is impaired, the diagnosis of enteral protein loss may be difficult and may require a ^{51}Cr-albumin test and/or a lymphography. Inherited intestinal lymphangiectasia primarily affects children and young adults and is characterized by an ectasia of enteric lymphatics. Valvular insufficiency of draining lymphatic vessels may lead to reflux of the lymph fluid and to chylointestinal fistulas. Chylous reflux due to acquired drainage disorders can develop secondarily, for example, due to abdominal tumors.

➤ *Hunger Edema.* Hunger edema as well as edema in cachetic conditions would also normally be considered as hypoproteinemic edema. The underlying cause of this type of edema is an unbalanced diet, especially in times of nutritional insufficiency. A typical example is the chronic alcoholic, who satisfies his/her caloric requirement mainly with carbohydrates. Specific queries as to the patient's diet will clarify the diagnosis.

➤ *Kwashiorkor.* In developing countries there is often a particular form of undernourishment that is called kwashiorkor. After infants have been weaned, they receive cereals as their main source of nourishment. This ultimately leads to underdevelopment and the formation of edema.

Edema Related to Glomerulonephritis

Clinical Symptoms. In cases of acute glomerulonephritis and of acute renal failure due to other causes, edema may occur without nephrotic syndrome. This edema has similar properties to those found in the edema of hypoproteinemic patients. The edema is pale, pits easily, and is found mainly on the face. In glomerulonephritis, there is evidence of a general increase in capillary permeability. However, in most cases of renal failure the tendency towards edema is primarily due to retention of sodium and water.

Diagnosis. A urinalysis showing haematuria, erythrocyte casts, and dysmorphia, usually accompanied by only moderate proteinuria, leads to the correct diagnosis. Newly developed hypertension and reduced renal function are frequently observed.

Edema Related to the Endocrine System

Myxedema is an important form of endocrine-related edema. Edema may occasionally develop in hyperaldosteronism. An overdose of mineralocorticoids, e. g., in the treatment of Addison disease, or the use of drugs with mineralocorticoid effect (Carbenoxolone, licorice) may lead to edema.

Myxedema. In myxedema, the edema is most commonly found in the pretibial area (Fig. 12.**3**). It does not pit on pressure. In severe cases, particularly those preceded by thyroidectomy or radioactive iodine treatment, its diagnosis is sometimes overlooked. False diagnoses are also frequent in oligosymptomatic cases. Inexplicable general fatigue, weight gain, increased sensitivity to cold, dry skin, deepening voice, and a low voltage electrocardiogram (ECG) will raise suspicion for the diagnosis. Appropriate laboratory evaluation of thyroid gland metabolism can confirm the diagnosis. Interstitial deposits of hydrophilic mucopolysaccharides and the resulting deterioration of lymphatic drainage are pathophysiologically significant. Pretibial myxedema, often accompanied by reddening of the skin, may occur in hyperthyroidism, albeit rarely. In this case, the clinical and hormonal findings are typical of hyperthyroidism.

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Edema Related to Electrolyte Imbalance

- *Hypokalemic edema* arises mainly as a result of chronic laxative abuse. Diagnosis can be established on the basis of medical history, general adynamia, and ECG changes.
- *The abuse of diuretics*, often practiced in order to lose weight, may also cause edema. In this case, edema does not occur until the medication has been discontinued, thus forcing the patient into a vicious circle whereby he/she starts taking the medication again if the doctor does not recognize the situation. Once the medication has been discontinued, the edema persists for a few weeks or months until it finally disappears completely. At the same time the hypokalemia and plasma renin return to normal levels.
- *Edema occurring as a result of hypertonic and hypotonic hyperhydration* is iatrogenic edema. The administration of excessive amounts of intravenous fluids leads to an increase in the extravasal fluid volume.

Edema Related to Scleroderma

In individual cases, edema may precede the other symptoms of scleroderma. Although it may initially be relatively soft, the edema becomes harder as the disease progresses. It then feels extremely dense and is difficult to press in. The normal skin creases disappear, e. g., of the face. Deposits of hydrophylic mucopolysaccharides, local inflammation, and increased microvascular permeability all play pathogenetic roles. The most recent findings suggest that there is also lymphatic microangiopathy (see Chapter 9). Other symptoms of the disease, such as secondary Raynaud syndrome, pulmonary fibrosis, renal involvement, and dysphagia, clarify the diagnosis.

Edema Related to Diabetes Mellitus

People with diabetes are prone to edema, particularly in the lower extremities, even in the absence of hypoproteinemia (glomerulosclerosis with nephrotic syndrome). This finding is based on the increased permeability of the capillaries, as demonstrated by clearance tests using radioactive substances and by flourescence videomicroscopy (see Chapter 9).

Drug-Related Edema

There are many drugs that can promote or cause edema. In particular, the adrenocortical hormones, certain antihypertensive drugs (hydralazine, α-methyldopa, minoxidil), and nonsteroidal antirheumatic drugs should be noted in this context. Treatment with calcium antagonists also relatively frequently leads to edema.

12.2 Localized Edema

Fig. 12.**4** demonstrates six different forms of localized, chronic edema and the differential diagnosis of the swollen leg.

Venous Edema

In cases of acute deep vein thrombosis a subfascial, or frequently epifascial painful edema, appears in the affected limb. The livid color is particularly striking when the patient is standing. Superficial veins, functioning as collaterals, appear congested and firm to the touch, when compared to the other limb. Once the acute phase is over, often following a relatively oligosymptomatic period, chronic venous insufficiency (Fig. 12.**4a**) may develop over a period of months or years. Edema which worsens upon standing or sitting (see Chapter 9) is one of the clinical characteristics in chronic venous insufficiency.

Lymphedema

While painful venous edema can be described as a "swollen blue leg," painless lymphedema could be referred to as a "swollen white leg" (Fig. 12.**4b**). Lymphedema is relatively firm, especially when the disease has reached a chronic stage. Typically lymphedema initially presents as a cushionlike swelling at the dorsum of the foot. The shape of the leg then becomes pillarlike (i. e., the ankle region loses its typical shape). The dorsal skin on the toes cannot easily be lifted with the finger and thumb (positive Stemmer sign). In severe cases verrucas may occasionally develop on the toes.

Primary Lymphedema

Pathogenesis. Primary lymphedema is a congenital disorder. It most commonly occurs in isolation, but may more rarely develop as part of a more complex congeni-

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a b c

d e f

Fig. 12.**4** Photographs of six patients with different forms of edema.

a Phlebedema of the left lower extremity related to congenital valvular agenesis of the deep venous system.

b Bilateral secondary lymphedema with a "pillarlike" deformation of both legs. History of vaginal carcinoma with resection and radiation therapy. Involvement of inguinal lymph nodes. "Cushionlike" swelling of the dorsum of the foot is easily visible on the left side.

c Lipedema. Swelling is restricted to both thighs ending with a "collarlike" appearance above the knee.

d Acrodermatitis chronica atrophicans of the right leg at the inflammatory preatrophic stage.

e Congenital angiodysplasia with hypertrophy of the right lower extremity (augmented growth in length and thickness), nevus flammeus (knee region), multiple small caliber arteriovenous fistulas and atypical varicose veins.

f Factitious edema of the right leg due to self-compression with a small bandage. A compression line is visible above the knee. Swelling abruptly starts distally.

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tal angiodysplasia. If a baby is born with an edematous leg (rare), this is referred to as hereditary congenital Nonne–Milroy disease, with autosomal dominant inheritance. A familial form, which develops later in life, is more common (hereditary lymphedema praecox; Meige disease). The most common form of primary lymphedema is sporadic lymphedema. In these cases, family history does not usually give any clues to the diagnosis. The edema generally begins in one leg after puberty. In 50% of cases, the contralateral leg is also affected as the disease progresses.

Primary lymphedema begins in more than 80% of patients before they have reached the age of 40. If it develops during adulthood, it is referred to as lymphedema tarda. Females are affected more often than males, making up 80% of all cases. The severity of the disease is defined according to three stages:

- I: reversible lymphedema (edema subsides overnight)
- II: irreversible lymphedema (edema does not subside overnight)
- III: elephantiasis.

Diagnosis. The presence of primary lymphedema can be confirmed by lymphography. If less than four to six lymph vessels are visualised in the lower leg, or less than eight to 12 in the upper leg, this is referred to as hypoplasia (Fig. 12.**5**). Usually the lymph nodes are also hypoplastic. Total aplasia (absence of puncturable lymph vessels), and dilation of the lymph vessels with valve insufficiency ("varicose" lymph vessels), are less common.

Since lymphography using contrast medium is a relatively invasive procedure, diagnosis is usually established only on the basis of the typical clinical signs. To some extent lymphography has been replaced by lymphscintigraphy. The diagnosis can also be supported by a pathological dye test, indirect lymphography using a subcutaneously administered contrast medium, or flourescence microlymphography (Fig. 12.**6**). As a result of lymphatic congestion, flourescence microlymphography, which is a virtually noninvasive procedure, demonstrates a more extensive lymphatic capillary network in lymphedema as compared to a healthy subject. In Nonne–Milroy syndrome microlymphatics are aplastic or hyperplastic.

Chylous Lymphedema. Chylous lymphedema is a special form of lymphedema. Lymphatic valve insufficiency extends as far as the cisterna chyli and there may be a reflux of lymph containing chyle from the bowel. Lymphedema of the genitalia and legs may ensue. Inguinal swellings may be mistaken for a hernia. Milky lymphatic fluid may occasionally be discharged from lymphatic fistulas (superficial blisters). In rare cases, chylous ascites may develop. In cases of so-called "yellow nail syndrome" there are pleural effusions in addition to lymphedema of the extremities.

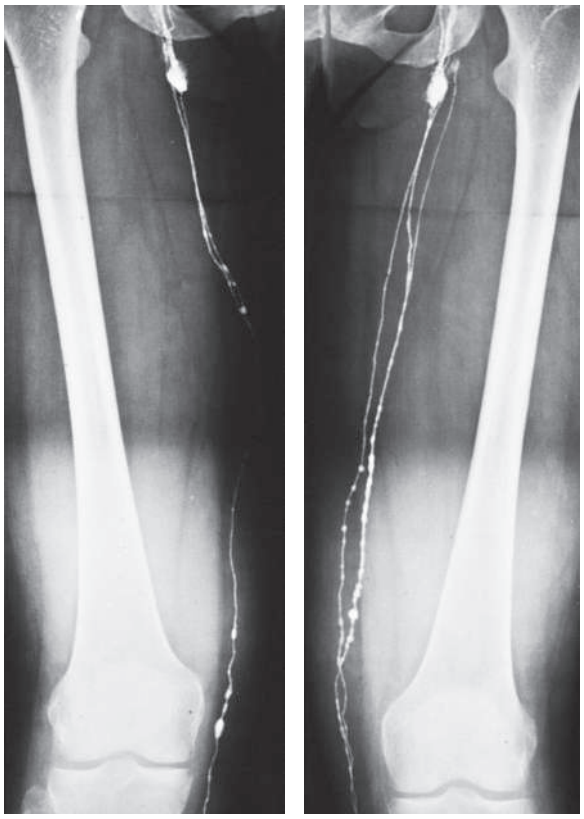

Fig. 12.**5** Lymphography with a water-soluble contrast medium in a patient with bilateral primary lymphedema. Instead of at least eight lymph collectors only one to two collectors are visible at the thigh region (hypoplasia).

Secondary Lymphedema

Etiology. Secondary lymphedema must always be ruled out, if swelling of the leg first appears when a patient is over the age of 40 (Fig. 12.**4b**). The most common causes of secondary lymphedema are:

- tumors of the lower pelvis (ovarian, bladder, rectal, and prostate gland carcinoma)
- malignant disease of the lymph nodes
- recurring bacterial lymphangitis (erysipelas)
- direct trauma to the anteromedial lymph vessel bundles (bottlenecks: medial knee area, groin)
- radiotherapy of the groin and pelvis
- tropical filarial infection (Fig. 12.**7**).

Lymphedema of the arm is most commonly seen following mastectomy. Chronically recurring nonspecific infections, e. g., originating from tinea pedis, can lead to occlusive lymphangiopathy.

Not until all of these possibilities have been carefully eliminated can a late-manifesting primary lymphedema be diagnosed.

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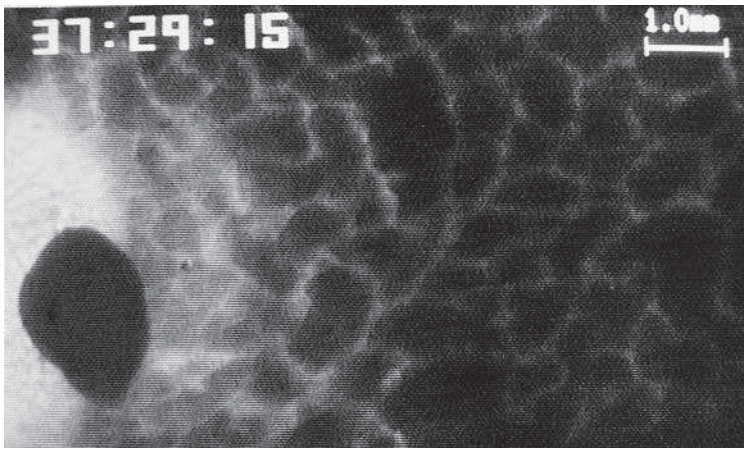

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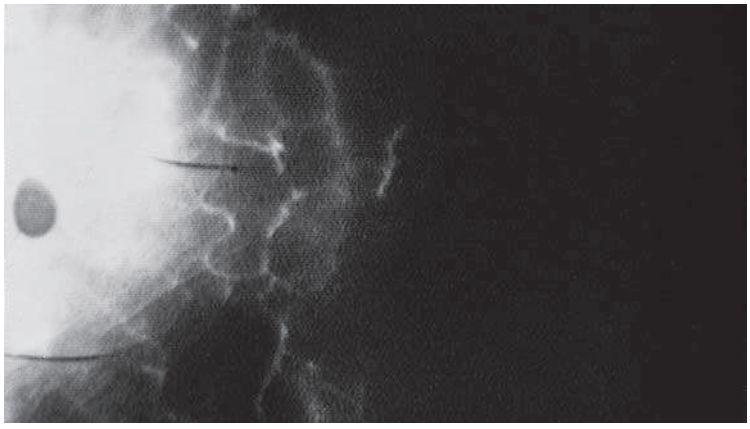

b

Fig. 12.**6** Fluorescence microlymphography.
a In a young patient with primary lymphedema an extensive network of microlymphatics fills from the dye deposit (left side of figure) after an intracutaneous injection of FITC–dextran 150 000 at the region of the medial malleolus.
b Young healthy control patient. The microlymphatic network is much less extensive (time point of maximal extension) since drainage to the deep collectors is not impaired.

Clinical Symptoms. Whereas secondary lymphedema usually commences proximally and extends distally (the upper leg is affected first and most seriously), it is typical for the primary form to take the opposite direction. In rare cases, with aplasia or hypoplasia of the pelvic and para-aortal lymph vessels, primary lymphedema may develop in the cranio-caudal direction.

Diagnosis. In addition to taking a thorough medical history, imaging techniques including ultrasound examination or, if necessary, CT or MRT scans are used to rule out pelvic or retroperitoneal tumors.

Complications. The most common complication of both primary and secondary lymphedema is erysipelas, which can be easily distinguished from superficial thrombophlebitis through local examination (a large hot and red area of skin) and through observation of the general symptoms (fever and chills). The protein-rich edema is evidently an ideal medium for pathogenic organisms (particularly *Streptococcus* and *Staphylococcus*). Less common complications include lymphatic fistulas and angioplastic sarcoma (Stewart–Treves syndrome), which is almost always fatal.

Lipedema

This condition is peculiar to women. Both legs become symetrically swollen with pads of fat. In contrast to lymphedema, the dorsum of the foot is not affected (Fig. 12.**4c**). The edema pits only slightly, or not at all, and is painful on pressure. It is often, but not always, accompanied by general obesity. The skin shows signs of peau d'orange ("cellulite").

Inflammatory Edema

Edema as a result of bacterial infection is characterized by the three classic symptoms: rubor, calor, and dolor (see Chapter 9). It must be kept in mind that, occasionally, the cause may be a tropical parasitic disease. The filarial worm Loa loa causes brief, sporadic recurrences of swelling of various parts of the body. The outlines of filariae can sometimes be seen directly beneath the skin. Eosinophilia, elevated levels of antibodies, the presence of filariae in the blood, and skin biopsy (Fig. 12.**7**) all contribute to the diagnosis.

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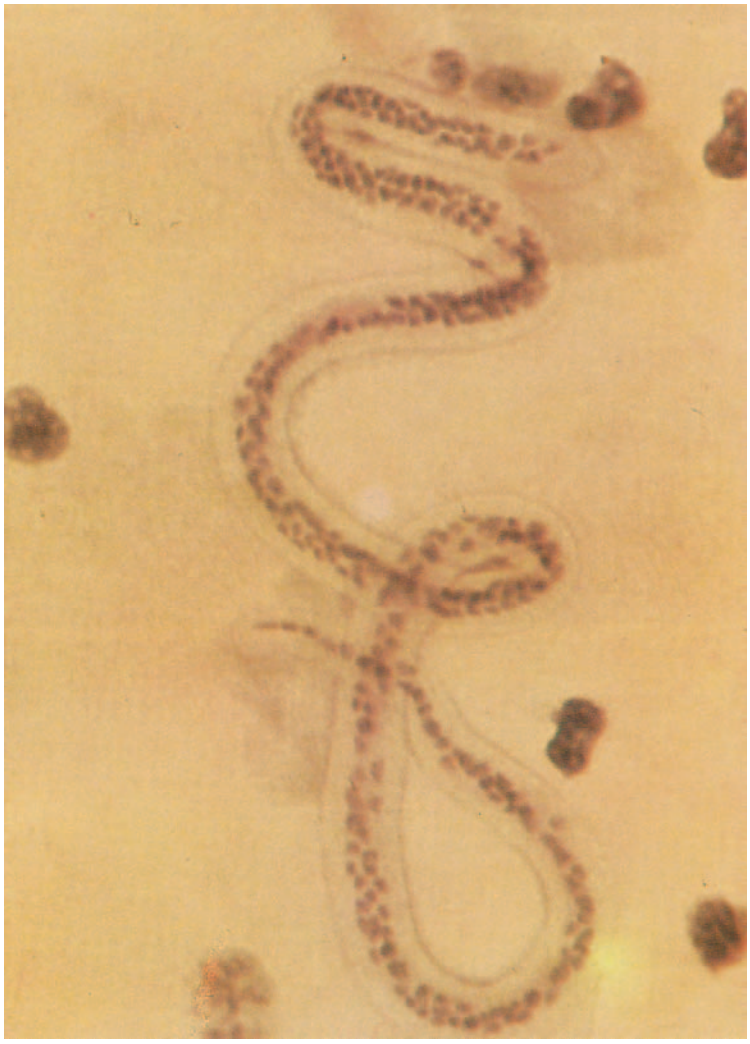

Fig. 12.**7** Microfilaria species *Wucheria bancrofti* on a blood smear. This species exhibits noctural periodicity. For detection blood should be drawn during the night.

During its edematous, preatropic phase, acrodermatitis chronica atrophicans may often be mistaken for other diseases, such as venous thrombosis, lymphedema, arthritis, or multiple arteriovenous fistulas (Fig. 12.**4d**). The illness is more easily diagnosed in the advanced stage, in which the skin characteristically becomes atropic and parchmentlike. The cause of the disease is an infection with *Borrelia burgdorferi*.

Congenital Angiodysplasia

The causes of edema in angiodysplasia include atypical varicose veins or angiomas, arteriovenous fistulas, and aplasia or hypoplasia of the lymph vessels. These are to be distinguished from soft tissue hypertrophy (Fig. 12.**4e**).

Urticaria and Angioedema

Clinical Symptoms. The characteristics of this distinctive form of edema are that it is transient (episodes lasting minutes or hours), starts suddenly in any part of the body (Fig. 12.**8**) and causes itching. If the cutis alone is affected, it is referred to as urticaria. If the subcutaneous layer and the mucuous membranes are affected, it is referred to as angioedema. The lips and eyelids are most commonly affected and it is, therefore, important not to confuse the diagnosis with Melkersson–Rosenthal syndrome (recurrent facial swelling, facial paresis, lingua plicata), the etiology of which is unknown. Angioedema of the upper respiratory tract may lead to life-threatening compression of the glottis. When the intestine is involved, colic and vomiting may be present.

➤ *In allergic edema (Quincke edema),* blood tests may show eosinophilia and raised IgE antibody levels immediately and/or at a subsequent time. Usually the cause can be identified. Nonsteroidal

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Fig. 12.**8** Quincke edema of the lower lip.

anti-inflammatory drugs, acetylsalicylic acid, ACE inhibitors, contrast dyes, blood products, and penicillin may trigger the development of allergic edema.

- *Drug-induced angioedema* may also be the result of a process induced by IgE, by circulating immune complexes or a direct activation of the complement pathway. Urticaria and angioedema may also be accompanied by cutaneous or systemic angiitis and paraproteinemia.
- *Hereditary angioedema ("angioneurotic" edema)* is a disturbance of the capillary permeability due to a congenital, autosomal dominantly inherited enzyme deficiency (C_1-esterase inhibitor). The disease manifests itself in distinctive attacks of edema occurring mainly in the extremities, the face, the laryngeal area (causing death by asphyxia in approximately one quarter of cases), and in the gastrointestinal tract. In addition to family history, it is essential to determine the C_1-esterase inhibitor level in order to obtain a definitive diagnosis. Acquired forms of C_1-esterase inhibitor deficiency occur in lymphoproliferative diseases and in systemic lupus erythematosus. In these cases, of course, there is no positive family history of the disease. In both the inherited and the acquired forms there are low levels of complement components.

Ischemic and Postischemic Edema

Both of these forms of edema may be attributable to an ischemic damage of the capillary walls. After revascularization of an obstructed artery, arterial pressure distal to the obstruction sharply increases, which affects the ischemically damaged peripheral microvascular network, resulting in transient postischemic edema due to increased microvascular permeability.

Edema in Sudeck Atrophy

This posttraumatic swelling involves persistent pain and is therefore dealt with in Chapter 9.

Local Edema Occurring at High Altitudes

Edema of the legs, backs of hands, and face can be a symptom of acute mountain sickness, which may occur at altitudes of more than 2500 meters above sea level. Edema appears after a latency of six to 12 hours (other symptoms include headache, nausea, vertigo, and insomnia). The symptoms usually disappear spontaneously if the patient remains at the same altitude. Climbing further, despite persistent symptoms, may result in serious cerebral or pulmonary edema.

Factitious Edema

The possibility of factitious edema must be considered in cases of unaccountable edema. Self compression with bandages can give rise to a pronounced swelling. Compression lines on the upper arm or thigh are signs that will aid diagnosis (Fig. 12.**4f**).

Edema of the hand is sometimes artificially induced by repeatedly slapping the back of the hand. It sometimes may be necessary to apply a plaster cast in order to protect the hand from further manipulation, to allow the edema to subside and thus confirm the suspected diagnosis.

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Hematological Symptoms

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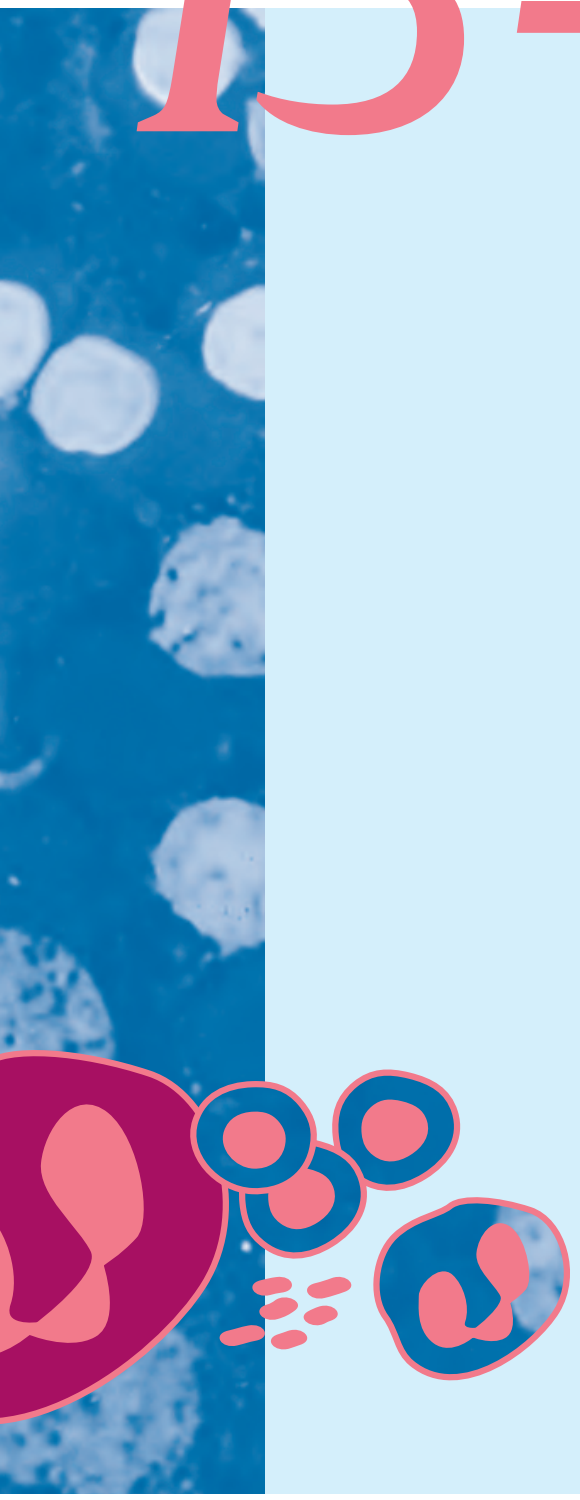

13 Anemia
P. E. Peghini, A. Knuth, and J. Fehr

14 Disorders of the Lymphatic System
U. Schanz, D. Jaeger, and J. Fehr

15 Bleeding Diathesis and Thrombophilic Diathesis
E. Baechli and T. Bombeli

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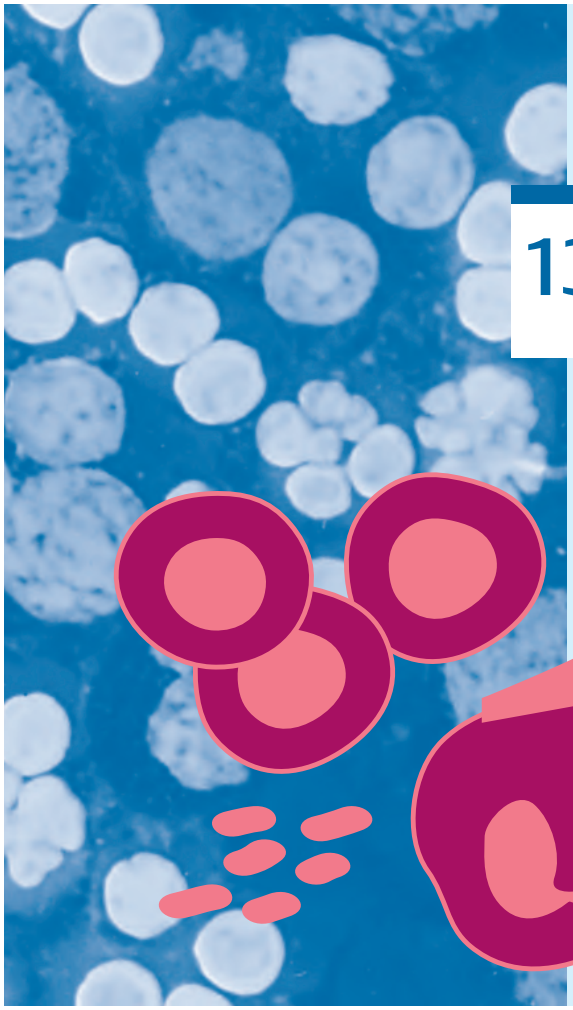

13 Anemia

P. E. Peghini, A. Knuth, and J. Fehr

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Definitions and Laboratory Techniques

The oxygen transport capacity of the blood is dependent on the hemoglobin concentration. Therefore, this value represents the most useful measurement for the definition of anemia. Historically the lower normal value, as published in many hematology text books, was set somewhat higher than the value determined in the large NHANES trial conducted in the USA. Subsequently, many laboratories have corrected the lower limit of the normal range. At our institution we use a lower limit of normal value of 11.7 g/dL for women and 13.5 g/dL for men (Tab. 13.**1**). By definition, anemia is present if the hemoglobin concentration is below the lower limit of the normal range. In addition, the hematocrit reading (packed-cell volume) and erythrocyte (RBC) number per microliter are routinely determined. Normal ranges have been defined for these measurements. Yet, their importance lies rather in calculation of the following indices:

Erythrocyte Indices

- Mean corpuscular volume (MCV):

$$\text{MCV (fL)} = \frac{\text{Hematocrit (\%)} \times 10}{\text{erythrocyte count } (10^6/\text{mm}^3)}$$

Normal range = 80–100 fL

- Mean corpuscular hemoglobin (MCH):

$$\text{MCH (pg)} = \frac{\text{hemoglobin (g/dL)} \times 10}{\text{erythrocyte count } (10^6/\text{mm}^3)}$$

Normal range = 26–34 pg

- Mean corpuscular hemoglobin concentration (MCHC):

$$\text{MCHC (g/dL)} = \frac{\text{hemoglobin (g/dL)} \times 100}{\text{hematocrit (\%)}}$$

Normal range = 32–36 g/dL Ec

These values are calculated automatically by modern hematology analyzers. Besides these calculated values, certain flow cytometric devices, which analyze laser-light scattering properties of cells, determine RBC indices by direct measurement of single cells. This makes it possible to display the distribution of these values in the sample and allows the quantification of subpopulations of cells which lie beyond the limits of the normal range (e. g., hypochromic RBC in %). This significantly increases the sensitivity for the detection of nonnormocytic and nonnormochronic erythrocytes.

Reticulocytes. The number of reticulocytes is important for the classification of anemia and for the selection of further diagnostic steps. Therefore, it should be determined early in the diagnostic work-up of anemia. Reticulocytes represent the young form of erythrocytes that have recently entered the peripheral blood. Their fraction is a measure of the production of new cells by the bone marrow.

The reticular substance can be visualized by brilliant cresyl blue stain. The reticular substance is composed of RNA and mitochondria which are present in the erythroblast. After the reticulocyte enters the blood, it will degrade the reticular substance within one to two days. Microscopically determined reticulocyte values are dependent upon the clinician. Modern blood cell analyzers can count the reticulocytes automatically after staining the reticular substance with fluorescent dyes. This procedure circumvents the clinician–dependent variability.

RBC Creatine. Another way to measure the bone marrow capacity is to determine the creatine content of erythrocytes. The mean erythrocytic creatine concentration is expressed in $\mu g/10^{10}$ erythrocytes. Because this concentration decreases continuously over the lifetime of an erythrocyte, its mean is a measure of the average age of the entire erythrocyte population. This value increases with increased turnover.

Table 13.**1** Normal values

Test	Units	Men	Women
Hemoglobin	g/dL	13.5–17.4	11.7–15.3
Hematocrit reading	%	40–53	34–42
Erythrocytes (RBC)	$10^6/\mu L$	4.4–5.5	4.0–5.0
Reticulocytes	‰	4–25	4–25
Reticulocytes	$10^3/\mu L$	17–125	17–125
MCV	fL	80–100	80–100
MCH	pg	26–34	26–34
MCHC	g/dL	32–36	32–36
Microcytes	%	0–1.5	0–1.5
Macrocytes	%	0–1.5	0–1.5
Hypochromic RBC	%	0–1.5	0–1.5
Hyperchromic RBC	%	0–1.5	0–1.5
Ferritin	ng/mL	15–300	15–300
RBC creatine	$\mu g/10^{10}$ RBC	37–93	37–93
Haptoglobin	mg/dL	40–190	40–190
Bilirubin	µmol/L	< 25	< 25
Lactate dehydrogenase	U/L	150–420	150–420
C-reactive protein	mg/L	< 3	< 3

Fig. 13.**1 a–d** Characteristic morphologic findings in peripheral blood.
a Normal blood
b Hypochromic anemia in iron deficiency with anulocytes.
c Spherocytosis with small, spheric erythrocytes, lacking central pallor. ▷
d Macrocytosis in ethylic liver cirrhosis, rare targetlike cells.

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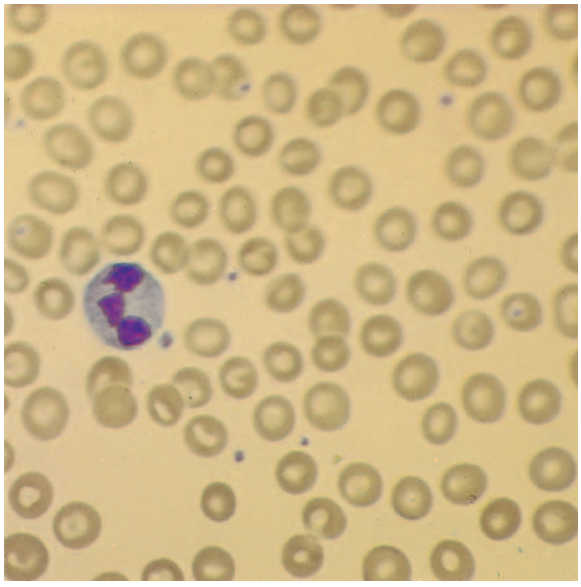
Classification of Anemia

Anemia can be classified according to two different systems. One system is based primarily on morphology (Fig. 13.**1**) and the erythrocyte indices. The other is determined by pathophysiologic considerations. In everyday practice, the erythrocyte indices are always available at the beginning of a diagnostic work-up, therefore we will start with the first classification system and will consider the mechanisms responsible for the anemia only in the second step.

We recommend determining the reticulocyte number early in the diagnostic work-up. In this way, a hemolytic anemia can easily be identified. Because of this practical aspect, we will divide hemolytic anemias that are normochromic and normocytic, or hypochromic and macrocytic into a separate group from other anemias.

The mean corpuscular hemoglobin concentration (MCHC), not the mean corpuscular hemoglobin content (MCH), subdivides anemias into hypochromic, normochromic, and hyperchromic types. The mean corpuscular volume (MCV) subdivides anemias into microcytic, normocytic, and macrocytic types.



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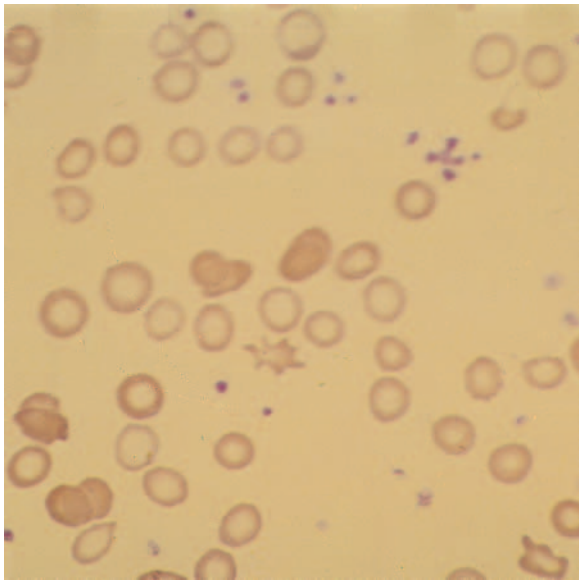

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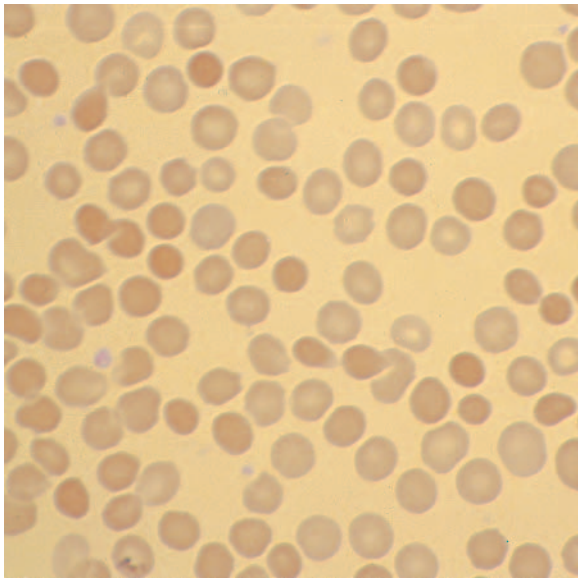

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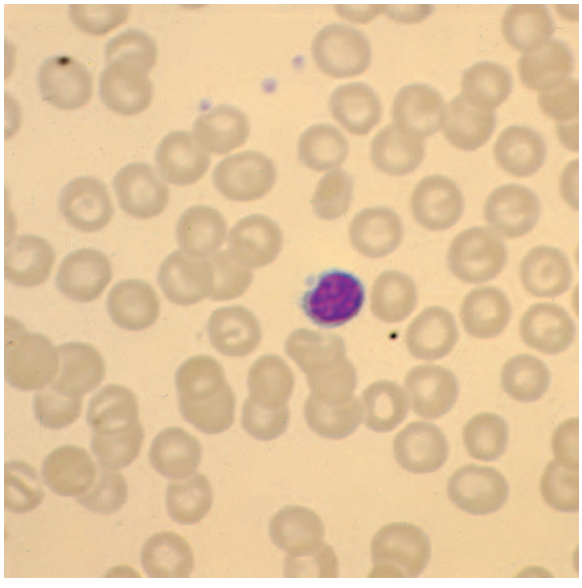

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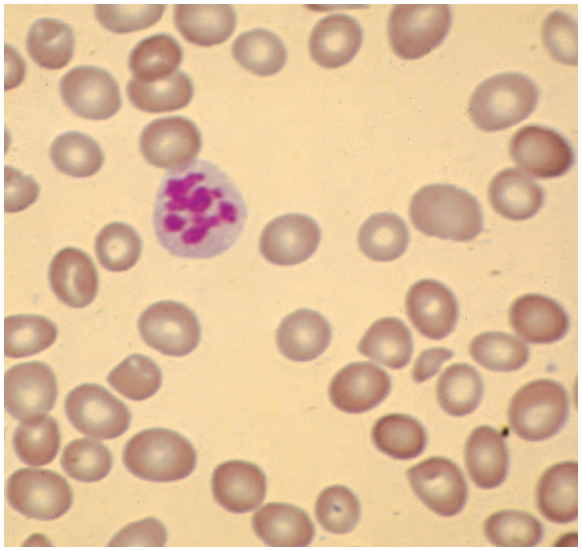

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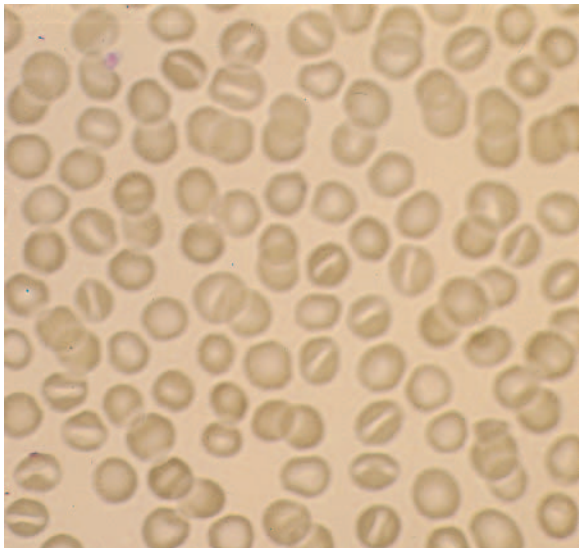

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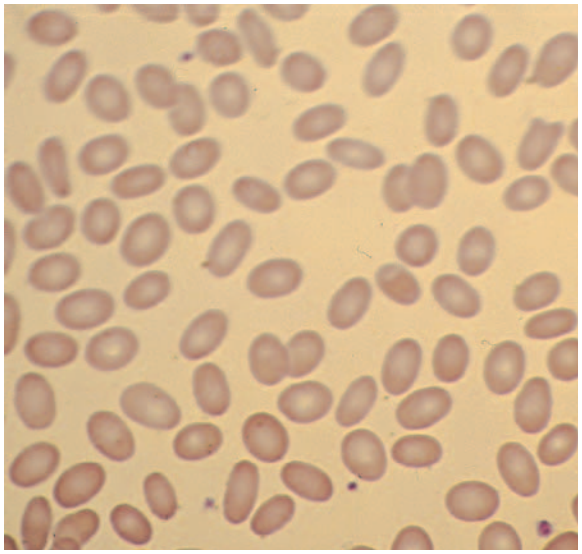

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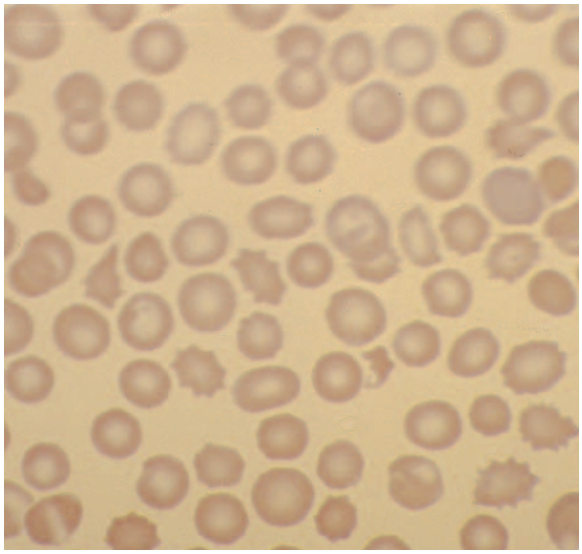

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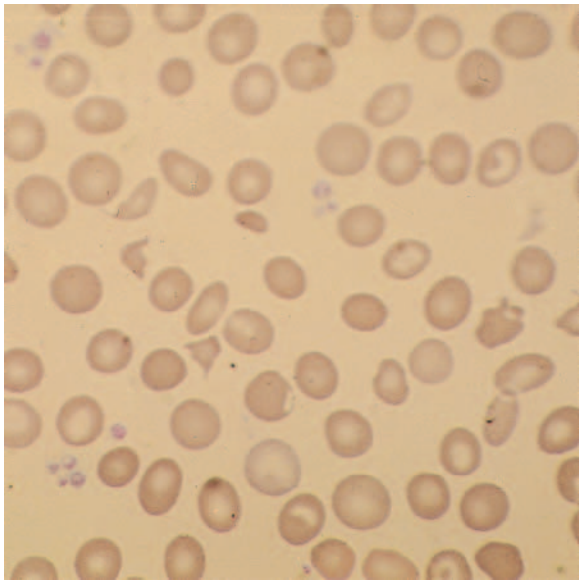

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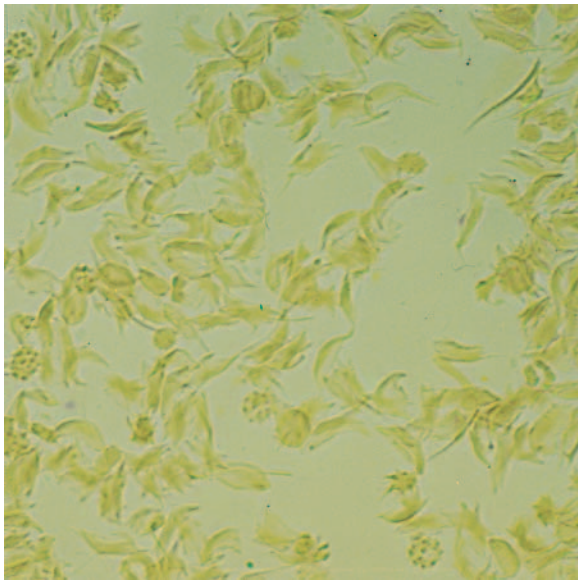

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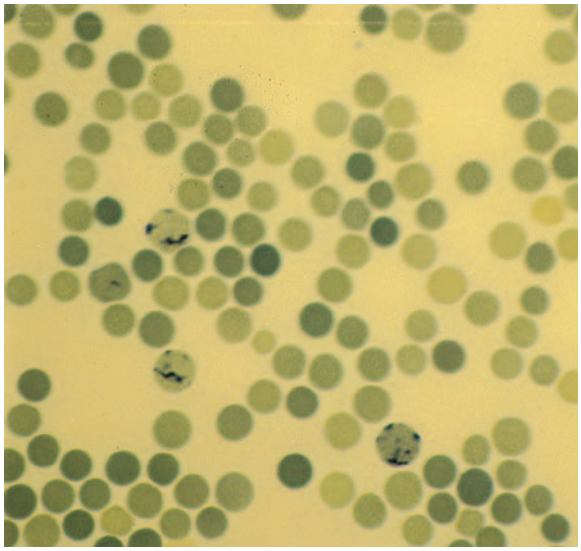

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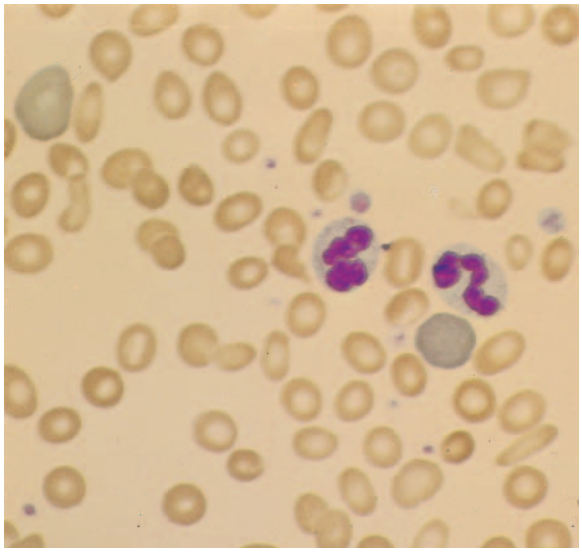

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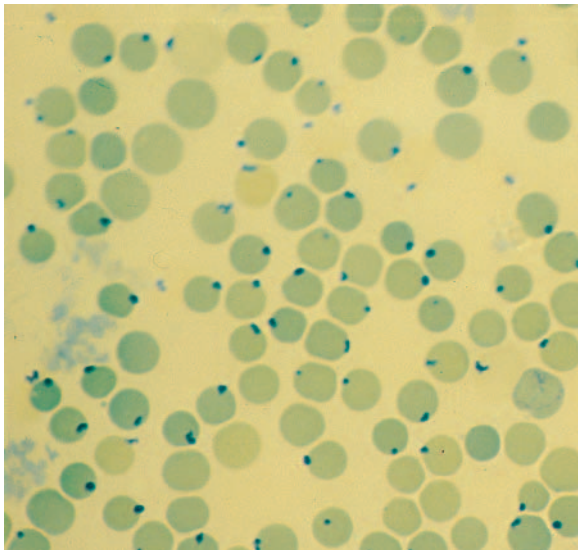

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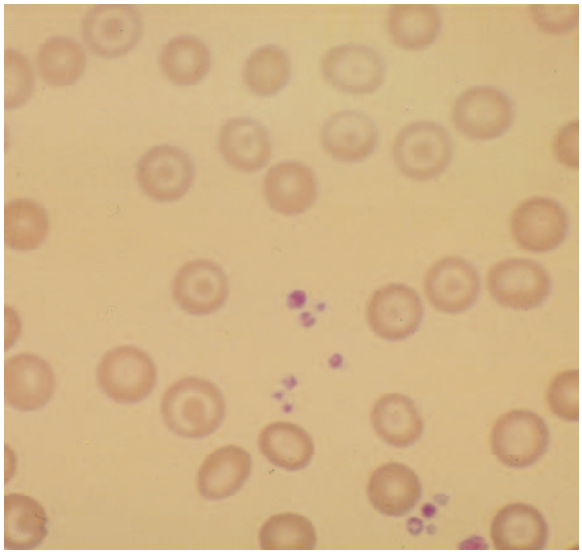

n

Fig. 13.**1 e–n**

e Megalocytosis in pernicious anemia with typical, large elliptoid cells and a hypersegmented neutrophil.
f Stomatocytosis
g Ovalocytosis
h Acanthocytes in liver cirrhosis or uremia.
i Fragmentocytes in disseminated, intravascular coagulation.
j Sickle cells (unstained cells under oxygen deprivation)
k Reticulocytes (brilliant cresyl-blue stain)
l Polychromatic erythrocytes (May–Grünwald Giemsa stain) correspond to a reticulocyte containing RNA.
m Heinz bodies (brilliant cresyl-blue stain), e. g., in reduced, oxidative resistance or unstable hemoglobin variations.
n Target cells in thalassemia.

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13.1 Microcytic Hypochromic Anemia

Table 13.**2** Pathogenetic classification of microcytic, hypochromic anemia

Disoders of iron metabolism
- Iron deficiency anemia
- Anemia of chronic disease
- Rare: atransferrinemia, Shahidi–Nathan–Diamond syndrome, familial microcytic anemia with decreased iron absorption and iron metabolism, antibodies to transferring receptor, aluminum intoxication, congenital aceruloplasminemia

Disorders of globin synthesis
- Thalassemia
- Hemoglobin E
- Hemoglobin C

Disorders of porphyrin and heme synthesis: sideroblastic anemia
- Hereditary
  - coproporphyrinogen oxidase deficiency
  - heme synthetase deficiency (ferrochelatase)
  - diminished activity of aminolevulinic acid synthase activity
- Vitamin B_6 deficiency
- Disorders of vitamin B_6 metabolism caused by medications and toxins
  - isoniazide, pyrazinamide, chloramphenicol
  - lead intoxication
- Copper deficiency

This group is defined by an MCV and MCHC below the normal range or an increased microcytic and hypochromic subpopulation. These changes result from a decreased production of hemoglobin. For a normal biosynthesis of hemoglobin, the availability of the three components, iron, protoporphyrin, which together comprise the heme molecule, and globin protein is required. The lack of any of these three components categorizes the resulting microcytic hypochromic anemia into three classes (Tab. 13.**2**).

Iron Deficiency Anemia

Iron Metabolism

The daily iron cycle is depicted in Fig. 13.**2**. The human body contains 3–6 g (35–50 mg/kg) of iron. Two-thirds of this amount (2–4 g), circulate bound to hemoglobin. One-third (0.5–1.5 g) is stored as ferritin and hemosiderin in the reticuloendothelial system (RES) in the spleen, the bone marrow, and the liver. The liver also stores iron in hepatocytes. Hemosiderin can be detected by Prussian-blue stain. About 120–150 mg of iron are located in myoglobin. Although vital to many other tissues (e. g., respiratory chain), the iron in other locations comprises only a few milligrams.

Iron reaching the plasma, after acquisition from food or released from stores in macrophages, is bound to transferrin. The transferrin concentration in plasma correlates with the total iron binding capacity (TIBC = serum iron plus unsaturated iron binding capacity). It can also be measured directly by immunologic methods in mg/dL. Normally one-third of the TIBC is saturated.

Three to four milligrams of iron circulate in plasma. The bone marrow synthesizes about 6 g of hemoglobin daily, which requires about 20 mg of iron. After the breakdown of hemoglobin, transferrin transports the free iron to the RES, where it is stored by macrophages, until it is required again for the synthesis of hemoglobin. Only minute amounts of iron are absorbed from the plasma by nonerythropoietic cells.

Iron Requirement. Daily iron requirement amounts to about 1 mg, and 1–3 mg in menstruating women. The daily loss of iron (skin and intestine) is about 1 mg. A normal diet contains 10–15 mg of iron on average daily. Only 10–20 % of this amount is absorbed in the duodenum and jejunum.

A negative iron balance results from:
- increased loss of iron
- increased iron requirements
- decreased iron stores
- insufficient availability of iron
- any combination of these factors.

Iron resorption. Iron resorption depends on various factors:
- It is increased by: ferrous iron Fe^{2+}, inorganic iron, acids (HCl), vitamin C, iron deficiency, increased erythropoiesis, pregnancy, and primary hemochromatosis.
- It is decreased by: ferric iron Fe^{3+}, organic iron, alkaline pH (antacids), precipitating substances, iron overload, decreased erythropoiesis, infections, and chelating substances (desferoxamine, deferiprone).

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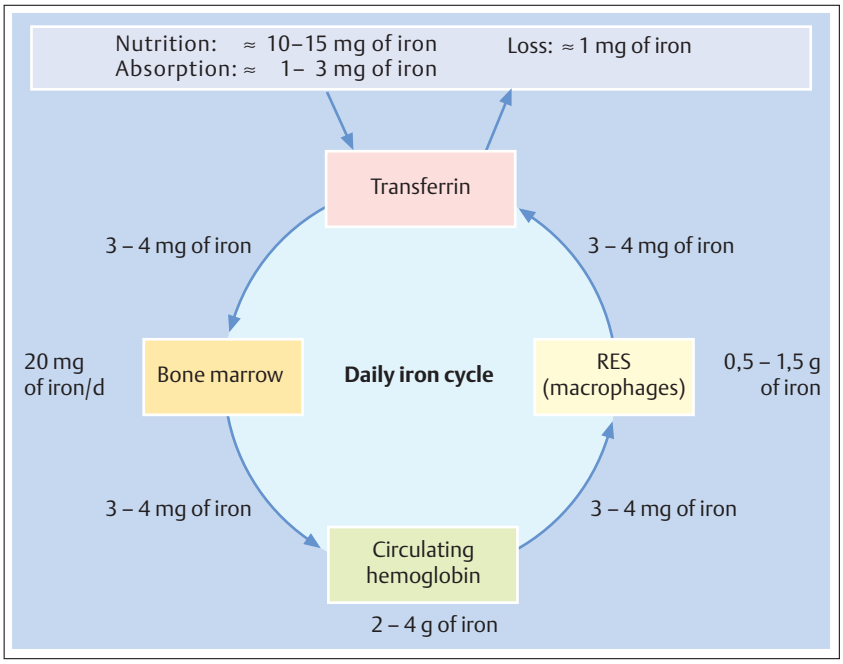

Fig. 13.**2** Daily iron cycle

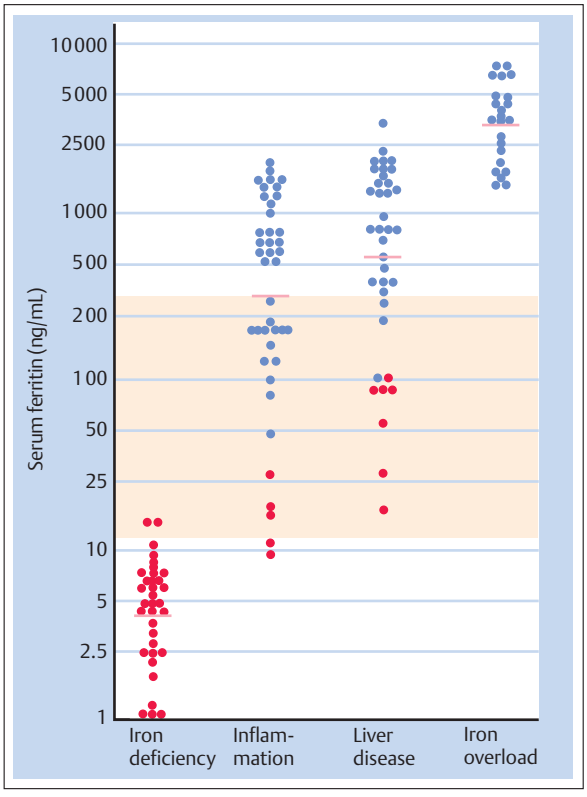

Fig. 13.**3** Values for serum ferritin in uncomplicated iron deficiency anemia, inflammation, liver disease, and iron overload. Horizontal line: mean for each group. Red circles, patients with iron deficiency; blue circles, patients without iron deficiency. The normal range is shaded.

Diagnosis. Erythrocytes in a blood smear are small and contain very little hemoglobin, so-called anulocytes (Fig. 13.**1b**). Iron is stored in the high molecular weight complex ferritin, in macrophages, and in the liver. An iron deficiency anemia only results when all iron stores are exhausted. Therefore, the serum ferritin level, which shows a particularly close quantitative correlation with whole body ferritin and whole body iron levels, is by far the most important parameter in the diagnosis of iron deficiency anemia. Serum ferritin values below the normal range are absolutely specific for iron deficiency. Values at the lower end of the normal range do not exclude iron deficiency, because inflammation, liver damage, and hemolysis can cause increased liberation of ferritin (Fig. 13.**3**). Therefore, every determination of serum ferritin must be accompanied by a measurement of C-reactive protein (CRP). If hypochromia and microcytosis are present, in spite of normal serum ferritin and CRP levels, then transaminases and reticulocyte levels must be determined. Still, in most instances including inflammation, a serum ferritin value > 100 ng/mL excludes iron deficiency. If the aforementioned conditions with spuriously elevated ferritin are considered, then the measurement of serum iron and transferrin levels is unnecessary, as these parameters are also influenced by the same confounding factors. For the rare cases that still remain unclear, the determination of iron in the bone marrow by Prussian-blue staining remains the "gold standard" for the assessment of iron stores (Fig. 13.**4**).

As mentioned above, the proportion of hypochromic and microcytic erythrocytes (in percent) is significantly more sensitive for the diagnosis of hypochromasia and microcytosis than MCH and MCV. Typically in iron deficiency, the fraction of hypochromic erythrocytes is higher than that of microcytes. In contrast, the ratio is

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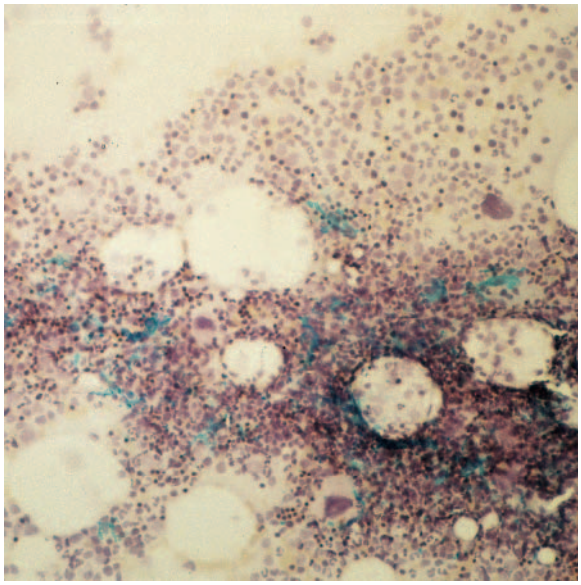
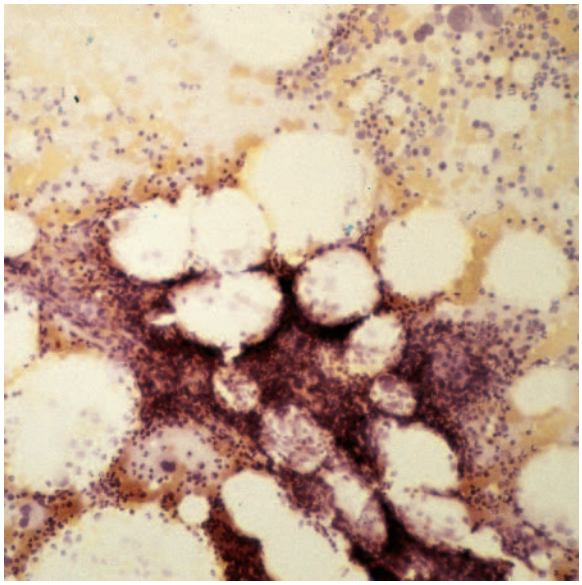


a



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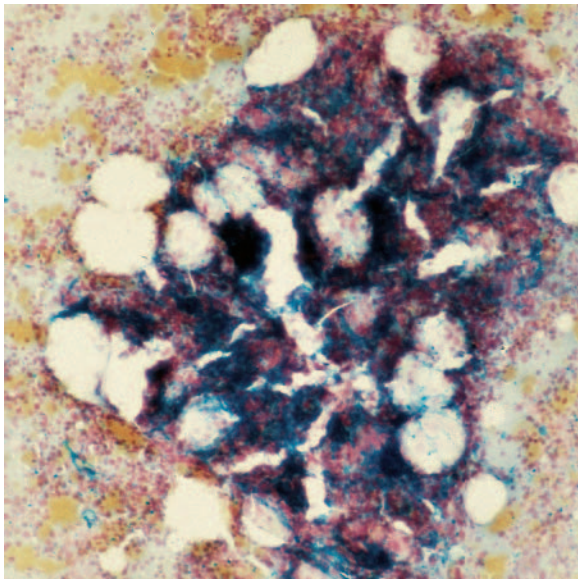

c

Fig. 13.4 Prussian-blue stain of a bone-marrow smear.
a Normal interstitial iron.
b Absent interstitial iron (iron deficiency anemia).
c Increased interstitial iron (sideroblastic anemia and post-transfusional hemosiderosis).

reversed in disturbances of globin synthesis of the thalassemia type. The number of reticulocytes is decreased or normal, but always insufficient for the degree of anemia.

Etiology. By far the most common cause of iron deficiency is chronic blood loss, for which the most frequently encountered reasons are hypermenorrhea and occult gastrointestinal bleeding. Iron deficiency should be suspected with excessive blood loss during menstruation. For example, if the blood flow can not be controlled with tampons alone, more than 12 pads per menstruation, or four pads per day are used, clots larger than 2 cm are observed or persist beyond the first day, or the period lasts for more than seven days. In case of iron deficiency without any evident source of bleeding, an endoscopic investigation of the gastrointestinal tract in search of malignancy is indicated. This is also true for premenopausal women, if hypermenorrhea is not clearly present.

Other possibilities of chronic blood loss are repetitive epistaxis, blood loss with intravenous drug abuse, especially if intra-arterial injections are also performed, frequent blood donations, hematuria, e. g., with carcinoma of the bladder, hemoglobinuria, and rarely, factitious anemia.

Iron deficiency in patients on dialysis results from blood loss associated with the dialysis process, frequent diagnostic phlebotomies, and disturbed platelet function due to uremia, with consecutive small bleedings. Also aluminum hydroxide, which is used to control hyperphosphatemia, leads to malabsorption of iron.

Dietetic iron deficiency is seen in vegetarians, because meat is not only rich in iron but, in addition, it also enhances iron absorption in the gut.

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Gastric acid also enhances iron absorption. Achlorhydria in chronic atrophic gastritis, after gastrectomy, or vagotomy leads to malabsorption. Antacid drugs usually do not induce iron deficiency. Iron absorption takes place mainly in the jejunum. Therefore, it is diminished after bypass operations e. g., Billroth II or Y–Roux. Gluten-sensitive enteropathy and tropical sprue can induce iron deficiency. The increased iron requirement during pregnancy, lactation, and growth can all induce or aggravate iron deficiency.

Tab. 13.**3** summarizes the causes of iron deficiency anemia.

Clinical Findings. Typical symptoms of iron deficiency are:

- pallor
- fatigue, irritability
- headache
- cold intolerance
- atrophy of the lingual mucosa (Fig. 13.**5**)
- cheilosis (angular stomatitis) (Fig. 13.**6**)
- dysphagia (Plummer–Vinson syndrome)
- bristly hair and brittle fingernails.

Fig. 13.**5** Atrophic tongue in iron deficiency anemia.

Calculation of Sufficient Iron Substitution

Intravenous Substitution. For an increase in hemoglobin of 1 g/dL, 200 mg of iron are necessary. Storage iron accounts for an additional 1000 mg.

- The amount of elementary iron to be supplemented is: (target value hemoglobin − actual hemoglobin [g/dL]) × 200 mg + 1000 mg

This amount is slowly injected intravenously in the form of 200 mg doses of iron sucrose, with the frequency being once per week (maximally every two days).

Oral Supplementation. The calculation of the required total dose is the same as for the intravenous application. Because only 10–20 % of the oral iron will be absorbed, the total dose must be multiplied by a factor of five to 10. One should aim at a daily dose of 200 mg elementary iron. Lower initial doses, which can be increased subsequently, reduce the frequency of gastrointestinal side effects, and thus improve compliance. The resulting duration of the administration is usually in the range of two to three months.

To monitor the success of the therapy, the serum ferritin level is determined. This should not be done while iron supplementation is still ongoing, because the test will give a value that is falsely elevated. Instead one should wait for a month after completing the supplementation before measuring ferritin.

Anemia of Chronic Disease

Mild to moderate anemia is often encountered in patients with infectious, inflammatory, or neoplastic diseases which last more than one to two months. Here, we abstain from listing the vast variety of possible underlying diseases. In particular, inflammatory diseases of the connective tissues and joints, and tumors tend to induce this type of anemia. When tumors are the inducing agent, anemia develops independently from bone marrow infiltration. The term anemia of chronic disease is somewhat problematic, because bone marrow infiltration, blood loss, hemolysis, renal insufficiency, liver diseases, and endocrine diseases, although also chronic, are not what is meant. The principle pathogenic event in this type of anemia is inflammation, accompanied by elevation of C-reactive protein (CRP), triggered by an underlying disease. Therefore, anemia of inflammation would be more appropriate.

Lack of an elevated CRP casts doubt on this diagnosis, in which case other causes for the anemia, such as bone marrow infiltration, should be considered.

Laboratory Findings. Erythrocyte indices are normal or slightly hypochromic and microcytic. Therefore, the differentiation of iron deficiency anemia from an iron deficiency accompanying a chronic inflammatory disease, becomes difficult. The serum ferritin, being an acute phase protein, tends to increase in patients with

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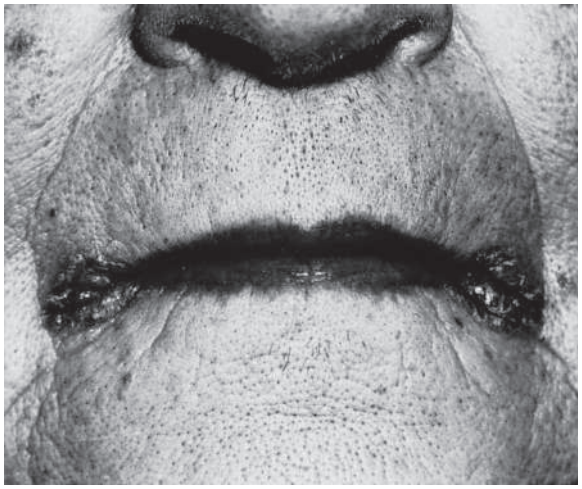

Fig. 13.**6** Cheilosis in iron deficiency.

Table 13.**3** Causes of iron deficiency anemia

Blood loss
- Gastrointestinal bleeding
  - hemorrhoids
  - angiodysplasias of the colon
  - hereditary, hemorrhagic, teleangiectasia syndrome (Osler–Weber–Rendu syndrome)
  - peptic ulcer
  - nonsteroidal, antiinflammatory drugs
  - oral anticoagulation
  - hiatal hernia
  - Meckel diverticulum
  - diverticulosis of the colon
  - intestinal polyps
  - carcinoma
  - inflammatory bowel disease
  - hookworm: *Necator americanus*, *Ancylostoma duodenale*
  - *Schistosoma mansoni*, *Schistosoma hematobium* (the latter causes blood loss via urine)
  - trichuris
- Menstruation
- Frequent, blood donations
- Erythrocyturia: bladder neoplasm
- Hemoglobinuria
  - paroxysmal, nocturnal hemoglobinuria
  - erythrocyte fragmentation in prosthetic heart valves
- Factitious anemia
- Intravenous and intra-arterial drug abuse
- Hemodialysis
- Nosocomial blood loss due to frequent venisection

Diet

Malabsorption
- Achlorhydria
- Chronic, atrophic gastritis
  - gastric resection and bypass
  - vagotomy
  - intestinal bypass operations
- Celiac disease (= nontropical sprue)
- Tropical sprue

Increased iron requirements
- Pregnancy and lactation
- Growth

inflammation. In a study at our institution, serum ferritin values were compared with the "gold standard" bone marrow iron stains. All patients with a serum ferritin value $< 30–40\ \mu g/L$ had iron deficiency. A serum ferritin value $> 100\ \mu g/L$ and elevated inflammatory markers (such as CRP) excluded iron deficiency. Values in between were not diagnostic. As a discriminative parameter for such situations, the serum transferrin level has been proposed, which tends to be elevated in iron deficiency anemia and decreased in inflammation. In our experience, this strategy is not reliable, especially in cases where iron deficiency accompanies inflammation. The same is true for soluble transferrin receptor levels. Thus, in unclear situations, the answer to the question as to whether iron deficiency is involved in a case of anemia or not, can be provided only by an intravenous iron trial or by a Prussian-blue stained bone marrow specimen.

Pathogenesis. Anemia due to inflammation probably ensues from tumor necrosis factor (TNF)- and interleukin-6-mediated activation of macrophages. Macrophages increase their production of ferritin, which binds iron and traps it in the macrophage (the so-called "iron block"). In addition, erythropoietin excretion is diminished. The latter fact most probably explains why this form of anemia sometimes responds to injections of erythropoietin. It should, however, be mentioned at this point that, in such situations, blood transfusions (as necessary) are less costly and more efficient.

Other Disorders of Iron Metabolism

A number of disorders of iron metabolism produce the clinical picture of iron deficiency, due to a disturbed iron utilization. Atransferrinemia is an autosomally recessive-inherited disease that manifests in childhood. It is extremely rare, as are most of the syndromes listed in Tab. 13.**2**. A condition that used to be diagnosed quite frequently is microcytic anemia triggered by aluminum intoxication, which in turn was caused by contaminated water used for dialysis in chronic renal failure. In addition, such patients were treated with phosphate binders containing aluminum. Measures have since been introduced to prevent this complication.

Disorders of Hemoglobin Synthesis (Thalassemia)

Clinical Findings. Also in thalassemia, quantitatively reduced hemoglobin synthesis leads to microcytosis and hypochromia, just as in iron deficiency anemia. Here, microcytosis outweighs hypochromia, as opposed to the case in iron deficiency anemia. This estimation is easier to perform by means of analysis of erythrocyte subpopulations, than with the mean values MCV and

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MCHC. The proportion of microcytic cells in percent is higher than that of hypochromic cells. In addition, despite anemia, the number of erythrocytes is normal or even increased. The blood smear frequently, although in thalassemia minor inconsistently, shows typical target cells (Fig. 13.**1n**). Because thalassemia major always manifests hemolysis and ineffective erythropoiesis, expansion of the hematopoietic marrow ensues. This can be seen on a radiograph as the so-called "hair on end" appearance of the skull (Fig. 13.**7**). The diagnosis of β-thalassemia is performed by hemoglobin electrophoresis, or currently by high performance liquid chromatography (HPLC). In β-thalassemia minor, hemoglobin Hb A_2 is increased. In β-thalassemia major, Hb F and Hb A_2 are increased, with various amounts of Hb A_1 present, depending on the exact genetic mutation in the β-globin genes. In contrast, α-thalassemia exhibits normal fractions of Hb A_2. Therefore, for this diagnosis molecular biologic investigations are necessary.

Epidemiology. Thalassemia occurs in an area including the Mediterranean basin, Central Africa, the Middle East, the Indian subcontinent, and Southeast Asia. These areas correspond more or less to the malaria belt. Diagnosing minor forms of thalassemia is important for two reasons. Firstly, iatrogenic iron overloading due to a false diagnosis of iron deficiency must be prevented, and secondly, major forms of thalassemia can be prevented by genetic counseling and/or family planning. For the same reasons, the family of a patient diagnosed with thalassemia should also be screened by blood count.

Other Hemoglobin Defects. In most of the qualitative hemoglobin defects, the synthesis is quantitatively normal. Therefore no microcytosis ensues. Exceptions to this rule exist, e. g., Hb Lepore, Hb E, and Hb C. Hypochromia without microcytosis is observed in cases of unstable hemoglobin, because the erythrocyte loses the heme molecule after denaturation of the unstable Hb (see Hemolytic Anemia, p. 412).

Sideroachrestic Anemia

Clinical Findings. A disturbed synthesis of the heme molecule leads to accumulation of iron in mitochondria of erythroblasts. These are visible in the Prussian-blue staining of the bone-marrow smear, producing typical, ringed sideroblasts (Fig. 13.**8**).

Etiologically a number of congenital enzyme deficiencies have been described. Ringed sideroblasts can be seen in alcohol abuse, where they are probably the consequence of the toxic or vitamin B_6 inhibitory action of alcohol. The tuberculostatic drug isoniazide, and probably also pyrazinamide and cycloserine, interfere with vitamin B_6 metabolism, resulting in sideroachrestosis. Also during treatment with chloramphenicol, anemia with ringed sideroblasts has been observed. In rare cases, a sideroachrestic anemia has been observed due to copper deficiency after gastrectomy or in parenteral nutrition over an extended time.

Sideroachrestosis also occurs in a fraction of myelodysplastic syndromes (see Macrocytic Normochromic Anemia, p. 406).

Fig. 13.**7** "Hair on end" appearance of the skull in thalassemia major.

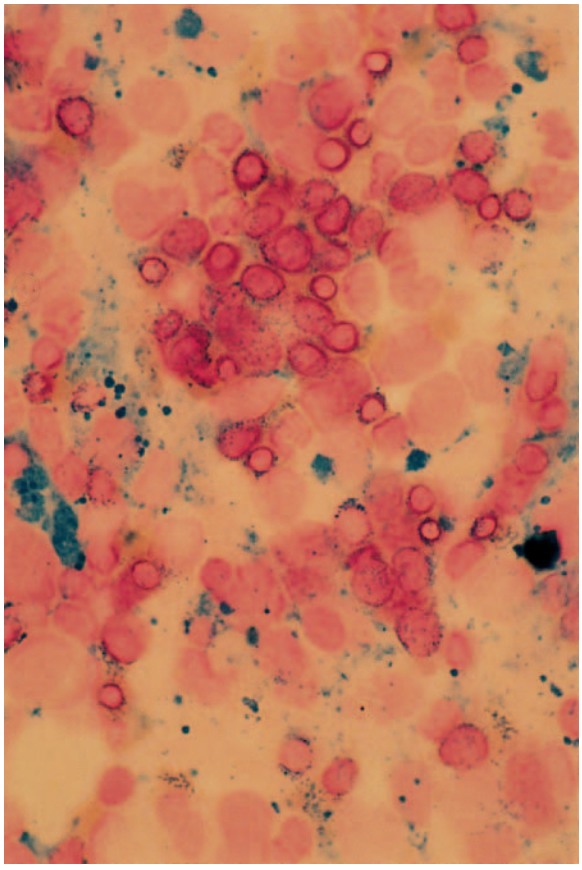

Fig. 13.**8** Ringed siderblasts in sideroachrestic anemia (bone marrow).

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Diagnostic Strategy in Microcytic Hypochromic Anemia

1. Determine serum ferritin and CRP levels.
2. Low serum ferritin is always diagnostic for iron deficiency.
3. If serum ferritin is in the normal range, but < 100 μg/L and CRP is elevated, iron deficiency is still possible. The diagnosis must be obtained by an intravenous iron trial or by bone marrow aspiration followed by Prussian-blue staining.
4. Once iron deficiency is excluded, then anemia of chronic disease (anemia of inflammation) is present if the CRP is elevated and a causative underlying disease can be diagnosed.
5. If CRP and serum ferritin are normal, a hemoglobin electrophoresis (or HPLC) must be performed.
6. If no hemoglobinopathy is found, then molecular biology techniques must be employed to detect α-thalassemia.
7. If the result is negative, then bone marrow examination for sideroachrestosis follows.

13.2 Macrocytic Normochromic Anemia

Definition. Macrocytic anemia is characterized by an increase in the MCV. The hemoglobin content increases proportionally to the erythrocyte volume. Thus, the MCHC remains constant. Therefore, as a rule, macrocytic anemia is normochromic. In a blood smear, very often a loss of the central pallor may be observed. This is due to an increased thickness of the erythrocyte and has led some authors to describe this type of anemia as macrocytic hyperchromic, which in a strict sense is incorrect.

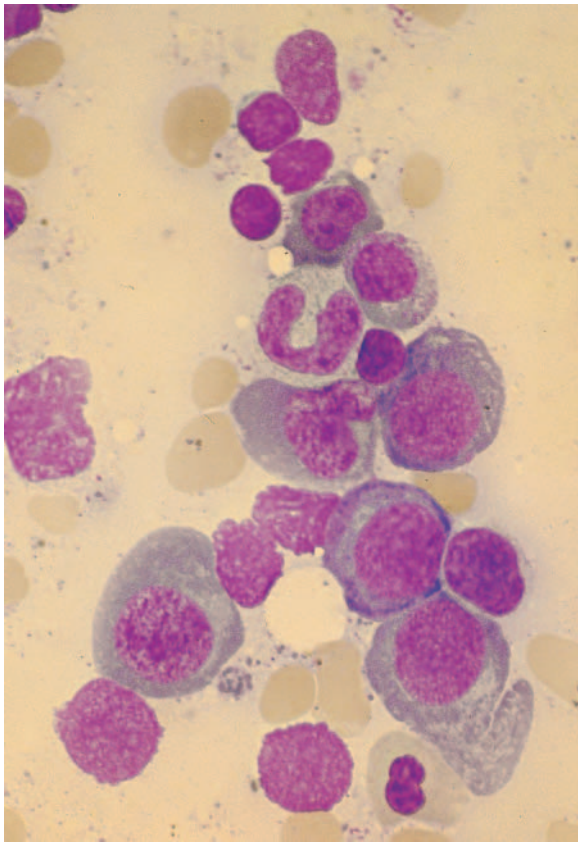

Fig. 13.**9** Megaloblastic bone marrow with markedly increased erythropoiesis.

Classification. Based on pathophysiological considerations, macrocytic anemias are divided into a main group, which is caused by defective synthesis of DNA and that therefore displays megaloblastic precursors of erythropoiesis in the bone marrow (Fig. 13.**9**), and a heterogeneous, remaining group (Tab. 13.**4**).

Most often, the disturbance in DNA synthesis is caused by a deficiency of folic acid and/or vitamin B_{12}, or by toxic effects of a drug. In both cases, diminished cell division, combined with conserved production of plasma proteins, results in larger cells. Only rarely is it caused by defects in the genes coding for enzymes involved in DNA synthesis.

Pernicious Anemia

Pathogenesis. Pernicious anemia is the classic presentation of vitamin B_{12} deficiency. Lack of intrinsic factor, a glycoprotein that is secreted by the gastric mucosa and that is necessary for absorption of vitamin B_{12} in the terminal ileum, is responsible for pernicious anemia. Hereditary intrinsic factor deficiency is very rare. It follows an autosomally recessive pattern of inheritance and manifests early in childhood. Consanguinity of the parents is common. Intrinsic factor deficiency in the adult form of pernicious anemia is caused by atrophic gastritis.

> Although in a high percentage of the adult population, signs of atrophic gastritis can be found upon biopsy, only a small proportion develops pernicious anemia.

Clinical Findings. The classic triad is weakness, burning tongue, and paresthesia. The lingual mucosa is atrophic (Fig. 13.**10**) and the sense of taste becomes weak. These clinical symptoms are known as Hunter glossitis. In addition, patients complain of loss of appetite, weight loss, vomiting, flatulence, abdominal discomfort, and fever. In the nervous system, demyelination with consequent

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axonal disruption can affect all parts, but typically it predominates in the dorsal and lateral tracts of the spinal cord. Normally, the peripheral nerves are less susceptible to this process, but can still be involved. Possibly, this is a secondary degeneration due to loss of proximal fibers. These changes manifest as dysesthesia, paresthesia, gait disturbance, and reduced position sense. The Romberg test becomes positive. Cerebral symptoms of cognitive and emotional types are possible. Accompanying autoimmune diseases of the thyroid with pathologic TSH values were observed in almost half of the patients with pernicious anemia.

Diagnosis. The blood count shows macrocytic anemia. Leukocytopenia and thrombocytopenia are possible. The blood smear is characterized by macro-ovalocytosis, anisocytosis, poikilocytosis, and hypersegmented neutrophils (Fig. 13.**1e**).

Usually the level of lactate dehydrogenase (LDH) is elevated. The serum vitamin B_{12} level is diminished. In the case of borderline values, a functional deficiency of vitamin B_{12} can be identified by measuring the serum homocysteine level. For this determination, blood must be drawn strictly from a fasting patient, because the value increases after food intake. The serum homocysteine level is also elevated in folic acid deficiency. To discriminate between these two states, the serum level or 24-hour urinary excretion of methylmalonic acid may be measured, because this value increases only in the case of vitamin B_{12} deficiency.

The bone marrow displays increased erythropoiesis, which is macroblastic. Antibodies to parietal cells are found significantly more frequently in patients with pernicious anemia. However because of their high prevalence in normal individuals (9.2% of men and 22.3% of women over 55 years of age) they are not specific. Anti-intrinsic-factor antibodies have a high specificity. They are found in less than 1% of healthy persons. Therefore, in spite of their poor sensitivity (only 56% of patients with pernicious anemia are positive), they are useful in the diagnostic work-up. If anti-intrinsic factor antibodies are positive in a patient with vitamin B_{12} deficiency, then a diagnosis of pernicious anemia is established. In the case of a negative test result, pernicious anemia is not excluded.

The vitamin B_{12} urinary excretion test (Schilling test), demonstrates defective absorption caused by intrinsic factor deficiency. Radioactively labeled cyanocobalamin is given orally to a patient, vitamin B_{12} uptake into tissues is blocked by a concomitant intramuscular dose of 1000 μg cobalamin, and the amount of radioactivity excreted in the urine after 24 hours is measured. Values below 8% are considered pathologic. Upon administration of the same dose, together with intrinsic factor, this value becomes normal in cases of endogenous intrinsic factor deficiency.

Other causes of vitamin B_{12} malabsorption (Tab. 13.**4**) are not reversible by addition of intrinsic factor. The Schilling test requires normal renal function and careful collection of the urine over 24 hours.

Fig. 13.**10** Hunter glossitis in pernicious anemia in a 75-year-old woman.

Other Causes of Vitamin B_{12} Deficiency

- A vegetarian diet, devoid of meat, eggs, and dairy products may result in vitamin B_{12} deficiency. Also, children of mothers adhering to such diets during pregnancy or lactation may become vitamin B_{12} deficient.
- Total or subtotal resection of the stomach causes diminished production of intrinsic factor, which is produced by the gastric mucosa.
- Anatomic abnormalities of the small intestine such as diverticula, anastomoses, fistulae, and blind loops or pockets, as well as motility disorders such as those found with strictures, scleroderma, amyloidosis, or autonomic neuropathy in diabetes, result in bacterial overgrowth. The micro-organisms bind cobalamin, competitively. In such cases, the megaloblastic anemia is accompanied by weight loss and steatorrhea. For diagnosis, radiologic examinations are important. Quantitative cultures of the bowel fluid or $^{14}CO_2$ breath tests after ingestion of ^{14}C-labeled xylose or bile salts are other possibilities.
- Because vitamin B_{12} is absorbed mainly in the terminal ileum, resections, bypasses, and involvement of this region by Crohn disease may cause vitamin B_{12} deficiency.
- Around 2–3% of fish tapeworm (*Diphyllobothrium latum*) carriers are deficient in vitamin B_{12}.
- Tropical sprue and celiac diseases more typically lead to deficiency in folic acid, but vitamin B_{12} deficiency is also possible.
- The familial Imerslund–Graesbeck syndrome results from selective vitamin B_{12} malabsorption, manifests early in childhood, and is accompanied by proteinuria. It is caused by genetic defects in ileal intrinsic factor receptor. Inheritance is autosomal recessive.
- About 20–30% of HIV-infected patients have diminished vitamin B_{12} concentrations, mostly with normal blood counts. The pathogenesis and importance of this finding are still unclear.

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Table 13.4 Causes of macrocytic anemia

Disorders of DNA synthesis – Vitamin B_{12} deficiency – dietary – pernicious anemia – gastrectomy or gastric bypass – bacterial overgrowth in blind loop syndrome, sclerodermia, achlorhydria – fish tapeworm – familial selective vitamin B_{12} malabsorption (Imerslund–Graesbeck syndrome) – exocrine pancreatic insufficiency – Zollinger–Ellison syndrome – hemodialysis – ileal resection – regional enteritis Crohn disease – Folic acid deficiency – dietary – increased requirements: pregnancy, growth – extensive jejunal resection – congenital malabsorption of folic acid – combined deficiency of vitamin B_{12} and folic acid – tropical sprue – celiac disease – Hereditary disorders of DNA synthesis – orotic aciduria – Lesch–Nyhan syndrome – thiamine-responsive megaloblastic anemia – enzyme deficiencies in folic acid metabolism: glutamate formiminotransferase, dihydrofolate reductase – transcobalamin II deficiency and abnormal transcobalamin II – homocystinuria, methylmalonyl aciduria – Drug-induced and toxic disorders of DNA synthesis – folic acid antagonists (methotrexate, trimethoprim [Bactrim]) – purine analogs (6-mercaptopurine), pyrimidine analogs (cytosine arabinoside) – alkylating substances (cyclophosphamide, chlorambucil) – hydroxyurea – virostatic drugs (zidovudine) – antiepileptics (phenytoin, primidone, carbamazepine, phenobarbital) – arsenic, insecticides (chlordane)
Erythroleukemia
Reticulocytosis: hemolysis, posthemorrhagic anemia
Myelodysplastic syndrome
Myeloid metaplasia (osteomyelofibrosis)
Aplastic anemia and pure red-cell aplasia
Sideroachrestic anemia
Hereditary dyserythropoietic anemia type 1
Liver disease, obstructive icterus
Hypothyroidism
Benign familial macrocytosis

Folic Acid Deficiency

Clinical Findings. The hematologic changes caused by lack of folic acid are the same as in vitamin B_{12} deficiency: macrocytic anemia, hypersegmented neutrophils, and megaloblastic precursors in bone marrow. Neurologic changes are more commonly observed in vitamin B_{12} deficiency, but have also been described in folic acid deficiency.

Etiology. Folic acid deficiency has many possible causes:

- The most common cause of folic acid deficiency is dietary, especially an insufficient consumption of fruit, vegetables, and dairy products. The macrocytosis seen in alcoholics is caused by folic acid deficiency, due in part to improper diet, but also in part to a compromised metabolism of folic acid.
- Folic acid requirements are increased during pregnancy and growth, but also in situations of increased cell proliferation, such as in hemolytic diseases.
- Antiepileptic drugs cause a mild deficiency of folic acid by a mechanism that is not fully understood. This applies to all of the commonly used medications

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(phenytoin, primidone, carbamazepine, and phenobarbital).

- Tropical sprue and gluten-sensitive enteropathy (celiac disease) often cause a combined deficiency of folic acid, vitamin B_{12}, and iron. Usually folic acid decreases first.
- A number of rare genetic defects resulting in defective DNA synthesis have been described. They are observed mostly in children. They will not be discussed here.
- Methotrexate and other folic acid antagonists act by inhibition of dihydrofolic acid reductase. A milder inhibition of this enzyme is observed as a side effect of other substances such as: proguanil (Paludrin, Malarone), pyrimethamine (Daraprim, Fansidar), triamterene (Dyrenium), pentamidine (Pentacarinat) and trimethoprime (Bactrim).

Other Causes of Macrocytic Anemia

Pure red-cell aplasia typically presents with macrocytosis, but it can be normocytic. It is related to aplastic anemia and will be discussed in the section on Hyporegenerative Normochromic Normocytic Anemia (below).

A rare cause of macrocytic anemia is congenital dyserythropoietic anemia type I. It is diagnosed by bone marrow smear examination, where binucleated erythroblasts with chromatin bridges can be observed (Fig. 13.**11**).

Liver diseases, the myelodysplastic syndrome, osteomyelofibrosis, anemia accompanying hypothyrosis, and aplastic anemia are macrocytic or normocytic and will be discussed in the section on Hyporegenerative Normochromic Normocytic Anemia (below).

Chronic alcohol abuse induces macrocytosis.

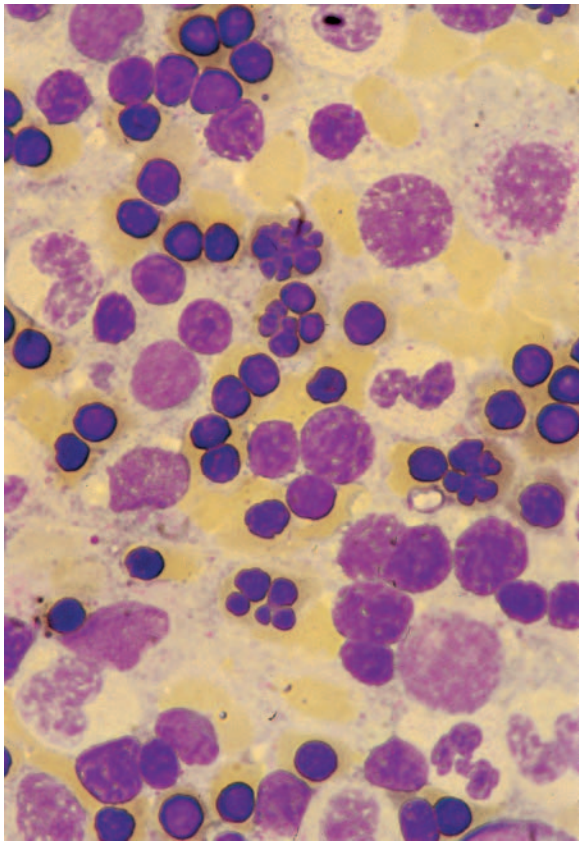

Fig. 13.**11** Bone marrow in congenital, dyserythropoietic anemia.

13.3 Hyporegenerative Normochromic Normocytic Anemia

It should be borne in mind that most of the anemias discussed in this section have normal MCV and MCHC, although macrocytic or microcytic and hypochromic cases are encountered. Especially, erythrocytic subpopulations that lie beyond the normal range are often observed.

Classification. The most reasonable classification of the normochromic normocytic anemias is to group them by hyporegenerative and hyperregenerative states. To this end a reticulocyte count is necessary. Hyporegenerative situations are characterized by a diminished or normal fraction of reticulocytes, whereas hyperregenerative states show an increase in reticulocytes, which corresponds to the severity of the anemia. Hyperregenerative conditions are limited to posthemorrhagic anemia with, usually, clinically manifest bleeding and hemolysis, which will be discussed separately in the section on Hemolytic Anemia (p. 412).

The hyporegenerative normochromic normocytic anemias are diverse and are listed in Tab. 13.**5**.

Renal Anemia

Primarily, a diminished production of erythropoietin, but also toxic effects of uremic substances on the bone marrow, and a mildly diminished erythrocyte survival time produce the normochromic normocytic anemia of renal failure. This anemia is independent of the cause of renal failure. Only in polycystic kidney disease is the erythrocyte production often normal, or even increased, because of cysts producing erythropoietin. Renal anemia does not ensue before the creatinine clearance rate falls below 40 mL/min. The reticulocyte count is normal or slightly elevated, but compared to the severity of the anemia, always too low.

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Table 13.**5** Hyporegenerative normochromic normocytic anemia

Renal anemia
Hepatic anemia
Anemia associated with endocrine disorders – hyperthyroidism/hypothyroidism – Addison disease – orchiectomy – panhypopituitarism
Aplastic anemia and pure red-cell aplasia
Drug-induced and toxic hyporegeneratory conditions – chemotherapy in oncologic therapy – nucleoside analogs in HIV therapy (zidovudine) – immunosuppressants (mycophenolate, sirolimus) – benzene exposure – radioactive accidents
Bone marrow infiltration – leukemia – myeloma, lymphoma – myelofibrosis – metastastatic cancer
Myelodysplastic syndromes
Dyserythropoietic anemia

It is likely that stored iron is also poorly mobilized. This may result in a functional iron deficiency despite adequate amounts of stored iron. The best parameter indicating a functional iron deficiency is an increased percentage of hypochromic erythrocytes. This problem is managed best by the intravenous application of iron until the serum ferritin level reaches a value in the upper reference range. If the serum ferritin level is higher than 600 ng/mL no additional iron should be given, because this leads to an increase in free iron radicals, which may promote atherosclerosis and induce tumors.

Hepatic Anemia

Three-quarters of patients with liver cirrhosis are anemic. Many mechanisms are involved, such as alcoholic suppression of the bone marrow, folic acid deficiency, and bleeding from esophageal varices or hemorrhoids due to portal venous hypertension. But even in cases without the aforementioned complications, anemia may be observed. It results from a combination of hypervolemia due to splenomegaly (dilution of hemoglobin), hemolysis, and compromised function of the bone marrow.

Some patients develop a severe hemolytic anemia associated with morphologically abnormal erythrocytes (acanthocytes or spur cells, Fig. 13.**1h**). The triad of fatty liver (with or without cirrhosis), acute hemolytic anemia, and hyperlipoproteinemia (type V) in alcoholic disease is also known as Zieve syndrome.

Clinical Findings. The erythrocyte indices are usually normal, but macrocytosis is observed quite frequently, although alcohol abuse and folic acid deficiency may be responsible for this finding. In cases of severe hepatic hemolysis, the aforementioned spur cells—large erythrocytes with five to 10 spikelike projections—are seen and the reticulocyte count is increased.

Anemia Associated with Endocrine Disorders

A normocytic or slightly macrocytic anemia is found in 21–60 % of patients with hypothyroidism. It is caused by a diminished production of erythrocytes in the bone marrow and probably represents a physiologic adaptation to the diminished needs for oxygen of the body in hypothyrosis.

Between 10–15 % of patients with hyperthyroidism are also anemic. The pathogenesis of this anemia is not clear. The MCV is normal or slightly diminished.

After puberty, the hemoglobin value for men is higher than for women. After orchiectomy in men it decreases to the normal range for women. These findings suggest that male steroid hormones are responsible for the higher hemoglobin value in men. We observed two cases of unclear anemia, where antiandrogens had been given after prostatectomy for cancer of the prostate.

A mild anemia is often observed in Addison disease. An insufficiency of the pituitary gland causes anemia that is related to the conditions mentioned, by reducing the hormone production of the thyroid gland, the adrenal glands, and the gonads. This anemia is reversible with hormone substitution.

Aplastic Anemia

Definition. The term “aplastic anemia” is reserved for pancytopenias with diminished production of all cell lineages in the bone marrow, and is associated with reduced cellularity, and lack of an apparent cause for the aplasia. Aplasia following chemotherapy, or other medications that interfere with cellular division, is excluded from this category.

Etiology. A number of medications, whose inherent mechanism of action is not expected to compromise bone marrow function, can cause aplastic anemia. The causal relationship has been demonstrated convincingly for only a few substances. These are chloramphenicol, phenytoin, gold preparations, and probably the sulfonamides. Recently, infections have also been identified as an initiating cause of aplastic anemia. Thus, cases of aplastic anemia following non-A, non-B, non-C hepatitis, or acute mononucleosis, have been described.

In about half of all patients with aplastic anemia, no initiating cause can be found. These idiopathic cases represent in the strict sense aplastic anemia.

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Laboratory findings are characterized by profound pancytopenia. Erythrocyte indices are normal or macrocytic, the reticulocyte count is close to zero. The diagnosis is confirmed by bone marrow analysis. The most difficult differential diagnosis is hypoplastic myelodysplastic syndrome (MDS). This differentiation can be made by a careful morphologic analysis. A complicating factor is that aplastic anemia can develop into MDS and therefore, a mixed clinical picture may be encountered.

Erythroblast Aplasia (Pure Red-Cell Aplasia)

This rare condition is related to aplastic anemia. It manifests as normochromic, normocytic anemia with a reticulocyte fraction near zero. Bone marrow cellularity is normal, but erythropoietic precursors are completely absent (Fig. 13.**12**).

In about 10–15% of these patients pure red-cell aplasia is caused by a thymoma. Occasionally an associated autoimmune disease, such as lupus erythematosus, or an infection with B19 virus is diagnosed, but most cases are idiopathic. We have observed cases of pure red-cell hypoplasia with strongly diminished, but not absent, erythropoiesis. This finding is important because these cases, like pure red-cell aplasia, respond to therapy with cyclosporine.

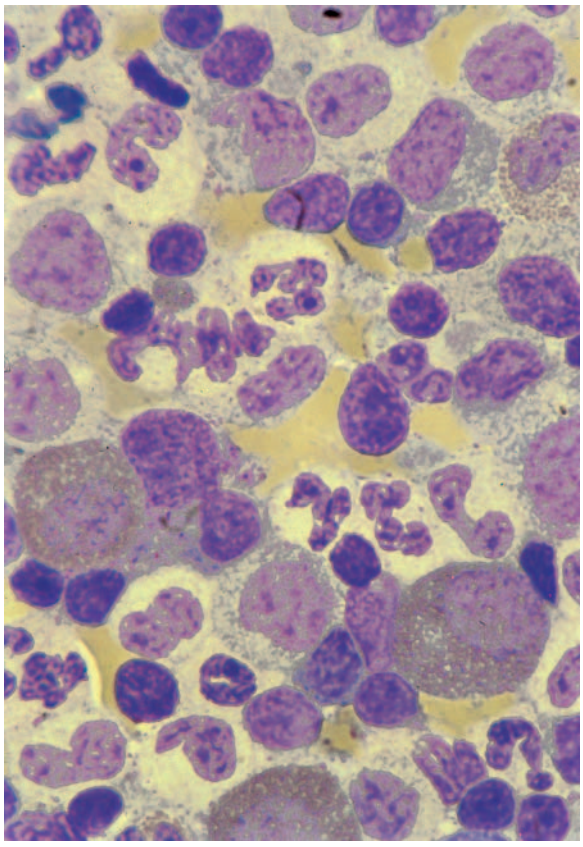

Fig. 13.**12** Erythroblast aplasia (pure red-cell aplasia).

Myelodysplastic Syndrome

Definition. Myelodysplastic syndrome is a clonal disease of bone marrow stem cells, which manifests as an ineffective hematopoiesis. This term denotes a condition of increased apoptotic death in the bone marrow. MDS is associated with abnormalities in cell maturation before cells enter the circulation, resulting in various combinations of cytopenia. The incidence increases with age.

Diagnosis. The diagnosis is made by morphologic analysis. Changes in morphology suggesting MDS are often visible in peripheral blood smears. The diagnosis is then confirmed by bone marrow. The most important diagnostic criterion is the finding of morphologic signs of dysplasia in one, two, or all three, cell lineages. The most important signs are: macrocytosis, teardrop erythrocytes, abnormal or absent granulation in neutrophils, Doehle bodies in neutrophils but no other evidence of inflammation (normal CRP), pelgeroid (i.e., hyponucleated) nuclei, agranular platelets, or giant platelets. The degree of bone-marrow cellularity typically is increased, reflecting ineffective erythropoiesis, but hypoplastic MDS is possible. Morphologic alterations are observed in the form of micromegacaryocytes, giant band forms, macroblastic erythrocyte precursors, and atypical erythroblasts (such as nuclear protrusions, cloverleaf forms, and binucleated elements). Sideroachrestic anemia with the appearance of ringed sideroblasts is also a sign of MDS.

Bone Marrow Infiltration

Neoplastic processes infiltrating the bone marrow, such as metastatic tumors, lymphomas, leukemias, and osteomyelofibrosis, produce a hyporegenerative anemia. In these cases the diagnosis can be obtained only by bone marrow examination (Fig. 13.**13**). Peripheral blood is, however, also typically leukoerythroblastic. This term denotes the appearance of erythrocytic and myeloid precursors (erythroblasts, promyelocytes, myelocytes, and metamyelocytes) in the peripheral circulation, usually accounting for only a few percent of total leukocytes.

Plasma Volume Expansion

Rarely, the cause of a diminished hemoglobin concentration lies in an expansion of the plasma volume. Strictly speaking, this is not an anemia because the total erythrocyte mass is normal, but represents rather a

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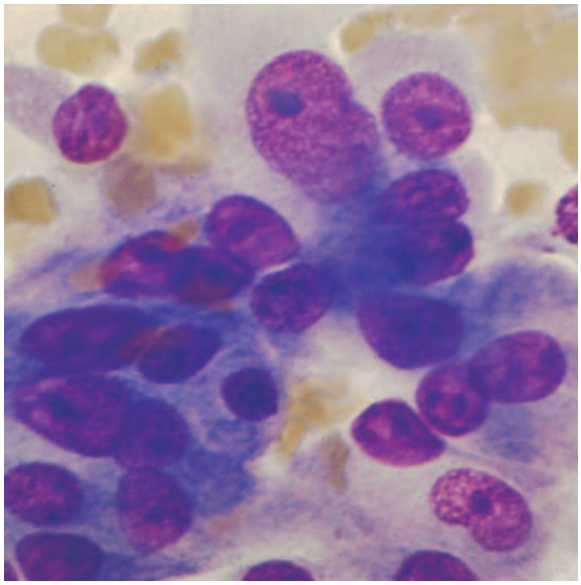

dilution effect. This condition can be observed in pregnancy, with splenomegaly, in cardiac or renal failure, and in hypoalbuminemia. In patients with edema, one hour after assuming a supine position, a reduction of the hematocrit reading of up to 16% has been observed.

Fig. 13.**13** Tumor cells in sternal bone marrow from a patient with breast cancer. The tumor cells exhibit fine chromatin and a large nucleolus.

Diagnostic Strategy in Normochromic Normocytic Anemia

1. Determine reticulocytes and hemolysis parameters (bilirubin, LDH, erythrocyte creatine, haptoglobin).
2. If the reticulocytes are increased then, depending on the results of the hemolysis tests, either bleeding or hemolysis is present (for hemolysis see Hemolytic Anemia).
3. If reticulocytosis is absent, then a renal (creatinine), hepatic (transaminases), or endocrine (thyroid-stimulating hormone, Addison disease) cause should be sought.
4. The next step is a bone marrow examination for hypoplastic or aplastic anemia, infiltration, or myelodysplastic syndrome.
5. Finally, a plasma volume expansion must be excluded by measurement of the erythrocyte and plasma volume.

13.4 Hemolytic Anemia

Definition. All anemias belonging to this large and heterogeneous group have in common a decreased erythrocyte survival time. In response, a regenerative reticulocytosis ensues. The causes and pathogenic mechanisms leading to hemolysis are diverse (Tab. 13.**6**).

Diagnosis. Hemolytic anemias are either normochromic and normocytic or, because of the reticulocytosis, slightly macrocytic and hypochromic. In addition, the so-called signs of hemolysis can be found:

- reticulocytosis (Fig 13.**1k, l**)
- increase in LDH
- increase in erythrocyte creatine
- hyperbilirubinemia, due to increased degradation of hemoglobin
- reduction in haptoglobin concentration, due to binding to free hemoglobin.

It must be kept in mind that only the reticulocytes and the erythrocyte creatine levels rise reliably, whereas the other parameters may remain in the normal range. The latter happens especially in cases of extravascular hemolysis, i. e., if erythrocytes are phagocytosed in the reticuloendothelial system. Another sign of hemolysis is the pink or red color of the plasma in a sedimentation tube (Fig. 13.**14**).

Clinical Findings. Besides the general symptoms of anemia, jaundice (sometimes subclinical) is often observed. This sign is most evident in the sclerae. If the hemolysis is severe enough to completely saturate the available haptoglobin with liberated hemoglobin, then the excess free hemoglobin is excreted by the kidneys, resulting in hemoglobinuria with red coloration of the urine.

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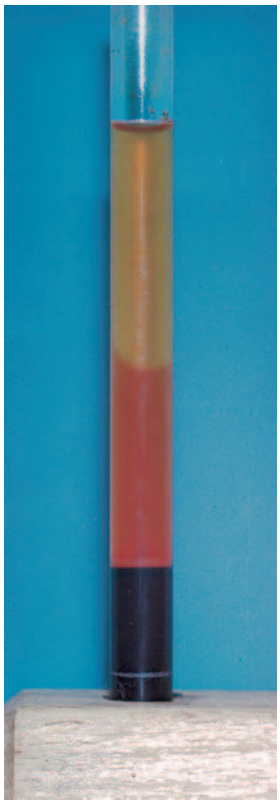

Fig. 13.**14** Characteristic appearance of sedimentation tube in hemolytic anemia. The more slowly sedimenting reticulocytes are visible between the yellow plasma and the dark-red erythrocytes.

Table 13.**6** Hemolytic anemia

Acquired hemolytic anemia
- Alloimmune hemolytic anemia
  - transfusion of incompatible blood
  - alloimmune, hemolytic disease of the fetus and newborn
- Autoimmune hemolytic anemia: warm active antibodies, paroxysmal cold hemoglobinuria
- Paroxysmal nocturnal hemoglobinuria
- Erythrocyte fragmentation syndromes
- Infections
  - malaria, toxoplasmosis, leishmaniasis, trypanosomiasis, babesiosis, bartonellosis, infections with clostridia, cholera, typhus
  - chemicals, drugs, toxins
  - oxidative agents
  - nonoxidative chemicals
  - snake venoms and insect stings
- Hypophosphatemia
- Liver disease

Congenital hemolytic anemia
- Abnormalities of the erythrocyte membrane
  - hereditary spherocytosis
  - hereditary ovalocytosis
  - abetalipoproteinemia (acanthocytosis)
  - hereditary stomatocytosis
  - hereditary xerocytosis
  - lecithin cholesterol acyltransferase deficiency
  - Rh null disease
  - McLeod phenotype
- Enzyme deficiency of erythrocyte glycolysis
  - pyruvate kinase, phosphoglucose isomerase, phosophofructokinase, triosephosphate isomerase, hexokinase, phosphoglycerate kinase, aldolase, diphosphoglyceromutase
- Enzyme deficiency in erythrocyte nucleotide metabolism
  - pyrimidine-5′-nucleotidase, adenylate kinase
  - excess of adenosine deaminase
- Enzyme deficiency in hexose monophosphate shunt and glutathione metabolism
  - glucose-6-phosphate dehydrogenase, glutamyl cysteine synthetase, glutathione synthetase, glutathione reductase
- Disorders of globin synthesis
  - unstable hemoglobins
  - sickle-cell anemia
  - other hemoglopinopathies (C, D, E)
  - thalassemia and hemoglobin H

Exogenous Hemolytic Anemia

Based on medical history and clinical examination, infectious and toxic causes of hemolysis can be suspected or excluded:

- Among these causes are malaria and bartonellosis (Oroya fever, Peru), which are diagnosed in the peripheral blood smear by demonstration of the intraerythrocytic parasites. Septicemia caused by *Clostridium perfringens* is associated with septic abortion, cholangitis, gangrene, leukemia, endocarditis, arteriovenous malformations of the gastrointestinal tract, and necrotizing enterocolitis of the newborn. It causes a rapidly progressive hemolysis. The diagnosis is obtained by performing blood cultures. In addition, many other Gram-positive and Gram-negative bacteria can cause hemolysis.
- A number of drugs induce hemolysis in patients with diminished resistance to oxidative stress (see below). There are also a number of substances that may denature normal hemoglobin by oxidative damage, leading to hemolysis. The substances that have been most often described are naphthalene (mothballs), nitrofurantoin (Furadantin), salicylazosulfidine, sulfamethoxypyridine, aminosalicylic acid, dapsone, and phenazopyridine.
- By the same mechanism, exposure to 100% oxygen results in a mild hemolysis, e. g., in mechanical ventilation.
- Industrial toxins such as arsine (a colorless and nonirritating gas that is used in metal processing, e. g., galvanizing, soldering, etc.). Accidental exposition to copper and copper liberated into the circulation in Wilson disease may lead to hemolysis.
- Spider venoms and snake venoms (especially of the cobra) or multiple bee stings have been described as the cause of hemolysis.
- Severe hypophosphatemia due to prolonged therapy with phosphate-binding antacids, intravenous alimentation lacking phosphate, or severe malnutrition (e. g., alcoholics) may cause hemolysis. Other signs are confusion, weakness, and paresthesia.

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Fig. 13.**15** Necrotic spots on the fingers in a 61-year-old woman with cold agglutinin disease.

Table 13.**7** Causes of secondary autoimmune hemolytic anemia

Autoimmune diseases – SLE – rheumatoid arthritis – sclerodermia – ulcerous colitis
Chronic lymphocytic leukemia
Hodgkin disease
Non-Hodgkin lymphoma
Multiple myeloma, Waldenström macroglobulinemia
Thymoma
Ovarian dermoid cyst
Teratoma
Carcinoma
Hypogammaglobulinemia
Dysglobulinemia
HIV infection
Mycoplasma pneumoniae infection
Syphilis

The causes of hemolytic anemia described above, while rare, can generally be excluded by taking a detailed history or by noting that the patient has no signs of infection.

Alloimmune Hemolytic Anemia

Alloimmune hemolytic anemia occurs following blood transfusions due to transfusion of incompatible blood, to immunization by multiple previous transfusions, or during pregnancy, usually by Rhesus immunization of the mother.

Autoimmune Hemolytic Anemia

Clinical Findings. Suspicion of an immune hemolytic process may arise from a routine blood count, if a fraction of microcytic hyperchromic erythrocytes is present. These cells appear as microspherocytes in the blood smear. Especially with IgM autoantibodies, erythrocyte agglutination is visible in the blood smear. So-called cold agglutinins, which usually are of the IgM type, may also cause acral necroses (Fig. 13.**15**). In this situation antierythrocytic antibodies must be sought using the Coombs test. If it is positive, then a diagnosis of autoimmune hemolytic anemia is established.

Etiology. Autoimmune hemolytic anemia is often secondary, therefore an underlying cause should be sought. A medical history and physical investigation aimed at the diseases mentioned in Tab. 13.**7** should be performed. In addition, a bone marrow examination to exclude a lymphoma or multiple myeloma, serologic tests for lupus erythematosus, and radiologic examinations searching for enlarged lymph nodes and splenomegaly should be performed. A self-limiting, though severe, autoimmune hemolysis with cold-acting IgM antibodies may occur after infections with *Mycoplasma pneumoniae* or Epstein–Barr virus (mononucleosis).

Drugs that have been repeatedly described as provoking an autoimmune hemolytic anemia are: α-methyldopa, penicillin, cephalosporins, tetracycline, tolbutamide, chinidin, and stibophen. For a number of other medications, case reports have been published with variably convincing evidence of causality.

> In autoimmune hemolysis, an unstable balance between cell destruction and regeneration is often present, which may worsen rapidly, leading to severe anemia and death.

Paroxysmal Cold Hemoglobinuria

Antibodies that bind to erythrocytes only at low temperatures, but then activate complement, cause hemolysis, which becomes severe in cold environments. They were discovered in 1904 by Donath and Landsteiner in a patient with advanced syphilis. Currently, this occurs only rarely, with other infections or idiopathically.

The clinical picture is one of fever, back and leg pain, abdominal cramps, headache, nausea, vomiting, and diarrhea. The first urine after such an episode is deep red. The antibody must be demonstrated by incubation of the test blood at low temperatures.

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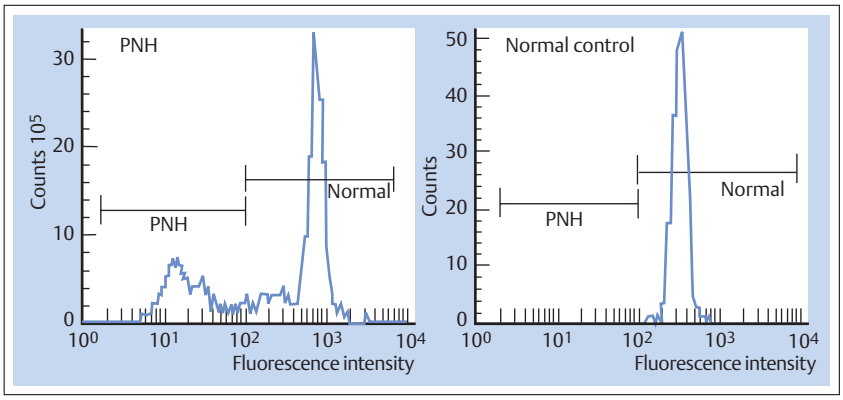

Fig. 13.**16** Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by FLAER staining and fluorescence activated cell scanning (FACS).

Paroxysmal Nocturnal Hemoglobinuria (PNH)

This is a monoclonal, rarely oligoclonal, expansion of an atypic stem cell. The underlying genetic defect in the enzyme phosphatidylinositol glycan class A (PIG-A) results in the inability of the cell to synthesize glycosylphosphatidylinositol (GPI), which is necessary for the anchoring of a number of proteins in the membrane of erythrocytes, leukocytes, and platelets. Among the GPI-bound membrane proteins are two inhibitors of complement: decay activating factor (DAF), which enhances the inactivation of complement factor C3, and membrane inhibitor of reactive lysis (MIRL). The lack of these proteins from the surface of erythrocytes causes a diminished resistance towards complement-mediated lysis.

Clinical Findings. There is a hemolytic activity of changing intensity with consequent reticulocytosis. Exacerbation of the process leads to saturation of haptoglobin, with renal excretion of excess hemoglobin, leading to hemoglobinuria. Iron is lost by this mechanism, resulting in an iron deficiency, which may aggravate the anemia. The leukocyte count is normal during the initial phase; the platelets are normal or slightly decreased. Later, the cytopenia may worsen, but the disease may also enter a spontaneous remission. It is important to know that PNH is complicated by thromboembolic events. Therefore in case of thromboses with atypical localization, e. g., mesenteric, portal, or hepatic veins, the presence of PNH should be investigated.

Diagnosis. For many years the diagnosis of PNH was made by demonstrating the susceptibility to complement-mediated lysis. Later, demonstration of the absence of GPI-anchored proteins from the cell surface using antibodies and fluorescence activated cell sorting (FACS), largely served to replace this approach. In different cell populations, various antigens are investigated.
Aerolysin, the toxin of the bacterium *Aeromonas hydrophila*, binds directly to the GPI anchor. Coupling a fluorescent marker to aerolysin produces a reagent (FLAER), which stains cells containing GPI proteins but not PNH cells lacking GPI. These cells can be identified by FACS. This simple test reliably demonstrates the presence of PNH cells (Fig. 13.**16**).

Hemolysis with Erythrocyte Fragmentation

Another cause for hemolytic anemia is mechanical fragmentation of erythrocytes. The hallmark in these cases is fragmented red cells, also called fragmentocytes or schistocytes. These cells can be seen in the peripheral blood smear in the form of crescents, helmets, or triangles (Fig. 13.**1i**). They are the product of mechanical, intravascular trauma to erythrocytes. It should be stressed that the erythrocyte may close a membrane defect in a spherocytic manner, therefore red-cell fragmentation can also produce microspherocytes with only a few of the above-described forms. In flow cytometry these forms are identified as a hyperchromic microcytic subpopulation.

Etiology. Surgically implanted prosthetic heart valves, including all mechanical types, produce red-cell fragmentation. Bioprostheses, such as porcine xenografts, are less prone to this complication, but erythrocyte fragmentation has also been observed with this type of heart valve. In addition, severe aortic valve disease, especially stenosis, may cause erythrocyte fragmentation. Rarely, patients with mitral valve disease are affected. Also, the **t**ransjugular **i**ntrahepatic **p**orto**s**ystemic **s**hunt (TIPSS) may produce schistocytes.
The examples mentioned above represent abnormalities of the large vessels. In the following sections, conditions which result in erythrocyte fragmentation occurring in small vessels will be discussed. These conditions are grouped under the term **mi**cro**a**ngiopathic **h**emolytic **a**nemia (MAHA).

Tab. 13.**8** summarizes the causes of hemolysis with erythrocyte fragmentation.

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Table 13.8 Hemolysis with erythrocyte fragmentation

Macroangiopathic erythrocyte fragmentation
– Prosthetic heart valves
– Severe valvular heart disease
– Endocarditis with large vegetations
– TIPSS
Microangiopathic erythrocyte fragmentation
– HUS/TTP
– Disseminated metastatic carcinoma
– Chemotherapy-associated microangiopathic hemolytic anemia
– Organ transplantation
– Malignant hypertension
– Disseminated intravascular coagulation
– Giant hemangiomas

Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Clinical Findings. TTP and HUS, in addition to hemolysis with fragmentocytes, are characterized by renal insufficiency. In TTP, thrombocytopenia, fever, and central nervous system dysfunction, due to microinfarctions, are also typically present. The propensity to vascular occlusion may also result in myocardial infarction. The clinical manifestations do not always allow a clear distinction between the two diagnoses.

Pathogenesis. HUS is caused by damage to vascular endothelia. This process predominantly affects the kidneys. This results in microthrombosis with resultant damage to the organ. Also, the smooth surface of the endothelia is lost due to deposition of platelets and fibrin. Erythrocytes flowing past are thus damaged, resulting in schistocytes.

Etiology. HUS can be triggered by infections. Especially enterohemorrhagic *E. coli*, (serotype O157:H7) and *Shigella dysenteriae* may cause epidemic outbreaks of HUS in children. Rarely, other bacteria such as *Streptococcus pneumoniae* have also been held responsible for triggering HUS.

In TTP, absence of the protease that cleaves von Willebrand factor (vWF) (ADAMTS-13, **a** **d**isintegrin **a**nd **m**etalloprotease with **t**hrombo**s**pondin motif 13) plays an important role. There is an inherited form as well as an inhibitor-induced form of ADAMTS-13 deficiency. In most cases, an inhibitor to this enzyme is the causative factor. This inhibitor is an immunoglobulin. Diminished cleavage of large vWF multimers leads to their increased concentration. Because the strongest procoagulant activity is found in these large vWF multimers, their increased concentration activates platelets, which in turn results in the observed thrombosis of small vessels.

Diagnosis. TTP and HUS are suspected if hemolysis with schistocytes is accompanied by renal failure or central nervous system dysfunction. In typical examples of TTP, fever and thrombocytopenia are present. This type of hemolysis is intravascular and, therefore, the LDH is always elevated. Usually, no reduction in coagulation factors and prothrombin time are observed. This fact is useful in the differentiation from disseminated intravascular coagulation. Tests to measure the activity of the vWF cleaving protease ADAMTS-13 have been developed and are available in specialized laboratories.

Metastatic Carcinoma

In disseminated malignant diseases hemolytic anemia with schistocytes is sometimes observed. The pathogenic mechanism proposed is a deposition of fibrin in the pathologic vessels of the tumor. The differential diagnosis is disseminated intravascular coagulation.

Chemotherapy

A number of antineoplastic substances may cause microangiopathic hemolysis. This complication is observed in 2–10% of patients after administration of mitomycin C. Less frequently it results from cisplatin, carboplatin, bleomycin, or gemcitabine. It usually starts four to eight weeks after administration. Most of the patients also suffer from noncardiogenic pulmonary edema.

Transplant-Associated Microangiopathy

Microangiopathic hemolysis can be seen after transplantation of solid organs or bone marrow. It is possible after allogenic, as well as after autologous, bone-marrow transplantation. Important risk factors are total body irradiation and administration of substances with endothelial toxicity such as cyclosporin A.

Pregnancy

A number of conditions occurring peripartum demonstrate some relation to TTP and HUS. These are preeclampsia, eclampsia, HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets), TTP of pregnancy, and postpartum HUS. In all of these conditions, a systemic dysfunction of varying severity affects liver, kidney, central nervous system, and heart. In addition, a microangiopathic hemolysis with production of schistocytes is always present.

Malignant Hypertension

The mechanism leading to erythrocyte fragmentation with excessive hypertension is not clear. Still, this phenomenon is observed very frequently in malignant hypertension. Some of the patients additionally exhibit mild thrombocytopenia.

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Disseminated Intravascular Coagulation (DIC)

DIC, independent of its cause, leads to erythrocyte fragmentation. Important diagnostic signs are low plasma levels of fibrinogen and coagulation factors due to increased consumption. This consumption also leads to a prolonged prothrombin time. Also due to increased consumption, the platelet count is decreased. In addition, signs of damage to different organ systems are present.

Autoimmune Diseases

A microangiopathic hemolysis has been observed in various diseases of connective tissue and in vasculitis, e. g., lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, polyarteritis nodosa, polymyositis, scleroderma, Wegener granulomatosis, and giant cell arteritis. The presumed mechanism is an endothelial deposition of immune complexes with consecutive alterations of the endothelium and deposition of fibrin.

Hemoglobinopathy

Classification. Hemoglobinopathy is classified into two large groups. The first is characterized by quantitative changes in the synthesis of globin resulting in the clinical conditions known as thalassemia. This is discussed in the section Microcytic Hypochromic Anemia. The second group represents the qualitative changes in globin synthesis. In most cases, genetic mutation leads to a single amino acid substitution, but there are cases with a shortened (e. g., Hb Lyon, Hb Freiburg) or extended (e. g., Hb Constant Spring, Hb Icaria) amino acid chain in the globin molecule. Fusion hemoglobins have also been described (e. g., Hb Lepore, which is a fusion molecule consisting of parts of hemoglobin δ and β chains). More than 600 hemoglobin variations have been described.

Pathogenesis. Thalassemia is characterized by a diminished production of either the α or β chain of the globin molecule. This results from total loss of a globin gene or from mutations in the promoter region or the splice sites of these genes. The blood count shows a microcytic hypochromic anemia (see above).

Hemoglobins with qualitative changes, i. e., changes in the amino acid sequence, are often unstable or are subject to increased methemoglobin formation. This leads to denaturation of the globin protein. Denatured globin is visible as a Heinz body in the supravital stain performed for counting reticulocytes (Fig. 13.**1m**). Such erythrocytes are phagocytosed in the reticuloendothelial system, leading to extravascular hemolysis. Some of the abnormal hemoglobins tend to polymerize, resulting in sickling of erythrocytes (sickle cell anemia with Hb S and Hb C). Another possible consequence of amino acid changes is an increased affinity for oxygen. Because this compromises tissue oxygenation, polyglobulia ensues.

Diagnosis. Sickle cell anemia is investigated by the sickling test. Deprivation of oxygen produces the characteristic morphologic change (Fig. 13.**1j**). The pathologic hemoglobin can also be identified using electrophoresis (Fig. 13.**17**) or high performance liquid chromatography (HPLC).

The various unstable hemoglobins cause hemolytic anemias of varying severity. Most cases are normochromic and normocytic, or hypochromic and mildly microcytic. The blood smear is characterized by anisochromasia, poikilocytosis, basophilic stippling, and sometimes bite cells. In cases of suspected unstable hemoglobin, a reticulocyte stain should be performed and investigated for the presence of Heinz bodies. These consist of denatured globin and are located adjacent to the cell membrane (Fig. 13.**1m**). However, this test is not appropriate to exclude unstable hemoglobin because, in many patients, Heinz bodies can be demonstrated only after splenectomy or during an acute hemolytic phase. Further diagnostic steps are the demonstration of reduced hemoglobin stability by heat denaturation or precipitation with isopropanol. We prefer investigating these conditions using oxidative resistance tests (Tab. 13.**9**), because these tests reliably detect unstable hemoglobin variations and enzyme defects of oxidative detoxification (see below). The electrophoresis of hemoglobin (and HPLC) does not detect all unstable hemoglobin variations (Fig. 13.**17**).

Erythrocyte Shape Variations

Deficiency of certain proteins of the erythrocyte membrane causes hereditary spherocytosis. The blood count exhibits a hyperchromic subpopulation of erythrocytes, as measured by flow cytometry. The blood smear shows spherocytes (Fig. 13.**1c**). Osmotic resistance is decreased. Splenomegaly is almost always present. Because autoimmune hemolytic anemia also exhibits spherocytes, a Coombs test should be performed to exclude this differential diagnosis.

Hereditary elliptocytosis or ovalocytosis is related to spherocytosis and clinical findings overlap. The same genetic defects in membrane and cytoskeleton proteins can also be found, in both conditions. The characteristic elliptocytes in the blood smear are diagnostic. The osmotic resistance may be normal or decreased (Fig. 13.**1g**).

Various defects in ion transport through the cell membrane cause hereditary stomatocytosis (Fig. 13.**1f**), cryohydrocytosis, and xerocytosis. Stomatocytes also occur in acute alcoholic intoxication, severe hepatobiliary diseases, and with administration of certain drugs such as vincristin. In cases of pronounced stomatocytosis, mild hemolysis ensues.

Acanthocytosis is characterized morphologically by spikelike projections (spur cells). Acanthocytes occur in

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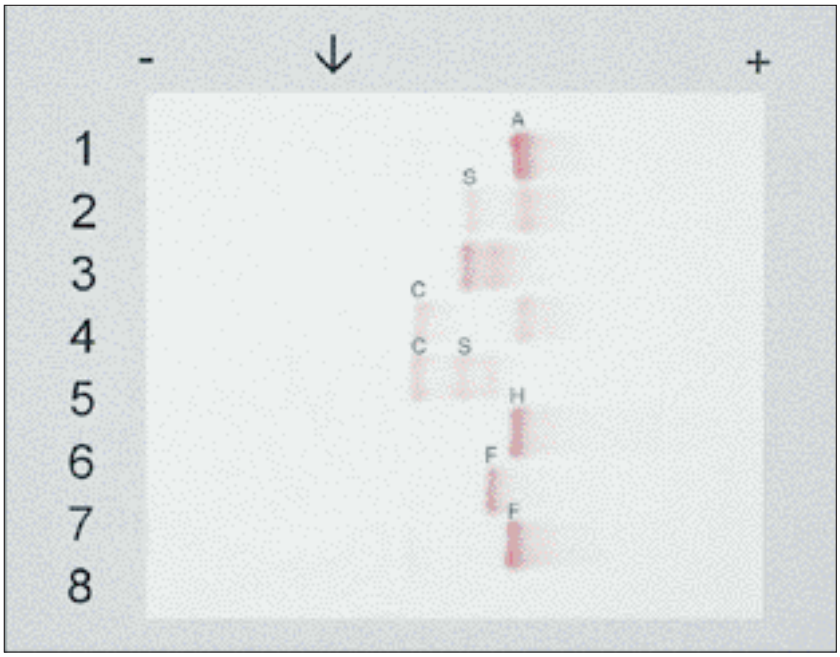

Fig. 13.**17** Electrophoresis of hemoglobin, lanes 1–8 as indicated.
1 Normal
2 Hb S heterozygous
3 Hb S homozygous
4 Hb C heterozygous
5 Hb S/Hb C compound heterozygous
6 Hb H–α-Thalassemia
7 β-Thalassemia minor
8 β-Thalassemia major
(after A.R. Huber, Kantonsspital Aarau, Switzerland).

malnutrition, e. g., in anorexia nervosa, hypothyroidism, after splenectomy, and with severe hepatocellular insufficiency. Hereditary causes are abetalipoproteinemia and McLeod phenotype, i. e., absence of the Kell blood group antigen. McLeod phenotype is investigated by serologic methods. The hemolysis in acanthocytosis is of variable severity and may necessitate transfusions.

Defects of Erythrocyte Enzymes

Diverse enzymatic defects of glycolysis or of nucleotide metabolism (see Tab. 13.**6**) cause hemolysis by various mechanisms. Most of these are very rare. The precise molecular investigation of such conditions is difficult and often unsuccessful, and therefore should be undertaken only if a considerable benefit is expected from establishing the exact diagnosis.

Table 13.**9** Tests for the evaluation of increased oxidative resistance

- Spontaneous sulfmethemoglobin
- Sulfmethemoglobin after vitamin C exposure
- Provocation of Heinz bodies with acetylphenylhydrazine
- Hemolysis after H_2O_2 exposure

Enzyme Deficiencies in the Hexose Monophosphate Shunt and Glutathione Metabolism

Pathogenesis. Oxidative substances (H_2O_2 and O_2^-) are generated during the metabolism of certain drugs, during the reaction of hemoglobin with oxygen, and are produced by leukocytes during infection.

Glutathione protects cells from oxidative stress. The hexose monophosphate shunt is the only source of reduced nicotinamide adenine dinucleotide phosphate (NADPH) for erythrocytes, which is necessary for the reduction of glutathione. Enzyme defects in this system cause an increased fragility of erythrocytes upon oxidative stress. From this fragility, denaturation of hemoglobin and the formation of Heinz bodies ensue, resulting in hemolysis.

Diagnosis. Heinz bodies should be identified using brilliant cresyl-blue stain (reticulocyte stain). Increased susceptibility of erythrocytes towards oxidative stress can be demonstrated by the tests listed in Tab. 13.**9**. Identification of the precise enzyme deficiency is then often not necessary.

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Diagnostic Strategy in Case of Suspected Hemolysis

Steps four to nine may vary in sequence depending on the findings from steps one to three.

1. Confirm hemolysis by counting reticulocytes, RBC creatine, and haptoglobin. LDH is very sensitive for intravascular, but less so for extravascular, hemolysis.
2. If spherocytes are present in the blood smear or hyperchromic cells in flow cytometric analysis, then the differential diagnosis is narrowed to autoimmune hemolysis, mechanical hemolysis (macroangiopathic and microangiopathic hemolysis), or hereditary spherocytosis.
3. Exclude exogenous toxic hemolysis in the medical history.
4. Confirm/exclude autoimmune hemolytic anemia by Coombs test.
5. Confirm/exclude fragmentation hemolysis (TTP/HUS, DIC, MAHA) on clinical grounds and laboratory findings and by seeking schistocytes in the blood smear.
6. Confirm/exclude hereditary variations of erythrocyte shape by examination of a blood smear and if necessary by determination of the osmotic fragility.
7. Confirm/exclude an increased susceptibility towards oxidative stress by the tests listed in Tab. 13.**9.**
8. Confirm/exclude paroxysmal nocturnal hemoglobinuria in the medical history, demonstration of hemoglobinuria, FLAER test, or immunophenotyping.
9. Confirm/exclude unstable hemoglobins by the following tests: Heinz bodies in reticulocyte stain, oxidative susceptibility, denaturation by heat, isopropanol precipitation, electrophoresis of hemoglobin or HPLC (Fig. 13.**17**).

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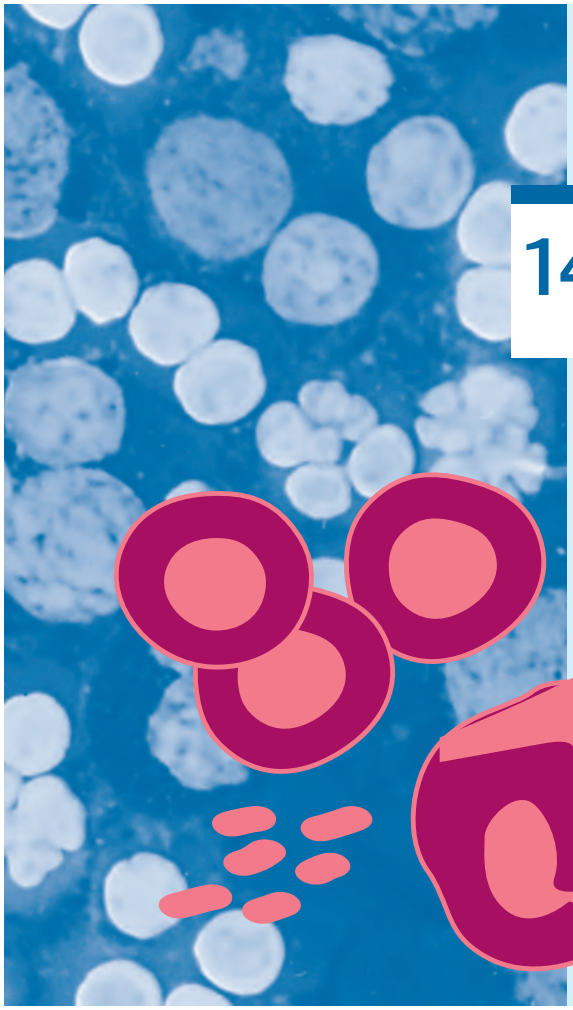

14 Disorders of the Lymphatic System

U. Schanz, D. Jaeger, and J. Fehr

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14.1 Hemopoietic Neoplasia

General Information

Malignant, hemopoietic neoplasia can be divided into the following groups of diseases:
- leukemia
- myelodysplastic syndrome (MDS)
- myeloproliferative syndrome (MPS).

Pathogenesis. All of these diseases characteristically involve various forms of malignant clonal proliferation of a certain cell type or several cell types in the bone marrow. Evidence of the clonal nature of these diseases is provided by analysis performed with molecular biologic methods, by the detection of chromosomal anomalies, as well as analysis of surface or cytoplasmic markers.

Diagnosis. Depending on the form and stage of disease, the most important diagnostic indicators are clinical or hematological changes e. g., those reflected in a pathological blood count, splenomegaly, and/or pathological findings upon examination of the bone marrow. In the diagnosis of some of these diseases cell morphology, cell chemistry, histology, immunological phenotyping, analysis of chromosomal alteration, and molecular biologic findings all play major roles, whereas for other diseases these methods play only a subordinate role.

Leukemia

In the diagnosis of all types of leukemia, the blood count, cell morphology, and cell chemistry are decisive factors. Immunological phenotyping, as well as chromosomal and molecular biological abnormalities, play a more supplemental role. The neoplastic proliferation in the bone marrow suppresses normal hemopoiesis to a greater or lesser extent, depending on the stage and form of leukemia involved. This suppression results in the development of various grades of anemia, granulocytopenia, and thrombopenia accompanied by unspecific clinical symptoms such as pale skin, fatigue, lowered resistance to infections, and hemorrhagic diathesis.

Classification. The five major forms of leukemia are:
- ➤ acute lymphocytic leukemia (ALL)
- ➤ acute myelogenous leukemia (AML)
- ➤ chronic myelogenous leukemia (CML)
- ➤ chronic lymphocytic leukemia (CLL)
- ➤ hairy cell leukemia (HCL).

Distribution by Age and Gender. The age and gender distribution is shown in Fig. 14.**1**. Age is a particularly relevant factor for the diagnosis. However, in individual cases only diagnoses based on blood count and bone marrow examination are decisive.

Acute Forms of Leukemia

Clinical Symptoms. These forms of leukemia (AML, ALL) are termed acute because, although they often begin with unspecific symptoms, they develop very rapidly (i. e., within just a few weeks). Pale skin, fatigue, hemorrhagic diathesis in the form of petechia, epitaxis, gingival bleeding, or menorrhagia and metrorrhagia (in women) are often observed. If, at the same time, the humoral coagulation is activated, as is the case in certain forms of leukemia (e. g., promyelocytic leukemia), the symptoms of hemorrhagic diathesis may be more pronounced and may also lead to suffusion and hematoma. Often, the disease begins with an acute infection such as pneumonia, angina, or a life-threatening sepsis. Occasionally, particularly in certain forms of myelogenous leukemia, the first symptoms are swollen gingiva (leukemic infiltration of the gingiva) or the development of lumps under the skin (chloroma).

Diagnosis. Patients usually consult a physician because they are suffering from symptoms of anemia, granulocytopenia, and/or thrombopenia. A blood count showing a rise in the number of leukocytes (10–50 × 10^9/L), combined with normochromatic, normocytic anemia (60–90 g/L), and pronounced thrombopenia (< 50 × 10^9/L) make the diagnosis of an acute leukemia very probable. However, in some, not entirely rare, cases the number of leukocytes is normal or even lower than normal (typical of promyelocytic leukemia) or there is no, or only a very mild, anemia and/or thrombopenia. For this reason it is very important to obtain a differential blood count, which usually shows the blast cells that are typical in acute leukemia. However, in the aleukemic forms of the diseases, the peripheral blood tests show no, or very few, blast cells. Consequently, it is very important to carry out an examination of the bone marrow as a further procedure for diagnosing acute leukemia. Bone marrow taken from patients with this form of leukemia, and with the other forms of AML and ALL, is usually hypercellular and infiltrated with blast cells.

A bone marrow examination (aspiration and biopsy) must always be performed in diagnosing an acute leukemia. A blood count as the only diagnostic procedure does not suffice.

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Acute Lymphocytic Leukemia (ALL)

Classification. ALL is divided into two main forms in accordance with the WHO:

- precursor B, acute lymphoblastic leukemia (B-ALL)
- precursor T, acute lymphoblastic leukemia (T-ALL).

B-ALL, as well as T-ALL, can be subdivided according to the expression of certain cytoplasmic or surface antigens (immunological phenotyping) or by certain immunoglobulin components (Tab. 14.**1**). The division into various types of ALL has prognostic and therapeutic significance. Figures 14.**2** and 14.**3** show findings obtained from blood counts and bone marrow examinations that are typical of ALL.

Clinical Symptoms. ALL primarily affects children (75% of the patients with ALL are under six years of age) and adolescents (B-ALL is the form of neoplasia that most frequently affects children) and is rarely diagnosed in adults (see Fig. 14.**1**). Besides the general symptoms caused by anemia, granulocytopenia, and thrombopenia, symptoms such as swelling in the lymph nodes, hepatomegaly, splenomegaly, as well as bone pain and arthralgia (joint pain), occur. Mediastinal tumor, caused by enlarged lymph nodes, is a frequent symptom, particularly of T-ALL. It is not unusual for leukemia to affect the central nervous system, although this does not cause the symptoms that show up in the initial diagnosis, but must be searched for by means of a diagnostic spinal tap.

When planning differential diagnosis it is very important, especially with children, to explore and exclude the possibility of *viral infections* such as mononucleosis (Epstein–Barr virus, EBV) that can cause similar symptoms and changes in the blood count.

Acute Myelogenous Leukemia (AML)

Clinical Symptoms. AML, in contrast to ALL, is extremely rare in children and consequently is considered to be primarily a disease of adults. The majority of the patients affected by this disease are older than 60 (see Fig. 14.**1**). The symptoms of AML are mainly caused by anemia, granulocytopenia, and/or thrombopenia. Swelling of the lymph nodes, hepatomegaly, splenomegaly, as well as involvement of the CNS are rare. If they occur, then they do so only in patients with particular subtypes of AML. Test results revealing activated, or even manifest, disseminated intravasal coagulation (DIC) are very typical in promyelotic forms of leukemia.

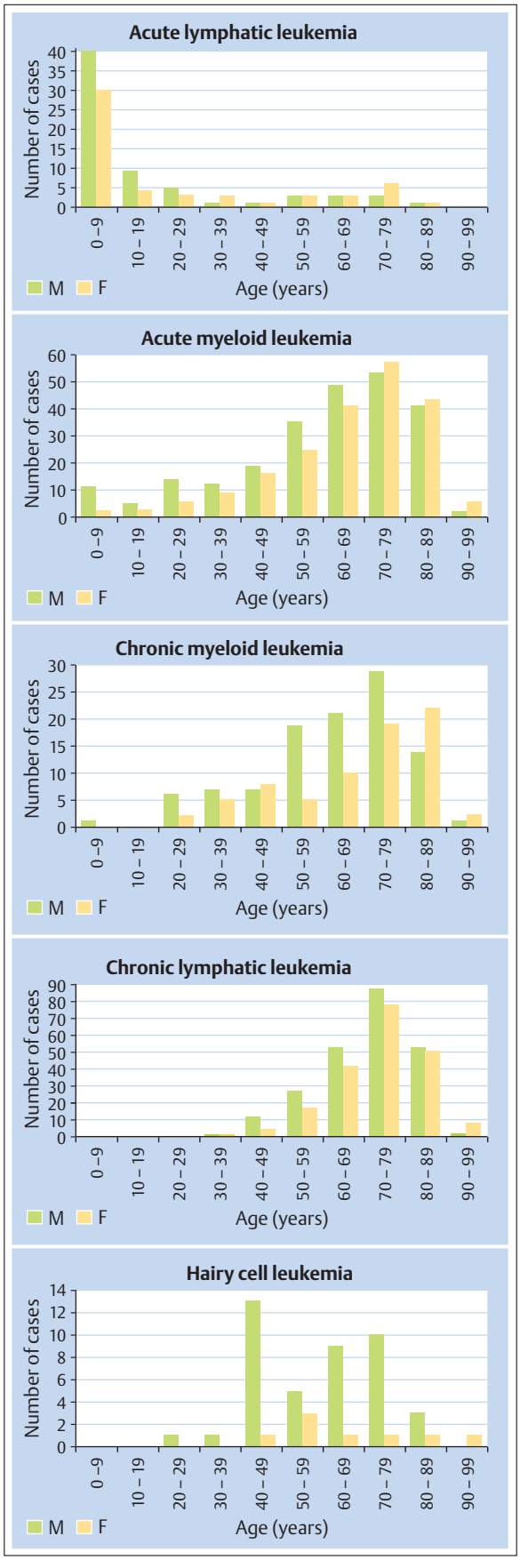

Fig. 14.**1** Incidence of patients with leukemia in the canton of Zurich, Switzerland,1985–1994 (G. Schüler, cancer registery Zurich). M (male), F (female).

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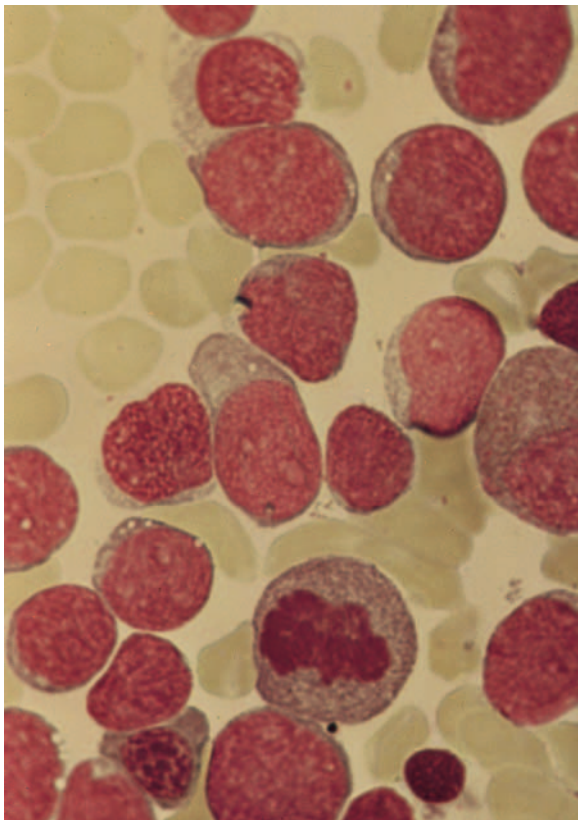

Fig. 14.**2** Acute lymphocytic leukemia (ALL). Bone marrow: leukemic cells, some containing a nucleolus. Peroxidase reaction is negative.

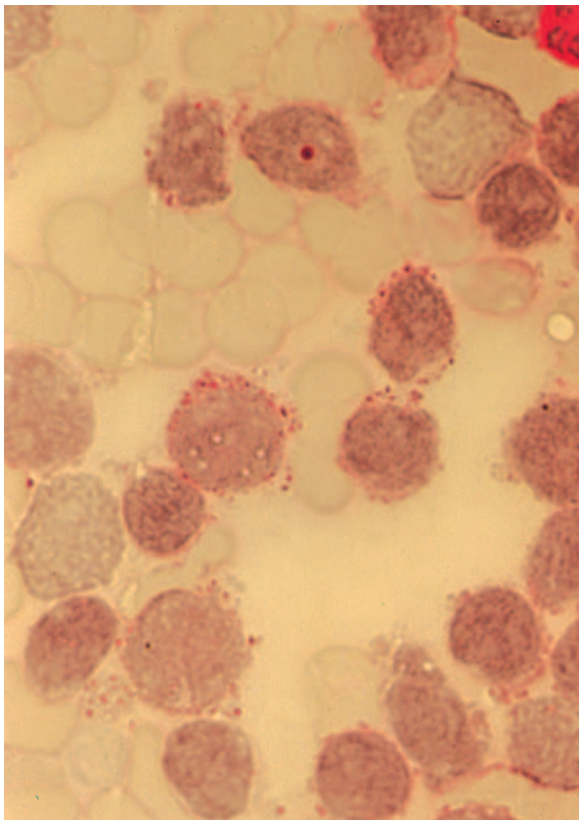

Fig. 14.**3** Acute lymphoblastic leukemia. PAS (periodic acid–Schiff reaction) shows granular positivity in a fraction of the cells.

Table 14.**1** Classification of acute lymphocytic leukemia (ALL) according to the EGIL (European Group for the Immunological Characterization of Leukemias)

Subtype	EGIL	Surface antigen marker	Frequent chromosomal aberrations
B-cell type		HLA-DR$^+$, TdT$^+$, CD19$^+$, and/or CD79a$^+$ and/or CD22$^+$	
– Pro-B-ALL	B–I	no additional markers	t(4;11)(q21;q23)
– Common ALL	B–II	additionally CD10$^+$	t(9;22)(q34;11), del(6q)
– Pre-B-ALL	B–III	additionally CD10±, cylgM$^+$	t(9;22)(q34;q11), t(1;19)(q23;p13)
– B-ALL	B–IV	additionally CD10±, slgM$^+$ or cyλ or κ light chains, TdT possibility negative	t(8;14)(q24;q32), t(2;8)(p12;q24), t(8;22)q(24;q11)
T-cell type		cyCD3$^+$ or sCD3$^+$	
– Pre-T-ALL	T–I	cyCD3$^+$, CD 7$^+$	t/del(9p)
– T-ALL	T–II, III, IV	CD7$^+$, CD2$^+$ and/ or CD5$^+$ and/or CD8$^+$, CD1a±	t(8;14)(q24;q11), t(10;14)(q24;q11), t(11;14)(p13;q11)

s = surface; cy = cytoplasmatic

Diagnosis. Blood and bone-marrow tests reveal mainly the presence of blasts, promyelocytes, and individual granulocytes, but rarely any intermediary forms of the myeloid cell series, a phenomenon which is referred to as *hiatus leukemicus*.

Immunological phenotyping and chromosome analysis, in addition to classical bone marrow morphology and cell chemistry, are part of the standard diagnosis for this disease. Moreover, a chromosome analysis is necessary to determine the AML subtypes in accordance with the new WHO classification system, and is of considerable significance for the prognosis as well as the choice of therapy. Tab. 14.**2** shows the chromosome anomalies which occur most frequently in AML.

Classification. Until recently, the various leukemic diseases were successfully classified for 25 years according to the FAB (French–American–British) classifica-

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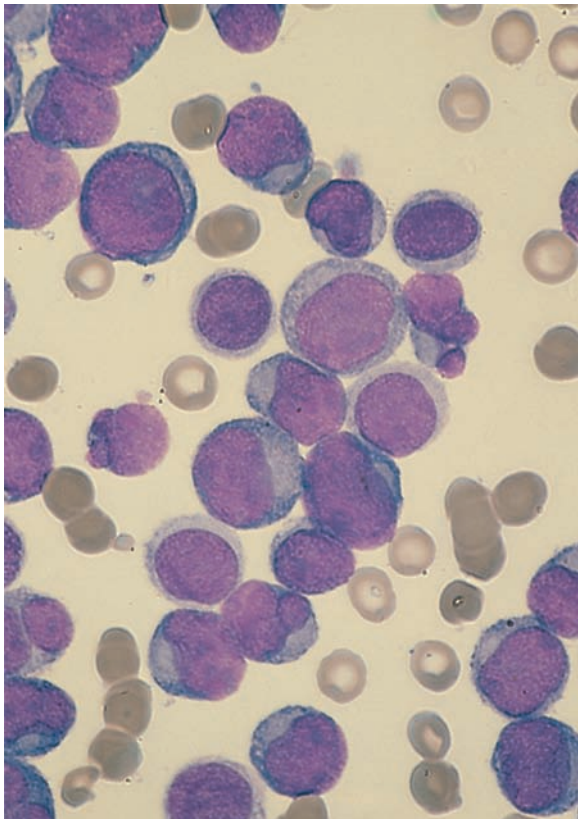

Fig. 14.**4** Acute myelogenous leukemia (AML), type M1. Bone marrow: large polymorphic blasts with multiple nucleoli. Cytoplasm without apparent granulation.

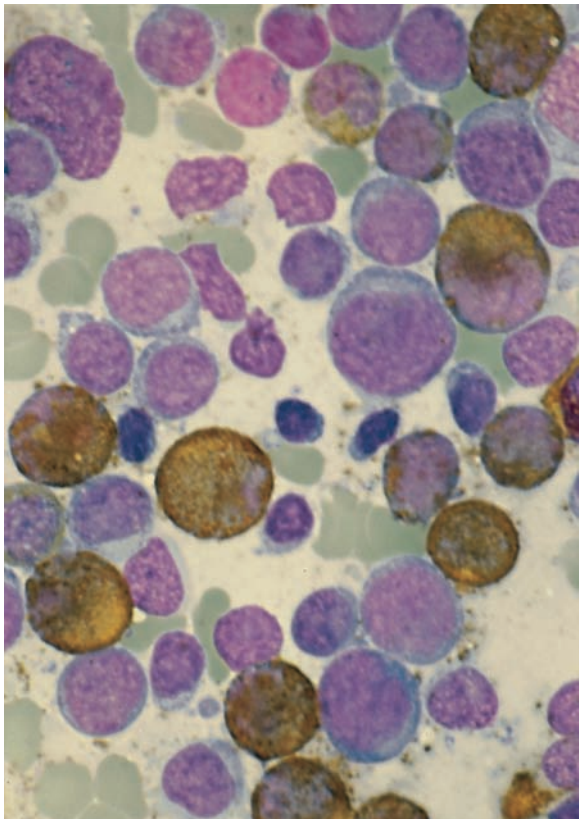

Fig. 14.**5** Acute myelogenous leukemia (AML), type M2. Peroxidase reaction strongly positive.

tion system and were divided into seven forms using the morphology and cytochemistry of the leukemic cells as criteria. The classifications prescribed by WHO are currently in use and chromosome analysis, signs of dysplasia in the hematopoesis, previous treatment with a leukemogenic form of chemotherapy, and various other factors are applied as criteria for dividing AML into four main groups and several subgroups.

In addition, there is an acute leukemia group of unknown origin (myelogenous or lymphatic) which encompasses undifferentiated acute leukemia, bilinear acute leukemia, and biphenotypical acute leukemia. Since these two different classification systems are often applied simultaneously, both are presented (Tabs. 14.**3**, 14.**4**). Figs. 14.**4**–14.**11** show blood and bone marrows smears from patients with the various forms of acute myelogenous leukemia.

Characteristics of Some Forms of AML. The symptoms and clinical parameters of the various forms of acute myelogenous leukemia do not differ significantly. However, there are some characteristic manifestations that will be described specifically.

The previously mentioned *promyelocytic leukemia* (AML M3 in the FAB classification, AML with t(15;17) in

Table 14.**2** Most frequent chromosomal aberration in acute myelogenous leukemia (AML)

FAB	Chromosomal aberration
M0	–
M1	t(9;22)(q34;q11.2)
M2	inv(3)(q21;q26), t(6;9)(p23;q34), t(8;21)(q22;q22), del(12)(p12)
M3	t(15;17)(q22;q21)
M4	inv(3)(q21;q26), t(6;9)(p23;q34), t(8;16)(p11;p13), t(8;21)(q22;q22), t(10;11)(p13;q23), del (12)(p12), inv(16)(p13;q22), t(16;16)(p13;q22), del(16)(q22)
M5	t(8;16)(p11;p13), t(9;11)(p21;q23), t(11;19)(q23;p13), t(10;11)(p13;q23)
M6	inv(3)(q21;q26), t(3;5)(q25.1;q34)
M7	t(1;22)(p13;q13)
General myelogenous	t(3;21)(q26;q22), del (5)(q13;q33), (-5), del(7q), (-7)

Except for t(15;17), which is pathognomonic for AML M3 in the FAB system, other cytogenetic abnormalities have only limited FAB class specificity.

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Table 14.3 FAB classification of acute myelogenous leukemia (AML)

M0 (myeloblastic leukemia without maturation)	– myeloblasts without granula or Auer rods – all cytochemical reactions negative – incidence < 5 %
M1 (myeloblastic leukemia with minimal maturation)	– myeloblasts with no or few Auer granula and/or Auer rods – the majority of cells have a rim of pale to slightly basophilic agranular cytoplasm – nuclei with one or more nucleoli – few blasts are peroxidase positive – incidence 15–20 %
M2 (myeloblastic leukemia with maturation)	– maturation more distinct and beyond the promyelocytic stage – 50 % of bone marrow cells are myeloblasts or promylocytes – numerous leukemic cells with azurophilic granula, partially with Auer rods – numerous leukemic cells are peroxidase positive – incidence 25–30 %
M3 (hypergranular promyelocytic leukemia)	– the majority of bone marrow cells are pathologic promyelocytes, packed with large purple granula – single cells with Auer rods (pathognomonic) – nucleus in variable form and size, frequently kidney-shaped or bilobed – incidence 10 %
M4 (myelomonocytic leukemia)	– granulocytic or monocytic differentiation – percentage of monocytic cells in bone marrow and blood > 20 %, percentage of myeloblasts and promyelocytes usually also > 20 % – leukemic cells partially with specific or unspecific, esterase staining – lysosome concentration in the serum is elevated – incidence 15 %

M5 (monocytic/monoblastic leukemia)	– M5a (little differentiation)
	  – 80 % of bone marrow cells are monoblasts, whose nucleus contains one to three large, bullous nucleoli
	  – nonspecific esterase reaction is positive and lysosomal reaction in the serum is elevated
	  – incidence 5 %
	– M5b (differentiated)
	  – 20 % of leukemic cells show maturation (promonocytes!), nucleus is convoluted or notched
	  – number of monocytes in the blood higher than in bone marrow
	  – nonspecific esterase and lysosomal reactions are the same as in M5a

M6 (erythroleukemia)	– 50 % of the bone marrow cells are megaloblastic erythrocyte precursors, some with a bizarre-shaped nucleus – 30 % of the bone marrow cells are myeloblasts and promyelocytes, some with Auer rods – erythroblasts in the blood – PAS staining of erythoblasts is positive – incidence < 5 %
M7 (megakaryoblastic leukemia)	– positive reaction with thrombocyte peroxidase and antibodies against thrombocytes – incidence 3 %

the WHO system) is characterized by activated coagulation, usually detectable in the first diagnostic tests. The activation rate increases at the beginning of treatment and desists only after several days of therapy, when there is a rapid drop in the number of leukemia cells.

In *acute myelomonocytic and monocytic/monoblastic leukemia* (M4 and M5a/b [FAB]) leukemic infiltration of the gingiva and skin are common. Coagulation is occasionally activated.

Acute myelomonoblastic leukemia, which is characterized by an inversion or translocation on chromosome 16 (inv[16] or t[16;16]), shows a distinct blood eosinophilia and, above all, bone marrow eosinophilia. The prognosis is favorable for this form of AML.

In addition, *acute erythroblastic leukemia* and the very rare *megakaryoblastic leukemia*, which is characterized by neoplastic changes in the erythropoesis and megakaryopoesis, are classified as forms of acute myelogenous leukemia.

AML as a Secondary Neoplasia. The increasing prevalence of these forms of acute myelogenous leukemia is reflected in the WHO classification, where they comprise an independent group entitled "therapy-related AML." Patients who are considered to be cured after being treated for lymphomas or solid tumors, often with high-dose chemotherapy combined with re-transfusion of autologous stem cells, comprise the largest group of

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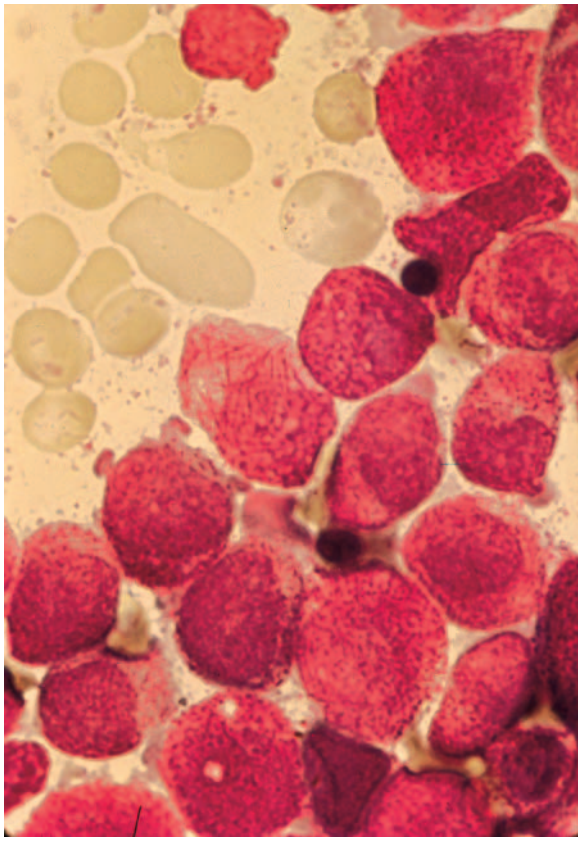

Fig. 14.**6** Acute myelogenous leukemia (AML), type M3 (acute promyelocytic leukemia). Bone marrow smear: nuclei of pathologic promyelocytes are almost completely masked by coarse granula. One cell shows many Auer rods (pathognomonic).

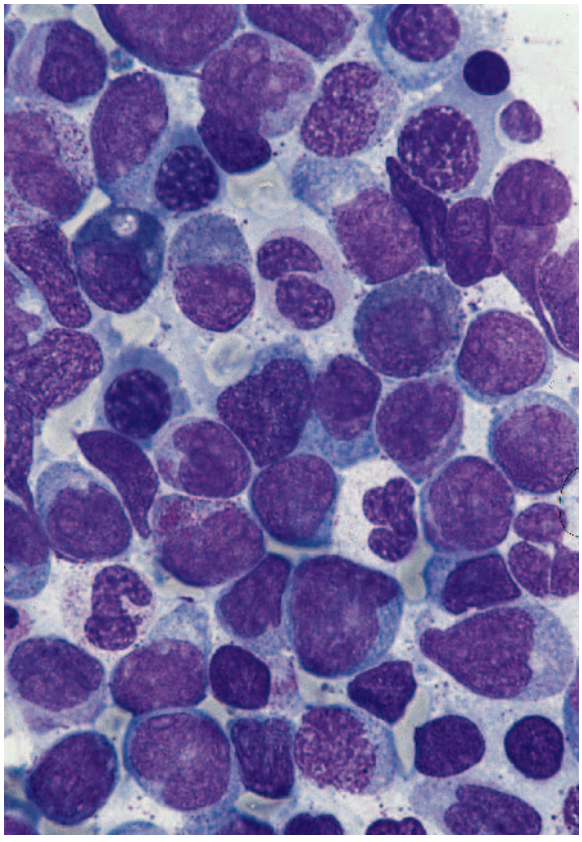

Fig. 14.**7** Acute myelomonocytic leukemia, type M4. Bone marrow smear: immature granular myeloid cells and monocytic cells with notched nucleus and broad plasma.

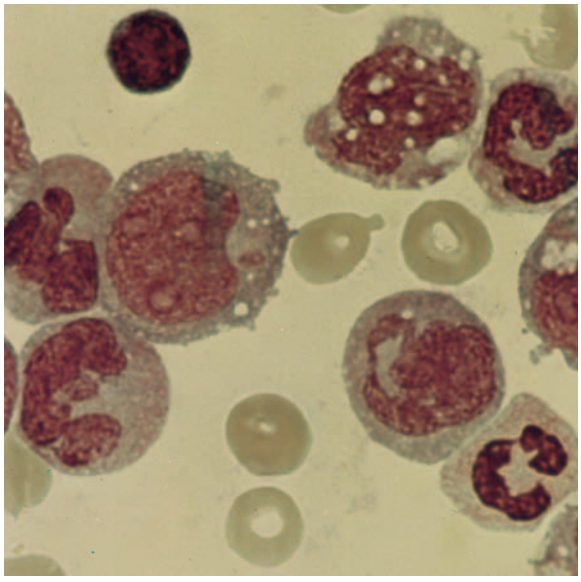

Fig. 14.**8** Acute monoblastic leukemia, type M5, differentiated form, type M5b. Peripheral blood smear.

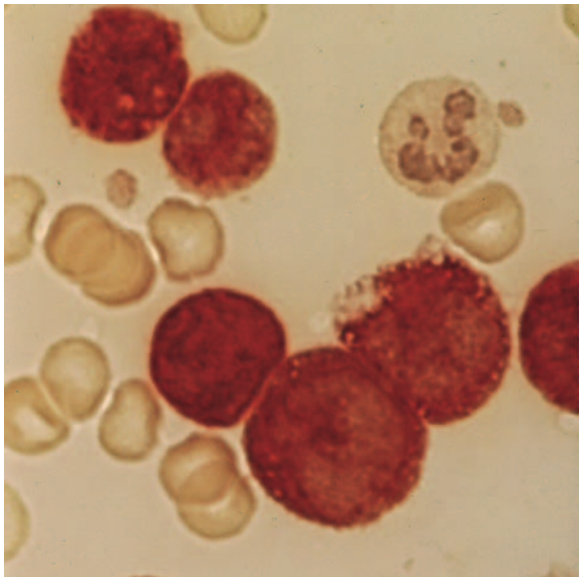

Fig. 14.**9** Acute monoblastic leukemia, type M5, differentiated form, type M5b. The α-naphthyl-acetate-esterase reaction is strongly positive (one granulocyte is negative).

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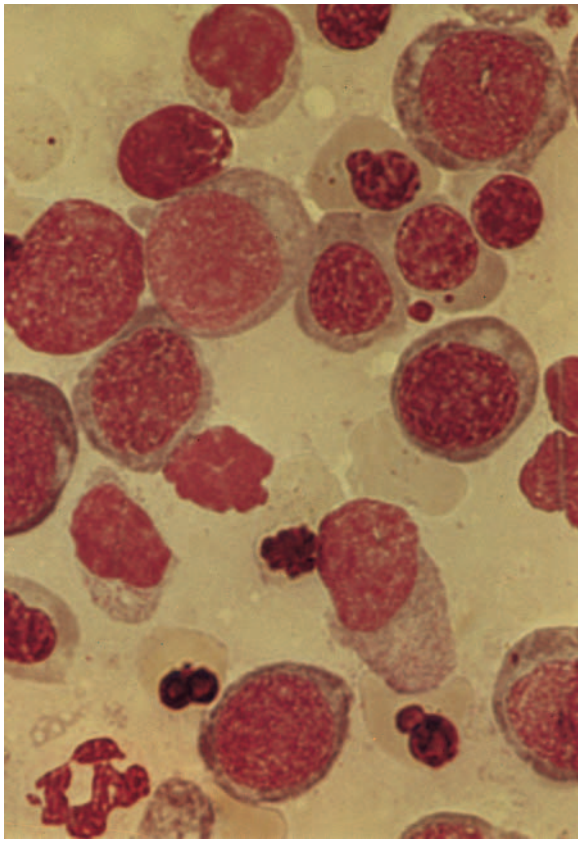

Fig. 14.**10** Acute erythroleukemia, type M6. Bone marrow smear: a large fraction of erythropoietic cells in all stages of maturation, macrocytic with forms of karyorrhexis.

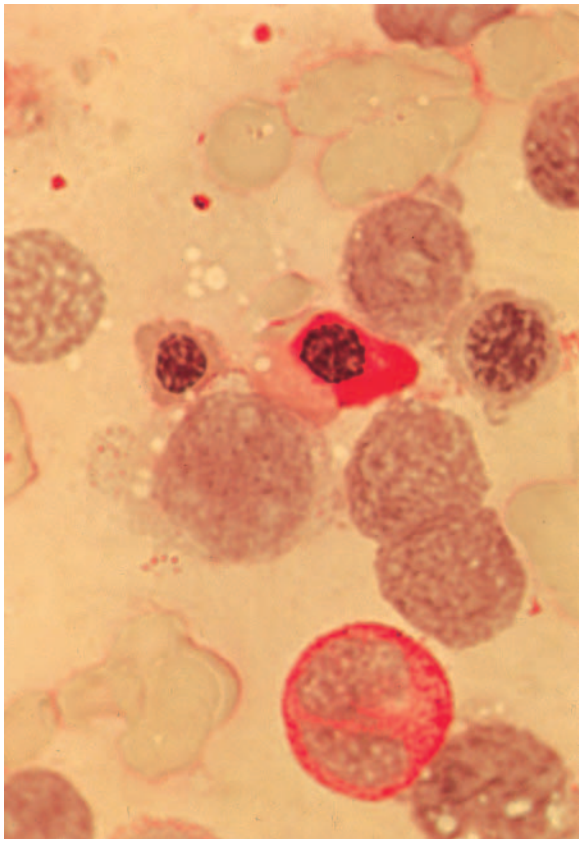

Fig. 14.**11** Acute erythroleukemia, type M6. PAS (periodic acid–Schiff reaction) shows abnormal positivity in one young binuclear and one mature mononuclear erythroblast.

patients diagnosed with this form of leukemia. The incidence of this form of AML is steadily increasing. This disease is divided further into two subgroups according to the leukemogenic substances used for treatment: alkylating agent and/or radiotherapy-related AML, and the topoisomerase-II inhibitor-related AML.

Alkylating agent and/or radiotherapy-related AML becomes apparent on average five to six years after exposure, with a range of 10 to 192 months. The risk of incidence is correlated with the cumulative administered dose and the age of the patient. Usually the leukemic phase is preceded by myelodysplastic syndrome (MDS). Cytogenetic analysis often reveals unbalanced translocations and delegations on the long arm of chromosome 5 or 7.

Topoisomerase-II inhibitor-related AML usually appears, in patients of all ages, after a short latency period of three years, on the average with a range of 12 to 130 months. This form of AML usually manifests itself without a preceding MDS and exhibits the characteristics of myelomonocytic or monoblastic leukemia. Cytogenetic analysis often reveals balanced translocations on band 11q23 (the so-called *MLL* [mixed lineage leukemia] gene), usually t(9;11), t(11;19), or t(6;11).

Chronic Forms of Leukemia

Chronic Myeloid Leukemia (CML)

A pronounced splenomegaly is a leading clinical symptom of chronic myelogenous leukemia. This symptom, together with an extreme leukocytosis ($> 100 \times 10^9$/L) in the peripheral blood count, is a typical finding in all early stages of myelopoesis and makes up the complete diagnostic picture of this disease.

Clinical Symptoms. The initial symptoms of CML are often not specific and include increased fatigue, reduced stamina, weight loss, night sweats, and a pronounced splenomegaly, which can lead to a feeling of pressure in the abdomen. Although patients with CML often have a thrombocytosis, they show no increased tendency to develop thrombosis. Around 20–40% of the patients have no symptoms when the diagnosis is made. In these cases, the disease shows up in a routine examination,

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performed usually because of some other illness, and can be diagnosed on the basis of the blood count.

Prognosis. In order to estimate how long the chronic phase will last, the most important factors to be considered after the diagnosis of CML is confirmed are:

- age
- size of the spleen under the rib cage, in centimeters
- percentage of blasts in the peripheral blood count
- percentage of basophilic cells in the peripheral blood count
- percentage of eosinophilic cells in the peripheral blood count
- number of thrombocytes per 10^9/L in the peripheral blood count.

These parameters can be used to calculate the Hasford score using a program found on the Internet site http://www.pharmacoepi.de.

The chronic phase of chronic myelogenous leukemia persists on average three to five years after the diagnosis, and then develops into an acute leukemia in a process referred to as a *blastic crisis*. The acute leukemia is usually myelogenous, but in one-third of cases it is lymphatic and, as a rule, resistant to treatment and ends fatally within a few months. The blastic crisis is usually preceded by a state which lasts three to 18 months, called the *accelerated phase*. In this phase, the response to therapy and the patient's general condition worsen, the spleen is enlarged, and the percentage of blasts in the peripheral blood increases.

Diagnosis. In the *chronic phase*, the blood count shows a typical increase in the number of leukocytes, often exceeding 100 × 10^9/L (50–70% of the cases), accompanied by myelemia (leaking of the premature, myelopoietic cells) (Fig. 14.**12**). The peripheral blood is basophilic and the granulocytes do not contain leukocyte alkaline phosphatase (LAP). It is not unusual for patients to have thrombocytosis at the level of 600–700 × 10^9/L (15–34% of patients). Most patients suffer from mild anemia. The bone marrow is distinctly hypercellular, due to the proliferation of granulocytes and their precursors. The number of blasts is less than 10%, usually under 5%. The megakaryocytes are smaller than the normal size (characteristic micromegakaryocytes) and have hypolobated nuclei. They can be decreased in number, but an increase is also not unusual. The erythopoiesis is reduced. Up to 40% of the patients show an increase in reticulin fibers at the time the diagnosis is made.

Characteristic test results in the *accelerated phase* and during the *blastic crisis* are listed in Tab. 14.**5**.

Philadelphia Chromosome. At the time the diagnosis is made the characteristic cytogenetic translocation t(9;22)(q34;q11) is discovered in 90–95% of the patients. This translocation unites parts of the *BCR* (breakpoint cluster region) gene on chromosome 22 with sections of the *ABL* (Abelson leukemia virus) gene on chromosome 9. The altered chromosome 22 is called

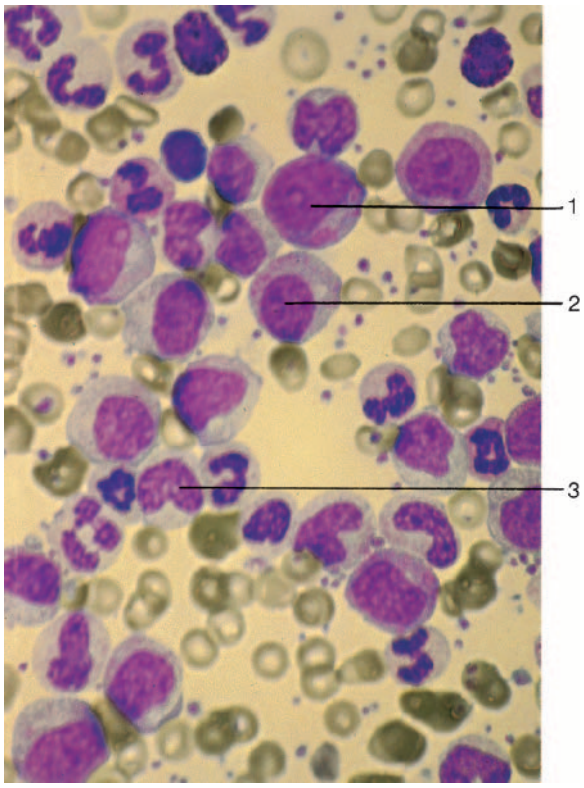

Fig. 14.**12** Chronic, myelogenous leukemia (CML). 1 = promyelocyte, 2 = myelocyte, 3 = metamyelocyte.

Table 14.**4** WHO classification of acute myelogenous leukemia (AML)

Acute myelogenous leukemia with typical chromosomal aberrations
– AML with t(8;21)(q22;q22); (AML1/ETO)
– AML with eosinopilic bone marrow inv(16)(p13:q22) or t(16;16)(p13;q22); (CBFβ/MYH11)
– AML with t(15;17)(q22;12); (PML/RARα) (AML M3 in FAB)
– AML with 11q23(MLL) anomalies
Acute myelogenous leukemia with multilineage dysplasia
– AML with prior myelodysplastic or myeloproliferating syndrome
– AML without prior myelodysplastic syndrome
Acute myelogenous leukemia, therapy related
– Alkylating agent related
– Topoisomerase-II inhibitor related
Acute myelogenous leukemia, not otherwise categorized
– AML without maturation (AML M0 in FAB)
– AML with minimal maturation (AML M1 in FAB)
– AML with maturation (AML M2 in FAB)
– Acute myelomonocytic leukemia (AML M4 in FAB)
– Acute monoblastic and monocytic leukemia (AML M5a, b in FAB)
– Acute erythroid leukemia (AML M6 in FAB)
– Acute megakaryoblastic leukemia (AML M7 in FAB)
– Acute basophilic leukemia (AML M2B in FAB)
– Acute panmyelosis with myelofibrosis
– Chloroma (granulocytic sarcoma)

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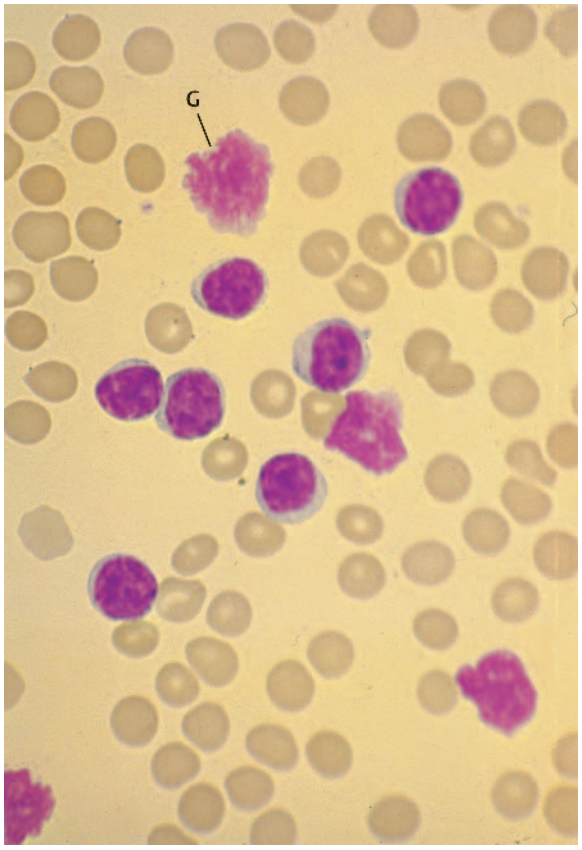

Fig. 14.**13** Chronic lymphatic leukemia (CLL). G = Gumprecht shadows.

Table 14.**5** Chronic myelogenous leukemia (CML): findings in the accelerated or blastic phase

Accelerated phase	Blastic phase
– 10–19 % blasts in peripheral blood or bone marrow – ≥20 % basophilic cells in peripheral blood – < 100 × 10^9/L thrombocyte count (not therapy related) or > 1000 × 10^9/L thrombocytes (therapy resistent) – increased spleen size (therapy resistent) – additional cytogenetic aberrations	– ≥20 % blasts in peripheral blood or bone marrow – extramedullary proliferation of blasts

the Philadelphia chromosome. It contains the fusion gene, termed *BCR–ABL*, which is responsible for the disease. In the rest of these cases, either an additional chromosomal aberration or a cryptic translocation of 9q34 and 22q11 is detected using molecular biologic methods, but cannot be detected at the cytogenetic level.

Differential Diagnosis. The forms of chronic leukemia that used to be considered variant, but that are now categorized as independent rare entities, are juvenile CML (now called juvenile myelomonocytic leukemia), chronic neutrophilic leukemia, chronic eosinophilic leukemia and the Philadelphia-positive form of ALL.

Chronic Lymphocytic Leukemia (CLL)

Clinical Symptoms. Approximately 25 % of patients do not have any symptoms at the time of diagnosis, and the only indication of the disease is an absolute lymphocytosis in the peripheral blood count. Frequently, however, there are further indications such as a generalized lymphadenopathy, splenomegaly (although not as pronounced as in CML), hepatomegaly, as well as anemia, and thrombopenia. It is also possible that patients complain of symptoms such as fatigue, lowered resistance to infections, weight loss, fever, and night sweats. In some, not entirely rare, cases, CML is accompanied by an autoimmune hemolytic anemia of the warm antibody type.

CLL typically becomes manifest at around age 60.

Prognosis. The average survival period for patients with CLL is seven years, depending on: which stage the patient is in when the disease is discovered, the time it takes for the number of lymphocytes to be doubled (< 12 months if the prognosis is poor), cytogenetic factors (trisomy 12 and 11q22–23 deletions with a poor prognosis, 13q14 anomalies with a good prognosis), and the mutations in the variable region of the Ig genes (the prognosis is better if there are mutations, worse if there are none). In a small number of cases, approximately 3–4 %, the disease is transformed into a high-grade lymphoma (Richter syndrome), usually a large B-cell lymphoma.

Diagnosis. The total number of lymphocytes is always increased, but there is disagreement in the relevant literature as to which blood count is indicative of a CLL. Examination of blood smears reveals mainly morphologically typical small lymphocytes (B lymphocytes) that have clumped chromatin but no nucleoli. These cells disrupt easily. This leads to the typical nuclear shadows, called Gumprecht shadows or smudge cells, which are seen when the blood is spread out on a microscope slide (Fig. 14.**13**). The pathological changes in the bone marrow can be follicular, interstitial, or in an advanced stage, diffuse. In the latter case, there is usually suppression of hematopoiesis.

Immunological phenotyping shows that the lymphocytes are strongly positive for the markers CD5 and CD23, only slightly positive for the surface markers CD79b and CD22, and negative for FMC7.

The architecture of the enlarged lymph nodes and spleen is disintegrated and follicular. Pale-looking areas contain large cells surrounded by small lymphocytes, which appear to be darker.

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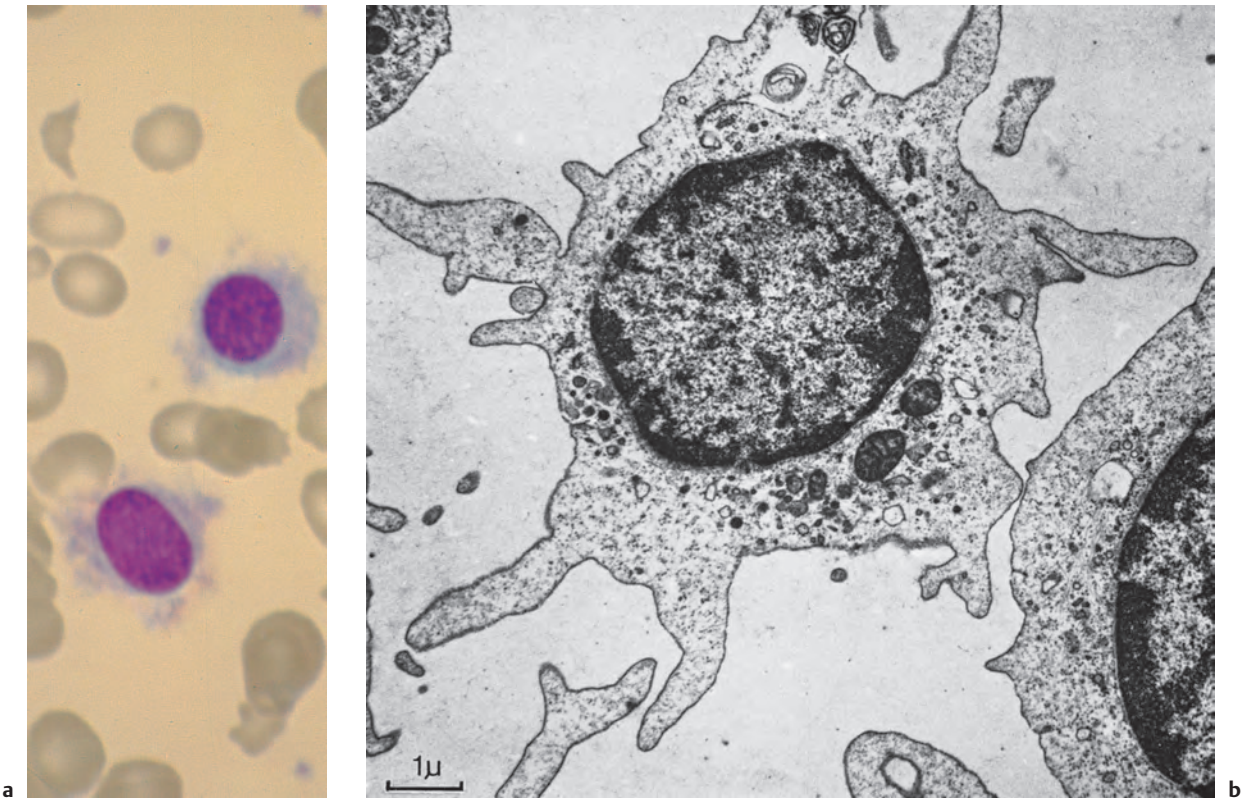

Fig. 14.**14** Hairy cell leukemia (HCL). Notice the hairlike protoplasm.
a blood smear
b electron micrograph.

Staging. Tab. 14.**6** shows the staging system for CLL developed by Rai and Binet indicating the median survival period.

Table 14.**6** Chronic lymphocytic leukemia (CLL) staging according to Rai and Binet

	Clinical findings	Median survival (years)
RAI Stages		
0	Lymphocyte count > 10 × 10^9/L	12.5
I	Lymphadenopathy	7
II	Splenomegaly ± hepatomegaly	
III	Anemia < 110 g/L	1.5
IV	Thrombopenia < 100 × 10^9/L	
Binet Stages		
A	< 3 Enlarged lymphnode locations, no anemia, no thrombopenia	12
B	≥ 3 Enlarged lymphnode locations, no anemia, no thrombopenia	7
C	Anemia < 100 g/L, and/or thrombopenia < 100 × 10^9/L	2

Hairy Cell Leukemia (HCL)

Clinical Symptoms. Laboratory tests reveal splenomegaly, pancytopenia with a characteristic monocytopenia, and only a few hairy cells circulating in the periphery in most of the patients. Hairy cell leukemia occurs rarely and manifests itself on average at 55 years of age and its incidence is significantly more frequent in men than in women (ratio of 5:1).

Prognosis. Since highly effective therapeutic measures are now available (splenectomy, interferon-α, purine analogs), the prognosis is very favorable.

Diagnosis. Hairy cell leukemia is a neoplasia consisting of small B lymphocytes that have characteristic hairlike protoplasm (Fig. 14.**14**). The hairy cells express not only B-cell antigens, but also very strongly express the CD103, CD25, CD11c, and FMC7 markers, are negative for CD5, CD10, and CD23 markers, and, in addition, are usually characterized by a diffuse tartrate-resistant acid-phosphatase positivity. An increase in the number of reticulin fibers can be observed in the bone marrow, which often leads to a "dry tap."

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Myelodysplastic Syndrome (MDS)

The various forms of myelodysplastic syndrome constitute a highly variable group of clonal diseases of the hematopoietic stem cells characterized by ineffective hematopoiesis and dysplasia in one or more cell lineages. The number of myeloblasts can go up as high as 19%. If the threshold of 20% or more is reached, the disease fulfills the definition of acute myelogenous leukemia and the diagnosis is made accordingly. MDS is a disease that normally afflicts elderly people (the median age is 70 years). The cause of the MDS cannot usually be identified clearly (i. e., the syndrome is idiopathic). However, the frequency of a secondary form of MDS, following treatment of malignancies that have been treated with chemotherapy (usually with alkylating agents) and/or radiotherapy, is increasing and this form now comprises 20% of all MDS.

Staging. Until recently, MDS was divided into five groups in accordance with the FAB classification system. Since this system is still partially being used, it is represented in Tab. 14.**7**. Currently, this syndrome is classified according to the nomenclature recommended by WHO (Tab. 14.**8**). In addition to the forms already included in the FAB system, the WHO classification system includes refractory cytopenia with multilineage dysplasia, refractory cytopenia with multilineage dysplasia with ringed sideroblasts, nonclassifiable MDS, and MDS with isolated del(5q). The chronic myelomonocytic form of leukemia, which has not only dysplastic, but also myeloproliferative aspects, was omitted from this section of the WHO classification system, and is now listed under the new category for myelodysplastic/myeloproliferative diseases.

Clinical Symptoms. Most patients exhibit the symptoms of anemia, neutropenia, and/or thrombopenia. Organomegaly is rarely seen and does not belong to the clinical picture which is typical for MDS.

Diagnosis. One or more cell lineages found in blood smears and bone marrow show signs of dysmorphism:

- *Erythropoiesis*: erythroblasts with nuclear buds and bridges, polynuclear, karyorrhectic, megaloblastoid, vacuolated cytoplasm, and ringed sideroblasts
- *Myelopoiesis*: small-sized granulocytes with nuclear hypolobulation (pseudo-Pelger nuclear anomaly), hypersegmentation, and hypogranulation
- *Megakaryopoiesis*: hypolobulated micromegakaryocytes, nonlobulated nuclei, megakaryocytes in highly variable sizes.

The bone marrow is usually hypercellular or normocellular, in rarer cases hypocellular. The latter case is difficult to differentiate from aplastic anemia in the diagnosis. The cytopenia on the periphery is a result of inadequate hematopoiesis.

In the *differential diagnosis* it is very important to distinguish MDS from other nonclonal diseases that are also characterized by dysplasia caused by changes in the hematopoiesis. In particular these are vitamin B_{12} and folic acid deficiencies, heavy metal poisoning (especially arsenic), congenital, dyserythropoietic anemias, virus infections, and reversible pathological changes caused by chemotherapeutic agents and granulocyte colony stimulating factor (G-CSF).

Cytogenetics. Analysis of MDS samples reveal a number of chromosomal aberrations, some of which are associated with certain characteristic morphological changes. These changes are divided into three groups, "good," "intermediate," and "poor," depending on their significance for the prognosis.

Prognosis. The percentage of blasts in the bone marrow and the number of cytopenic cell lineages in the peripheral blood of MDS patients, combined with the cytogenetic aberration, can be used to calculate a prognostic

Table 14.**7** FAB classification of myelodysplastic syndrome (MDS)

MDS subtype	Percentage of peripheral blasts	Percentage of bone marrow blasts	AML transformation	Median survival (months)
Refractory anemia (RA)	< 1	< 5	10–20	30–65
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5	10–35	34–83
Refractory anemia with excess blasts (RAEB)	< 5	5–20	> 50	8–18
Refractory anemia with excess blasts in transformation (RAEB-t)	> 5	21–29	60–100	4–11
Chronic myelomonocytic leukemia (CMML)	< 5	< 20	> 40	15–32

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Table 14.**8** WHO classification of myelodysplastic syndrome (MDS)

MDS subtype	Blood findings	Bone marrow findings
Refractory anemia (RA)	– anemia – no or few blasts	– erythroid dysplasia – < 5 % blasts – < 15 % ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	– anemia – no blasts	– erythroid dysplasia – < 5 % blasts – ≥15 % ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	– bi- or pancytopenia – no or rare blasts – < 1 × 10^9/L monocytes – no Auer rods	– dysplasia in ≥10 % of cells in two or more myeloid cell lines – < 5 % blasts in marrow – < 15 % ringed sideroblasts – no Auer rods
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	– bicytopenia or pancytopenia – no or few blasts – < 1 × 10^9/L monocytes – no Auer rods	– dysplasia in ≥10 % of cells in two or more myeloid cell lines – < 5 % blasts – ≥15 % ringed sideroblasts – no Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	– cytopenias – < 5 % blasts – no Auer rods – < 1 × 10^9/L monocytes	– unilineage or multilineage dysplasia – 5–9 % blasts – no Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	– cytopenias – < 5 % to 19 % blasts – ± Auer rods – < 1 × 10^9/L monocytes	– unilineage or multilineage dysplasia – 10–19 % blasts – ± Auer rods
Myelodysplastic syndrome, unclassified (MDS-U)	– cytopenias – no or few blasts – no Auer rods	– unilineage dysplasia in granulocytes or megakaryocytes – < 5 % blasts – no Auer rods
MDS associated with isolated del(5q)	– anemia – platelets normal or increased – < 5 % blasts	– normal to increased megakarocytes with hypolobated nuclei – < 5 % blasts – no Auer rods – isolated del(5q)

Table 14.**9** International Prognostic Scoring System (IPSS) for myelodysplastic syndrome (MDS)

Score	0	0.5	1.0	1.5	2.0
Bone marrow blast percentage	< 5	5–10	–	11–20	21–30
Karyotype	good	intermediate	poor		
Cytopenia	0–1	2–3			

Definitions:

Karyotype:
Good = normal, –Y, del(5q), del(20q)
Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities
Intermediate = all other abnormalities

Cytopenias:
Hb < 100 g/L neutrophils < 1.5 × 10^9/L
Platelets < 100 × 10^9/L
* By definition, AML is already present.

index referred to as the "international prognostic scoring system (IPSS)" (Tab. 14.**9**). The score and age of the patient are used to determine the prognostic median survival time (Tab. 14.**10**).

Table 14.**10** International Prognostic Scoring System (IPSS) for myelodysplastic syndrome (MDS): age and median survival

Score	Median survival (years) Age < 60	Median survival (years) Age > 60
0	11.8	4.8
0.5–1.0	5.2	2.7
1.5–2.0	1.8	1.1
≥2.5	0.4	0.5

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Myeloproliferative Syndrome (MPS)

In addition to chronic myelogenous leukemia, chronic neutrophilic anemia, chronic eosinophilic leukemia, and the nonclassifiable myeloproliferative diseases there are three diseases that are defined as myeloproliferative syndromes in the narrower sense of the term:

- polycythemia rubra vera (PV)
- chronic idiopathic myelofibrosis (osteomyelofibrosis OMF)
- essential thrombocythemia (ET).

The myeloproliferative syndromes are clonal diseases of the hematopoietic stem cells, which are characterized by the proliferation of one or more myeloid cell lineages in the bone marrow. The proliferation leads to an increase in the number of mature cells of the affected diseased cell lineage in the peripheral blood.

Polycythemia Rubra Vera

Increased erythropoiesis, myelopoiesis, and megakaryopoiesis due to clonal anomalies in hematopoietic stem cells are the most important characteristics of polycythemia rubra vera. Accordingly, the hemoglobin levels and hematocrit counts are necessarily always elevated and this symptom is often accompanied by thrombocytosis and neutrophilia, a phenomenon referred to as trilinear proliferation.

Clinical Symptoms. Patients frequently complain of tinnitus, dizziness, headache, high blood pressure, breathing difficulties, unexplainable weight loss, disturbance of vision, and undue fatigue. The examining physician often observes a *typical redness* in the face (plethora), as well as reddening of the mucous membranes and conjunctiva. Patients often feel pressure in the epigastric region due to a distinctly palpable *splenomegaly* (50–80% of cases), or in rarer cases, due to a supplementary hepatomegaly. Further symptoms that can appear are painful paraesthesia in the palms of the hands and soles of the feet, so-called *erythromelalgia*. An increased *tendency towards thrombosis* in the larger arteries and veins is also typical and can lead to cerebrovascular insults, transitory ischemic attacks, acute coronary syndrome, venous thromboembolism, and stenosis of the portal vein, mesenteric veins, and splenic vein. Besides the increased risk of thrombosis, hemorrhagic diathesis with epistaxis, and gastrointestinal bleeding have also been observed, although much less frequently.

These symptoms are the signs of a variety of physiologic changes such as increased secretion of inflammatory mediators, defective microcirculation, augmented viscosity of the blood due to the relatively larger volume of erythrocytes, and increased cell turnover, which can lead to splenomegaly and attacks of gout.

Diagnosis. Blood tests reveal a greater number of normocytic, normally colored erythrocytes (the exception is when there is an iron deficency caused by recurrent bleeding, which makes the erythrocytes microcytic and hypochromic). There is often neutrophilia, as well as basophilia, leakage of myeloid precursors and some of the erythroblasts, and an increase in the number of thrombocytes. The degree of cellularity of the bone marrow is augmented, whereas erythropoiesis and granulopoiesis remain morphologically normal. Megakaryopoiesis is in contrast abnormal, with the formation of clusters around the medullary sinus and a pleomorphic aspect, accompanied by the appearance of characteristic micromegakaryocytes. An increase in the number of reticulin fibers is not unusual, although a genuine myelofibrosis generally appears in more advanced stages of the disease.

The World Health Organization has listed the following criteria as the decisive factors for diagnosing polycythemia rubra vera:

- A1: increase in the volume of the erythrocytes to 25% above the normal count, or a hemoglobin count that is higher than 185 g/L in men and higher than 165 g/L in women
- A2: differential exclusion of the causes of a secondary polycythemia such as familial erythrocytosis, or an increase in the erythropoietin (EPO) level for the following symptoms:
  - hypoxia ($Po_2 \leq 92\%$)
  - pathological hemoglobin with increased oxygen affinity
  - mutations in the erythropoietin receptors
  - paraneoplastic, erythropoietin production
- A3: splenomegaly
- A4: clonal anomalies other than those that are characteristic of the Philadelphia chromosome
- A5: spontaneous growth of erythroid colonies in vitro
- B1: thrombocytosis $> 400 \times 10^9$/L
- B2: leukocytosis $> 12 \times 10^9$/L
- B3: increased erythropoiesis and megakaryopoiesis in the bone marrow
- B4: lower level of erythropoietin in blood serum.

The diagnosis of polycythemia rubra vera can be considered to be correct when criteria A1 and A2, as well at least one further A criterion and at least two B criteria, are fulfilled.

Prognosis and Course of Disease. The disease can usually be kept under control by performing blood-letting to lower the hematocrit reading and by administering antithrombotic and antineoplastic medication. The survival period is, as a rule, relatively long (> 10 years). Patients may die of a thrombosis, bleeding, or the disease may develop into osteomyelofibrosis, myelodysplastic syndrome, or an acute leukemia.

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Chronic Idiopathic Myelofibrosis (Osteomyelofibrosis)

Chronic idiopathic myelofibrosis is a clonal disease affecting the hematopoietic stem cells, which is characterized by a fibrosis of the bone marrow and extramedullary blood formation. Cytogenetic aberrations are not uncommon. Proliferation of fibroblasts is nonclonal and consequently does not show up in cytogenetic analysis and is, therefore, considered a reactive process.

Clinical Symptoms. Laboratory tests often reveal anemia or thrombocytosis, and patients complain of unspecific symptoms such as fever, weight loss, breathing difficulties, night sweats, fatigue, and hemorrhagic diathesis. The *spleen* and *liver* are *extremely enlarged* (the spleen often extends down to the minor pelvis) due to the extramedullary hematopoiesis. Less frequently (10%), patients develop a lymphadenopathy.

Diagnosis. In addition to anemia and thrombocytosis or thrombopenia, blood tests often typically show a leakage of the myeloid precursors and erythroblasts, a configuration that is referred to as an *erythroleukemoid hematologic picture*. The erythrocytes are poikilocytotic and display a typical teardrop shape (dacryocytes) and blood smears show characteristic *giant thrombocytes* (Fig. 14.**15**). Bone marrow aspiration is usually not possible because of reticulin fibrosis (dry tap). A biopsy is an indispensable diagnostic procedure for this disease, and may show a more or less pronounced myelofibrosis (collagenization). The level of alkaline phosphatase is elevated.

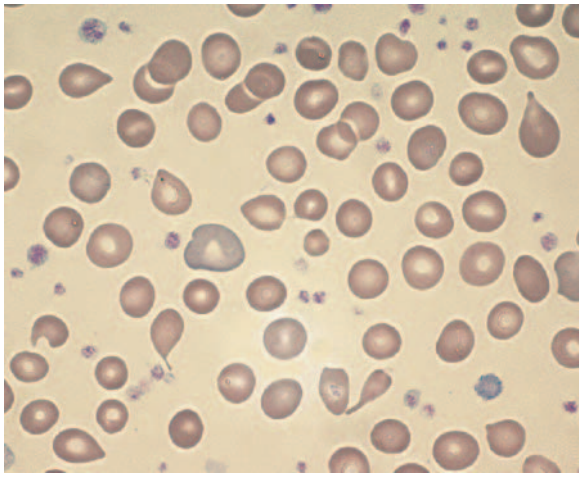

Fig. 14.**15** Blood smear, osteomyelofibrosis. Anisocytosis and poikilocytosis with teardrop erythrocytes and giant thrombocytes, some of which are hypogranular.

Prognosis and Course of Disease. The median survival time, after the diagnosis has been made, is three to five years. The main causes of death are failure of bone marrow function, thromboembolic complications, portal hypertension, heart failure, or transition to an acute leukemia.

Essential Thrombocythemia

See Chapter 15, Thrombocytosis (p. 468).

14.2 Malignant Lymphomas

Basic Information

The following diseases are classified as malignant lymphomas:

- Hodgkin lymphoma
- non-Hodgkin lymphoma
- multiple myeloma
- Waldenström syndrome.

Non-Hodgkin lymphoma can be divided into T-cell or B-cell lymphomas, depending from which cell they originate, and into mature or immature cell lymphomas, depending on the stage of maturity. Their growth can be follicular or diffuse. Multiple myeloma and Waldenström syndrome belong to the group of mature cell neoplasias.

Hodgkin Lymphoma

Hodgkin lymphoma is a special entity among the malignant lymphoma. The actual neoplastic cells that derive from the B cells are the scattered large mononuclear Hodgkin cells and the multinuclear Reed Sternberg giant cells (Fig. 14.**16**). They are surrounded by a large number of neoplastic, inflammatory and accessory cells. The tumor cells are, as a rule, surrounded by T cells arranged in a rosette pattern. Currently, Hodgkin lymphoma is divided into two main forms:

- classical Hodgkin lymphoma (CHL), which includes four subtypes
- nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL, paragranuloma).

Classical Hodgkin lymphoma encompasses 95% of all Hodgkin lymphomas and typically becomes manifest between 15–35, or after 50, years of age. The NLPHL represents 5% of all Hodgkin lymphomas and usually manifests itself between 30 and 50 years of age.

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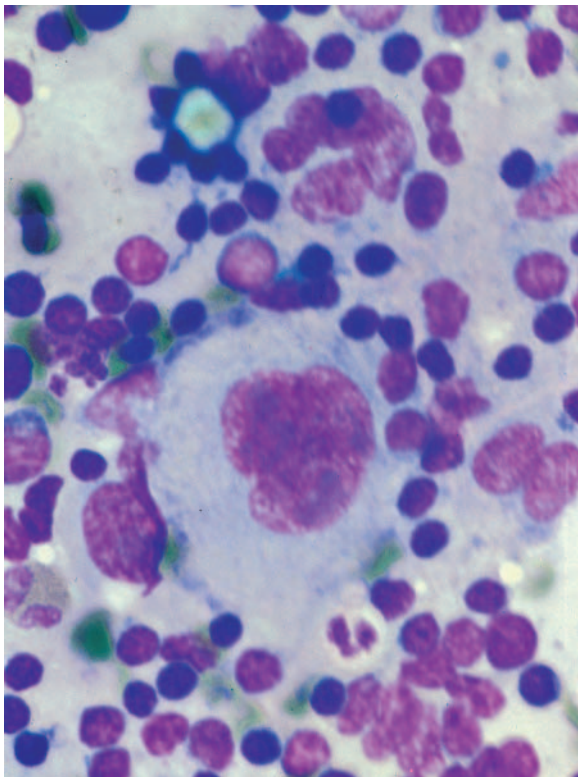

Fig. 14.**16** Sternberg giant cell.

Clinical Symptoms. Hodgkin lymphoma can become clinically manifest in two forms:

- The appearance of a *painless lymphadenopathy* is typical, usually in the area of the neck, which slowly expands. The lymph nodes are hard, not painful, movable relative to the skin, and often adhere to each other. The lymphadenopathy also appears frequently in the mediastinum (Fig. 14.**17**) or axillary area. It is rare for the abdominal and inguinal lymph nodes to be affected in the primary stage. The patients feel well, in their own subjective judgement.
- A considerable portion of the patients have systemic symptoms, called *B symptoms*, which become evident before the lymphadenopathy is discovered. These include noninfectious fever above 38 °C, loss of weight (> 10% in six months), and night sweats. There may also be a generalized pruritus and, in rare cases, patients feel pain in the affected part of their bodies after drinking alcoholic beverages (alcohol pain).

Diagnosis. The diagnosis of Hodgkin lymphoma must always be made with histomorphological methods. Cytological analysis is usually not particularly helpful and is often negative, especially if there is a mature cell lymphoma. Even though the results of laboratory tests and the clinical symptoms are typical for this disease, this is not diagnostic proof. The laboratory tests can show an

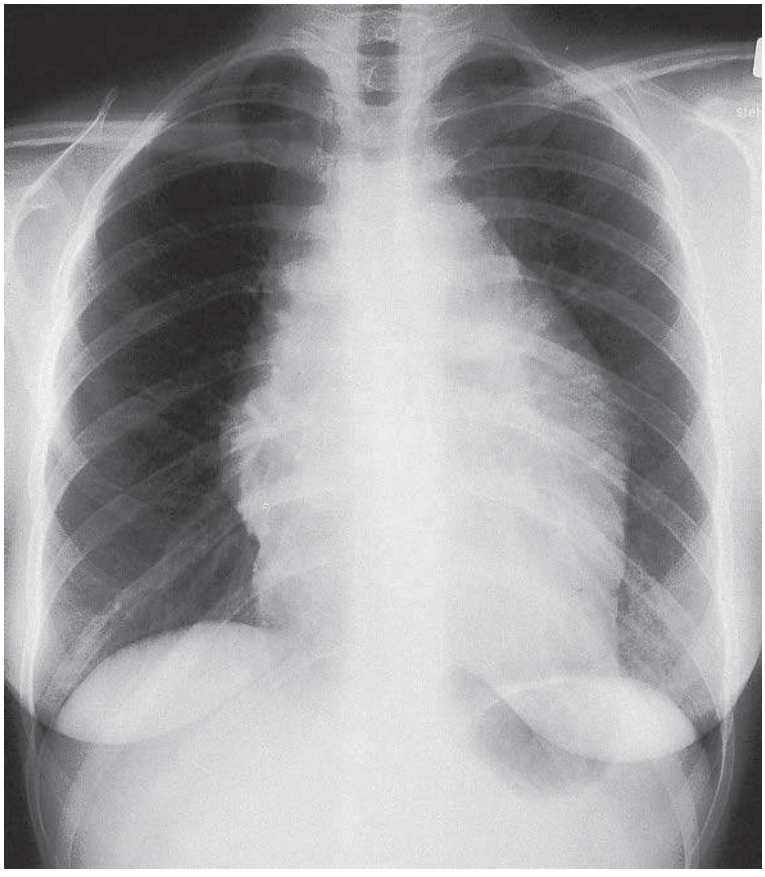

Fig. 14.**17** Extensive involvement of the mediastinal lymph nodes (bulky disease) in a patient with Hodgkin lymphoma.

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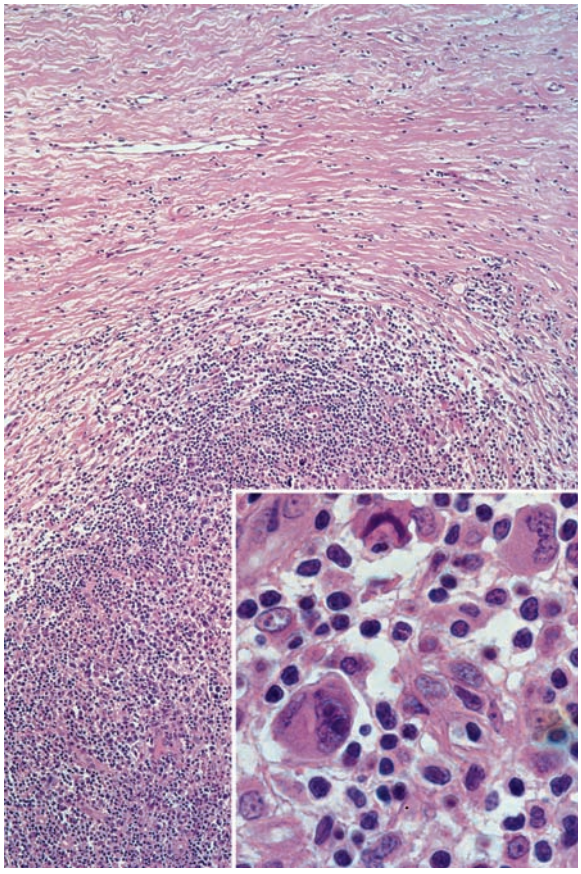

Fig. 14.**18** Hodgkin lymphoma, nodular sclerosis; sclerosis (above), mixed cellularity (below). Insert: higher magnification showing Sternberg giant cells, Hodgkin, and lacunar cells, as well as lymphocytes.

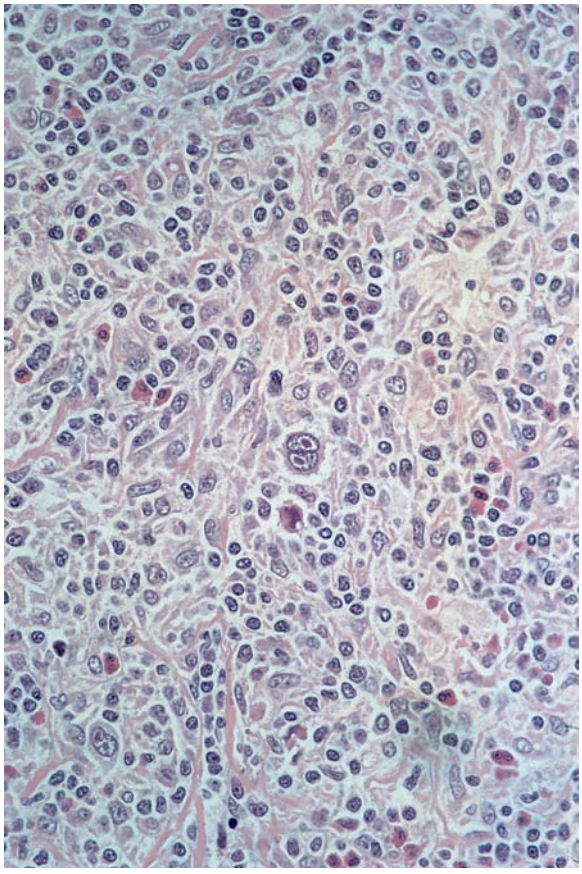

Fig. 14.**19** Hodgkin lymphoma, mixed cellularity (lymphocytes, histiocytes, lacunar cells, in the center a Sternberg giant cell).

accelerated sedimentation rate and increased CRP and LDH levels, and the differential blood count can reveal a lymphopenia and occasionally an eosinophilia. As the disease progresses, the function of the T cells is defective with frequent herpes zoster infections. A Mantoux test that had previously been positive, can now yield negative results.

Histology. The diagnosis is typically based on a *lymph node biopsy*. Nodular lymphocyte predominant Hodgkin lymphoma is a rare diagnosis. The classical Hodgkin lymphoma is diagnosed in most cases, which can be divided into four subtypes:

- classical lymphocytic type
- nodular sclerosis type
- mixed cell type
- lymphopenic type.

Nodular sclerosis type (Fig. 14.**18**) accounts for about 70%, and the mixed cell type (Fig. 14.**19**) about 20–25% of all classical Hodgkin lymphoma diagnoses. The lymphopenic type is very rare.

With the introduction of modern chemotherapeutic reagents, the prognostic value of the different subtypes is no longer relevant.

Stages. The original Ann Arbor classification (Fig. 14.**20**) is still being used with modifications. The most recent version is the Cotswold classification:

- *Stage I:* involvement of one lymph node region or one lymphatic organ (spleen, thymus, Waldeyer ring).
- *Stage II:* involvement of two or more lymph node regions on one side of the diaphragm.
- *Stage III:* involvement of lymph node regions on both sides of the diaphragm.
- *Stage IV:* involvement of one or more extralymphatic organs (bone marrow, liver, etc).

In addition to stages, other classifications are: A = no B symptoms, B = B symptoms, X = bulky disease (more than one-third of the thoracic diameter, or lymph node mass larger than 10 cm), E = extranodal disease.

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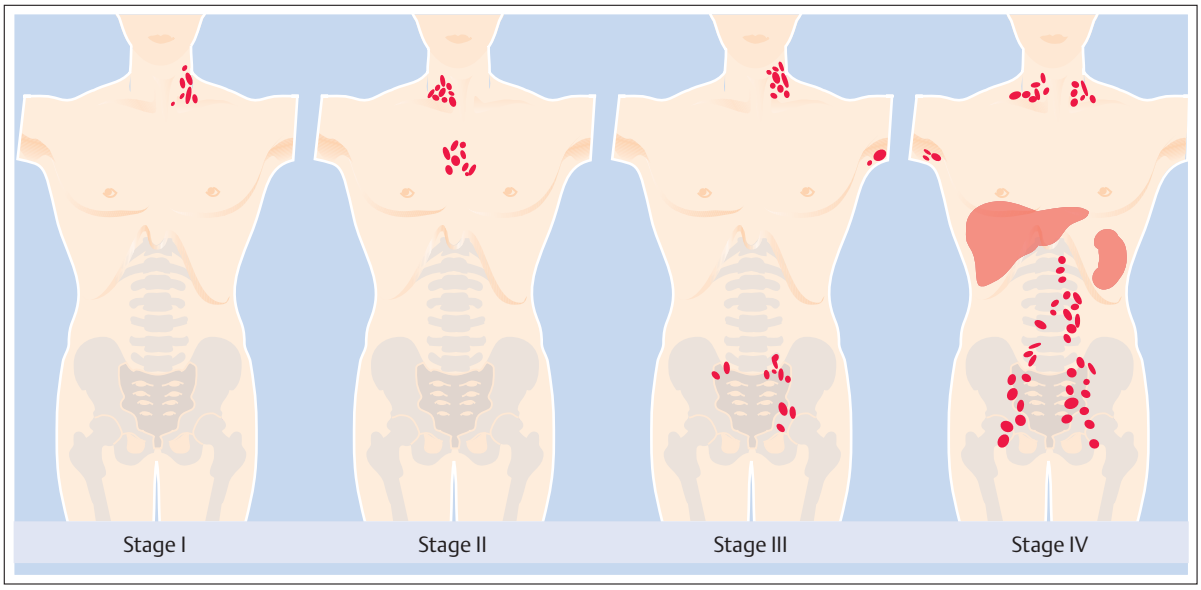

Fig. 14.**20** Ann Arbor staging of Hodgkin lymphoma.

Non-Hodgkin Lymphoma (NHL)

NHL comprises a group of lymphomas with various degrees of malignancy. Based on the prognosis of the different lymphomas, three groups can be differentiated:

- low grade (indolent) lymphomas (median survival of many years)
- intermediary malignant (aggressive) lymphomas (median survival of months or several years)
- high grade (highly aggressive) lymphomas (median survival of several weeks).

The characteristic histologic feature of B-cell lymphoma is a follicular or diffuse proliferation of malignant lymphatic cells, either derived from B cells or T cells. In most cases, NHL is already systemic when diagnosed; bone marrow involvement is not a rare event. The staging classification is analogous to the Hodgkin lymphoma. About 40% of patients diagnosed with NHL will have B symptoms.

Immunocompromised patients (HIV infection, organ transplantation) have a higher risk for NHL. The prevalence of NHL in this risk group contributes to an overall increase of NHL in the population.

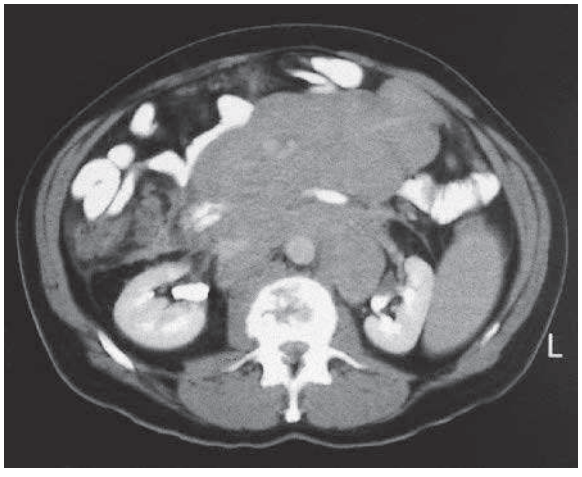

Fig. 14.**21** Computed tomography (CT) scan of the abdomen in a patient with NHL. Large vessels are enclosed by a bulky tumor.

Clinical Symptoms. Most patients have a *peripheral lymphadenopathy*. Lymph nodes are usually soft but can be hard and painful in cases of rapidly progressing disease. Involvement of lymph nodes in the retroperitoneum is common. Mediastinal lymph nodes are involved to a lesser extent. Swelling of the abdomen, in some cases with development of ascites, can be a symptom that leads to diagnosis. In those cases, a bulky tumor in the retroperitoneum and mesentrium is detected in most cases (Fig. 14.**21**). Thoracic outlet syndrome, as a sign for mediastinal bulky disease, can be seen in some cases.

A *primary extranodal disease* occurs in 10–35% of all patients, either as involvement of the gastrointestinal tract, the skin, or other organs. *Primary CNS lymphoma* is diagnosed more frequently since the prevalence of HIV infection and immunosuppressive drug treatment is increasing.

In *indolent lymphoma*, involved lymph nodes can grow and then disappear again (waxing and waning). Liver and spleen infiltration is more significant compared to aggressive lymphoma.

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Diagnosis. The blood smear is usually uncharacteristic. In cases of bone marrow infiltration, anemia, thrombocytopenia, and leukopenia occur. Lymphatic tumor cells can be detected in the peripheral blood.

> Diagnosis of NHL is based on the histopathologic analysis of a lymph node biopsy.

Histology and Classification. Histologic findings are based on the increasing understanding of the normal development of lymphatic cells and the architecture of lymphatic organs. Over the past three decades, different classification systems have been introduced. These are the Kiel classification, IWF (International Working Formulation), REAL (revised European–American classification) and the WHO classification, for example. Progress in understanding the biological and molecular pathways involved has been the driving force behind these classification systems. Tables 14.**11** and 14.**12** summarize the IWF and the WHO classifications, which are, with minor modifications, very similar to the REAL classification.

In general, NHL is categorized into:

- precursor B-cell and T-cell NHL
- mature B-cell and T-cell NHL
- NK-cell NHL.

The differentiation into B-cell, T-cell, and NK-cell NHL is primarily based on the detection of *cell surface antigens*. The most important are:

- T cells: CD2, CD3, CD4, CD7, and CD8
- B cells: CD5, CD19, CD20, CD22, and CD79a.

Typical *chromosomal aberrations* can be detected in many lymphomas, e. g., t(14;18), t(11;14)(q13;q32) leading to molecular biologically detectable changes in BCL2, BCL1, and cyclin D1 levels. The detection of cell-surface antigens and cytoplasmatic immunoglobulins adds to the diagnostic toolbox.

The *histology* of NHL is very broad, ranging from indolent lymphoma with a follicular architecture and differentiated lymphatic cells, to highly aggressive lymphomas with undifferentiated lymphatic cells and diffuse growth (Figs. 14.**22**–14.**25**). Treatment strategies are based on the histological type and the classification into indolent, intermediary, and aggressive lymphomas. We use aggressive chemotherapy for the aggressive lymphomas. Indolent lymphomas can rarely be cured with aggressive chemotherapy. High-dose chemotherapy, with autologous or allogeneic stem cell transplantation, is a promising treatment strategy, but still in its experimental phase.

Some NHL occurs atypically and manifests as CLL or HCL variations. Lymphoblastic (B-cell and T-cell) lymphoma can also occur atypically, with a diffuse primarily bone marrow involvement, which is essentially ALL. These three forms are discussed above under Leukemia. Lymphoplasmocytic lymphoma (Waldenström disease) and plasma-cell neoplasia (multiple myeloma) are accompanied by the production of paraproteins. These entities are discussed below.

Table 14.**11** IWF classification of NHL

Low grade	
A	follicular, small lymphocytic, consistent CLL
B	follicular, predominantly small cleaved cells
C	follicular, mixed small cleaved and large cells
Intermediate	
D	follicular, large cells
E	diffuse, small cleaved cells
F	diffuse, mixed small cleaved and large cells
G	diffuse, large cells (cleaved and noncleaved)
High grade	
H	large cells, immunoblastic
I	lymphoblastic
J	small noncleaved cells, Burkitt
K	others, mycosis fungoides, histiocytic, etc.

Table 14.**12** WHO classification of NHL

B-cell non-Hodgkin lymphoma
Precursor B-cell neoplasm
– precursor B-lymphoblastic leukemia/lymphoma
Mature (peripheral) B-cell neoplasm
– small lymphocytic lymphoma
– B-cell prolymphocytic leukemia
– lymphoplasmacytic lymphoma
– splenic marginal zone B-cell lymphoma
– hairy cell leukemia
– plasma cell myeloma/plasmacytoma
– extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT)
– nodal marginal zone lymphoma
– follicular lymphoma
– mantle cell lymphoma
– diffuse large cell B-cell lymphoma
– Burkitt lymphoma/Burkitt-cell leukemia
T-cell and natural killer (NK)-cell non-Hodgkin lymphoma
Precursor T-cell neoplasm
– precursor T-lymphoblastic lymphoma/leukemia
– blastic NK lymphoma
Mature (peripheral) T-cell and NK-cell neoplasms
– T-cell prolymphocytic leukemia
– T-cell granular lymphocytic leukemia
– aggressive NK-cell leukemia
– extranodal NK-/T-cell lymphoma
– hepatosplenic gamma-delta T-cell lymphoma
– subcutaneous panniculitis-like T-cell lymphoma
– mycosis fungoides/Sézary syndrome
– primary cutaneous anaplastic large cell lymphoma T/null cell
– peripheral T-cell lymphoma, other unclassified
– angioimmunoblastic T-cell lymphoma
– anaplastic large cell lymphoma

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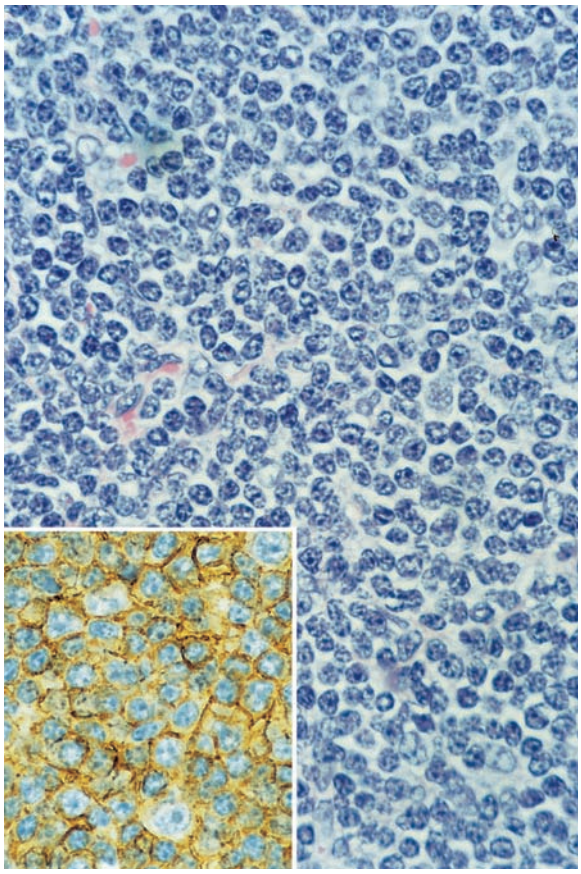

Fig. 14.**22** Lymphocytic diffuse NHL = CLL (B-cell type). Insert: labeled surface marker CD20.

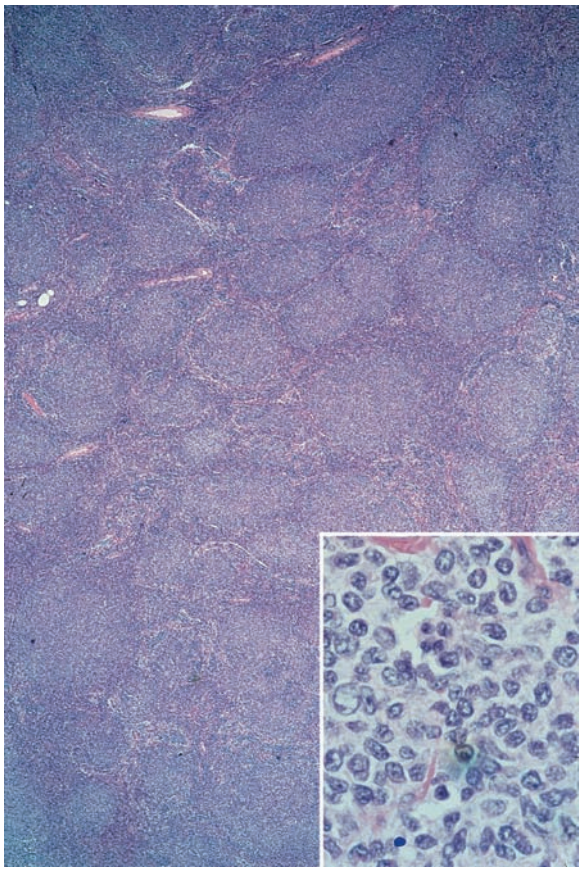

Fig. 14.**23** Follicular NHL. Insert: few centroblasts, many centrocytes.

MALT Lymphoma

Typically, chronic inflammations, such as autoimmune diseases, precede the development of extranodal marginal B-cell lymphomas of the **m**ucosa-**a**ssociated **l**ymphatic **t**issue (MALT). Examples are *Helicobacter pylori*-associated chronic gastritis, Sjögren syndrome, and Hashimoto thyroiditis.

Approximately 50% of all extranodal lymphomas are located in the gastrointestinal tract, especially in the *stomach*. Other locations are lung, head and neck area, eye, skin, thyroid, and the mammary gland. This disease is pathogenetically unique, in that a chronic inflammatory stimulus can give rise to the development of the lymphoma and that antibiotic treatment of *Helicobacter pylori*-induced lymphoma can bring about the elimination of a neoplasm.

Mantle Cell Lymphoma

Typically, mantle cell lymphoma involves lymph nodes. Spleen and bone marrow are also frequently involved. Extranodal manifestation can occur in the gastrointestinal tract. In more than 80% of the cases the translocation t(11;14)(q13;q32) can be detected, which leads to an overexpression of cyclin D1 messenger RNA (mRNA). Median survival is three to five years; there is no realistic chance for a cure with chemotherapy.

Rare Non-Hodgkin Lymphoma

Burkitt Lymphoma. There are three different forms of Burkitt lymphoma, the EBV-associated *endemic* form in African children, the *sporadic* form in western countries, and the *immunodeficiency-associated* form (mostly HIV associated).

Mycosis Fungoides/Sézary Syndrome. There are two variations of the same disease. Mycosis fungoides is characterized by a chronic *T-cell lymphoma of the skin*, whereas

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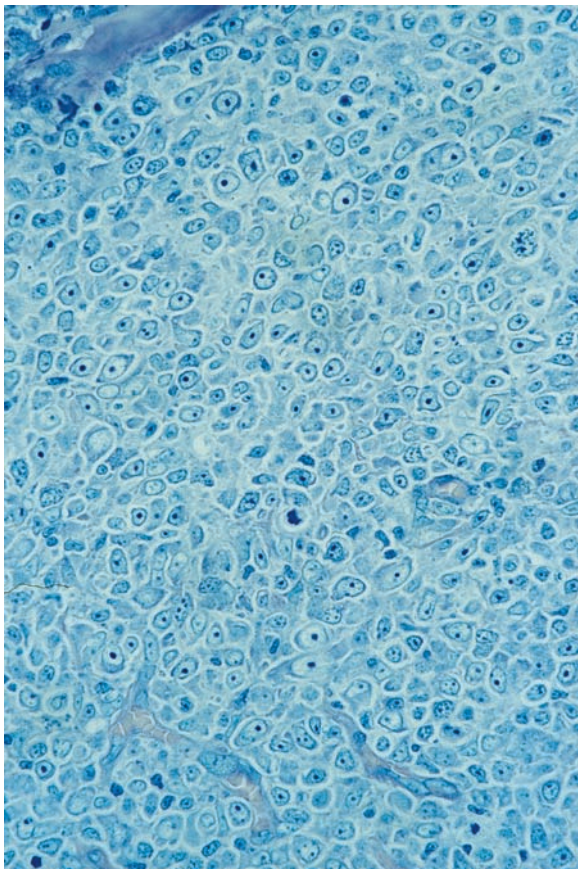

Fig. 14.**24** Polymorphic centroblastic non-Hodgkin lymphoma (NHL).

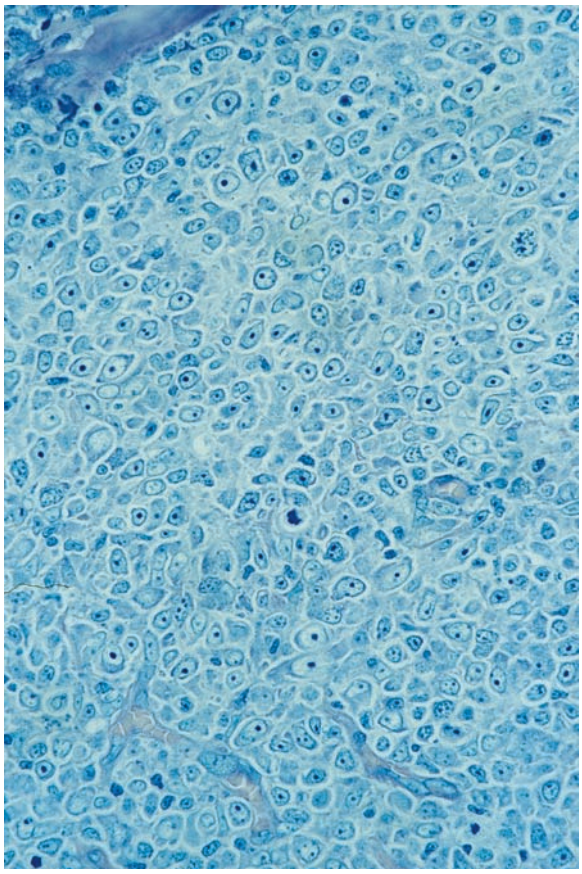

Fig. 14.**25** Immunoblastic non-Hodgkin lymphoma (NHL) (B). Typical plasmoblasts with prominent nucleoli. (Figs. 14.**18**, 14.**19**, 14.**22**–14.**25** provided by R. Maurer, Institute of Pathology, Stadtspital Triemli, Zürich, Switzerland.)

Sézary syndrome characterizes the *generalized disease*. Neoplastic T cells have the typical cerebriformous nuclei.

Adult T-Cell Lymphoma/Leukemia. This lymphoma is associated with the HTLV-1 virus (human T-cell leukemia virus) and occurs in Japan, the Carribean, and in Central Africa. There are different variations of the disease, which can occur as leukemia or as lymphoma.

Angioimmunoblastic lymphadenopathy occurs with a generalized, peripheral lymphadenopathy, with hepatomegaly, and skin rashes. Concurrently, edema, pleural effusions, ascites, and arthritis can occur. Symptoms, such as fever, may accompany hypergammaglobulinemia. The architecture of lymph nodes can be partially destroyed. Polymorphic small to mediumsized lymphocytes can be seen between reactive lymphocytes, eosinophils, histiocytes, and plasma cells. A *proliferation of venules* is characteristic, with a *thick endothelial layer*. This hyperreactive lymphoproliferation is monoclonal and can transform into an aggressive T-cell lymphoma.

Multiple Myeloma and Waldenström Disease

These diseases are characterized by a pathological enrichment of plasma cells in the bone marrow (multiple myeloma) or lymphoplasmocytoid cells in lymph nodes, spleen, and bone marrow (Waldenström) accompanied by a *paraproteinemia* (M gradient in serum electrophoresis). In cases of multiple myeloma, IgG, IgA, IgD, or IgE paraproteins are detectable; in Waldenström disease an IgM paraprotein is found. Like normal immunoglobulins, paraproteins consist of two heavy chains and two light chains. The light chains are divided into two classes, either kappa (κ) or lambda (λ) type chains. Additionally, in 15% of all multiple myelomas, free light chains (Bence Jones protein in the urine) or in exceptional cases only light chains (light-chain disease) or

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only heavy chains (heavy-chain disease) are produced. In very rare cases, there are no immunoglobulins (nonsecretory myeloma) being produced.

In cases where only paraprotein is detectable, without enrichment of lymphoplasmocytoid cells or plasma cells in the bone marrow, the disease is termed *monoclonal gammopathy*. In elderly persons this phenomenon becomes more frequent and, because those patients are at risk of transformation of the disease into multiple myeloma or Waldenström disease, they must be closely monitored.

Multiple Myeloma (Plasma Cell Myeloma)

Clinical Symptoms. Multiple myeloma is a frequent disease. About 15% of all hemotological malignancies are multiple myelomas. It is more frequent in elderly patients and the incidence is three to five per 100 000 per year. The median age at diagnosis is 70. In patients under 30 years of age, multiple myeloma is a very rare disease. Clinical symptoms are weakness, tiredness, loss of physical fitness, symptoms of anemia, recurrent infections, and diffuse arthritis-like symptoms.

Typically, the differential diagnosis of joint pain, (renal dysfunction, spontaneous bone fractures, etc.) leads to the diagnosis of multiple myeloma.

Radiologic Findings. In more than 60% of all cases, osteolytic foci can be detected, typically in the proximal part of the femur, humerus, the ribs, or the skull (characteristic hollow lesions, Fig. 14.**26**). A *generalized osteoporosis* occurs in about 20% of all patients, with signs of compression fractures of the spine (Fig. 14.**27**), in some patients with compression of the spinal cord. Osteosclerotic foci are rare. A similar clinical picture can be observed in POEMS syndrome with **p**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **M** gradient in serum electrophoresis, and **s**kin lesions.

Diagnosis. The detection of hypergammaglobulinemia, by a sharp peak (M gradient) in the gamma, beta, or alpha region of the serum electrophoresis (Fig. 14.**28**), which appears monoclonal in the immune electrophoresis, is diagnostically decisive. The ESR is greatly accelerated. In addition, in 75% of patients, light chains can be detected in the urine (Bence Jones protein). About 50% of the paraproteins are IgG (typically > 35 g/L), 20% are IgA (> 20 g/L), and 2% are IgD. IgG and IgA paraproteins have 60–70% κ light chains, IgD paraproteins have more than 90% λ light chains. Biclonal gammopathies, as well as the absence of paraproteins (nonsecretory myeloma) are rare. The IgE myeloma is very rare. In 15% of all cases, a monoclonal light chain in the serum is not detectable by serum electrophoresis and must be detected in the urine. Heavy-chain disease is again a rare disease. Bacterial infections occur due to the suppression of normal myelogenesis with low levels of normal immunoglobulins. Paraproteins can occur transiently in other diseases like hepatitis C or lymphoproliferative diseases.

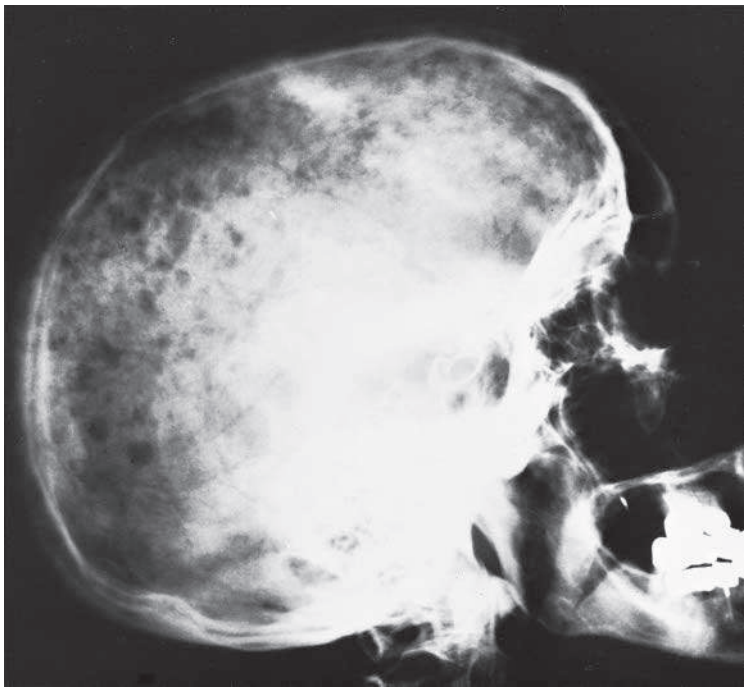

Fig. 14.**26** Radiograph of the skull showing multiple hollowed-out lesions in a patient with multiple myeloma.

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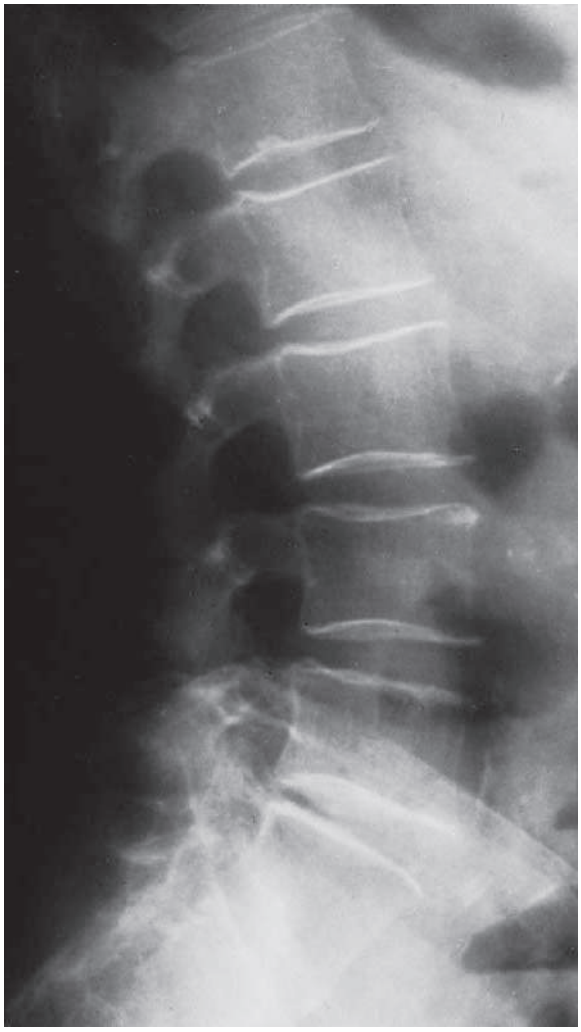

Fig. 14.**27** Radiograph of the spine showing diffuse osteoporosis in a patient with multiple myeloma.

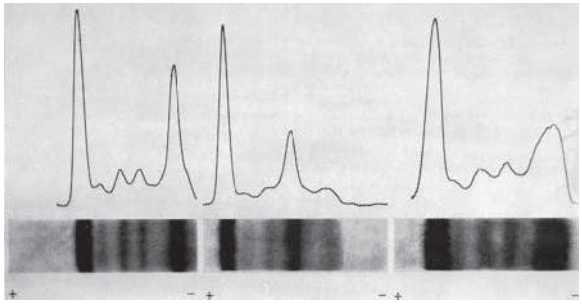

Fig. 14.**28** Paper electrophoresis in a patient with multiple myeloma (M gradient in the γ and β fraction) and liver cirrhosis (broad γ peak).

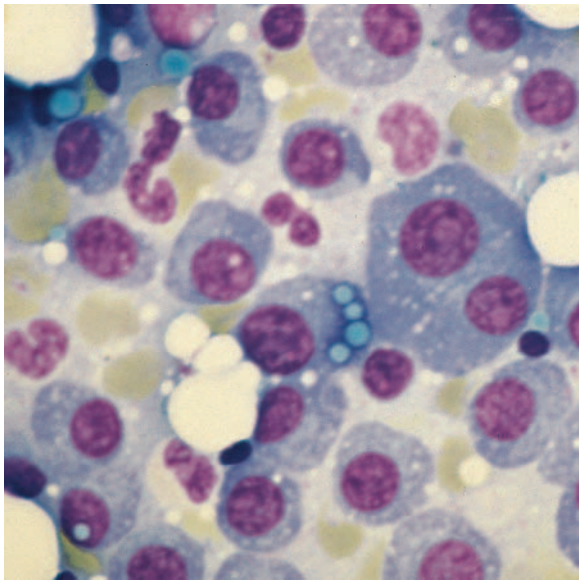

Fig. 14.**29** Multiple myeloma with highly polymorphic plasma cells.

Patients have anemia and the blood smear shows signs of agglutination (rolls of erythrocytes). Leukopenia and thrombopenia occur in later stages of the disease. The anemia is a sign of suppression of normal myelogenesis, as well as low erythropoietin production. This is due to impaired renal function, caused by tubular damage of light chains proteins. Hypercalcemia is frequent. The bone marrow shows a clearly diffuse proliferation of plasma cells (typically > 30%) which are either highly differentiated (phenotypically normal), or show signs of dedifferentiation up to plasmoblastic myeloma (Fig. 14.**29**). Plasmocytoma is a monolocular myeloma in the bone marrow or is an extramedullary localized disease.

Differential Diagnosis and Classification. Classical myeloma must be differentiated from *monoclonal gammopathy* (MGP) and *smoldering myeloma* (SMM). MGP shows a weaker M gradient, which is sometimes a coincidental finding in the investigation of an elevated ESR, for example. In some patients with MGP, a classical multiple myeloma or Waldenström disease may develop over time. SMM shows a strong M gradient and fulfils the criteria for diagnosis of multiple myeloma. However, patients are completely asymptomatic and have no bone lesions or other symptoms of multiple myeloma. Tab. 14.**13** summarizes the WHO criteria for the diagnosis of MGP and SMM. Tab. 14.**14** lists the diagnostic criteria for multiple myeloma.

Staging. The Durie and Salmon staging system is shown in Tab. 14.**15**. The three stages have a *prognostic value*, such that the median survival of patients in:

- stage I is > 60 months
- stage II is 41 months
- stage III is 23 months.

Impairment of renal function worsens the prognosis significantly.

Modern treatment of multiple myeloma can usually temporarily reduce symptoms and prolong survival.

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Table 14.**13** Criteria for monoclonal gammopathy of unknown significance (MGUS) and "smoldering myeloma" (SMM)

	MGUS	SMM
Plasma cells in bone marrow	< 10 %	10–30 %
M gradient	IgG < 35 g/L, IgA < 20 g/L, IgM	IgG > 35 g/L, IgA > 20 g/L
Osteolytic lesions	negative	negative
Symptoms	negative	negative

Table 14.**14** Criteria for plasma-cell myeloma (multiple myeloma)

Major criteria
- > 30 % Plasma cells in bone marrow aspirate
- Plasma cell tumor on biopsy result
- Monoclonal band on electrophoresis > 35 g/L for IgG, 20 g/L for IgA, or > 1 g of light chains excreted in urine per day

Minor criteria
- 10–30 % Plasma cells in bone marrow aspirate
- Abnormal monoclonal band but levels less than for major criteria
- Lytic bone lesions
- Immunosuppression (IgG < 6 g/L, IgA < 1.0 g/L, IgM < 0.5 g/L)

The diagnosis of multiple myeloma requires:
- one major criterion plus one minor criterion *or*
- three minor criteria (including at least the first two minor criteria) *and*
- a symptomatic patient.

Table 14.**15** The Durie–Salmon staging system for plasma-cell myeloma

Stage I
All of the following:
Hemoglobin > 100 g/L
Serum calcium value normal
Bone radiograph normal
Bence Jones protein < 4 g/24 h
Low M-component production rate (IgG value < 50 g/L; IgA value < 30 g/L)

Stage II
Neither stage I nor stage III criteria are met

Stage III
Hemoglobin value < 85g/L
Serum calcium value > 12 mg/dL
Advanced lytic bone lesions
High M-component production rate (IgG value > 70 g/L; IgA value > 50 g/L
Bence Jones protein > 12 g/24 h

However, as a rule, (including aggressive treatment modalities such as high-dose chemotherapy with autologous stem cell transplantation) it cannot cure the disease.

Amyloidosis. Every diagnosis of paraproteinemia must also consider the possibility of amyloidosis. Primary (idiopathic) amyloidosis and secondary amyloidosis as a consequence of multiple myeloma are characterized by an AL (amyloid light chain) amyloid protein, which is a product of altered light chains. Such proteins can deposit in organs such as heart, liver, kidney, intestine, nerves, or tongue and cause symptoms including heart and kidney failure and polyneuropathy. Amyloidosis as a consequence of a long-standing, usually untreated, chronic inflammatory disease and is characterized by an AA (amyloid A) amyloid protein. Familiar amyloidosis, caused by various amyloid proteins, is rare.

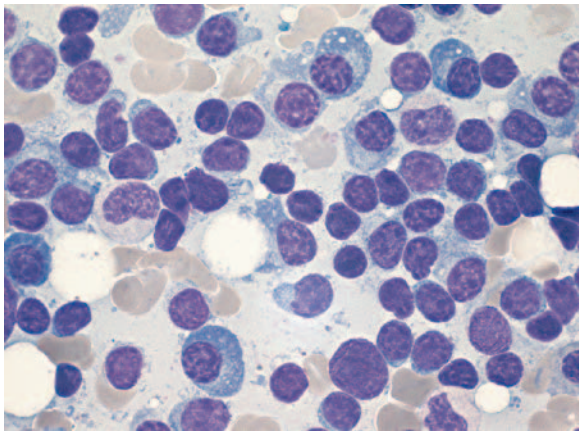

Fig. 14.**30** Bone-marrow aspiration in Waldenström macroglobulinemia (WM) with lymphoplasmacytic infiltration.

Waldenström Disease (Lymphoplasmocytic Lymphoma, Macroglobulinemia)

Clinical Features and Diagnosis. Waldenström disease is a rare disease occurring at an average age of 65. An IgM paraprotein (in most cases > 20 g/L) is responsible for the disease, which in 10–30 % of patients leads to a *hyperviscosity syndrome* causing impairment of retinal and cerebrovascular blood flow. A characteristic finding is *fundus paraproteinemicus* with dilated retinal veins and fundal bleeding. *Spontaneous bleeding* is frequent and may be due thrombocytopenia or hyperviscosity syndrome or may result from the binding of IgM paraprotein to platelets and coagulation factors. Paraprotein desposits may form in the skin, intestine, and peripheral nerves, leading to *diarrhea and polyneuropathy*. The abnormal IgM may have either cryoglobulin or cold agglutinin properties. This may result in cryoglobulinemia or a cold-antibody type of autoimmune hemolysis.

Anemia is usually present at the time of diagnosis. Thrombocytopenia is less common and is usually less pronounced but is also a consequence of splenomegaly. On histologic examination, the lymph nodes, spleen, and bone marrow in particular are found to be diffusely permeated by lymphoplasmocytic cells (Fig. 14.**30**).

Prognosis is better than in multiple myeloma. The median survival is 5 years, and 20 % of the patients live more than 10 years.

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14.3 Histiocytosis

Histiocytosis encompasses various benign (reactive) and malignant neoplastic diseases, whose proliferating tissues consist of various organ-localized macrophages, which, in turn, are derived from monocytes that have left the bloodstream. Malignant histiocytosis symptoms overlap with those of acute monocytic/monoblastic leukemia (M5a, b, see Acute Myelogenous Leukemia, above). Histiocytosis can be classified as follows:

- Langerhans cell histiocytosis
- non-Langerhans cell histiocytosis
- malignant histiocytosis.

Langerhans Cell Histiocytosis

This rare disease occurs in children and young adults. The cell of origin is the Langerhans cell, an antigen-presenting cell derived from the macrophage lineage. The classification in eosinophilic granuloma, Hand–Schüller–Christian disease, and Abt–Letterer–Siwe disease is no longer used, instead the pattern of organ involvement is characterized. Interestingly, proliferating cells are monoclonal, and thereby represent a disease in between the benign reactive and malignant proliferative classifications. In two-thirds of patients, only one organ is involved, in one-third, two or more organs are involved:

- *Eosinophilic granuloma* involves the skull, mandibula, sometimes the spine, pelvis, or the long bones e.g., femur and humerus. Lesions with a punched-out contour are characteristic, and spontaneous fractures occur.
- In *Hand–Schüller–Christian disease* the lesions are also localized to the skull and mandibula, as in eosinophilic granuloma. Osteolysis is more frequent, which leads to the characteristic radiologic finding. Infiltration of the retrobulbar space or hypophysis can lead to exophthalmus or diabetes insipidus, respectively. Typically, there is involvement of spleen, liver, lymph nodes, and lungs.
- The acute form of disseminated Langerhans cell histiocytosis, previously designated as *Abt–Letterer–Siwe disease*, is associated with high fever, anemia, thrombopenia, and enlargement of lymph nodes, liver, and spleen.

Histology. Large ovoid mononuclear cells with folded nuclei, poorly defined nucleoli, and weakly eosinophilic cytoplasm can be observed. In addition, scattered eosinophils and lymphocytes are seen. The detection of Birbeck granules by electron microscopy is characteristic.

Non-Langerhans Cell Histiocytosis

This group of diseases is characterized by a proliferation of histiocytes and lymphocytes that are not Langerhans cells. Specific examples are *familiar hemophagocytotic lymphohistiocytosis* and *reactive hemophagocytosis syndrome*. The latter can be caused by viral infections or occurs as a paraneoplastic syndrome with malignant lymphoma and acute monoblastic leukemia (AML M5 [FAB]). Characteristic features are excessive phagocytosis of erythrocytes and thrombocytes and less pronounced phagocytosis of granulocytes from macrophages in the bone marrow resulting in a peripheral pancytopenia.

Malignant Histiocytosis. Rare diseases like histiocytic sarcoma, Langerhans cell sarcoma, and other very rare, malignant disorders of dendritic cells belong to this group.

14.4 Reactive Lymphadenopathy and/or Splenomegaly

In addition to metastatic solid tumors and malignant hematopoietic malignancies, some inflammatory processes can lead to lymphadenopathy and/or splenomegaly (see Chapter 4).

Examination of Lymph Nodes and Spleen

Enlarged Lymph Nodes. Depending on the disease, lymph nodes can be enlarged locally or in general.

> The inspection and examination of all lymph node locations is part of every basic physical examination.

It is important to examine lymph nodes for the following qualities:

- size
- consistency
- painfulness
- mobility.

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Reactive (*infectious or inflamed*) enlarged lymph nodes can vary in size, are typically soft, painful, and mobile relative to the surrounding tissue. In chronic inflammations, lymph nodes can become hard and they lose their mobility. Metastatic infiltrated lymph nodes are typically hard and indolent, most of the time still mobile; lymphoma-infiltrated lymph nodes are typically softer and also indolent.

Splenomegaly. The normal spleen is covered by the lower thorax and typically not palpable. A spleen that can be examined by palpation is always pathologically enlarged. The estimated size should be recorded below the thoracic apertura. A more accurate calculation of the size can be done with ultrasound. Figure 14.**31** shows how spleen size correlates to different diseases.

Diagnosis. A number of imaging techniques can be used to analyze the extent of enlarged lymph nodes and splenomegaly:

- ultrasound
- thorax radiograph (mediastinal and hilar, lymph nodes)
- CT scan
- MRI
- positron emission tomography (PET) for particular problems.

Cytology and Histology. In cases where there is no clear correlation of enlarged lymph nodes to inflammation or already known malignant diseases, a biopsy of the enlarged lymph nodes with histological examination should always be performed. Cytological analyses can be misleading and should be confirmed by histology.

Localized Lymphadenopathy

Localized viral, as well as bacterial, infections of the skin, the nasopharynx, etc. can cause reactive swelling of regional lymph nodes. Regional cervical lymph nodes as well as lymph nodes in the axilla, the cubital area, and the groin can be examined by palpation. Other areas must be analyzed by imaging techniques.

Diseases that typically accompany reactive regional lymphadenopathy are: lymphadenitis, tuberculosis, syphilis, lymphogranuloma inguinale, *Bartonella* infections, and sarcoidosis.

Generalized Lymphadenopathy with or without Splenomegaly

Systemic infections like toxoplasmosis, mononucleosis (Epstein–Barr virus), Cytomegalovirus infection, and HIV infection can lead to a generalized lymphadenopathy, sometimes after initial swelling of regional lymph nodes. Additional symptoms like fever, fatigue, splenomegaly, and elevated levels of liver enzymes are frequent. The blood smear shows atypical lymphocytes (virocytes), in cases of viral infections in general and particularly in cases of mononucleosis.

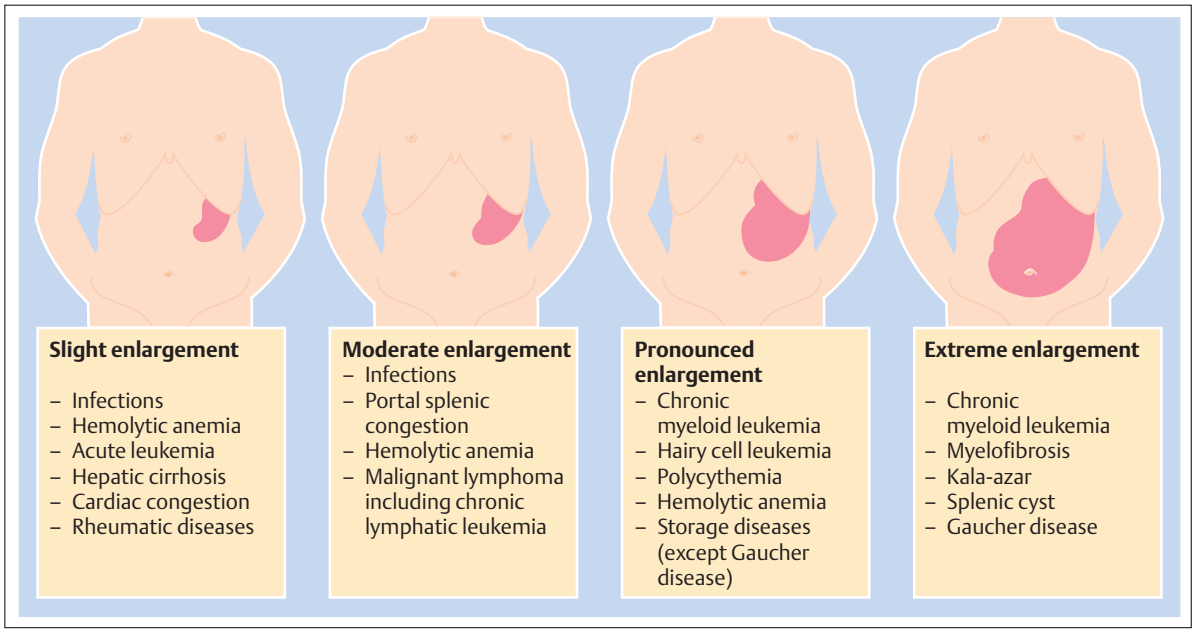

Fig. 14.**31** Relevance of spleen size for differential diagnosis.

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Diagnosis. Depending on the type of infection, additional serologic tests to identify specific antibodies, microbiologic cultures, molecular biological analysis using PCR, or biopsy may be necessary.

A biopsy for histological analysis should always be performed if there is any doubt as to the origin or benign or malignant nature of a lymph node swelling.

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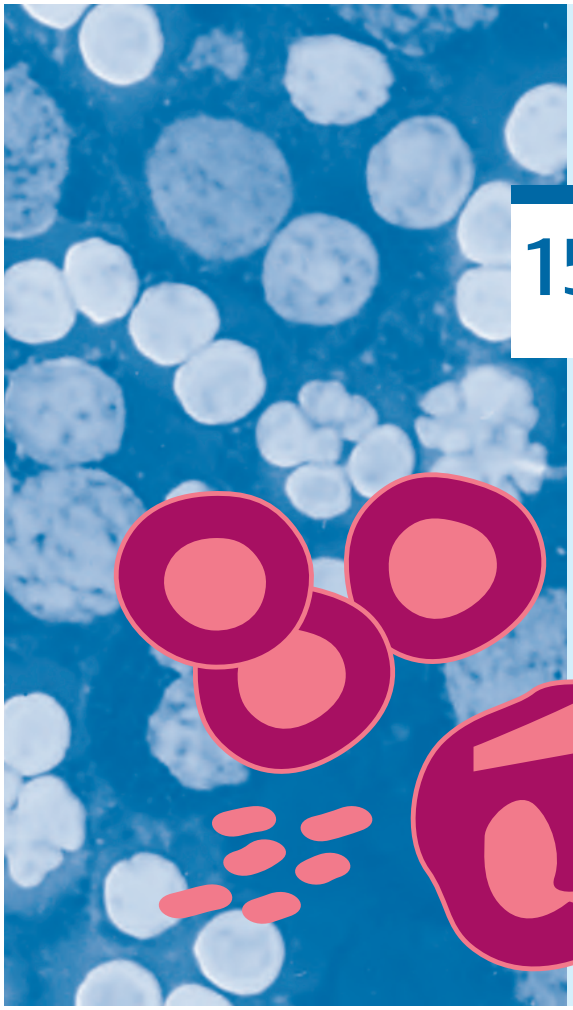

15 Bleeding Diathesis and Thrombophilic Diathesis

E. Baechli and T. Bombeli

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Abbreviations (listed in alphabetical order):

AD	autosomal dominant
ADAMTS-13	**a** **d**isintegrin **a**nd **m**etalloprotease with **t**hrombo**s**pondin motifs, a vWF–splitting protease
ADP	adenosine diphosphate
ALK-1	activin receptor-like kinase 1
AML	acute myelogenous leukemia
APA	antiphospholipid antibody
APC	activated protein C
aPTT	activated partial thromboplastin time
BSS	Bernard–Soulier syndrome
CHS	Chediak–Higashi syndrome
DIC	disseminated intravascular coagulation
EBV	Epstein–Barr virus
EDTA	**e**thylene**d**iamine **t**etra**a**cetic acid (an anticoagulant)
ET	essential thrombocythemia
F	factor
Fbg	fibrinogen
GP IIbIIIa	glycoprotein IIbIIIa
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HPS	Hermansky–Pudlak syndrome
HUS	hemolytic uremic syndrome
Ig	immunglobulin
INR	international normalized ratio
ITP	idiopathic thrombocytopenic purpura
LMWH	low-molecular-weight heparin
LYST	name of the gene whose changes are responsible for Chediak–Higashi syndrome
MRC	membrane receptor complex
NSAID	nonsteroidal antiinflammatory drug
OAC	oral anticoagulation
PAI-I	plasminogen activator inhibitor type I
PS	pentasaccharide, fondaparinux (Arixtra)
PV	polycythemia vera
PF4	platelet factor 4
PFA-100	platelet function analyzer 100 (for whole blood aggregometry)
PT	prothrombin time
QPD	Quebec platelet defect
SPD	storage pool defect (decreased, absent, or nonfunctioning granules contained in platelets; two subtypes: alpha (α) granules and dense (δ) granules
tPA	tissue plasminogen activator
TTP	thrombotic thrombocytopenic purpura
UFH	unfractionated heparin
WASP	Wiskott–Aldrich syndrome protein
vWF	von Willebrand factor

Importance of Coagulation in Disease Processes

Acquired coagulation disorders are often the result of an underlying disease that has shifted the balance between the tendency to clot and the tendency to bleed. In some conditions, the presence of a coagulation disorder has implications for the prognosis of the underlying disease. Disseminated intravascular coagulation (DIC) in the setting of sepsis or venous thrombosis in cancer is considered a poor prognostic sign.

For the first time since the advent of the platelet aggregation inhibitor, acetylsalicylic acid (aspirin) and of heparin-type and coumarin-type anticoagulants, medications with new mechanisms of antithrombotic action have been introduced into clinical use during recent years. These drugs inhibit platelet function by acting as adenosine diphosphate (ADP) receptor antagonists (clopidogrel) or glycoprotein IIbIIIa-receptor antagonists (abciximab, tirofiban). The thrombin inhibitor, ximelagatran is a new oral anticoagulant that is awaiting clinical approval. A recombinant form of human activated protein C, drotrecogin alfa activated (brand name Xigris), has been shown to be beneficial for DIC in patients with sepsis.

Congenital thrombophilia has been the subject of extensive research in recent years. With the discovery of congenital resistance to activated protein C (APC resistance), the FV–Leiden gene mutation, and the prothrombin gene mutation, we can now account for approximately 60% of familial thrombophilia cases. Increasingly, it has been recognized that these inherited forms of venous thrombophilia often become symptomatic only if acquired thrombogenic factors are additionally present (e.g., immobilization, childbirth, aging, estrogenic effects).

Principles of Laboratory Diagnosis in Coagulation Disorders

The foundation for the clinical therapeutic management of both hemorrhagic and thrombotic disorders is an accurate and comprehensive laboratory work-up. Serial measurements are often necessary for establishing a diagnosis and evaluating response to treatment. This is particularly important in patients with DIC.

Global Tests. The laboratory work-up generally begins with global tests that evaluate the coagulation process as a whole. Specific analyses are second-line studies that should follow the global tests. Moreover, a distinction is drawn between tests for primary (platelet-induced) hemostasis and tests for secondary (plasmatic) hemostasis. The global tests that are most widely used in clinical laboratories are reviewed in Tab. 15.**1**.

Specific Coagulation Tests. The results of the global tests direct the selection of more specialized coagulation tests. For example, if a prolonged closure time in whole blood aggregometry (PFA-100) raises suspicion of a defect in primary hemostasis, then further laboratory analysis should be based on classical platelet aggregation test-

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ing and flow cytometry. Platelet aggregation testing evaluates platelet function in vitro in response to the presence of an agonist such as collagen or ADP. Flow cytometry measures the composition of surface receptors and the content of α-granules and δ-granules in the platelets. If the prothrombin time or activated partial thromboplastin time (aPTT) is found to be prolonged, individual coagulation factors should be measured so that the coagulation disorder can be characterized more precisely (Figs. 15.**1**, 15.**2**). In patients with a thrombotic disorder, it is also necessary to determine coagulation activation markers (mostly D-dimers), coagulation inhibitors (e. g., protein C, protein S, and antithrombin), and antiphospholipid antibodies (see Thrombophilic Diathesis, p. 466). Figs. 15.**1** and 15.**2** show the standard diagnostic algorithms that are applied in patients with a prolonged prothrombin time and a prolonged aPTT. The process of plasmatic coagulation and fibrinolysis is shown schematically in Fig. 15.**3**.

Table 15.**1** Laboratory methods for evaluating coagulation disorders

	Test	Method	Detectable disorders	Comments
Primary hemostasis	Bleeding time	Standard 5 × 1 mm lancet puncture in the forearm (Simplate) with a blood pressure cuff inflated to a constant pressure of 40 mmHg; normally < 8 min	Prolonged in thrombocytopenia, thrombocytopathy, vWF disease, or a vascular disorder	Low sensitivity to disorders of primary hemostasis, low predictive value for intraoperative bleeding risk
	Platelet function analyzer (PFA-100)	Determines the clotting time of blood flow through a membrane in a microcapillary system; occlusion occurs by platelet aggregation	Prolonged in thrombocytopenia, thrombocytopathy, or vWF disease	Very sensitive to aspirin use, vWF disease, and severe thrombocytopathies
Primary and secondary hemostasis	Thrombo-elastography	Detection of increased rigidity of a clot due to plasmatic and platelet induced coagulation disturbances with a sensor, which gives a continuous readout in a whole blood sample	"Hemorrhagic curve" in thrombocytopenia, thrombocytopathy, factor deficiency, or anticoagulant therapy; "fibrinolytic curve" in DIC, fibrinolytic therapy, or liver transplantation; "thrombotic curve" in thrombocytosis, treatment with coagulation factors, DIC, etc.	Very sensitive to disorders of primary and secondary hemostasis, reasonably good predictive value for intraoperative bleeding, effective in the detection of hyperfibrinolytic states and prothrombotic states
Secondary hemostasis	Prothrombin time (Quick test, INR)	Measures the time to formation of a soluble fibrin clot after the addition of tissue factor, calcium, and phospholipids (tissue thrombokinase) to the plasma	Prolonged in hereditary or acquired deficiencies of fibrinogen, FII, FV, FVII, and FX, also in vitamin K deficiency (coumarin therapy, nutrition)	Sensitivity varies for different factor deficiencies and also depends on the reagent; very sensitive to vitamin K deficiency and coumarin therapy; spontaneous bleeding may occur with a prothrombin value < 10%
	Activated, partial thromboplastin time (aPTT)	Measures the time to the formation of a soluble fibrin clot after the addition of an activator (e. g., ellagic acid), calcium, and phospholipids to the plasma	Prolonged in hereditary or acquired deficiencies of fibrinogen, FII, FV, FVIII, FIX, FX, FXI, and FXII, also in patients on heparin therapy	Sensitivity varies for different factor deficiencies and also depends on the reagent; very sensitive to unfractionated heparin

DIC: disseminated intravascular coagulation; F: factor; INR: international normalized ratio; vWF: von Willebrand factor.

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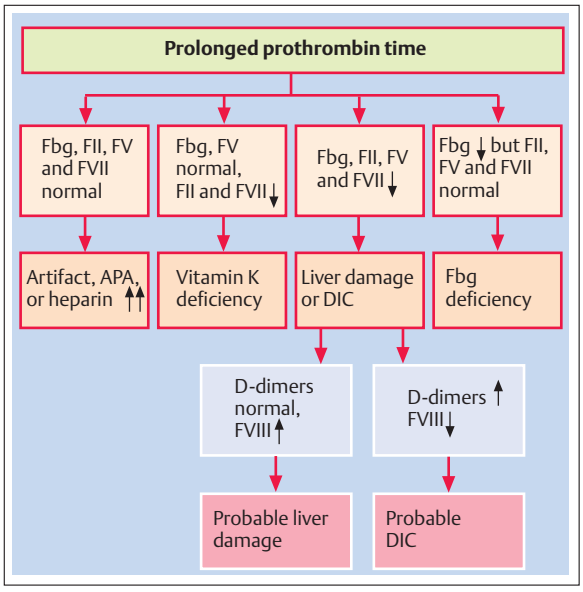

Fig. 15.**1** Diagnostic algorithm for investigating a prolonged prothrombin time. APA: antiphospholipid antibodies; DIC: disseminated intravascular coagulation; F: factor; Fbg: fibrinogen.

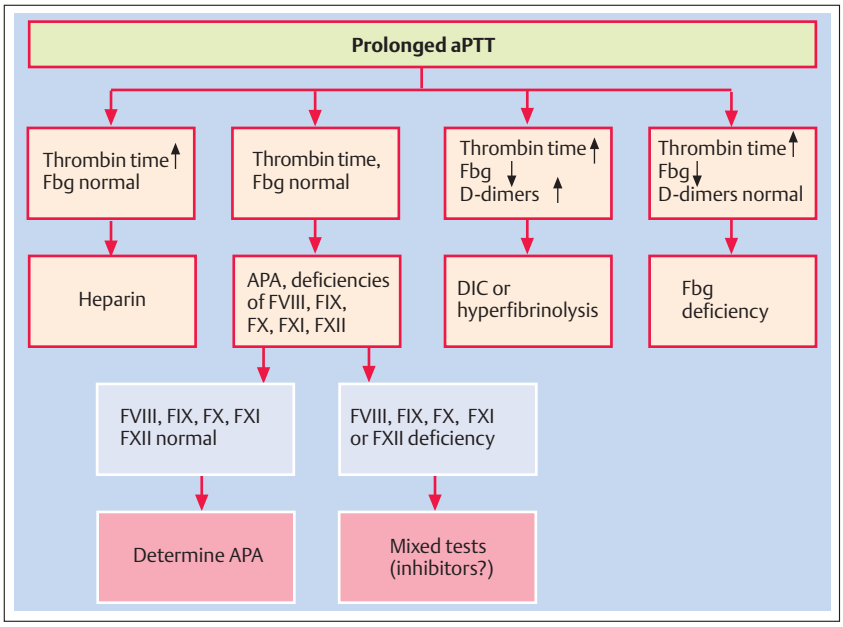

Fig. 15.**2** Diagnostic algorithm for the further investigation of a prolonged activated partial thromboplastin time (aPTT). APA: antiphospholipid antibodies; DIC: disseminated intravascular coagulation; F: factor; Fbg: fibrinogen.

15.1 Bleeding Diathesis

A bleeding diathesis (hemorrhagic diathesis) is a condition characterized by an *increased susceptibility to bleeding*. We distinguish between congenital and acquired forms of bleeding diathesis, which are further classified as disorders of primary or secondary hemostasis and vascular pathology. Primary hemostasis may be compromised due to abnormalities of platelet count or platelet function, and secondary hemostasis may be impaired due to a change in plasmatic coagulation factors. Vascular pathology may increase the susceptibility to bleeding by increasing the permeability of blood vessels. The types of bleeding diathesis most commonly seen in routine settings are acquired forms caused by medications or organic diseases such as gastric bleeding due to aspirin use or a bleeding diathesis secondary to cirrhosis of the liver.

The *medical history, type of bleeding, and laboratory tests* are the keys to recognizing the severity of the bleeding diathesis and instituting appropriate precautionary measures. When a new bleeding diathesis

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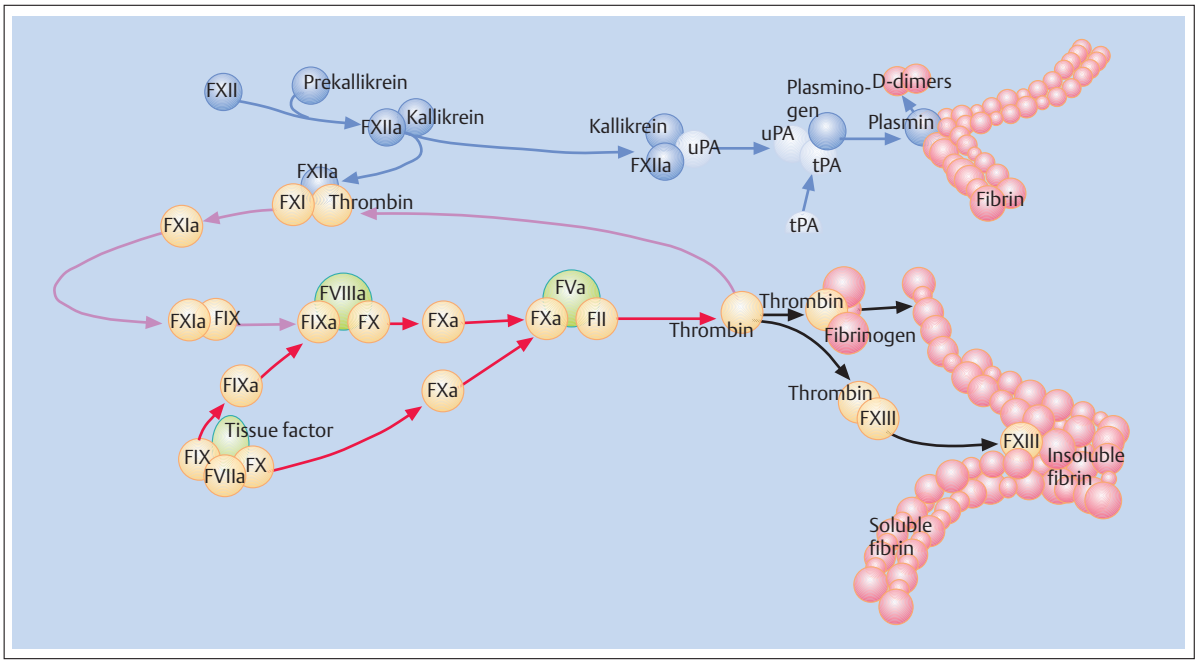

Fig. 15.**3** Coagulation and fibrinolytic pathways. Schematic representation of the three phases of the coagulation process leading to fibrin formation and the process (fibrinolysis) by which fibrin is broken down again.
Phase 1 (initiation phase, red arrows): activated factor VII (FVIIa) binds to tissue factor (tissue thrombokinase) exposed on cells. This step activates FX to FXa, which is then helped by FVa in converting FII to FIIa (thrombin). This factor complex (FXa, FVa, and FII) is called the prothrombinase complex.
Phase 2 (amplification phase, purple arrows): the small amount of thrombin formed in the initiation phase is still not sufficient for activating fibrinogen to fibrin. Through a positive feedback mechanism, thrombin activates FXI to FXIa, which then activates FIX to FIXa. At the same time, FIX is also activated by the FVIIa/tissue factor complex. The newly formed FIXa now activates FX to FXa with the aid of FVIIIa. This factor complex (FIXa, FVIIIa, FX) is called the tenase complex.
Phase 3 (propagation and stabilization phase, black arrows): now present in large amounts, thrombin activates fibrinogen, which spontaneously polymerizes to form soluble fibrin strands. Meanwhile, the thrombin also activates FXIII to FXIIIa, which crosslinks the soluble fibrin strands to form a stable meshwork (insoluble fibrin). Thrombin also sustains the coagulation process by its continuing activation of FV and FVIII (not shown).
Fibrinolysis (gray arrows): the fibrin is broken down by plasmin to produce fibrin fragments of varying size. Among the breakdown products are D-dimers (composed of two D fragments from two fibrin molecules), which are frequently determined in routine tests. Plasmin is produced by the activation of plasminogen, which is activated mainly by urokinase (uPA) and tissue plasminogen activator (tPA). Several mechanisms are responsible for the release and activation of uPA and tPA, such as activation by FXIIa and kallikrein. F: factor; uPA: urokinase; tPA: tissue plasminogen activator.

occurs in adulthood, it often stems from the interaction of several pathogenic factors. Gastrointestinal bleeding, for example, may reflect a combination of drug-induced platelet dysfunction (e. g., aspirin, NSAIDs) and the presence of a local inflammatory process (gastritis) or lesion (ulcer).

Clinical Approach

A detailed medical history and physical examination are crucial in the investigation of a bleeding diathesis. The examiner should be sure to cover the following points when taking the history and performing the physical examination:

Family History:

- Questions regarding spontaneous bleeding or bleeding complications relating to surgical operations or childbirth that have occurred in relatives.
- Questions regarding early deaths in relatives.
- Questions regarding mode of inheritance:
  - autosomal dominant (the disease is present in every generation)
  - X-linked (only male family members are affected).
- Questions regarding the type of bleeding:
  - mucosal bleeding occurs mainly in disorders of primary hemostasis
  - postoperative or posttraumatic bleeding occurs mainly in disorders of secondary hemostasis.

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Table 15.**2** Overview of different types of bleeding and possible underlying coagulation disorders

Type of bleeding	Description	Distribution	Causative disorders
Purpura (Fig. 15.**4**)	Pinhead-sized hemorrhages in the skin	Often occur in clusters on the arms or legs	Thrombocytopathy, thrombocytopenia
Petechiae (Figs. 15.**5**, 15.**6**)	Small red spots caused by bleeding from capillaries in the skin and mucosae; larger than purpura	Mostly on the lower extremities (do not confuse with telangiectasias)	Thrombocytopathy, thrombocytopenia, vascular disorder
Bruising, ecchymosis (Fig. 15.**7**)	Bleeding covering a larger area, often after mild trauma; hemorrhagic areas are not palpable	Forearms and legs	Thrombocytopathy, thrombocytopenia, vascular disorder
Hematoma (Figs. 15.**8**, 15.**9**)	Bleeding into the skin and subcutaneous tissue, sometimes into muscle; palpable bleeding with swelling	Often follows trauma, or may occur spontaneously in the abdominal wall (e. g., due to anticoagulant therapy or coughing)	Plasmatic coagulation disorder
Bleeding into organs, such as hemarthrosis (Fig. 15.**10**)	Swelling or mass with loss of function	Joints (especially in hemophiliacs), brain (e. g., anticoagulant bleeding)	Plasmatic coagulation disorder

Fig. 15.**4** Purpuric rash on the lower leg of a patient with idiopathic thrombocytopenic purpura (ITP). The cutaneous hemorrhages resemble pinpricks.

Personal History:

- Often it is difficult for patients to assess the severity of their bleeding diathesis. Patients should be asked specifically about objective details such as the need for a transfusion during a bleeding complication and whether they were later diagnosed with iron deficiency anemia.
- Questions regarding the type of bleeding and the age at which bleeding first occurred are important in assessing the severity of the bleeding. The different types of bleeding are described in Tab. 15.**2**.
- The precise circumstances of the bleeding should be elicited. The following information would be consistent with a congenital bleeding diathesis:
  - bleeding since childhood
  - lifelong history of severe nosebleeds
  - bleeding after dental procedures or tonsillectomy
  - heavy menstrual bleeding since menarche
  - spontaneous internal bleeding (e. g., hemarthrosis).
- The following would be consistent with an acquired bleeding diathesis:
  - history of taking medications that affect platelet function (e. g., aspirin, NSAIDs, antibiotics) or plasmatic coagulation (oral anticoagulants, heparin)
  - history suggestive of a disease that may be associated with coagulopathy (liver diseases, infections, renal diseases).
- Patients should be asked about the timing of bleeding in relation to an injury:
  - bleeding that does not stop shortly after an injury suggests a defect of primary hemostasis or a vascular disorder
  - bleeding that is well controlled initially but recurs after a period of hours or days suggests a disorder of secondary hemostasis.

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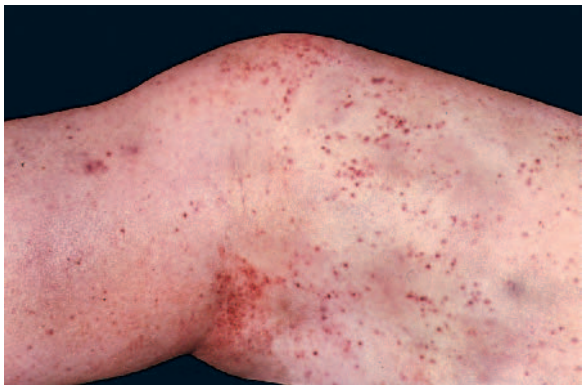

Fig. 15.**5** Petechial skin hemorrhages in a patient with thrombocytopenia.

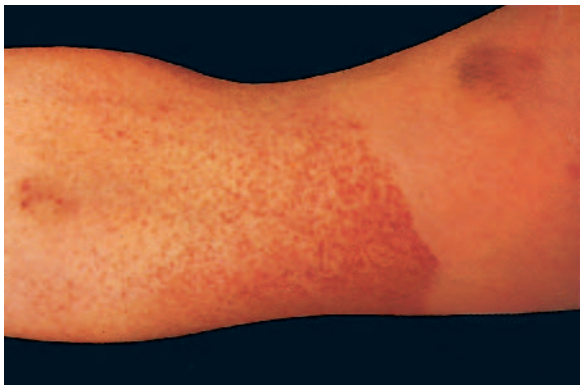

Fig. 15.**6** Rumple–Leede phenomenon, most pronounced in patients with a thrombocytic or vascular bleeding diathesis. When a blood pressure cuff is applied and inflated to a pressure that is between the arterial blood pressure and diastolic pressure, petechial skin hemorrhages appear on the arm within five minutes.

Fig. 15.**7** Petechial skin hemorrhages, bruising, and thrombotic occlusions of cutaneous vessels in a patient with meningococcal sepsis ("purpura fulminans"). Note the fresh necrosis involving the distal middle finger.

Fig. 15.**8** Fresh hematoma in a patient with a plasmatic coagulation disorder. Bleeding in the lower leg was caused by excessive anticoagulant medication. ▷

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Fig. 15.**9** Large hematoma in the left hand of a patient with a combined acquired defect of primary and secondary hemostasis. The patient had abciximab-induced (chimeric anti-GPIIbIIIa receptor antibody) thrombocytopenia and was also being treated with aspirin, clopidogrel, and heparin.

Fig. 15.**10** Large pseudotumor of the left hip and groin in a patient with hemophilia A. The mass was produced by chronically recurring episodes of bleeding into a joint (hemarthrosis) with further extensive hematoma in surrounding soft tissues.

Clinical Examination:

- The location and type of the bleeding should be accurately documented (Tab. 15.**2**).
- The patient should be examined for evidence of liver or kidney disease.

If the medical history or clinical findings suggest a disorder of primary hemostasis, then the bleeding time and platelet count should be determined and a PFA-100 analysis should be performed (Tab. 15.**1**). If the findings suggest a disorder of secondary hemostasis, the following laboratory values should be determined: Quick PT (INR), aPTT, fibrinogen, thrombin time, and D-dimers. The possible combinations of findings are reviewed in Figs. 15.**1**, 15.**2**.

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Disorders of Primary Hemostasis

Disorders of primary hemostasis may be caused by congenital or acquired disorders of platelet function (*thrombopathy*) or by a congenital or acquired low platelet count (*thrombocytopenia*). Congenital thrombopathies are rare and lead to severe bleeding manifestations, whereas acquired forms of platelet dysfunction are quite common and are less likely to cause serious bleeding. Platelet function may be compromised due to a low platelet count (thrombocytopenia) or, rarely, due to an abnormally high platelet count. The latter condition, called thrombocytosis, may develop in response to inflammations or certain tumors, and it may occur after splenectomy. Reactive forms of thrombocytosis with platelet counts higher than 1500 × 10^9/L are not associated with bleeding but with thrombosis. Thrombocytosis occurring in myeloproliferative diseases such as essential thrombocythemia (ET) or polycythemia vera (PV) may be associated with bleeding, regardless of the platelet count.

In thrombocytopenias, as well as thrombocytosis, bleeding manifestations are markedly increased by medications that cause further compromise of platelet function.

Congenital Thrombocytopathies

Congenital thrombocytopathies (platelet function disorders) are rare in comparison with the acquired forms. Congenital thrombopathies may be caused by changes in surface receptors (receptor defects) or by changes in the platelet granules (α-granules or δ-granules, also called "storage pool defects" [SPD]). These disorders are reviewed in Tab. 15.**3**. Some forms may be acquired and are also listed in Tab. 15.**3**. Patients with these disorders should avoid all medications that may compromise platelet function (e. g., aspirin, NSAIDs, etc.), as this would markedly increase their bleeding diathesis.

Receptor Defects. In *Glanzmann thrombasthenia* and in *Bernard–Soulier syndrome* (BSS), heterozygous carriers are generally asymptomatic. Homozygous carriers have a lifelong mucocutaneous bleeding diathesis with epistaxis, gastrointestinal bleeding, menorrhagia, and cutaneous hemorrhages. Both diseases are very rare.

An important entity, requiring differentiation from BSS, is an autoimmune condition called idiopathic thrombocytopenic purpura (ITP). Patients with BSS who are falsely diagnosed with ITP have a marked bleeding tendency despite only a mild degree of thrombocytopenia. When the platelet count returns to normal (e. g., after splenectomy), the bleeding diathesis will be eliminated in patients with ITP, but will still be present in patients with BSS. The diagnosis of Glanzmann thrombasthenia or BSS is established by flow cytometry and platelet aggregation testing.

Storage Pool Defects (SPD). SPDs are defined as a deficiency or abnormality of the alpha (α) or dense (δ) platelet granules, whose contents normally are released during platelet activation.

These very rare congenital disorders include gray platelet syndrome and Quebec platelet syndrome, which involve the α-platelet granules, Hermansky–Pudlak syndrome, and Chediak–Higashi syndrome, which involve the δ-granules. Usually they are associated with other anomalies, which are listed in Tab. 15.**3**. Platelet function is impaired, and patients suffer a bleeding diathesis of variable degree. Diagnosis relies on a detailed clinical examination and platelet function tests (PFA-100, platelet aggregation study).

Acquired Thrombocytopathies

Aspirin and NSAIDs. Owing to its extremely wide use, the platelet aggregation inhibitor aspirin (acetylsalicylic acid) is the leading cause of acquired thrombopathies. Aspirin irreversibly inhibits the function of the platelet enzyme cyclooxygenase I, which is crucial for platelet aggregation. Normal platelets survive in the bloodstream for 14 days. This means that seven days after the last ingestion of aspirin, one-half of the circulating platelet population is again functionally competent and should be able to provide adequate primary hemostasis with no clinically significant bleeding tendency. In the Physicians' Health Study (1989), a total of 22 071 doctors who took either aspirin or a placebo were followed for five years. The incidence of bleeding was 27% in the aspirin group and 20% in the placebo group. As for bleeding serious enough to require a blood transfusion, the incidence was only 0.4% in the aspirin group and 0.3% in the placebo group. Aspirin was, however, associated with a significantly higher incidence of hematomas, epistaxis, and melena.

NSAIDs temporarily and selectively inhibit cyclooxygenase I and II. When these drugs are discontinued, the recovery of platelet function depends on the half-life of the NSAID in the blood and on the capacity for platelet regeneration.

Clopidogrel. This ADP receptor antagonist, which is often administered alone or in conjunction with aspirin, leads to a type of bleeding identical to that associated with aspirin use. Although clopidogrel is a stronger platelet aggregation inhibitor, patients who take this drug do not bleed more than patients who take aspirin. Clopidogrel is an inactive precursor compound that must be transformed in the liver to its pharmacologically active metabolite.

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Table 15.**3** Congenital thrombocytopathies and thrombocytopenias

Name	Inheritance	Defect	Features	Acquired form
Glanzmann disease (Glanzmann thrombasthenia)	AR	Deficiency or defect of the GPIIbIIIa MRC	Normal platelet count, normal morphology	ITP, Hodgkin disease; medications (abciximab, tirofiban)
Bernard–Soulier syndrome	AR	Deficiency of the GPIb-IX-V MRC	Thrombocytopenia; morphology: giant platelets with absent or decreased granules	AML, MDS, ITP, APA syndrome
Pseudo-von Willebrand disease	AD	Increased affinity of the GPIb-IX-V MCR for vWF	Normal or slightly decreased platelet count, normal morphology	Unknown
Gray platelet syndrome	Uncertain	Unknown	α-SPD, thrombocytopenia; morphology: absence of α-granules gives the platelets a "gray" color on Pappenheim staining	Unknown
Hermansky–Pudlak syndrome (HPS)	AR	Lysosomal storage disease with ceroid–lipofuscin inclusions; HPS 1–4: four different genes, requires further characterization	Oculocutaneous albinism, pulmonary fibrosis, ulcerative colitis, ceroid–lipofuscin inclusions in macrophages, δ-SPD, normal platelet count, normal morphology	Unknown
Chediak–Higashi syndrome (CHS)	AR	Functional defect of lysosomal organelles, caused by mutations of the *LYST* gene	Hypopigmentation of the skin, iris, and hair; neutropenia with recurrent infections, lymphomas, peripheral neuropathy; eosinophilic inclusions in myeloblasts, δ-SPD, normal platelet count, normal morphology	Unknown
Quebec platelet defect (QPD)	AD	Proteolytic degradation of the contents of the platelet α-granules	α-SPD, mild thrombocytopenia, normal morphology	Unknown
May–Hegglin anomaly	AD	Unknown	Giant platelets, inclusion bodies in granulocytes, thrombocytopenia	Unknown
Wiskott–Aldrich syndrome	X-linked recessive	Defect in the *WASP* gene	Functional defect in T lymphocytes, recurrent infections, eczematous dermatitis, increased cancer incidence; thrombocytopathy: δ-SPD, possible MRC defect, thrombocytopenia	Unknown

AD: autosomal dominant; AML: acute myelogenous leukemia; APA syndrome: antiphospholipid antibody syndrome; AR: autosomal recessive; CHS: Chediak–Higashi syndrome; GP: glycoprotein; HPS: Hermansky–Pudlak syndrome; ITP: idiopathic thrombocytopenic purpura; *LYST*: name of the gene responsible for CHS syndrome; MDS: myelodysplastic syndrome; MRC: membrane receptor complex; QPD: Quebec platelet defect; SPD: storage pool defect = a deficiency or defect of the alpha (α) or dense (δ) platelet granules; vWF: von Willebrand factor; *WASP*: Wiskott–Aldrich syndrome protein defect.

Dipyridamole. This drug, which is also used to inhibit platelet aggregation, increases the release of adenosine from red blood cells and increases the release of nitric oxide and prostacycline from endothelial cells. This leads to an indirect inhibition of platelet aggregation and to peripheral vasodilation. Treatment with dipyridamole is associated with only a mild bleeding diathesis.

Renal Failure. Severe renal failure leads to impairment of platelet function with a prolongation of bleeding time. Bleeding complications have become rare since the advent of erythropoietin therapy and the correction of renal anemia. This fact alone is evidence that anemia per se may contribute to a bleeding diathesis in some patients. The unusual sites of the bleeding, such as hemorrhagic pericarditis, pleuritis, and retroperitoneal hemorrhages, suggest that, besides a generalized platelet dysfunction, there must also be a local component such as an inflammatory process in the setting of uremia.

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Thrombocytopenia

Thrombocytopenia is present when the platelet count falls below 100 × 109/L. This condition may result from a deficiency of platelet production, the pooling of platelets in the spleen, or increased platelet consumption. A pseudothrombocytopenia (see below) should be excluded.

Bleeding Due to Thrombocytopenia. The following general principles apply to bleeding due to thrombocytopenia:

- Type of bleeding:
  - purpura, petechiae, bruising, hematomas, mucosal bleeding (Tab. 15.**2**).
- Bleeding diathesis:
  - *dependent on the platelet count:* generally a count $< 50 \times 10^9$/L is associated with an increased bleeding risk, while a count $< 10 \times 10^9$/L implies a severe bleeding risk.
  - *dependent on the cause of the thrombocytopenia:* with peripheral consumption, young and functionally competent platelets are circulating in the blood. In ITP, the bleeding risk is not significantly increased until the platelet count falls below 10×10^9/L.
  - *dependent on the drug history:* if the patient has used medications that impair platelet function or otherwise affect coagulation, the bleeding risk is markedly increased.

Exclusion of Pseudothrombocytopenia

EDTA-Dependent Pseudothrombocytopenia. This condition should be excluded at once in every newly discovered case of thrombocytopenia. When the anticoagulant EDTA (**e**thylene**d**iamine **t**etraacetic **a**cid) is present, it causes platelets to clump together due to the presence of calcium-dependent antibodies in the blood. In an automated machine count, this leads to a false-low determination of platelet numbers. Platelet clumps may be seen when the blood smear is examined under the microscope. This relatively common anomaly (0.1 % of the population) has no pathogenic significance because the antibodies will bind platelets in vitro only in the presence of a calcium-binding anticoagulant.
EDTA-dependent pseudothrombocytopenia is easy to diagnose and is not an indication for further testing. An EDTA tube and heparin tube should be drawn concurrently and a blood smear should be prepared. Typically a normal platelet count will be found in the heparin tube. The platelet count determined from the EDTA tube is low and the corresponding smear will often contain platelet clumps.

EDTA-Induced, Abciximab-Associated Thrombocytopenia. The phenomenon of pseudothrombocytopenia has assumed renewed importance since the advent of abciximab (Reopro), a chimeric human–murine antibody against platelet surface GPIIbIIIa that is used in the treatment of acute coronary syndrome. Abciximab therapy may lead to a harmless EDTA-induced and abciximab-associated thrombocytopenia, which is easily diagnosed using the above methods and has no therapeutic implications. This harmless form is distinguished from severe "true" abciximab-associated thrombocytopenia, which may lead to life-threatening hemorrhage.

Idiopathic Thrombocytopenic Purpura (ITP)

Clinical Features. ITP is a common autoimmune disease characterized by an increase in peripheral antibody-induced platelet consumption with a consequent reduction of platelet survival time. ITP is often manifested by petechial skin hemorrhages, mucosal bleeding, and hematomas. Severe bleeding usually does not occur until the platelet counts falls below 10×10^9/L. Patients who have a platelet count of approximately 40×10^9/L (and have not taken medication that impairs platelet function) do not have bleeding manifestations and may be completely asymptomatic.

Diagnosis. ITP is a diagnosis of exclusion. There is no reliable test for detecting the antiplatelet antibodies in the blood that cause ITP. Antiplatelet antibodies have also been found in other diseases that are associated with thrombocytopenia and therefore have little diagnostic value. The best way to diagnose ITP is by excluding other diseases that may be associated with thrombocytopenia (see below). Giant platelets, myelodysplastic syndrome, thrombotic, thrombocytopenic purpura/hemolytic–uremic syndrome (TTP/HUS), and EDTA-dependent pseudothrombocytopenia can be excluded by the morphological examination of a stained blood smear.

A bone-marrow examination in ITP will show a normal or increased megakaryocyte count and can exclude infiltration or displacement by neoplasia as the cause of the low platelet count. The spleen is not enlarged in ITP. A possible liver disease with associated portal hypertension should be excluded as the cause of thrombocytopenia. Viral diseases or autoimmune diseases that may be associated with persistent or transient thrombocytopenia should be excluded by clinical or serological examination (HIV, cytomegalovirus, Epstein–Barr virus [EBV], lupus erythematosus, etc.). Thrombocytopenia due to antiphospholipid antibody (APA) syndrome is typically characterized by thrombosis rather than bleeding.

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Fig. 15.**11** Facial eczematic lesions and petechial hemorrhages in a patient with Wiskott–Aldrich syndrome.

Thrombocytopenia Due to Abnormal Platelet Production

Bone-marrow infiltration and the suppression of megakaryopoiesis due to neoplasia, lymphoma, or leukemia may lead to isolated thrombocytopenia. Aplasia-inducing forms of chemotherapy, aplastic anemia, chronic alcoholism, paroxysmal nocturnal hemoglobinuria, or a severe vitamin B_{12} or folic acid deficiency may lead to bone-marrow insufficiency. In most cases, however, they are associated with defects of myelopoiesis and erythropoiesis and rarely lead to isolated thrombocytopenia. Viral infections often lead to a decrease in megakaryopoiesis. The thrombocytopenias that occur in viral infections are often mild and rarely lead to clinically significant bleeding. Petechial skin hemorrhages, mucosal bleeding, and cutaneous hematomas are typical features. If the patient has also taken drugs that inhibit platelet function, or has a febrile infection, platelet function will be further compromised and the bleeding manifestations will be more severe.

May–Hegglin Anomaly. This rare hereditary disease, which has an autosomal dominant mode of inheritance, is characterized by decreased megakaryopoiesis, giant platelets, mild thrombocytopenia, and inclusion bodies in the white blood cells. The genetic defect is unknown, and the clinical bleeding tendency is mild or completely absent in 40% of patients (see Tab. 15.**3**).

Epstein syndrome, Fiechter syndrome, and Alport syndrome are very rare syndromes that are associated with giant platelets, thrombocytopenia, and occasional lymphocytic inclusions. These forms are accompanied by other anomalies (nephritis, deafness, etc.).

Wiskott–Aldrich Syndrome. This is a very rare X-linked recessive disorder characterized by immunodeficiency, microthrombocytopenia, and eczematous dermatitis. Defects in the Wiskott–Aldrich syndrome protein (WASP), which are not yet fully understood, lead to immunodeficiency, thrombocytopenia, and platelet dysfunction (receptor defect and δ-granule SPD) (see Tab. 15.**3**, Fig. 15.**11**).

Initial bleeding episodes usually occur during adolescence and are severe (e. g., cerebral hemorrhage). Severe bacterial infections commence during childhood, and a consistent finding is eczematoid dermatitis predominantly affecting the face. Lymphomas frequently develop by young adulthood. Less common manifestations are autoimmune diseases such as ulcerative colitis and vasculitis.

Hypersplenism or Platelet Pooling

Even under physiological conditions, two-thirds of the platelets in the body are stored in the spleen. All diseases that cause portal hypertension or splenomegaly may lead to thrombocytopenia due to the increased pooling of platelets in the spleen. Involvement of the spleen by tumors, lymphomas, or storage diseases (e. g., Gaucher disease) or reactive splenomegaly in response to an infection (e. g., leishmaniasis, malaria) may lead to mild forms of thrombocytopenia.

Thrombocytopenia Due to Increased Peripheral Consumption

Disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and hemolytic–uremic syndrome (HUS) are prime examples of nonimmunogenic, peripheral platelet consumption (see Microcirculatory Disorders, p. 470).

Mild mechanical forms of thrombocytopenia are known to develop in association with mechanical heart valves or may occur temporarily after cardiac operations in which the patient was placed on a heart–lung machine.

During *pregnancy*, it is not uncommon (5%) for mild thrombocytopenia to develop during the third trimester. This form is often difficult to distinguish from ITP. After other causes of thrombocytopenia have been excluded, a history of a normal platelet count before

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pregnancy and the appearance of the condition during the third trimester should be sufficient to exclude ITP. Pregnancy-induced thrombocytopenia resolves after the delivery and, unlike ITP, has no adverse effects on the fetus.

Medications may lead to thrombocytopenia as a result of drug-induced antibodies directed against the platelets. Thrombocytopenia has been described in association with many pharmacological agents, but in many cases the link has not been well established. Thrombocytopenia has definitely been linked to treatment with quinidine, trimethoprim–sulfamethoxazole, amiodarone, sulfonyl ureas, and heparin. This type of thrombocytopenia is reversible after discontinuation of the drug. The clinically important entity of heparin-induced thrombocytopenia (HIT) is discussed below.

GPIIbIIIa-receptor antagonist-induced thrombocytopenia develops in approximately 1–4% of patients. It is frequently severe (platelet count $< 10 \times 10^9$/L) and leads to severe bleeding because GPIIbIIIa receptor antagonists are used together with heparin, clopidogrel, and aspirin in the treatment of acute coronary syndrome (see Fig. 15.**9**).

Disorders of Secondary Hemostasis

Disorders of secondary hemostasis are caused by changes in the concentration or function of plasma coagulation factors, resulting in an increased bleeding tendency. Among the more common congenital disorders are hemophilia types A and B and von Willebrand disease. Very rare congenital deficiency states have been described for all of the plasma coagulation factors (FII, FV, FVII, FX, FXI, FXIII, and fibrinogen); they occur with a variable bleeding diathesis and will not be explored here. The common acquired disorders include liver diseases, vitamin K deficiency, and anticoagulant medication. The processes involved in secondary hemostasis are shown schematically in Fig. 15.**3**.

Hemophilias A and B

Pathogenesis. Hemophilia is an X-linked recessive bleeding diathesis caused by a deficiency of FVIII (hemophilia A) or FIX (hemophilia B). The severity depends on how much the levels of the coagulation factors are decreased. Only about 40% of male newborns with hemophilia are known to have a family history of the disease. The prevalence is 1:5000 to 1:10 000 for hemophilia A and 1:25 000 to 1:30 000 for hemophilia B.

Clinical Features. Severe forms of hemophilia (FVIII or FIX: < 1%) occur clinically with spontaneous bleeding in the skin, joints, or muscles. Moderately severe forms (FVIII or FIX: 1–4%) and mild forms (FVIII or FIX: 5–40%) show less spontaneous bleeding, but may manifest very severe bleeding hours or days following an injury or surgical procedure. The milder the form of the disease, the later bleeding manifestations may appear during the patient's lifetime. In mild cases, initial manifestations may not occur until adulthood. The hemophilia may be unmasked by a surgical operation or by treatment with platelet aggregation inhibitors (aspirin, clopidogrel).

Acquired Immune-Inhibitor Hemophilia. The rare condition of acquired immune-inhibitor hemophilia should be suspected in cases where this type of bleeding first occurs in late adulthood or during the postpartum period. The disease is triggered by an acquired inhibitor, which is usually directed against FVIII. As in classic hemophilia, patients demonstrate a prolonged aPTT and a normal PT.

Von Willebrand Disease

Pathogenesis and Classification. Von Willebrand factor (vWF) circulates in the blood in the form of multimers of varying size. On the one hand, vWF functions as the transport protein for FVIII; at the same time, it has a key role in mediating the interaction of platelets and subendothelial structures in the presence of vascular lesions. The level of vWF in the blood depends on many factors, rising in response to stress, pregnancy, aging, and inflammation. The vWF level is also dependent on blood type (lower in type O than in the non-O blood groups).

Von Willebrand disease is classified as follows:

- *Type 1:* partial quantitative deficiency of vWF.
- *Types 2A, B, M, and N:* qualitative abnormalities of vWF:
  - A: reduction of high and medium molecular weight multimers
  - B: absence of high molecular weight multimers because of increased binding to platelets, possible mild thrombocytopenia
  - M: all multimers are present but show defective binding to platelets
  - N: decreased binding to FVIII, low concentration of FVIII.
- *Type 3:* severe quantitative vWF deficiency with absence of vWF.

The laboratory work-up of the vWF deficiency is challenging, and a routine genetic test is not yet available. The deficiency has an autosomal dominant (types 1, 2A, 2B, 2M) or autosomal recessive (types 2A, 2N, 3) mode of inheritance.

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Clinical Features. Type 1 disease is very common, with a prevalence of 0.5–1.0%, and the clinical bleeding tendency is usually mild. Type 2 occurs with a significant bleeding diathesis. Type 3 is characterized by a severe bleeding diathesis that occurs with muscular and joint bleeding at an early age. Mucosal bleeding is a typical manifestation of von Willebrand disease. Epistaxis, prolonged bleeding after a trivial injury, menorrhagia, excessive bleeding after dental procedures, and cutaneous bleeding are the classic manifestations of vWF deficiency types 1 and 2.

Acquired Von Willebrand Disease. Rarely, von Willebrand disease may be acquired at an adult age. This form may be caused by an antibody that inactivates the von Willebrand factor (monoclonal gammopathy, multiple myeloma), or there may be an increased expression of the vWF receptor on a tumor, in thrombocytosis, or in essential thrombocythemia that binds greater amounts of circulating vWF.

Vitamin K Deficiency

Pathogenesis. Vitamin K is a lipophilic vitamin and an essential cofactor of γ-carboxylase. This liver enzyme is responsible for modifying glutamine residues of coagulation factors II, VII, IX, X, and of proteins Z, S, and C. These glutamine residues are essential to the normal function of these coagulation factors. A vitamin K deficiency may result from deficient intake (parenteral nutrition), fat malabsorption (e. g., in cystic fibrosis or pancreatitis), disruption of the enterohepatic circulation (e. g., due to cholestasis), antibiotic therapy, or intoxication with vitamin K antagonists (coumarins, rat poisons).

Clinical Features. The bleeding diathesis is related to a fall in the PT or a rise in the INR. When the INR reaches a value of 4–5, the bleeding risk rises exponentially. Thus, an INR of 2–3 correlates with a 3% bleeding risk per 100 patient years, an INR of 3.0–4.5 with a 9.5% risk, and INR of 4.5–6.9 with a 40% risk, and an INR >7 with a 200% risk per 100 patient years. Bleeding may occur at any of the following sites, which are listed in order of frequency: gastrointestinal tract, brain, skin, urinary tract, and nose. In patients with high INR values, abdominal wall hematomas may occur in response to minimal trauma such as coughing.

Liver Disease

Pathogenesis. All plasma coagulation factors except vWF, plasminogen activator inhibitor 1, tissue plasminogen activator (tPA), and probably FVIII are synthesized and broken down in the liver. One criterion for the assessment of liver function in the Child–Pugh classification is the PT (see Chapter 25). Additionally, the concentration of FV, a nonvitamin K-dependent factor synthesized in the liver, is a useful prognostic indicator in patients with liver failure.

The following situations that promote coagulopathy may exist in various combinations in patients with liver failure:

- It is common to find a concomitant vitamin K deficiency caused by intrahepatic or extrahepatic cholestasis or by malabsorption secondary to portal hypertension.
- All coagulation factors synthesized in the liver decrease in accordance with their half-life, which vary widely.
- Dysfunctional proteins are synthesized in a failing liver. For example, the dysfibrinogen that is synthesized in liver failure is no longer able to polymerize and form a stable clot:
- Portal hypertension leads to hypersplenism with thrombocytopenia.
- Hyperfibrinolysis develops due to a deficiency of alpha1-antiplasmin and an excess of tPA.
- A coagulopathy may develop due to the loss of fibrinogen to ascites.

It may be difficult to distinguish liver failure from DIC. DIC is characterized by a consumption of all plasma coagulation factors including FVIII and VWF. In liver failure, however, FVIII and vWF are often normal or elevated because they are synthesized in the endothelium and not in the liver.

Clinical Features. Gastrointestinal bleeding from esophageal or fundal varices is common in patients with portal hypertension. Rectal bleeding, epistaxis, and cutaneous hemorrhages may also occur.

Oral Anticoagultion (OAC)

Mechanism of Action of Coumarins. Oral anticoagulants belong to the class of coumarins, vitamin K antagonists that inhibit γ-carboxylase, thereby causing a functional decrease in all vitamin K-dependent coagulation factors. Approximately 98% of ingested coumarins are bound to plasma proteins and metabolized by cytochrome P450. Coumarins have varying half-lives in the plasma, ranging from 168 hours for phenprocoumon (Marcumar) to 10 hours for acenocoumarol (Sintrom). The INR value is tested to monitor response. Oral anticoagulants may lead to bleeding in the therapeutic range (INR 2–3) and even more at excessive doses (INR >3).

> If a patient on OAC bleeds within the therapeutic dose range, the physician should look for an additional factor that may be contributing to the bleeding.

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A patient with gastrointestinal bleeding, for example, should be evaluated for a colon polyp, colon tumor, or a gastric or duodenal ulcer. Given the high plasma protein binding and metabolism of coumarins, interactions should be considered with each newly administered drug. If the PT value is outside the desired range, the patient should be questioned about the use of natural remedies. St. John wort, ginseng, ginko, and garlic are only a few examples of herbal remedies that may increase the INR value. Medical conditions that may cause higher INR values include liver dysfunction (heart failure, hepatitis, etc.), vitamin K deficiency, diarrhea, and hyperthyroidism. Vitamin K antagonizes the action of coumarins. When a patient with an INR value of 2–3 is given vitamin K by oral or intravenous administration, the PT value should return to normal within 12–24 hours.

Bleeding during Coumarin Therapy. The incidence of bleeding during coumarin use depends on the increase in the INR value and rises expotentially when the INR reaches 5 or more (40 bleeds/100 patient years). An INR of 2–3 is associated with 4.8 bleeds/100 patient years, one-fifth of which have a fatal outcome. Bleeding may occur virtually anywhere in the body (the sites are listed in order of frequency under Vitamin K Deficiency, above). Bleeding events are most likely to occur during the first three months after the initiation of OAC (one-third of all bleeding complications) and become more frequent with aging (the incidence doubles after age 70). Coumarin-induced necrosis is a feared complication that may occur during the initial phase of OAC in patients with a protein S or protein C deficiency. With the rapid decline of the inhibitor proteins S and C and the more gradual decline of other vitamin K-dependent procoagulant factors, a hypercoagulable state develops leading to skin necrosis due to the thrombosis of cutaneous vessels (Fig. 15.**12**).

Thrombin Inhibitor. A representative of a new class of drugs, the oral thrombin inhibitor ximelagatran is awaiting clinical approval. The efficacy of these direct thrombin inhibitors does not need to be monitored with a coagulation test. Hepatotoxicity is among the side effects already noted in patients taking the drug. As with all anticoagulants, it is reasonable to expect that bleeding events will also occur.

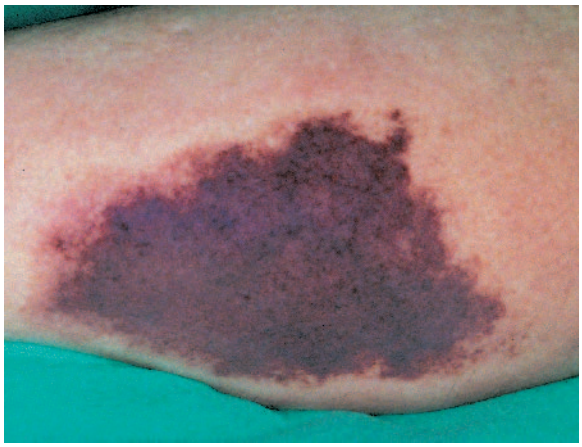

Fig. 15.**12** Coumarin-induced skin necrosis. The lesion, located on the inside of the thigh, was caused by the thrombotic occlusion of cutaneous and subcutaneous vessels in a patient with protein C deficiency, who had been placed on oral coumarin therapy. Concomitant heparin therapy would have prevented this necrosis.

Heparins

Heparins are a category of drugs that includes unfractionated heparins (UFH) and low molecular weight heparins (LMWH). A new class of drugs is the synthetically produced pentasaccharides (PS), whose mechanism of action is similar to that of heparins. Heparins and PS bind to antithrombin and inactivate thrombin (UFH, LMWH) or FXa (UFH, LMWH, PS). UFH is composed of high molecular weight glycosaminoglycans of animal origin, while LMWH is composed of shortened glycosaminoglycan chains produced from chemically or enzymatically treated UFH. PS (fondaparinux, Arixtra) are purely synthetic products. Response to UFH is monitored by testing the thrombin time or aPTT. LMWH and PS cannot be monitored with routine coagulation tests. If bleeding complications arise, a special anti-FXa test should be done to check for possible overdosage (e. g., in patients with renal failure). Preexisting lesions (gastric ulcer, colon carcinoma, etc.) may bleed at therapeutic dose levels, and the bleeding that occurs with overdosage is like the forms observed in OAC.

Vascular Bleeding Diathesis

Vascular bleeding diathesis includes the following:

- proliferative vascular disorders
- structural defects in perivascular tissue
- vascular trauma
- inflammatory disorders.

Proliferative Vascular Disorders

Bleeding may result from a localized or generalized proliferation of fragile blood vessels. Localized forms of vascular proliferation include all types of hemangioma, which cannot be fully discussed in this chapter. A clinically significant generalized form is Osler–Weber–Rendu

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Fig. 15.**13** Lesions of the lower lip and tongue in hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease).

disease, also known as hereditary hemorrhagic telangiectasia (HHT).

Osler–Weber–Rendu Disease

Pathophysiology. This disease has an autosomal dominant mode of inheritance and an incidence of 1:18 000 in the general population. It has been linked to mutations in two genes of the transforming growth factor β superfamily: endoglin and ALK-1 (activin receptor like kinase 1). A typical feature of this disease is a focal dilatation of the postcapillary venules. This malformation gives rise to arteriovenous shunts and increased bleeding from these fragile vessels (Fig. 15.**13**).

Clinical Features. Telangiectasia is often visible in the skin and mucous membranes (lips, tongue, etc.), but the vascular malformations may involve any vascular bed. Patients often suffer from chronic iron deficiency anemia due to recurrent episodes of gastrointestinal bleeding or epistaxis. Many patients require iron replacement therapy for the duration of their life.

Arteriovenous shunts in the lung may lead to cerebral abscess formation because the shunts bypass the normal filtering action of the pulmonary vascular bed. Neurological symptoms may also result from bleeding in cerebral vascular malformations or from the mass effect produced by malformed vessels in the brain. If high-volume shunts are present, they may create a volume overload leading to high-output heart failure.

The differential diagnosis of Osler–Weber–Rendu disease should include CREST syndrome, an acronym for its cardinal features of **c**alcinosis cutis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia. Patients with CREST syndrome do not have a positive family history or bleeding history and invariably exhibit scleroderma, which is not present in Osler–Weber–Rendu disease.

Structural Defects

Diseases that compromise the integrity of the perivascular tissue or vessel wall may lead to increased cutaneous or internal bleeding. This group includes the following disorders:

Abnormal Composition of the Vessel Wall

Collagen Defect:

- *Ehlers–Danlos syndrome:* Ehlers–Danlos syndrome encompasses a group of diseases that are marked by abnormalities of collagen production. All forms predispose to cutaneous hematomas. Type IV may also lead to the spontaneous rupture of large-sized and medium-sized arteries.
- *Corticosteroid therapy:* treatment with corticosteroids leads to decreased collagen synthesis resulting in cutaneous atrophy and an increased susceptibility to bruising of the arms and legs. These changes are especially pronounced in Cushing syndrome.
- *Senile purpura:* aging is accompanied by a generalized atrophy of the subcutaneous tissues. Small cutaneous hemorrhages occur mainly on the backs of the hands and forearms. The hemorrhages often leave relatively large brownish spots caused by hemosiderin deposits arising from repeated bleeding episodes.
- *Vitamin C deficiency:* a deficient intake of vitamin C that persists for two to three months leads to defects in collagen synthesis. Typical consequences are perifollicular bleeding, subperiosteal bleeding, and bleeding gums.

Elastin Defect:

- *Pseudoxanthoma elasticum:* in this very rare autosomal recessive inherited disease formation of connective tissue is altered. The skin of these patients is overexpandable, mostly in the neck and in the axilla. Additional teleangiectasia and yellowish discoloration of the skin may also occur. Excessive bleeding occurs in the skin, gastrointestinal and urogenital regions, and in the head.

Fibrillin Defect:

- *Marfan syndrome:* this is a hereditary syndrome with an autosomal dominant mode of transmission. A defect in fibrillin synthesis leads to tall stature with abnormal length of the extremities, arachnodactyly, dislocation of the lens, aortic dissection, and a bleeding diathesis, especially after surgical procedures.

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Infiltration of the Vessel Wall

- *Fabry disease (angiokeratoma):* this very rare, X-linked, α-galactosidase deficiency is characterized by an increased deposition of glycosphingolipids in the skin. Typical features include reddish-blue papules in the area between the umbilicus and knees.
- *Amyloid:* amyloid infiltration of the vessel walls occurs predominantly in the cutaneous and periorbital vessels. Even minimal trauma such as sneezing or a Valsalva maneuver may lead to periorbital or cutaneous hemorrhage. Rarely, the amyloid may also bind and absorb a coagulation factor (e. g., FX), resulting in a bleeding diathesis.

Traumatic Purpura

Heavy physical exertion, extreme altitude, coughing, or vomiting may lead to purpuric lesions in susceptible individuals. The cause of the disorder is unknown.

Inflammatory Disorders

The deposition of immune complexes in the vessel wall leads to localized extravasation that is visible in the skin as purpura.

Henoch–Schönlein Purpura

Pathogenesis. The deposition of immune complexes in the vessel wall (chiefly IgA) leads to a palpable cutaneous purpura. Lesions may develop in the kidney, gastrointestinal tract, skin, and joints. In most cases a precipitating cause for the disease cannot be determined (Fig. 15.**14**).

Clinical Features. The disease is most commonly observed in children and is rare in adults. Besides hemorrhagic exanthema, the manifestations include fever, joint pain, abdominal pain, and edema.
The following findings support a diagnosis of Henoch–Schönlein purpura:

- palpable hemorrhages located mainly on the legs, buttocks, and extensor surface of the arms
- arthritis, most commonly affecting the ankles, knees, finger joints, and elbows
- abdominal pain, sometimes associated with bloody diarrhea
- gross hematuria or microhematuria.

Fig. 15.**14** Henoch–Schönlein purpura (anaphylactoid or leukocytoclastic purpura). Older lesions have a brownish color caused by hemosiderin deposits. Newer lesions appear red due to fresh cutaneous bleeding.

Cryoglobulins

Pathogenesis. Cryoglobulins are serum proteins that reversibly precipitate at low temperatures, leading to immune complex deposition on vessel walls and complement activation. This process incites a systemic vasculitis involving the small and medium-sized arteries and veins. The presence of monoclonal IgG or IgM is known as isolated cryoglobulinemia and occurs in patients with multiple myeloma, Waldenström disease, and chronic lymphatic leukemia. The more common forms are mixed forms in which both IgG and IgM fractions are present; they occur in the setting of hepatitis C infection and autoimmune diseases (Fig. 15.**15**).

Clinical Features. Ninety percent of patients present with a palpable purpura on the legs, trunk, and buttock. Concomitant arthralgias and Raynaud phenomenon are often present. In 60% of cases, the involvement of small vessels and nerves leads to a sensorimotor polyneuropathy that predominantly affects the lower

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extremity. When the purpuric lesions heal, they leave behind areas of brownish discoloration caused by hemosiderin deposits in the skin. Cases with renal involvement require differentiation from Henoch–Schönlein purpura.

Fig. 15.**15** Hepatitis C-induced cryoglobulinemia with cutaneous vasculitis affecting both lower legs.

15.2 Thrombophilic Diathesis

Thrombophilia is an *acquired or hereditary coagulation disorder* characterized by a heightened susceptibility to thromboembolitic disease. In a narrow sense, it refers mainly to coagulation defects (e. g., antithrombin deficiency) that can be detected by clinical laboratory methods. But in its broader meaning, it also includes clinical situations or diseases that are known to be associated with an increased risk of thromboembolism (e. g., neoplastic diseases). It should be noted that venous thrombosis is much more common than arterial thrombosis in all forms of thrombophilic diathesis, and so the term usually refers tacitly to a propensity for venous thrombosis.

From a clinical standpoint, it is crucial to assess the severity of the thrombophilic diathesis based on the history and laboratory tests. This is essential in assessing the individual risk for initial or recurrent thromboembolic events and protecting the patient with appropriate thromboprophylaxis.

Clinical Approach

The medical history and physical examination are important in evaluating the individual risk of thrombosis. They should cover the following points:

- previous thromboembolic events (location, extent, situational risks such as surgical procedures, immobility, etc.)
- family history of thromboembolism
- age; the incidence of venous thrombosis rises steadily with aging (from approximately 0.01 % per year at age 15–25 to approximately 0.5 % per year over age 55)
- thrombogenic medications (e. g., estrogen containing medications, thalidomide, and many others)
- points to note during the physical examination: obesity, saphenous varicosity in the lower extremities, edema (heart failure, nephrotic syndrome, postthrombotic syndrome).

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Hereditary Thrombophilia

During the past 20 years, approximately 30 coagulation defects have been found that were initially felt to have an assocation with venous and/or arterial thromboembolism. To date, however, only a few coagulation defects have been found to have a consistent link with thromboembolism, and strictly with venous thromboembolism. Thus, only the following parameters have been definitely established as clinically significant thrombophilic markers for risk evaluation:

- antithrombin deficiency
- protein C deficiency
- protein S deficiency
- APC resistance in the FV–Leiden mutation R506Q
- prothrombin gene mutation G20 210A.

Clinical Features. These five thrombophilias lead to a significantly increased risk of venous thrombosis. Patients with a heterozygous defect typically experience venous thromboembolic complications prior to 40 years of age. Deep lower extremity venous thrombosis with or without pulmonary embolism is by far the most common manifestation. It has been shown that patients with these thrombophilias may also develop venous thrombosis at other sites such as the cerebral venous sinuses, visceral veins, and upper extremity veins. Except in children, none of these five thrombophilias have yet been found to be associated with arterial thrombosis. It is important to note that hereditary thrombophilias not only lead to idiopathic thrombosis, but that in approximately 50 % of cases the thrombophilia is not manifested until the patient is in a high-risk clinical situation (immobilization, postoperative period, etc.).

Recently it has been shown that these hereditary thrombophilias are also associated with an increased

Table 15.**4** Acquired thrombophilia

	Type	Frequency and relative thrombotic risk in heterozygous carriers	Pathophysiology	Clinical features
Antithrombin deficiency	Type I: quantitative deficiency; type II: qualitative defect	Healthy population: 0.1–0.3 %; patients with thrombotic disorders: 1–2 %; relative risk: 10–15 ×	Decreased inhibition of thrombin and FXa	Most severe thrombophilia; homozygous forms are lethal except in type II; most thrombotic episodes occur before age 25, mostly in large veins; high risk of recurrence; acquired deficiencies result from liver failure, heparin therapy, acute thrombosis, or plasma leakage
Protein C deficiency	Type I: quantitative deficiency; type II: qualitative defect	Healthy population: 0.2–0.5 %; patients with thrombotic disorders: 2–3 %; relative risk: 6–10 ×	Decreased inhibition of FVa, FVIIIa	Leads to thrombotic occlusion of large veins and possible superficial thrombophlebitis; high risk of recurrence; risk of skin necrosis in heterozygotes at the start of coumarin therapy and in homozygotes; acquired deficiency may result from liver failure, acute thrombosis, coumarin therapy, or vitamin K deficiency
Protein S deficiency	Type I: quantitative deficiency; type II: qualitative defect; type III: quantitative deficiency of free protein S	Healthy population: 0.2–0.5 %; patients with thrombotic disorders: 2–3 %; relative risk: 2–8 ×	Decreased inhibition of FVa, FVIIIa (protein S is a cofactor of protein C)	Leads to thrombotic occlusion of large veins and possible superficial thrombophlebitis; increased risk of recurrence; risk of skin necrosis in heterozygotes at the start of coumarin therapy and in homozygotes; acquired deficiency may result from vitamin K deficiency, liver failure, acute thrombosis, coumarin therapy, estrogen therapy, or pregnancy
APC resistance (FV–Leiden mutation)		Healthy population: 3–7 %; patients with thrombotic disorders: 25–30 %; relative risk: 6–8 ×	Decreased inhibition of FVa	Most common thrombophilia, leads to thrombotic occlusion of large veins and sometimes small subcutaneous veins; onset may be delayed until an advanced age; risk of recurrence is probably not increased; acquired APC resistance may result from increased FVIII, pregnancy, or antiphospholipid antibodies
FII mutation G20 210A		Healthy population: 1–3 %; patients with thrombotic disorders: 5–7 %; relative risk: 3–6 ×	Increased synthesis of FII	Second most common thrombophilia with a low risk of thrombosis; leads to thrombotic occlusion of large veins; risk of recurrence is probably not increased

APC: activated protein C; F: factor; G20 210A: prothrombin gene mutation at position 20 210, where a glutamine (G) is replaced by an alanine (A).

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incidence of obstetric complications such as habitual abortion, intrauterine fetal death, and fetal growth retardation. The underlying mechanism is probably placental thrombosis. There is also recent evidence that hereditary thrombophilias may be a risk factor for the early rejection of organ transplants. The incidence, risks, and typical clinical features of these hereditary thrombophilias are reviewed in Tab. 15.**4**.

Diagnosis. While the following parameters have been found to have an association with venous thromboembolism in most studies, they have not (yet) been consistently applied in routine diagnostic situations due to technical or socioeconomic issues:

- persistent elevated plasma level of FVIII, FIX, or FXI
- persistent elevated plasma level of D-dimers
- elevated plasma homocysteine (hyperhomocysteinemia), due either to a folic acid deficiency or a mutation in an enzyme in homocysteine metabolism (methylenetetrahydrofolate reductase C677T)
- elevated plasma level of lipoprotein A.

Acquired Thrombophilia

There are several clinical entities that are associated with a markedly increased risk for both venous and arterial thromboembolism.

> In the absence of a corresponding known disease, the thrombophilic work-up of a patient with thrombosis should include a search for acquired thrombophilic systemic diseases in addition to hereditary thrombophilias.

Antiphospholipid Antibody Syndrome (APA Syndrome)

Pathogenesis. APAs are autoantibodies that are directed against phospholipid-binding proteins. They bind to the vascular endothelium and to platelets, and their activation can induce a prothrombotic state. Also, numerous mechanisms have been described for how APAs can influence the coagulation cascade and can ultimately potentiate thrombin formation. The APAs of greatest clinical importance are: anti-beta-2-glycoprotein I antibodies, anticardiolipin antibodies, antiphosphatidylserine antibodies, and antiprothrombin antibodies. In addition to these APAs, aPTT or lupus anticoagulant (aPTT-like test) is also usually determined in clinical settings to prove that these APAs have "procoagulant activity." Certain APAs can prolong the coagulation time in vitro and thus can mimic anticoagulation. This has given rise to the paradoxical term "lupus anticoagulant," even though APAs lead to thrombosis.

Clinical Features. APAs may occur idiopathically or secondarily in the setting of various autoimmune diseases (e. g., systemic lupus erythematosus, Sjögren syndrome, Behçet syndrome, rheumatoid arthritis, and many others), and usually they persist for years. Transient APAs (e. g., after viral infections) are of no clinical importance. When high titers of APAs persist for months or years, they substantially increase the risk for the following complications:

- *venous thrombosis:* chiefly in the lower extremity but also in the brain and viscera
- *arterial thrombosis:* mostly cerebral (stroke, multi-infarct dementia)
- *thrombocytopenias:* caused by antiplatelet antibodies
- *valvular heart disease:* sterile endocarditis, mitral valve prolapse.

Myeloproliferative Diseases

Pathogenesis. The only myoproliferative diseases that lead to an increased risk of thrombosis are essential thrombocythemia (ET) and polycythemia cera (PV), whereas chronic myeloid leukemia and osteomyelofibrosis are not associated with thrombophilia. The main pathogenic mechanisms in both ET and PV are considered to be a rise in the platelet count and alterations in platelet function. These functional alterations are diverse and are often manifested by a capacity for spontaneous platelet aggregation, although they may also lead to an aggregation defect with a consequent bleeding diathesis.

Clinical Features. Arterial microthrombosis is the most common thrombotic manifestation in both ET and PV. Its classic features are painful ischemia of the fingers and toes ("erythromelalgia") and cerebral ischemia (visual disturbances, dysesthesias, etc.). It is also characterized by visceral, venous thrombotic conditions such as Budd–Chiari syndrome and portal, mesenteric, and splenic venous thrombosis. Studies have shown that ET or PV is found in approximately 50% of all patients with visceral venous thrombosis! Habitual abortion is also common. The overall incidence of thrombosis in patients with untreated ET and PV is 20–60% per year.

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Nephrotic Syndrome

Pathogenesis. Despite the description of numerous coagulation defects in the setting of nephrotic syndrome, such as a reduction in coagulation inhibitors (e. g., antithrombin, protein C, protein S), a decrease in fibrinolytic capacity, and an increase in blood viscosity and platelet counts, the actual cause of thrombophilia in nephrotic syndrome is not yet fully understood.

Clinical Features. The most frequent thrombotic event is renal vein thrombosis, which is particularly common in nephrotic patients with glomerulonephritis. There is also an increased incidence of thrombosis in other venous systems. Studies suggest that the risk of thrombosis is particularly great when the serum albumin level is < 20 g/L, fibrinogen is > 4.0 g/L, or antithrombin is $< 50\%$ of normal values.

Neoplastic Diseases

Pathogenesis. Malignant tumors are associated with a significantly increased risk of thrombosis. Various factors may contribute to this thrombophilia in cancer patients:

- direct invasion or compression of blood vessels by the tumor
- the activation of coagulation by the tumor cells. It is known that procoagulant substances such as tissue factor ("tissue thromboplastin") and cancer procoagulant are expressed on tumor cells, leading to procoagulant activation of the endothelium
- hyperviscosity caused by a paraneoplastic or neoplastic erythrocytosis, thrombocytosis, leukostasis, or paraproteinemia
- chemotherapeutic agents, which may cause endothelial cell damage or may activate coagulation as a result of tumor degeneration, or the decreased synthesis of coagulation inhibitors such as antithrombin, protein C and protein S.

Clinical Features. The incidence of venous thromboembolism in cancer patients is approximately 1–15%, depending on the type of tumor and chemotherapy regimen. It is also important to check for additional risk factors such as immobilization, surgery, and venous catheter use. Lower extremity venous thrombosis and pulmonary embolism are the most frequent manifestations, regardless of tumor type. Vascular invasion or compression by the tumor may also cause thrombosis to develop at unusual sites (venous sinuses, portal veins, etc.).

The risk of thrombosis appears to be greatest in patients with adenocarcinomas of the colon, stomach, lung, ovary, or breast. An association with arterial thrombosis has not been established. Not infrequently, venous thrombosis may be the initial manifestation of a malignant tumor. Several studies have shown that the incidence of newly diagnosed tumors is significantly increased in patients with venous thrombosis.

> In other words, thrombosis may be an early sign of malignant disease.

When deep venous thrombosis in a cancer patient is accompanied by a migratory thrombophlebitis that is refractory to treatment, Trousseau syndrome is said to be present.

Heparin-Induced Thrombocytopenia (HIT)

Pathogenesis. Patients on heparin therapy may occasionally form autoantibodies that have strong procoagulant activity and may lead to severe thrombosis despite (or even because of) the heparin therapy. The pathogenic mechanism of this phenomenon has been fairly well researched: The heparin binds platelet factor 4 (PF4) released by platelets, thereby inducing the formation of antiheparin-PF4 antibodies. These antibodies then stimulate platelet activation and aggregation, changing the endothelium from an anticoagulant state to a strongly procoagulant state. This antibody-mediated platelet aggregation leads both to thrombosis and to thrombocytopenia.

Clinical Features. HIT most commonly occurs after the administration of UFH and less commonly after LMWH. In typical cases the antibodies (and thrombocytopenia) appear approximately five to seven days after heparin administration. If the antibodies are already present in the blood (e. g., due to prior heparin administration within the past three months), the thrombocytopenia may develop within one day after reexposure to heparin. In most cases the platelet count falls to 50% of the initial value, reaching a level of approximately 50×10^9/L. Even so, bleeding complications are extremely rare. HIT is extremely thrombogenic, leading in many cases to venous or arterial thrombosis or to a rapid progression of preexisting thrombosis. Without alternative anticoagulant therapy, the incidence of thrombosis is approximately 50–60%. The following criteria, then, are necessary for a diagnosis of HIT: heparin administration, the detection of antiheparin-PF4 antibodies, and the presence of thrombocytopenia that cannot be attributed to other causes.

Heparin therapy may also be associated with a *mild transient thrombocytopenia* that is not antibody-mediated. This form of HIT, known also as HIT type 2, usually leads to platelet counts of $100–150 \times 10^9$/L, is not associated with thrombosis, and is clinically innocuous.

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15.3 Microcirculatory Disorders

Disseminated Intravascular Coagulation (DIC)

Pathogenesis. DIC is defined as an acquired, nonsegmental, global intravascular coagulation disorder that leads to the consumption of platelets and coagulation factors. Various factors may trigger the coagulation process, depending on the cause (e. g., bacteria, tumor cells, amniotic fluid, toxins, etc.), but proinflammatory cytokines (e. g., interleukin-6, TNF-α) play a key role in perpetuating and generalizing the coagulation process.

Clinical Features. A variety of diseases may be associated with DIC. Prime examples are sepsis, severe trauma, malignant tumors, obstetric complications, and major surgical operations.

Two clinical phases of DIC are distinguished:

- *Ischemic phase:* the microthrombosis of small vessels leads to organ tissue damage, leading in turn to impaired organ function (e. g., renal and liver failure). The coagulation factors are often still normal or slightly decreased at this stage, but activation markers (e. g., D-dimers) are greatly elevated. During the course of the disease, a continued rise in D-dimers, accompanied by declining fibrinogen levels and a falling platelet count are considered the most important indicators for the progression of DIC.
- *Hemorrhagic phase:* the continuing consumption of platelets and coagulation factors leads to severe thrombocytopenia and factor deficiency, causing a severe bleeding diathesis marked by generalized petechiae, bruising, and mucosal hemorrhages (see Fig. 15.**7**). In very severe cases the blood loses its ability to clot, i. e., global coagulation tests like the PT and aPTT show no coagulation and the individual coagulation factors fall to immeasurably low plasma levels. This condition is described as defibrination syndrome and has a very high mortality rate. This situation is characterized by very extensive microthrombosis, leading to ischemic necrosis that is especially pronounced in the end arteries (e. g., necrosis of the fingers and toes) (see Fig. 15.**7**).

Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic–Uremic Syndrome (HUS)

Pathogenesis. TTP is a disseminated, thrombotic microangiopathy characterized by the formation of fibrin-poor platelet aggregates in the microcirculation. The increased platelet aggregation results mainly from endothelial damage and the presence of ultra-large vWF molecules. The formation of these ultra-large molecules is caused by a congenital or acquired deficiency of the recently discovered vWF-splitting protease (ADAMTS-13 = **a d**isintegrin **a**nd **m**etalloprotease with **t**hrombo**s**pondin motifs).

Clinical Features. TTP is characterized clinically by thrombocytopenia, intravascular hemolysis with red cell fragmentation (fragmentocytes), neurological deficits, impaired renal function, and fever. Two forms are distinguished etiologically:

- *Primary TTP:* this type occurs in the absence of coexisting diseases. Generally it is based on a congenital or acquired autoantibody-induced deficiency of ADAMTS-13.
- *Secondary TTP:* coexisting diseases or circumstances are present that are associated with TTP, such as a malignant tumor, chemotherapy, or autoimmune disease (e. g., systemic lupus erythematosus, preeclampsia, infections, and many others; an autoantibody-induced ADAMTS-13 deficiency is not necessarily present).

The *differential diagnosis* includes *hemolytic–uremic syndrome (HUS)*, which is analogous to TTP but is characterized only by impaired renal function without neurological deficits and classically occurs after *E. coli* diarrhea or a *Shigella* infection. Often, however, it is difficult or impossible to distinguish clinically between TTP and HUS due to the frequent occurrence of mixed forms (TTP/HUS). An ADAMTS-13 deficiency is not present in classic HUS, however, and therefore the laboratory determination of this vWF-splitting protease is an important test.

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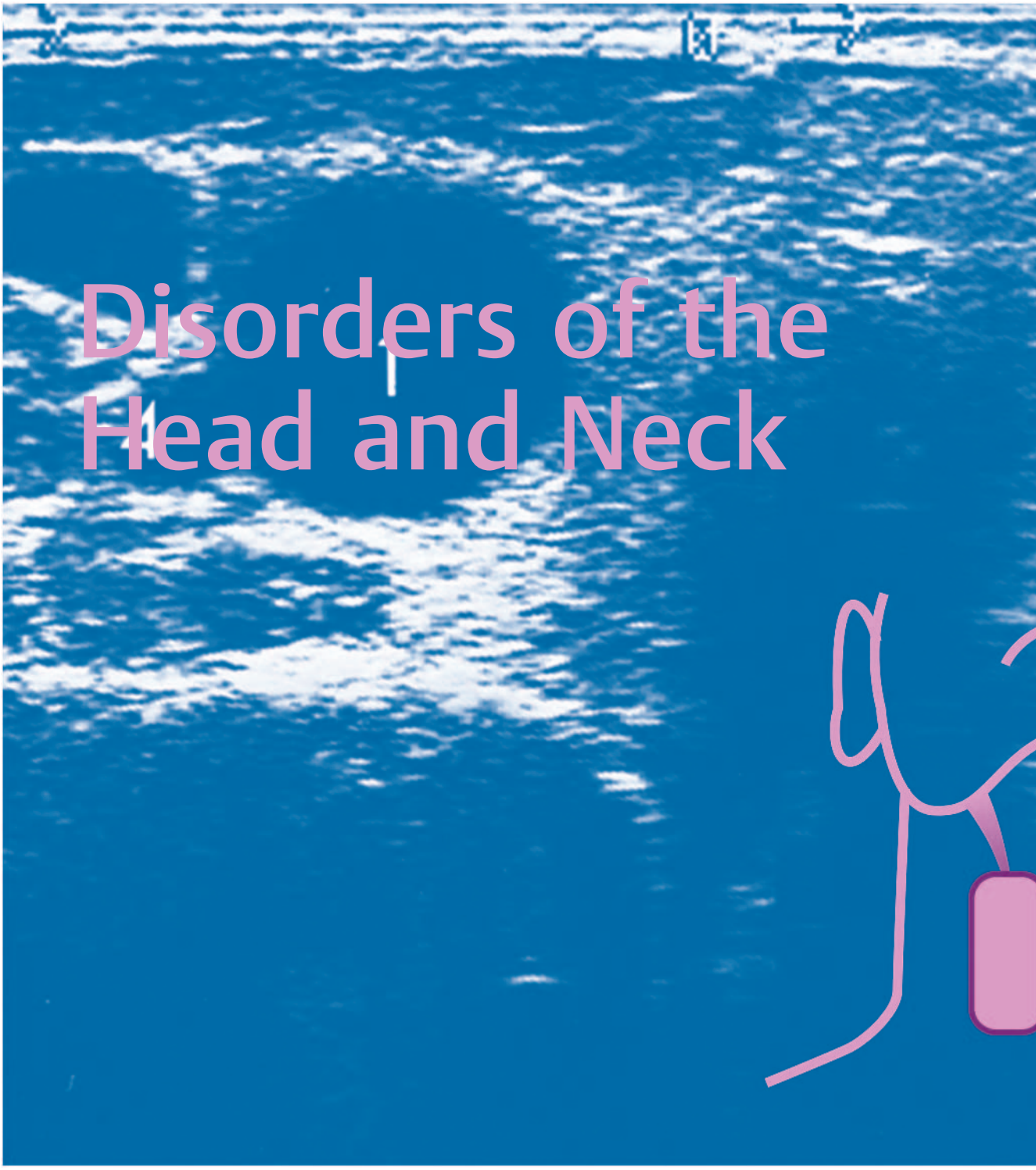
Disorders of the Head and Neck



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16 Disorders of the Head and Neck

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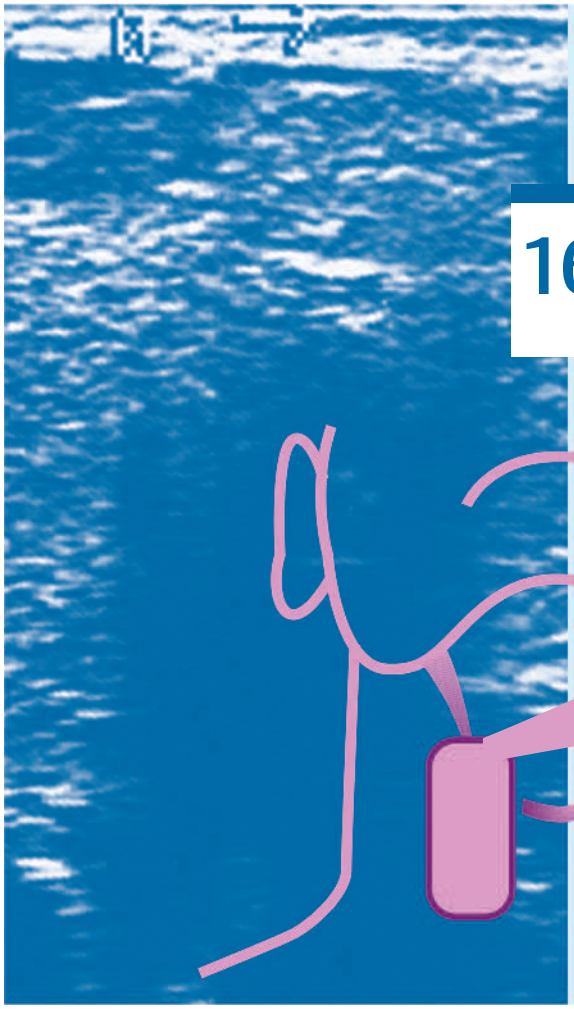

16 Disorders of the Head and Neck

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Examination and Differential Diagnosis of a Neck Mass

The neck is very well accessible for clinical examination. The thorough assessment of the medical history and a careful palpation of the cervical structures continue to be pivotal for the differential diagnosis of a neck disorder. The final diagnosis is supported by imaging modalities such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), and confirmed with the aid of fine-needle aspiration cytology or open biopsy. With regard to the many different organs in the neck, most diseases of the cervical area benefit from a multidisciplinary approach.

Neck Masses. Many diseases of the neck manifest as a mass. Any mass of the neck that lasts more than four weeks has to be further investigated. The main goal is to rule out a malignant disease.
A neck mass may occur as a result of congenital anomalies, inflammatory diseases, or tumors (Tab. 16.**1**).

Table 16.**1** Differential diagnosis of a cervical mass (thyroid excluded)

Anomalies
– Lateral cervical cyst (branchiogenic cyst)
– Thyroglossal duct cyst
– Vascular malformations (hemangioma, lymphangioma)
– Dysontogenic masses (teratoma, dermoid cyst)
Inflammations
– Acute nonspecific lymphadenitis (reactive, HIV, EBV)
– Specific lymphadenitis (tuberculosis, nontuberculous mycobacteriosis, sarcoidosis, toxoplasmosis, catscratch disease, syphilis)
– Chronic lymphadenitis (HIV, Castleman disease, Rosai–Dorfman syndrome)
– Deep neck infections (parapharyngeal space abscess, danger space infections, necrotizing fasciitis)
Neck tumors
– Benign tumors (lipoma, vagal schwannoma, carotid body tumor)
– Malignant tumors (lymph node metastases, lymphoma)

16.1 Congenital Anomalies of the Neck

The most common congenital neck anomalies are branchiogenic cysts and fistulae, thyroglossal duct cysts, vascular malformations (lymphangioma, hemangioma), and dysontogenic masses (teratoma, dermoid cyst).

Lateral Cervical Cysts. These cysts are branchiogenic in origin (Fig. 16.**1**). In general, they occur in young adults as a painless, fluctuant mass below the angle of the mandible, between the hyoid bone and the anterior border of the sternocleidomastoid muscle. In case of an infection, a lateral neck cyst may occur with a sudden and painful enlargement, similar to a neck abscess of other origin. The clinical suspicion of a branchial cyst is confirmed by the typical appearance and location in the ultrasound. Surgical excision is the treatment of choice.

If fine-needle aspiration cytology or the histopathologic work-up of the surgical specimen unexpectedly reveals malignant cells of a carcinoma, the most probable diagnosis is that of a cystic lymph node metastasis of an occult primary head and neck tumor. The existence of a primary branchiogenic carcinoma is debated controversially, but in any case is a very rare event.

Lateral Cervical Fistulae. These fistulae are also branchiogenic in origin. They commonly occur in early childhood with a recurrent suppurative discharge from a porus in the neck skin. The external opening of the fistulous tract is located at the anterior border of the sternocleidomastoid muscle. The main differential diagnoses are a tuberculosis or actinomycosis of the neck.

Thyroglossal Duct Cysts. These develop from remnants of the thyroglossal duct, which descends from the foramen cecum at the base of the tongue (Fig. 16.**2**). They occur as a fluctuant, painless neck mass in the midline between the hyoid bone and the thyroid cartilage of the larynx. During swallowing they follow the upward movement of the larynx. Infections may lead to a sudden painful enlargement with possible formation of a fistula through the otherwise intact skin. The diagnosis of a thyroglossal duct cyst is presumed by its clinical presentation and underlined by the typical appearance and location in the ultrasound.

Thyroglossal Duct Fistulae. These are the result of an infected thyroglossal duct cyst, either draining spontaneously or after surgical incision to the overlying skin. The porus of the fistula is typically located in the midline of the neck anterior to the hyoid bone.

Vascular Malformations. These mainly consist of hemangiomas and lymphangiomas. Hemangiomas are benign vascular neoplasms, which occur as reddish to bluish cutaneous or mucosal swellings. Spontaneous involu-

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Fig. 16.**2** Thyroglossal duct cyst

◁ Fig. 16.**1** Lateral cervical cyst

tion can be expected in 80 % of the cases. Involvement of multiple sites and organs has to be considered. Lymphangiomas (cystic hygromas) are benign, soft, and painless masses that are composed of ectatic and cystically enlarged degenerated lymph vessels. Spontaneous involution does not occur and slow progression is possible. Surgical excision is indicated in case of compression of adjacent structures.

Dysontogenic Masses. Teratomas and dermoid cysts are rare in adults. They occur as subcutaneous lesions. Teratomas may radiographically show opaque inclusions, which is indicative of the diagnosis. Due to their potential for malignant transformation, surgical excision is advised. Dermoid cysts are benign masses located in the midline, usually in the submental area. Treatment is by surgical excision.

16.2 Inflammatory Disorders of the Neck

In principle, inflammatory disorders of the neck are subdivided into those affecting superficial and those affecting deep neck structures. Superficial inflammations of the neck involve the skin and the cervical lymph nodes. Infections of the deep spaces of the neck may spread along the cervical fascias to the mediastinum and become the cause of a life-threatening mediastinitis.

Cervical lymphadenitis is a common accompanying finding for many underlying inflammatory diseases of the head and neck. It is subdivided, according to its temporal course, into acute (less than four weeks in duration) and chronic (more than four weeks in duration) cases. Infectious lymphadenitis is differentiated from noninfectious lymphadenitis. Furthermore, specific or nonspecific lymphadenitis is differentiated with reference to the histopathologic findings (see Chapter 4).

Acute Nonspecific Lymphadenitis

Etiology. An acute and painful cervical lymphadenitis occurs most commonly in association with an infection in the head and neck area (Fig. 16.**3**). The primary focus may be suspected with regard to the location of the involved lymph nodes. Patients frequently feel sick and show an elevated body temperature.

Epstein–Barr virus (EBV)-associated infectious mononucleosis occurs as an acute pharyngotonsillitis with voluminous lymphadenopathy. The tonsils are typically covered by a thick layer of grayish exudate.

After an incubation period of one to three weeks, some patients experience an acute lymphadenopathy as a result of a primary infection of HIV. Other symptoms include fever and malaise.

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Fig. 16.**3** Acute lymphadenitis with perifocal cellulitis in a patient with acute tonsillitis.

Fig. 16.**4** Cervical tuberculosis.

Diagnostic Evaluation. Initially, the search for an inflammatory focus is made by thorough physical examination of the entire head and neck area including the skin, the external auditory canal, the pinnae, the oral cavity including the teeth, and the pharynx including the tonsils. In some patients, laboratory findings (hematology, antibody titers) might be helpful. Further evaluation by imaging and cytology or histology is performed on a case-by-case basis.

Specific Lymphadenitis

Tuberculosis. Cervical tuberculosis occurs mainly as a secondary manifestation, through hematogenous spreading from another primary affected organ (Fig. 16.**4**). Therefore, tuberculosis of another organ, usually the lungs, has to be considered. Around 20% of cases show a bilateral, cervical lymphadenopathy. These nodes are multiple, firm or fluctuant upon palpation, and mostly nontender. The overlying skin can be reddish or bluish, and cutaneous fistulae may develop. The diagnosis is confirmed by the detection of acid-fast bacilli in cytologic smears. Histology of an affected node shows the specific epithelioid granulomas with giant cells and central caseous necrosis.

Differential Diagnosis. Initially, differential diagnosis of cervical tuberculosis from *nontuberculous mycobacteriosis*, which is quite frequent in children, is required.

Sarcoidosis is a multisystem granulomatosis with unknown etiology. The disease may occur in the neck, with bilateral painless enlargement of multiple lymph nodes. The general health status of affected patients is good. The diagnosis is confirmed through histopathology of involved nodes, which also have epithelioid granulomas, but without central caseous necrosis.

Acquired toxoplasmic lymphadenitis may occur with flulike symptoms. The diagnosis is confirmed by an elevated IgM titer during the acute phase or by histopathology (Piringer–Kuchinka syndrome).

The diagnosis of *catscratch disease* is based on a history of exposure to cats, but also to dogs or rodents. Histopathology shows a necrotizing granulomatous lymphadenitis with stellate abscesses.

Primary syphilis of the oropharyngeal area may manifest one to two weeks after an inoculation. The primary chancre is at the site of inoculation and a painless regional lymphadenopathy develops. The diagnosis is confirmed by dark-field microscopic examination of a smear.

Chronic Lymphadenitis

Diagnostic Evaluation. Chronic cervical lymphadenitis or cervical lymphadenopathy is defined by an enlargement of cervical lymph nodes, which lasts more than four weeks. It often presents a diagnostic challenge to clini-

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cians. It is of utmost importance not to miss the diagnosis of a malignant disease.

> In order not to miss the diagnosis of a malignant disease, the cytologic or histopathologic examination of an enlarged lymph node must not be omitted.

Further laboratory testing is based on the medical history. Travel destinations, exposure to animals, food habits, and occupation are among the topics that must be elucidated in this regard.

Etiology. Several months after an infection with HIV, painless lymphadenopathies with predilection of the posterior neck may occur.

Rosai–Dorfman syndrome is a chronic disease that is characterized by sinus histiocytosis with a massive painless cervical lymphadenopathy. The cause of the disease is not known. The disease is self-healing within few weeks.

Castleman disease shows histopathologically an angiofollicular lymph-node hyperplasia. The course of the disease is generally benign.

Deep Neck Infections

Abscess of the Parapharyngeal Space. Infections of the parapharyngeal space originate in the peritonsillar, parotid, masticator, or submandibular spaces. The most common causes are a peritonsillar abscess or an acute suppurative lymphadenitis. Other foci may be found in the teeth or in the floor of mouth. If an acute otitis media has preceded the infection, the possibility of a descending Bezold abscess should be considered. A parapharyngeal space infection or abscess occurs with fever, sore throat, odynophagia, and painful torticollis. The diagnosis is confirmed by ultrasound or CT analysis.

Danger Space Infections. The danger space is a space posterior to the retropharyngeal space with an open communication to the mediastinum. Any deep neck infection may spread to this space and cause a life-threatening mediastinitis. Immediate antibiotic treatment and surgical drainage of all affected spaces is mandatory.

Necrotizing Fasciitis. This severe, very difficult to treat, and potentially lethal infection of the cervical viscerae is caused by a mixed bacterial flora, usually containing *Streptococcus* species and anaerobic organisms. The patient's health status may severely deteriorate within a few hours from onset of the disease. Immediate admission to an intensive care unit, broad-spectrum and high-dose antibiotic treatment, and surgical drainage may save the patient's life.

16.3 Neck Masses

Masses of the neck tend to turn out to be malignant, more often than not. Therefore, the possibility of a malignant disease (lymph node metastasis, lymphoma) must be included in the differential diagnosis, and the appropriate evaluation must be performed.

Benign Tumors

Lipoma. The most common benign mass of the neck occurs as a single (or multiple) soft, well delineated, and freely movable, nontender lesion. Therapy is by surgical excision.

Vagal Schwannoma. Rare neurogenic tumors can arise from the cervical part of cranial nerve X. These tumors show a slow growth pattern and appear firm and sometimes tender upon palpation. They are typically only moveable in a lateral direction but fixed in a cephalic–caudal direction. With continued tumor growth the vagus nerve loses its function, and patients develop hoarseness and dysphagia.

Carotid Body Tumor (Paraganglioma). These tumors occur at the level of the common carotid artery bifurcation as nontender pulsating masses. On palpation they appear firm and only moveable in a lateral direction but fixed in a cephalic–caudal direction. They can produce a bruit on auscultation. The pathognomonic finding is a widening of the carotid artery bifurcation, which is observed in angiography or color-coded Doppler ultrasonography.

> In case of a suspected carotid body tumor no open biopsy should be attempted due to possible devastating hemorrhage.

Malignant Tumors

Lymph Node Metastases. Squamous cell carcinomas of the upper aerodigestive tract typically metastasize to cervical lymph nodes (Fig. 16.**5**). Enlarged unilateral or bilateral neck nodes can be the first manifestation of the

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Fig. 16.**5** Lymph node metastasis of a tonsillar carcinoma.

underlying disease. Metastases from other sites in the head and neck, or from organs of the chest and abdomen, are much less frequent. The medical history must be explored for risk factors such as smoking and alcohol abuse. Clinical palpation assesses the number, location, and size of the involved nodes. Imaging modalities are required for exact staging of the disease. The diagnosis is confirmed by fine-needle aspiration cytology. A thorough search for the primary tumor is mandatory.

Carcinoma of Unknown Primary (CUP Syndrome). In some patients with lymph node metastases of a carcinoma, the further thorough staging evaluation fails to reveal a primary tumor. The primary remains unknown and may never become evident.

Lymphomas. Approximately 10–15% of all lymphomas become clinically evident by the appearance of enlarged cervical lymph nodes. The most common, extranodal site in the head and neck region are the organs of the Waldeyer tonsillar ring. Presenting symptoms may include fever, night sweats, and weight loss. Fine needle aspiration cytology may result in suspicion of a lymphoma, but the exact diagnosis and classification is most reliably established by an open biopsy.

16.4 Salivary Gland Diseases

Most diseases of the salivary glands manifest with an enlargement of the affected gland. For the clinical differential diagnosis it is decisive to distinguish uniglandular from multiglandular, unilateral from bilateral, and painful from painless swellings. This allows, in most cases, allocation of the disorder to one of the following three categories: sialadenitis, sialadenosis, or salivary gland neoplasm (Tab. 16.**2**).

Table 16.**2** Differential diagnosis of salivary gland enlargements

Sialadenitis
– Acute suppurative
– Acute viral (mumps)
– Recurrent parotitis of childhood
– Sialolithiasis
– Sjögren syndrome
– Sarcoidosis
Sialadenosis
– Metabolic (diabetes mellitus, menopause, hypothyroidism)
– Malnutrition (hypovitaminosis, anorexia, bulimia, protein deficiency)
– Medication induced
Tumors
– Benign tumors (pleomorphic adenoma, Warthin tumor)
– Malignant tumors (mucoepidermoid carcinoma, acinic cell carcinoma, adenoidcystic carcinoma, non-Hodgkin lymphoma)

Sialadenitis

Acute suppurative sialadenitis of the parotid gland occurs as a sudden onset of a unilateral, painful swelling of the affected gland. In the oral cavity, purulent saliva can be seen draining from a swollen and reddened duct orifice. If the submandibular gland is involved, the presence of an underlying *sialolithiasis* must be suspected. These patients show a history of recurrent, painful swellings of the affected gland usually in association with eating.

The most common viral affection of the salivary glands is *mumps*. Mumps occurs as an acute, bilateral, painful swelling of the parotid glands. Mumps is well known for its rare, but severe, complications such as meningitis, encephalitis, orchitis, pancreatitis, and unilateral deafness.

Recurrent parotitis of childhood is a disorder of unknown origin in the pediatric population. It usually disappears at puberty, but may continue in some cases into adulthood. In some patients, surgical excision of the gland becomes necessary.

Sarcoidosis of the salivary glands is a granulomatous disease of unknown origin. In some patients it occurs with uveoparotid fever (Heerfordt syndrome) characterized by uveitis, parotitis, and facial palsy.

Sjögren syndrome is an autoimmune disease characterized by xerostomia and keratoconjunctivitis sicca. Patients are at elevated risk of developing a lymphoma.

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Sialadenosis

Sialadenosis is defined by a noninflammatory, painless, bilateral swelling of the salivary glands, usually the parotids (Fig. 16.**6**). Patients show a symmetric, diffuse, soft, and nontender enlargement of the parotids. Sialadenosis can be associated with metabolic disorders (diabetes mellitus, menopause, hypothyroidism), malnutrition (hypovitaminosis, protein deficiency, anorexia nervosa, and bulimia), and some medications.

Fig. 16.**6** Sialadenosis of the parotid glands.

Salivary Gland Neoplasms

Most salivary gland neoplasms are benign and manifest as nontender, slowly enlarging masses of the affected gland.

Benign Tumors. The most common benign tumor is the *pleomorphic adenoma* (benign mixed tumor) of the parotid gland (Fig. 16.**7**). The diagnosis is usually suspected from history and clinical examination, and confirmed by fine-needle aspiration cytology and imaging studies.

> Open biopsy of a pleomorphic adenoma leads to dissemination of tumor cells with subsequent development of a multilocular recurrent tumor. Therefore, open biopsy of a suspected pleomorphic adenoma is strictly contraindicated.

A sudden increase in size of a preexisting, pleomorphic adenoma, possibly in association with a facial palsy, suggests malignant transformation of the tumor. This occurs in about 3–5% of patients with long-standing adenomas.

Warthin tumor is the second most common benign tumor and usually affects elderly men who smoke. This tumor is soft upon palpation and is typically located in the tail of the parotid gland. Bilateral involvement is possible and malignant transformation has not been described.

Malignant Tumors. These show a rapid increase in size and infiltrate the overlying skin and adjacent deep structures. They are usually firm and, in the initial phase, nontender upon palpation. Malignancy is highly probable with the occurrence of a facial palsy or the appearance of enlarged lymph nodes. A wide variety of histologically distinct, malignant tumors with different prognoses exists. The most common are mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma.

Fig. 16.**7** Pleomorphic adenoma of the parotid gland.

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16.5 Diseases of the Thyroid Gland

Diseases of the thyroid gland may occur as diffuse or nodular enlargement of the thyroid alone or accompanied by:

- symptoms of thyroid hormone deficiency (hypothyroidism), or
- symptoms of thyroid hormone excess (hyperthyroidism), or
- ophthalmic complications (exophthalmus, diplopia), and/or
- thickening of the skin over the lower legs in the context of Graves disease.

An enlarged thyroid gland is easily distinguishable from branchiogenic cysts, dermoid cysts, etc., as it moves up and down, as the patient swallows. There are several ways to assess both the function of the thyroid gland and its morphology.

Diagnostic Tests to Assess Thyroid Morphology and Function

Evaluation of Thyroid Size and Morphology

Sonography. Inspection and physical examination of the thyroid gland (while swallowing) may be supplemented by ultrasonography. Radionuclide imaging should only be performed in specific situations. Thyroid ultrasonography is useful for measuring the size of the gland or thyroid nodules and particularly for differentiating solid from cystic nodules (Fig. 16.**8**).

Radionuclide Imaging. Scintigraphy with ^{123}I or ^{99m}Tc (technetium 99m pertechnetate) may be used for determining the functional activity of the thyroid gland, e. g., "hot nodules," indicating increased uptake of the radionuclide. Scintigraphy is particularly useful for identifying ectopic thyroid tissue (lingual thyroid, Fig. 16.**9**) or substernal extension of a goiter. Radioactive iodine (^{131}I) is used for treatment and followup of thyroid cancer.

Fine-Needle Aspiration Biopsy. Fine-needle aspiration biopsy is a reliable way to distinguish a benign nodule from a carcinoma.

Tests of Thyroid Function

The function of the thyroid gland can be evaluated by measuring the concentration of thyroid hormones in the serum or by assessing the thyroid stimulating hormone (TSH).

Measurement of TSH. Very sensitive and reliable methods for the measurement of TSH have been developed. Serum TSH levels reflect function of the anterior pituitary gland by sensing the level of circulating triiodothyronine and thyroxine (T3 and T4). The ultrasensitive measurement of TSH has become the most sensitive, most convenient, and most specific test for the diagnosis of both hyperthyroidism and hypothyroidism.

Measurement of Thyroid Hormone Concentrations in Serum. Most laboratories provide reliable immunoassays for the measurement of free triiodothyronine (fT3) and free thyroxine (fT4) concentrations in the blood. Measurement of total (protein-bound) T3 and total T4 concentrations should only be performed in specific situations. In most cases, measurement of TSH (and in case of hyperthyroidism) fT4 is sufficient to assess thyroid function.

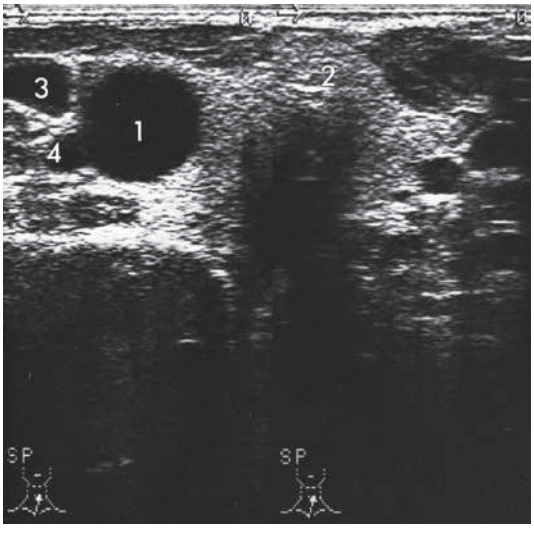

Fig. 16.**8** Ultrasonography of a thyroid cyst (1), surrounded by normal thyroid tissue (2), adjacent to the cyst, the jugular vein is seen (3), and the carotid artery (4).

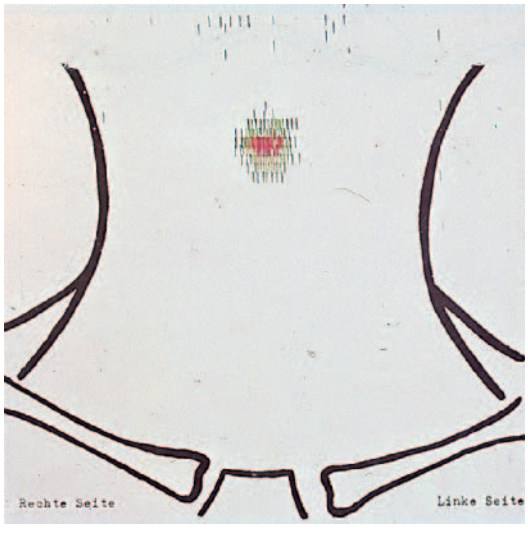

Fig. 16.**9** ^{123}I scintiscan showing an ectopic thyroid at the base of the tongue.

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Thyroid Enlargement (Goiter)

Several conditions may cause a diffuse or nodular enlargement of the thyroid (Tab. 16.**3**).

Table 16.**3** Causes of thyroid enlargement

Nontoxic goiter
– Iodine deficiency
– Goitrogens
– Inherited defects in thyroid hormone biosynthesis
– Generalized resistance to thyroid hormones
– Ectopic thyroid
Thyroiditis
– Subacute thyroiditis (de Quervain)
– Chronic autoimmune thyroiditis (Hashimoto)
Neoplasias
– Benign adenomas (follicular)
– Thyroid carcinoma
Hyperthyroidism
– Graves disease
– Toxic adenoma (Plummer disease)
– Toxic multinodular goiter

Nontoxic Goiter

Definition. Nontoxic goiter is defined as a noninflammatory, benign, diffuse or nodular enlargement of the thyroid without signs of hyper- or hypothyroidism.

Pathogenesis. Iodine deficiency used to be the most common cause of nontoxic goiter before iodized salt was introduced. However it may still exist in areas where iodine intake is deficient, e. g., alpine regions. If the daily intake of iodine falls below 50 μg/day goiter may develop. Optimal iodine requirements for adults are in the range of 150–300 μg/day, as suggested by the WHO.

Other causes of nontoxic goiter are: inherited defects in enzymes necessary for T3 and T4 biosynthesis, goitrogens such as amiodarone, kelp tablets, and lithium carbonate, or goitrogens found in certain food stuffs such as roots (Cassava), seeds, and cabbage which releases thiocyanates, and as a consequence of treatment with antithyroid drugs (methimazole, carbimazole).

The development of nontoxic goiter in patients with iodine deficiency, or defects in T3 and T4 biosynthesis, results in an increase in TSH secretion. This in turn causes diffuse thyroid hyperplasia followed by focal or nodular hyperplasia, which may become TSH-independent (autonomous). The result is a multinodular toxic or nontoxic TSH-independent goiter. The hyperplastic nodules may become necrotic and hemorrhagic. A multinodular goiter may therefore consist of "hot" (hyperplastic) nodules which can concentrate iodine and "cold" (necrotic, hemorrhagic, or microfollicular) nodules.

Thyroid enlargement manifestation may be diffuse or multinodular. In long-standing disease large goiters may develop and extend substernally, which leads to a narrowing of the trachea with inspiratory stridor or to a compression of the esophagus with difficulties in swallowing (dysphagia). An involvement of the recurrent laryngeal nerve may lead to vocal cord paralysis. Substernal extension of the thyroid can be assessed by ultrasound and/or CT analysis.

Differential Diagnosis. In areas with sufficient iodine supply, the most common cause of thyroid enlargement is chronic thyroiditis (Hashimoto thyroiditis) and subacute thyroiditis (see below). Thyroid cancer is a rare cause of nontoxic goiter (see p. 484, Thyroid Nodules).

Thyroiditis

The two most common forms of inflammatory thyroid disorders are subacute thyroiditis (de Quervain thyroiditis or granulomatous thyroiditis) and chronic autoimmune thyroiditis (Hashimoto thyroiditis).

Subacute Thyroiditis

Pathogenesis. Subacute thyroiditis is an inflammatory disorder, which is most likely caused by a viral infection. Several viruses including mumps virus, coxsackievirus, Epstein–Barr virus, and adenoviruses have been implicated, as these viruses have been found in biopsy specimens of the thyroid and/or increased titers of viral antibodies have been demonstrated during the course of an infection. Histologic examination may show mild inflammatory infiltrates and destruction of the thyroid parenchyma, and large phagocytic cells (giant cells).

Clinical Features. Subacute thyroiditis usually occurs with symptoms of malaise, fever, and pain in the neck, which may extend towards the inner part of the jaw or the ear lobes. The thyroid gland is usually tender and painful to pressure. At the beginning of the disease, patients may experience palpitations, nervousness, intolerance to heat, and weight loss (symptoms of transient hyperthyroidism). There is no ophthalmopathy.

Laboratory Findings. The erythrocyte sedimentation rate is markedly elevated, as are C-reactive protein levels. Thyroid hormone concentrations vary according to the course of the disease. Initially serum fT4 is increased, while TSH is suppressed (accompanied by a low iodine

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[^{123}I] uptake). As the disease progresses fT3 and fT4 levels drop into the hypothyroid range while TSH increases, which is accompanied by symptoms of hypothyroidism. Usually thyroid function will normalize and very seldom, permanent hypothyroidism ensues. Thyroid autoantibodies are usually not detectable or only slightly elevated (see below).

Course and Prognosis. The duration of the disease usually lies between one and three months and it resolves spontaneously but may occasionally reoccur within one to two years.

Chronic Autoimmune Thyroiditis (Hashimoto Thyroiditis)

Chronic autoimmune thyroiditis is the most common cause of hypothyroidism and goiter in areas with sufficient iodine supply. It occurs in children and young adults.

Riedel thyroiditis is a rare variant of chronic thyroiditis leading to a fibrous destruction of the thyroid. Riedel thyroiditis typically presents as a firm mass, extending outside the gland and involving surrounding tissues. It must be differentiated from thyroid cancer.

Pathogenesis. Hashimoto thyroiditis is an autoimmune disorder caused by a lymphocytic destruction of the thyroid tissue and is characterized by increased titers of autoantibodies in the serum against thyroid antigens. The most important thyroid autoantibodies are thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (Tg-Ab), and TSH receptor blocking antibodies (TSB-Ab). Chronic autoimmune thyroiditis is four times more common in women than in men, is often familial, and associated with other autoimmune disorders such as Addison disease, diabetes mellitus type 1, hypoparathyroidism, ovarian insufficiency, pernicious anemia, and vitiligo (autoimmune polyglandular disease, APG).

Clinical Features. Hashimoto thyroiditis usually occurs with a diffusely enlarged painless thyroid gland. Patients are usually euthyroid or have only mild hypothyroidism, but may also suffer from severe hypothyroidism. In these situations the thyroid gland is usually small and atrophic.

Laboratory Findings. The most characteristic laboratory finding in patients with chronic autoimmune thyroiditis is the presence of high titers of thyroid autoantibodies in the serum. Autoantibody tests may, however, be negative in patients with long-standing disease and atrophic glands. Thyroid hormone concentrations are usually normal or low. In the latter case TSH concentrations are elevated.

Other Forms of Thyroiditis

Occasionally the thyroid gland may become acutely infected, with abscess formation. In such situations, the gland is painful and swollen with redness of the overlying skin. The diagnosis may be confirmed by fine-needle aspiration biopsy. An abscess of the thyroid must be differentiated from an infected thyroglossal duct cyst.

Thyroid Nodules/Thyroid Cancer

Thyroid nodules are very common. Most of them are benign in origin including follicular adenomas, cysts of the thyroid, focal thyroiditis, or a hyperplastic nodule of a multinodular goiter (Tab. 16.**4**).

Thyroid cancer is a rare condition, occurring as a nodule of the thyroid gland. It is observed as a firm mass that has grown rapidly, is fixed to the overlying skin, and does not move during swallowing. Signs of invasion (vocal cord paralysis and hoarseness), metastasis (cervical lymphadenopathy), or family history of medullary carcinoma make it likely that the nodule is a carcinoma.

> A history of exposure to external radiation, particularly to the thymus, also indicates an increased risk of malignancy.

Histology. Histopathological classification of thyroid cancer is important for prognosis and therapy. Differentiated tumors (papillary carcinoma, follicular carcinoma) and medullary carcinoma usually have a favorable prognosis, while undifferentiated anaplastic carcinoma has a very poor prognosis.

Medullary thyroid carcinoma is a disease of the C-cells and is characterized by an increased concentration of calcitonin and carcinoembryonic antigen (CEA) in the serum, which are useful markers for diagnosis and follow-up. Patients with medullary C-cell carcinoma may also suffer from therapy-resistant diarrhea. Around 20% of medullary thyroid carcinomas are familial and these are differentiated into four types:

1. Familial and may manifest without associated endocrine disease (familial medullary thyroid carcinoma).
2. In the context of multiple endocrine neoplasias (MEN) consisting of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism (MEN2A).
3. In the context of multiple endocrine neoplasias (MEN) consisting of medullary thyroid carcinoma, pheochromocytoma, and multiple mucosal neuromas (MEN2B).
4. Associated with a pruritic skin lesion usually located on the upper back (cutaneous lichen amyloidosis, MEN2A variant).

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These familial syndromes are due to mutations in the *RET* proto-oncogene. Patients with medullary thyroid carcinoma and their family members need to be screened for the endocrine abnormalities occurring in MEN2.

Table 16.**4** Causes of thyroid nodules

- Focal thyroiditis
- Cysts (thyroid, parathyroid, thyroglossal cysts)
- Dominant nodules in a multinodular goiter
- Recurrence of goiter after surgery
- Benign neoplasias
  - follicular adenoma (microfollicular, macrofollicular)
  - rare causes: lipoma, teratoma, and hemangioma
- Malignant neoplasms
  - differentiated thyroid cancer (papillary and follicular carcinoma)
  - undifferientiated carcinoma
  - medullary thyroid carcinoma
  - rare forms: lymphoma, fibrosarcoma, squamous cell carcinoma, teratoma, and metastases

Hyperthyroidism

Definition. Hyperthyroidism is a clinical feature resulting from an excess of circulating triiodothyronine (T3) or thyroxine (T4). The different conditions leading to hyperthyroidism and thyrotoxicosis are presented in Tab. 16.**5**.

Causes of Hyperthyroidism. The most common cause of hyperthyroidism is Graves disease. Less common are toxic adenomas (Plummer disease) or toxic multinodular goiter. Occasionally subacute or chronic thyroiditis may occur with a transient hyperthyroid state. Other rare forms of hyperthyroidism include iodine-induced forms (treatment with amiodarone, radiocontrast dyes), excessive ingestion of thyroid hormones, metastatic thyroid cancer, TSH-secreting pituitary tumors, resistance to thyroid hormones, excessive human chorionic gonadotropin (HCG) production by a hydatidiform mole, struma ovarii, etc.

Graves Disease

Etiology and Pathogenesis. Graves disease is an autoimmune disease occurring with one or more of the following features:

1. hyperthyroidism with or without goiter
2. endocrine ophthalmopathy
3. dermopathy (pretibial myxedema).

Hyperthyroidism is brought about by autoantibodies directed against the TSH receptor (TSHR Ab). Lymphocytic infiltration can be found within the thyroid. Around 40% of patients with Graves disease have ophthalmopathy, whereby lymphocytes and cytokines activate fibroblasts in the orbital tissue, resulting in swollen orbital muscles, diplopia, proptosis of the globe, periorbital edema, etc. Similar mechanisms, involving lymphocyte infiltration and cytokine stimulation of fibroblasts in the subcutis, cause thyroid dermopathy, which occurs in 2–3% of patients with Graves disease.

Graves disease is associated with certain HLA class II antigens (HLA-DR3) and other autoimmune diseases such as diabetes mellitus type 1, Addison disease, and chronic polyarthritis. The disease is five times more common in women. The peak incidence of Graves disease is between 20–40 years of age.

Clinical Features. Graves disease may occur with a variety of symptoms depending on the age of manifestation. Younger patients typically complain of nervousness, hyperkinesia, excessive sweating, intolerance to heat, palpitations, weight loss in spite of increased appetite, diarrhea, muscle weakness, and insomnia. Women are often oligomenorrheic or amenorrheic. Older patients may suffer palpitations, dyspnea, nervousness, weight loss, and muscle weakness. Upon examination, patients usually have tachycardia, tremor, a diffusely enlarged goiter, and may exhibit signs of Graves eye disease. In older patients, myopathy may be so severe that the patient cannot rise from the sitting position without assistance (signe de tabouret).

Ophthalmopathy associated with Graves disease includes mild forms with congestion or redness of the conjunctiva, periorbital edema, proptosis, thickening of extraocular muscles, and more severe forms with involvement of the cornea (keratitis cornea), and compression of the optic nerve (Fig. 16.**10**). Ocular muscle

Table 16.**5** Causes of hyperthyroidism and thyrotoxicosis

- Graves disease
- Toxic adenoma (Plummer disease)
- Toxic multinodular goiter
- Hyperthyroid phase of subacute or chronic thyroiditis
- Iodine-induced hyperthyroidism (amiodarone, radiocontrast dyes)
- Rare forms: TSH-secreting pituitary tumours, anterior pituitary resistance to T3/T4, metastatic, thyroid carcinoma, struma ovarii, hydatidiform mole, thyrotoixicosis factitia

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Fig. 16.**10** Proptosis and periorbital edema in a patient with Graves disease.

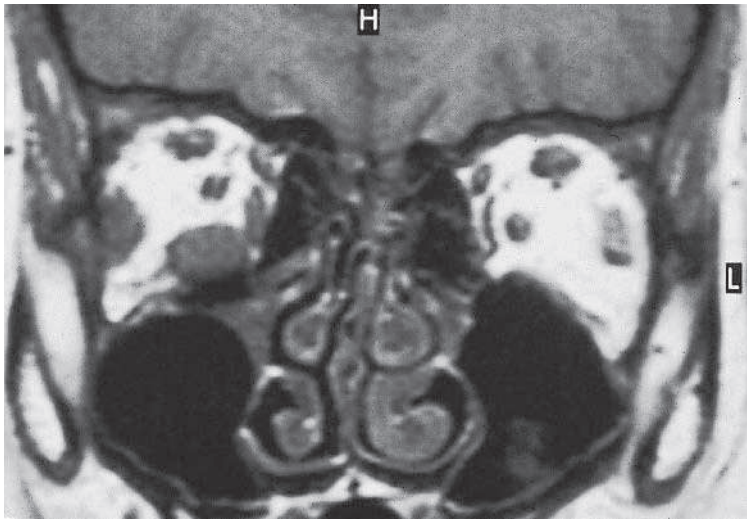

Fig. 16.**11** MRI of right-sided endocrine ophthalmopathy. The image shows pronounced ocular muscle swelling, particularly of the rectus inferior and lateralis.

enlargement can be assessed by orbital MRI (Fig. 16.**11**). Occasionally, endocrine orbitopathy may be unilateral (10%). In such situations MRI or orbital CT scanning can be helpful to exclude other intraorbital processes such as lymphomas, hemangiomas, malformations, pseudotumor orbitae, and meningiomas of the optic nerve. Endocrine ophthalmopathy may occasionally occur in the absence of hyperthyroidism (euthyroid Graves disease) or in hypothyroid patients.

Pretibial myxedema (thyroid myxedema) is characterized by thickening of the skin over the anterolateral part of the tibia as a consequence of accumulation of glucosamine glycans (Fig. 16.**12**) Dermopathy occurs in 2–3% of patients with Graves disease and is usually associated with endocrine ophthalmopathy. Rarely the dermopathy may involve the entire lower leg and feet (elephantiasis). Involvement of the bones with hypertrophy of the hollow bones, subperiosteal bone formation, and swelling (thyroid osteopathy) may occur, as well as onycholysis (separation of the finger nails from their beds, Fig. 16.**13**).

Diagnosis. Hyperthyroidism is diagnosed by an elevated fT4 and a suppressed TSH concentration in the serum. The presence of signs of an endocrine ophthalmopathy supports the diagnosis of Graves disease and no further tests are needed. The presence of thyroid autoantibodies, particularly of TSHR autoantibodies is diagnostic for Graves disease.

Toxic Adenoma (Plummer Disease)

Definition. Toxic adenomas are "hot" nodules on the thyroid scintiscan, representing follicular adenomas. These thyrocytes are constitutively activated and autonomously hypersecrete thyroid hormones due to a point mutation in the G-protein of the TSH receptor.

Clinical Features. Toxic adenomas usually occur in older (> 40 years of age) patients with thyroid nodules, which are often only detected by ultrasonography. The patients

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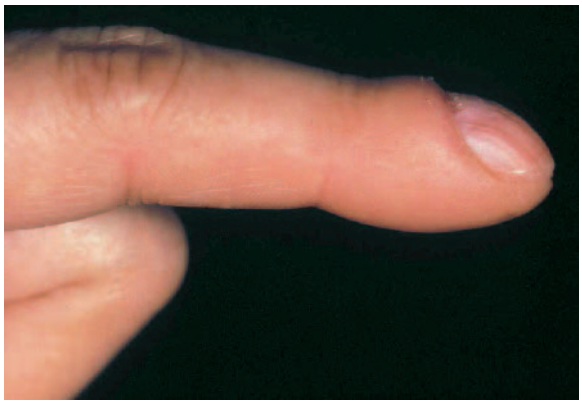

Fig. 16.**13** Onycholysis in Graves disease.

Fig. 16.**12** Pretibial myxedema in a patient with Graves disease.

are often oligosymptomatic. Toxic adenomas are often found incidentally in patients with cardiac arrhythmias, palpitation, history of weight loss, shortness of breath, or muscle weakness.

Diagnosis. Laboratory studies usually reveal suppressed TSH and elevated fT3 and fT4 concentrations. Usually serum fT3 is markedly elevated as compared to only slightly elevated fT4. Thyroid scintiscan typically reveals a "hot" nodule and no radionuclide uptake by the rest of the thyroid (suppression). Thyroid autoantibodies are not present (Fig. 16.**14**).

Toxic Multinodular Goiter

Causes. Hyperthyroidism may occur if multiple nodules in a multinodular goiter (autonomously) hypersecrete thyroid hormones. The disease typically occurs in patients with long-standing goiter, living in areas with iodine deficiency, and may be precipitated by the administration of iodides (radiocontrast dyes, amiodarone).

Amiodarone is an antiarrhythmic drug containing 37.3% iodine. The drug is stored in fat tissue, myocardium, liver, and the lungs and has a half life of 50 days. Some 10% of patients treated with amiodarone

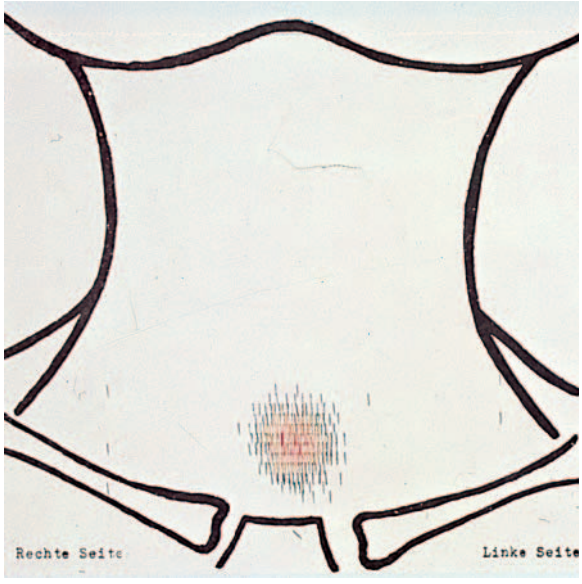

Fig. 16.**14** Solitary toxic nodule in a ^{123}I scintiscan, with suppression of the contralateral lobe.

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develop thyrotoxicosis. There are two forms of amiodarone induced thyrotoxicosis:

- a iodine-induced form (type I AIT), which often occurs in patients with preexisting autoimmune thyroiditis
- an inflammatory destructive form (type II AIT).

Clinical Features. Patients with toxic, multinodular goiter are usually older and have symptoms of muscle weakness, weight loss, and arrhythmia.

Laboratory Findings. As in patients with toxic adenoma, serum TSH is suppressed, serum fT4 concentrations are only slightly elevated, and serum fT3 is markedly elevated. Thyroid autoantibodies and ophthalmic symptoms are absent. Radioiodine scan typically shows multiple functioning "hot" nodules and nonfunctioning "cold" (degenerative) nodules.

Hypothyroidism

Definition. Hypothyroidism is due to an insufficient production or action of thyroid hormones leading to a slowing down of metabolism.

Causes of Hypothyroidism. Hypothyroidism can be due to a failure of the thyroid to produce thyroid hormones (primary hypothyroidism), to an insufficient production of TSH by the pituitary (secondary hypothyroidism), or to hypothalamic TRH deficiency (tertiary hypothyroidism) (Tab. 16.**6**). Primary hypothyroidism is the most common form and can be subdivided into neonatal or acquired hypothyroidism.

Neonatal hypothyroidism mainly results from failure of the thyroid to develop (aplasia, hypoplasia) or to descend during embryonic development, or from inherited defects in thyroid hormone biosynthesis. Very rarely it can occur as a result of peripheral resistance to the action of thyroid hormones. Neonatal hypothyroidism may also result from administration of anti-thyroid drugs or iodides during pregnancy, or because of iodine deficiency in iodine deficient areas (endemic cretinism).

The most common cause of *acquired hypothyroidism* is chronic autoimmune thyroiditis (Hashimoto disease). Other causes are treatment with radioactive iodine, subtotal thyroidectomy for nodular goiter, Graves disease, excessive intake of iodides (kelp tablets, radiocontrast dyes, amiodarone), and treatment with lithium carbonate or antithyroid drugs. Rarely, subacute thyroiditis may lead to hypothyroidism.

Secondary hypothyroidism may occur in patients with pituitary tumors after pituitary ablative therapy, as a consequence of postpartum pituitary necrosis (Sheehan syndrome), or after head/neck injury. The clinical presentation and the findings depend on the age of manifestation.

Table 16.**6** Causes of hypothyroidism

Primary hypothyroidism
– Chronic autoimmune thyroiditis (Hashimoto thyroiditis)
– Radioactive iodine therapy
– Subtotal thyroidectomy
– Excessive iodine intake
Secondary hypothyroidism
– Pituitary destruction/necrosis
– Hypopituitarism (partial/total) due to pituitary adenoma, hypophysectomy, etc.
Tertiary hypothyroidism
– Hypothalamic lesions
Neonatal hypothyroidism
– Congenital (athyreotic, hypothyreotic)
– Acquired in utero

Neonatal Hypothyroidism

Hypothyroidism in newborns manifests with poor feeding, respiratory difficulty, cyanosis jaundice, hypotonia, muscle weakness, umbilical hernia, and growth retardation.

Hypothyroidism in children is characterized by growth and mental retardation, retardation in bone maturation, a puffy face and hands, and as neurological signs of pyramidal and extrapyramidal tract abnormalities.

Acquired Hypothyroidism

In advanced hypothyroidism, the signs and symptoms are characteristic and easy to recognize. In mild forms and in elderly patients, symptoms may be subtle and hypothyroidism may occur with unusual features such as neurasthenia, paresthesias, muscle weakness and constipation.

Clinical Features. Common symptoms of hypothyroidism include chronic fatigue, inability to concentrate, coldness, weight gain, constipation, and menstrual irregularities. Patients often complain of dry, rough skin, periorbital swelling (Fig. 16.**15**), swollen hands and feet, a hoarse voice, and a thickening of the tongue. Muscle tendon reflexes are slow and patients may complain of paresthesia, muscle cramps, and muscle weakness.

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Laboratory findings often reveal anemia, which may be due to impaired hemoglobin synthesis or impaired intestinal absorption of iron or folic acid, or to pernicious anemia (occurring in the context of polyglandular autoimmune disease). Serum cholesterol and creatinine levels may be elevated. Secondary hypothyroidism usually occurs with uncharacteristic symptoms and may be accompanied by symptoms and signs of adrenocorticotropic hormone (ACTH) deficiency, gonadotropin hormone (GH) deficiency, or of secondary hypogonadism.

Diagnosis. The most important test to diagnose hypothyroidism is serum TSH. An elevated TSH in the presence of low serum fT4 is diagnostic for primary hypothyroidism. In secondary hypothyroidism fT4 concentrations are decreased and TSH is low (or normal). Increased titers of thyroid autoantibodies confirm the diagnosis of autoimmune thyroiditis.

If secondary hypothyroidism is diagnosed, MRI of the pituitary should be performed (pituitary tumors, empty sella).

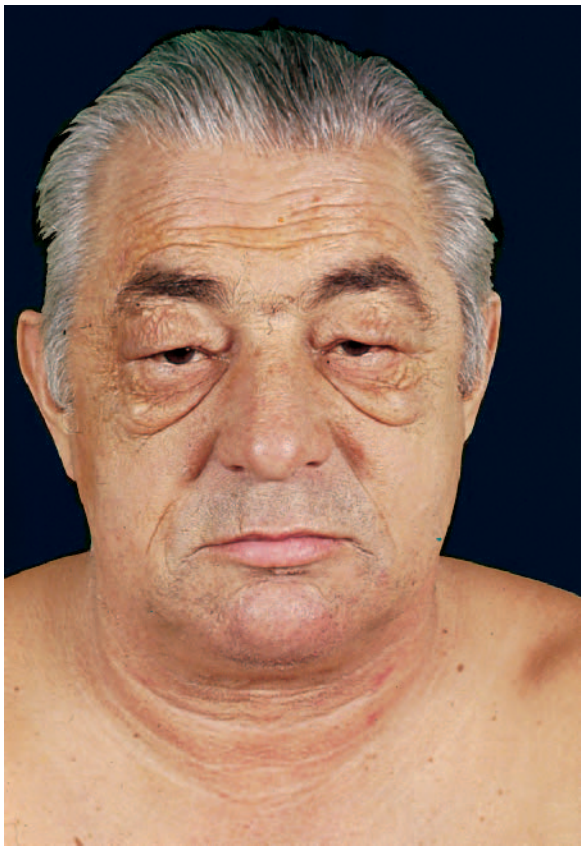

Fig. 16.**15** Hypothyroidism (myxedema) in a 60-year-old patient with a typical puffy face, and periorbital edema.

16.6 Diseases of the Parathyroid Glands

Disorders of the parathyroid glands including primary and secondary hyperparathyroidism as well as hypoparathyroidism are discussed in Chapters 11 and 30, respectively.

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Pulmonary Symptoms

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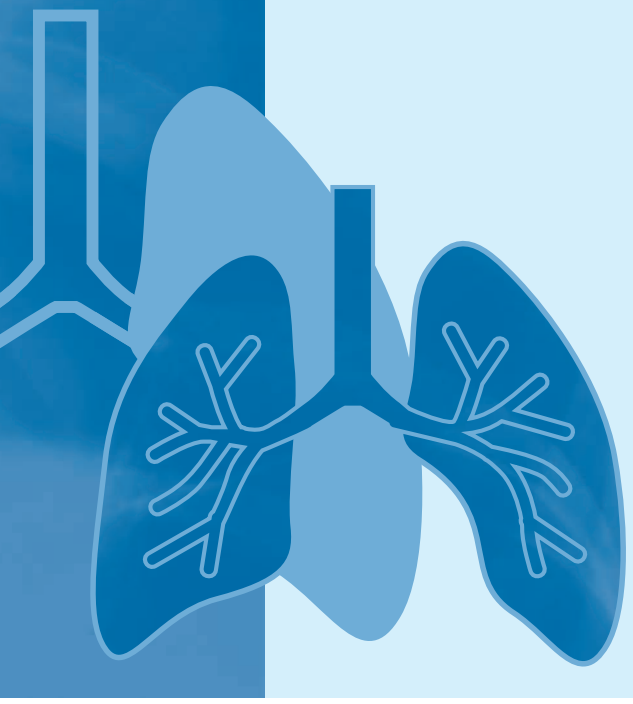

17 Cough, Expectoration, and Shortness of Breath
E. W. Russi and K. E. Bloch

18 Pulmonary Opacities
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19 Enlargement of the Hilum
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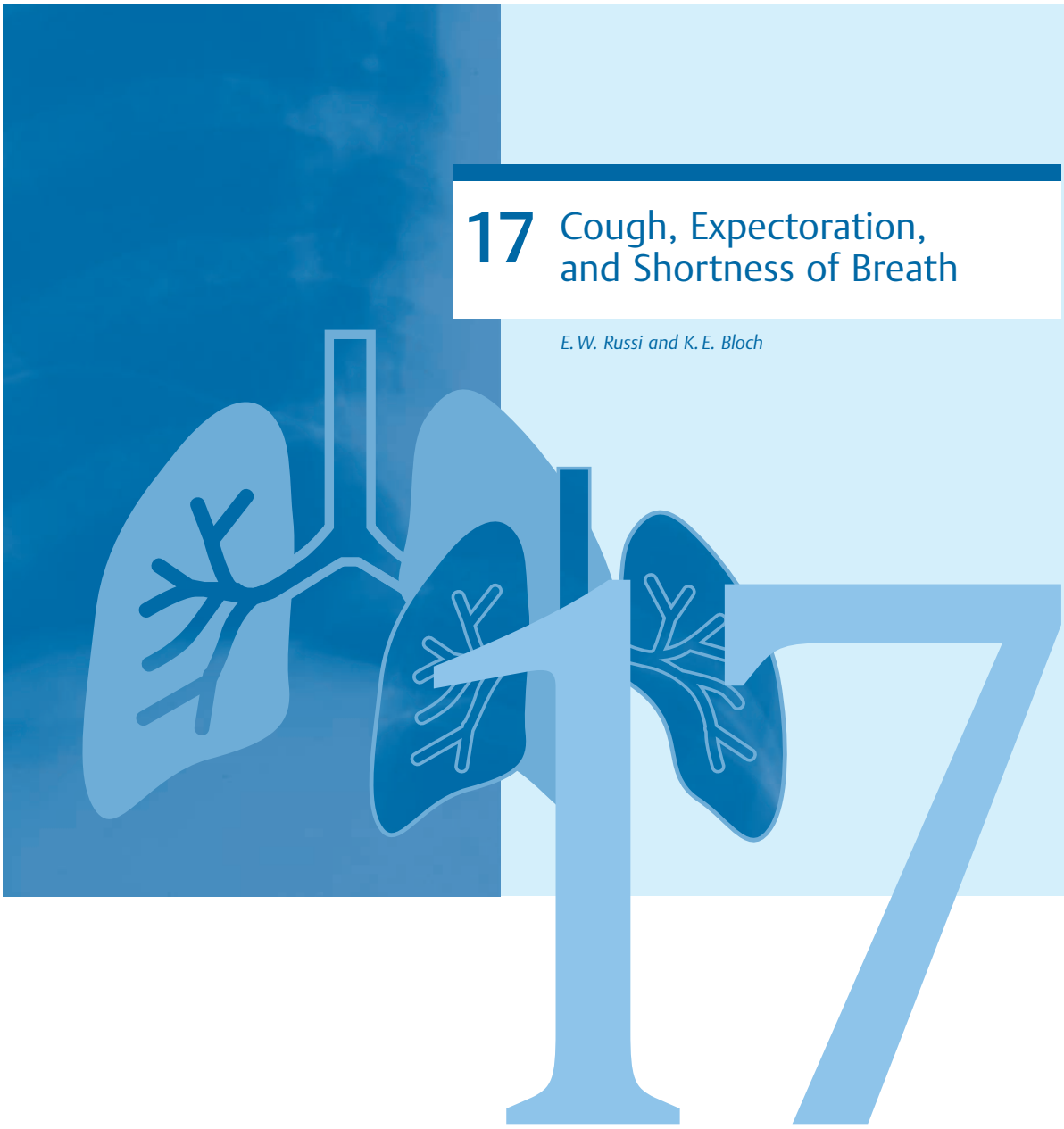

17 Cough, Expectoration, and Shortness of Breath

E. W. Russi and K. E. Bloch

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Cough, sputum production, and dyspnea are the cardinal features of respiratory diseases. One of these symptoms may prevail according to the underlying pathology, but quite often they occur concurrently. Cough and expectoration are particularly frequent in patients suffering from chronic airway diseases, such as chronic obstructive lung disease, bronchial asthma, bronchiectasis, and, in severe forms, i. e., at a certain level of functional impairment, patients complain about shortness of breath. However, in restrictive lung diseases dyspnea is often the leading complaint, whereas an unproductive cough remains a complementary symptom. Pulmonary infections are frequent causes of cough and expectoration. The volume of sputum may be particularly voluminous in patients with bronchiectasis or a lung abscess. Pulmonary vascular diseases, which are accompanied by an increase in pulmonary vascular pressure, are characterized by shortness of breath during exercise. Blood in the sputum or frank hemoptysis is a typical complication of lung cancer.

17.1 Cough

Pathophysiology. Cough is a complex reflex initiated by the irritation of cough receptors located in the upper and lower airways. Cough serves as a protective mechanism against noxious inhalants. It represents an important bronchial clearance mechanism, indicates air pollution, and is a cardinal symptom of various lung diseases. In healthy persons cough is a physiologic reaction to inhaled irritants, in sick people it is the most common and often the first symptom of a diseased lung. Cough may indicate impaired mucociliary clearance, which requires an intact respiratory epithelium and bronchial secretion of normal rheologic properties. Viral infections of the lower airways are the most common causes for transiently impaired mucociliary clearance, whereas cigarette smoking is the most common cause for a permanently damaged clearance.

Clinical Findings. A distinction should be made between *acute* and *chronic*, as well as between *unproductive*, i. e., dry and *productive* cough, i. e., cough accompanied by sputum production.

Acute episodes of cough are common at any age and are most often due to viral airway infections. In this case, cough is self-limiting and needs no further work-up. Treatment is either not necessary or only symptomatic.

Chronic cough lasts longer then eight weeks by definition. It is quite often a diagnostic challenge.

Etiology. The following diseases can cause chronic cough (Tab. 17.**1**). In *children*, cough is frequently due to prolonged viral infections or postviral bronchial hyperreactivity. In childhood, cough is quite often the single symptom of asthma. Other causes are: foreign body aspiration, cystic fibrosis, and other lung diseases, which lead to impaired development and growth.

In *adults*, the most common causes of cough are chronic bronchitis in cigarette smokers, bronchial asthma, chronic rhinosinusitis with postnasal drip, and gastroesophageal reflux. Other causes are bronchial carcinoma, tuberculosis, and diffuse infiltrative lung diseases. Chronic cough may also be due to left-sided heart failure or it is caused by treatment with angiotensin-converting enzyme (ACE) inhibitors. In elderly people cough may be due to recurrent aspiration or an aspirated foreign body.

Cough is rarely a leading symptom in diseases of the pleura, the diaphragm, or the pericardium. Rare cases have been reported in which cough was due to an irritation of the ear drum by hairs in the external ear channel.

Table 17.**1** Causes for chronic cough

	Children	Adults
Frequent	– bronchial hyperresponsiveness after viral infections – bronchial asthma – gastroesophageal reflux–pulmonary aspiration – "postnasal drip"	– chronic bronchitis (smokers) – "postnasal drip" – bronchial asthma – gastroesophageal reflux – congestive left-sided heart failure
Rare	– aspiration of a foreign body – bronchiolitis after viral infections – cystic fibrosis – primary cilicary dyskinesia	– ACE inhibitors – recurrent aspiration bronchial cancer – tuberculosis – bronchiectases – pneumonia – interstitial lung diseases – psychogenic

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17.2 Expectoration

Pathophysiology. Expectoration of sputum, i. e., tracheobronchial secretion mixed with saliva, is an important symptom of diseases of the respiratory tract. Under normal circumstances an approximately 5 μm thick mucus layer covers the airways and protects the bronchial epithelium against inhaled noxious substances. This continuously renewed mucus is transported by the respiratory cilia towards the oropharynx. It will be swallowed under normal circumstances and coughed up, if its quantity is increased. The normal amount of secretion is about 100 mL per day.

Sputum production is increased by any injury of the bronchial tree or the lung parenchyma due to inhaled noxious substances or by inflammation. Enhanced sputum production is a hallmark for airway injury or inflammation. Most inflammatory diseases of the bronchi (e. g., bronchitis, asthma, and bronchiectasis) and of the lung parenchyma (pneumonia) are associated with sputum production.

Appearance and Composition. According to the color of the sputum a distinction is made between mucous (whitish), mucopurulent, and purulent (yellowish) expectoration. The yellow or green color of the sputum is due to leucoproteins and leucoverdins, which mainly originate from decaying inflammatory cells, i. e., neutrophils and eosinophils and only partially from bacterial products. If sputum contains blood its color turns from faint red to dark brown according to the amount of blood and the time course of bleeding.

Sputum consists of 95 % water and only 5 % organic components, e. g., substances such as high molecular weight mucins, secretory IgA, etc. It contains substances that transude or exsude from the blood, such as fibrinogen or albumin. In addition, it contains cells from the blood or exfoliated epithelial cells. Cell products and mediators are further components of the complex composition of the secretion.

> Sputum is a product of secretion, transudation, exudation, and exfoliation of a highly complex mucous membrane. Its composition reflects inflammatory and neoplastic processes of the respiratory tract.

Cytologic and bacteriologic examination of the sputum (Giemsa and Gram preparations) allows characterization of airway inflammation, detection of neoplasms and identification of microorganisms responsible for bacterial and fungal infections.

Hemoptysis

Clinical Findings. The coughing up of blood is called hemoptysis. It can usually be distinguished from hematemesis without problems. Blood originating from the bronchial tree is coughed up and is of light red color. If blood is vomited, it is a dark color and often mixed with partially digested food ("coffee grounds vomiting").

A distinction should be made between small amounts of blood mixed with sputum (minor hemoptysis) and frank blood (major hemoptysis). Minor hemoptysis is often due to injured hemorrhagic mucous membranes. In patients with known bronchiectasis, minor hemoptysis is often self-limited and does not need further work-up in any case.

However, if a smoker experiences *minor hemoptysis*, meticulous work-up is mandatory and bronchial carcinoma is an assumed cause until proven otherwise. *Major hemoptysis* is caused by the bursting of a bronchial artery in the wall of an old tuberculous cavern, an aspergilloma, or due to lung cancer. The origin of the bleeding needs to be localized immediately, as it is important for further treatment (i. e., surgical resection or embolization of bronchial arteries). The risk of a patient dying from hemoptysis due to asphyxia depends on the severity of the bleeding. Major hemoptysis consisting of small amounts of blood may be a harbinger of sudden life-threatening hemorrhage.

Etiology. The following causes of hemoptysis need to be considered:

- *common causes*: bronchial carcinoma, bronchiectasis, chronic bronchitis, tuberculosis, aspergilloma, lung abscess, pulmonary embolism, mitral stenosis
- *rare causes*: foreign body, aortic aneurysm, Wegener granulomatosis, and other vasculitides involving the lung (alveolar hemorrhage), bronchial cysts, atrioventricular (AV) malformations, pulmonary endometriosis.

Diagnostic Work-Up. *Radiologic investigations*, particularly spiral computed tomography (CT) and *bronchoscopy*, are mandatory. These methods provide complementary information and allow in most cases a diagnosis of the underlying disease and a localization of the source of bleeding. It is not uncommon in smokers with chronic bronchitis and a normal CT scan to find only remnants of blood and no active bleeding source during bronchoscopy. In such cases no further work-up is mandatory, since recurrent hemoptysis is rare.

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17.3 Dyspnea

Definition. Dyspnea is defined by a subjective sensation of shortness of breath or air hunger. In other words, dyspnea is an individual's unpleasant perception of increased difficulty breathing.

Pathophysiology. Dyspnea is due to an imbalance between required gas exchange and the workload imposed on the breathing muscles. Dyspnea also occurs if the normal work of breathing has to be performed by insufficient respiratory muscles. Since dyspnea, by definition, is a subjective sensation, it can not be measured objectively by an investigator. However, dyspnea may indirectly be assessed by the changes in breathing pattern such as tachypnea, orthopnea, periodic breathing, etc.

Degree of Dyspnea

A frequently used scale to assess the degree of dyspnea due to lung diseases is that of the British Medical Research Council:

- Grade 0: dyspnea only during strenuous exercise
- Grade I: dyspnea only caused by brisk walking
- Grade II: brisk walking not possible due to shortness of breath
- Grade III: stopping due to dyspnea after 100 m walking
- Grade IV: does not leave the house due to shortness of breath.

Etiology. The following pulmonary and extrapulmonary pathophysiologic mechanisms and diseases are causes of dyspnea:

➤ **Pulmonary causes of dyspnea:**

– *obstructive lung diseases*: increased airway resistance caused by stenosis of the upper airways, bronchial asthma, chronic obstructive lung disease
– *restrictive lung diseases*: infiltrative pulmonary diseases, pulmonary fibrosis, following lung resection
– *vascular lung diseases*: pulmonary embolism, pulmonary arterial hypertension, intrapulmonary right–left shunt.

➤ **Extrapulmonary causes of dyspnea:**

– *extrapulmonary restriction*: excessive obesity, kyphoscoliosis, neuromuscular diseases, diaphragmatic paralysis
– *cardiovascular diseases*: systolic and/or diastolic impairment of ventricular function, valvular heart diseases
– *other causes*: hypobaric hypoxia, extreme anemia, metabolic acidosis, third trimester of pregnancy, impairment of breathing regulation (panic attack with hyperventilation, idiopathic alveolar hypoventilation).

Respiratory Failure

Pulmonary diseases as a cause of dyspnea are often accompanied by respiratory failure. Therefore, the differential diagnosis of respiratory failure is discussed below.

Definition. Respiratory failure is not a clinical but a pathophysiological term. It is defined by impaired oxygen uptake with or without hypercapnia. The diagnosis of respiratory failure requires an arterial blood gas analysis. A distinction is made between respiratory failure type I (Po_2 in the arterial blood < 60 mmHg or < 8.0 kPa) and respiratory failure type II (Pco_2 > 45 mmHg or > 6.5 kPa).

Respiratory Failure Type I. This type of respiratory failure is characterized by hypoxemia and normal or low levels of CO_2 in the blood at rest (hypoxemia, normo- or hypocapnia). Respiratory failure type I may be caused by *ventilation–perfusion inequality*, *impaired diffusion* due to a decreased surface, a thickening of the alveolocapillary membrane, or a reduced contact time between circulating red blood cells and the alveolar gas or by a *right–left shunt*.

Respiratory Failure Type II. In this type of respiratory failure the elimination of CO_2 is impaired due to *alveolar hypoventilation*. Respiratory failure type II is characterized by an increase in Pco_2 in the arterial blood accompanied by hypoxemia.

Differentiation of Causes. The various causes of respiratory failure may be differentiated to a certain degree according to their response to a particular intervention. Shunts are rarely caused by pulmonary AV malformations, but more commonly due to extensive pneumonia or acute respiratory distress syndrome (ARDS). While breathing 100% oxygen, arterial Po_2 increases only minimally if a shunt is present.

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If the arterial Po_2 increases promptly, hypoxemia is either due to *ventilation–perfusion inequality*, *diffusion impairment*, or *alveolar hypoventilation*. During exercise the arterial Po_2 drops with diffusion impairment and shunts, while Po_2 does not change or even increases in conditions of ventilation–perfusion inequality or certain forms of alveolar hypoventilation.

The calculation of the alveolar–arterial Po_2 gradient allows one to discriminate if hypoxemia in a hypercapnic patient is solely due to hypoventilation or if impairment of diffusion or ventilation–perfusion inequality is present as well. If the gradient is not increased (< 20 mmHg, < 2.7 kPa) hypoxemia is mainly or exclusively due to hypoventilation.

Advanced lung diseases are frequently accompanied by *pulmonary arterial hypertension*. Pulmonary arterial hypertension is due to a reduction in the cross-sectional area of the pulmonary vasculature caused by destruction or an obliteration of arterioles and capillaries in infiltrative lung diseases, pulmonary fibrosis, or severe pulmonary emphysema ("vanished lung"). Alveolar hypoxia causes locoregional vasoconstriction and therefore augments pulmonary vascular resistance. This component of pressure elevation may be alleviated by supplementary oxygen. Surprisingly, even in advanced emphysema pulmonary pressure and vascular resistance are often normal at rest.

Clinical Findings. Respiratory failure may be due to the lung diseases and pathophysiological abnormalities described below. Clinical findings alone are often insufficient to make a diagnosis, except in advanced stages of the disease, or to quantify the degree of impairment. Pulmonary function tests, particularly spirometry aid in differentiation between obstructive and restrictive ventilatory impairment.

Spirometry

Spirometry is of great value in daily clinical practice. Spirometry measures *static* as well as *dynamic lung volumes* such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1).

Pulmonary restriction is characterized by a proportional decrease in FVC and FEV_1. The ratio between FEV_1 and FVC remains normal since both volumes decrease proportionally.

However, in *airflow obstruction* the ratio between FEV_1 and FVC is decreased, since the FEV_1 is reduced more than the corresponding vital capacity (Fig. 17.**1**).

Spirometry Measurement. Flow is measured while the patient performs a maximal inspiration and exhales as fast, as forcefully, and as long as possible, for at least six seconds. Volumes are calculated by integrating flow over time. A graphic display allows an assessment of the promptness by which the air has been exhaled and hence the quality of spirometry (volume–time and flow–volume curves; Fig. 17.**1**).

The volume exhaled during the first second (FEV_1) is measured in liters, as a percentage of predicted and as a percentage of forced vital capacity (FEV_1/FVC) × 100 (Fig. 17.**1a**). Slow vital capacity (VC) is measured during a slow inspiratory maneuver: the patient exhales slowly, as maximally as possible, and subsequently inspires as deeply as possible.

Maximal flow during the expiratory maneuver is called *peak expiratory flow* (PEF) and is measured in liters per second or liters per minute (Fig. 17.**1**). After the flow has reached its maximal value it steadily declines toward zero. The last two-thirds of the descending part of the flow–volume curve do not depend on the strength of the respiratory muscles, i. e., this fraction is not cooperation dependent. It is determined by airway geometry, i. e., the resistance to airflow and the lung's retractile forces, and it reflects the flow properties of the peripheral airways. The flow–volume curve can also be characterized by the flow at 50 % of forced vital capacity ($FEF_{50\%}$). If upper airway obstruction is a concern, a forced inspiratory maneuver should be performed (forced inspiratory flow during the first second: FIV_1 and $FIF_{50\%}$). Reversibility of obstruction to airflow is checked by performing spirometry after the inhalation of a betaadrenergic drug.

Spirometry Results. *Obstructive ventilatory defects* are defined by a decreased FEV_1/FVC ratio (0.7). The degree of airflow obstruction is assessed according to the reduction in the FEV_1 as a percentage of the predicted value. An increase in the FEV_1 after the inhalation of a betaadrenergic drug by at least 12 % and by more than 0.2 L indicates a reversible obstructive defect.

In *pulmonary restriction* the ratio of FEV_1/FVC is normal or increased. If the situation remains unclear, particularly in combined obstructive restrictive defects, a more extensive functional work-up, which consists of body plethysmography, helium dilution, nitrogen washout, etc., is mandatory to determine resistance to airflow, residual lung volumes, and functional residual capacity. The shape of the inspiratory and expiratory flow–volume curve allows a distinction between variable and fixed upper airway obstruction (Fig. 17.**2**).

Obstructive Ventilatory Defects

Airway resistance is increased in the following conditions:

- *stenosis* of the upper (mouth to larynx) and central lower airways (trachea, bronchi; Figs. 17.**3**, 17.**4**)
- *chronic obstructive lung disease (COPD) corresponding to the prevalent pathology*: chronic obstructive bronchitis (central airways), bronchiolitis ("small airways"). In the presence of pulmonary emphysema the expiratory collapse of the small airways, which are insufficiently tautened by the inelastic lung tissue is a further component of airflow obstruction.

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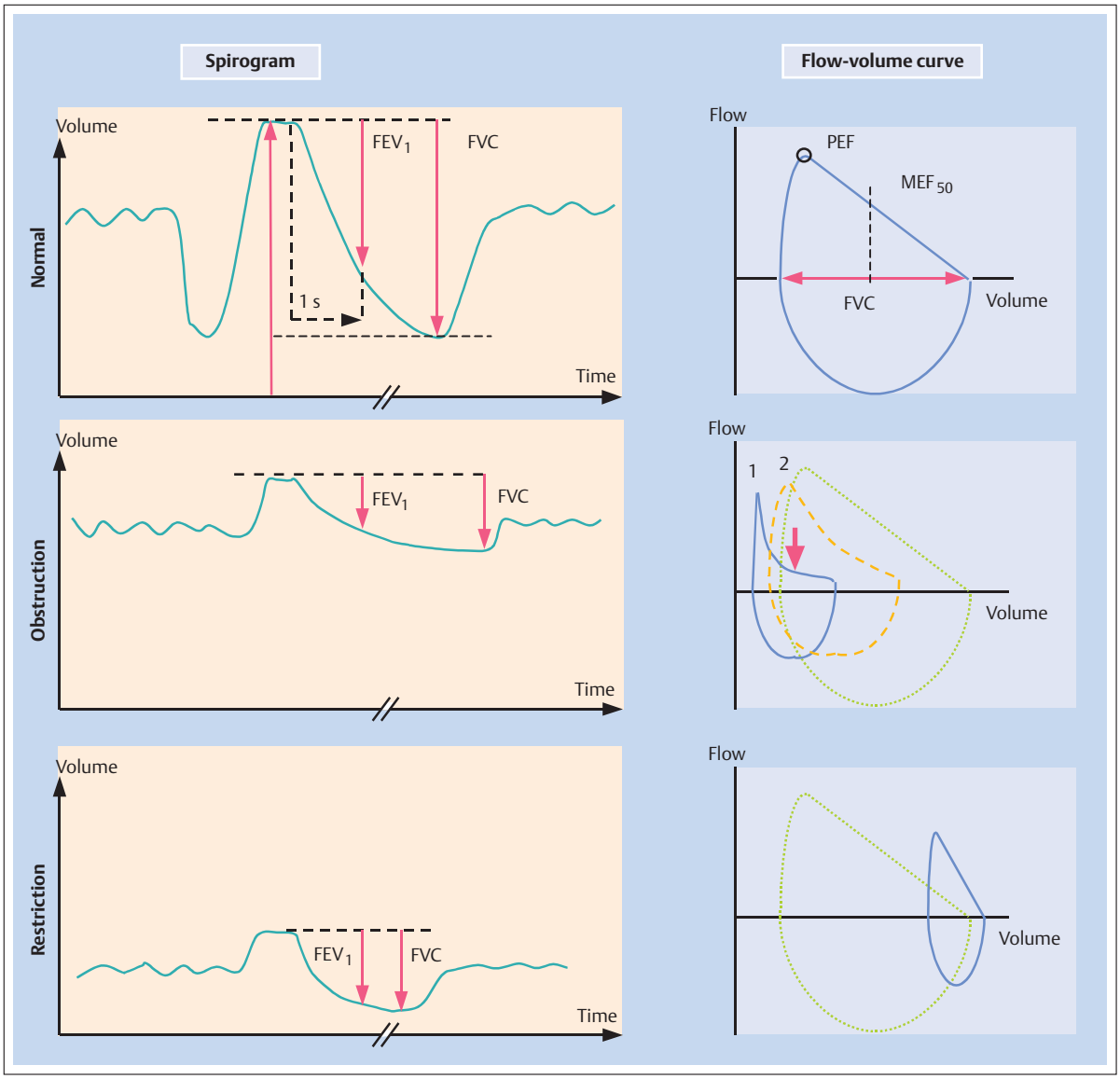

Fig. 17.1 Spirogram and flow–volume curve in a healthy person, in obstruction and restriction to airflow:
FEV_1: forced expiratory volume in the first second, i. e., the lung volume, which is expired during one second.
FVC: forced vital capacity: volume, which is measured after > 6 seconds maximal expiration.
PEF: peak expiratory flow: maximal flow (L/s).
In obstructive ventilatory defects the ratio FEV_1/FVC is < 0.7. In restriction, both volumes i. e., the FEV_1 and FVC are decreased by the same degree and the ratio FEV_1/FVC > 0.7. Notice the characteristic flow–volume curve 1: before, and curve 2: after, inhalation of a beta-adrenergic drug: characteristic for bronchial asthma.

- *bronchial asthma*: edema of the airways caused by inflammation, obstruction of the airways by infiltration of inflammatory cells, viscous mucus, and thickening of the bronchiolar walls.

Restrictive Ventilatory Defects

The following diseases are causes of *restriction*:

- *pulmonary*: atelectasis, pneumonia, infiltrative lung diseases and pulmonary fibrosis of various etiologies, pneumoconiosis, surgical resection
- *extrapulmonary*: pleural effusions, pneumothorax, kyphoscoliosis, thoracoplasty, pleural thickening, neuromuscular diseases.

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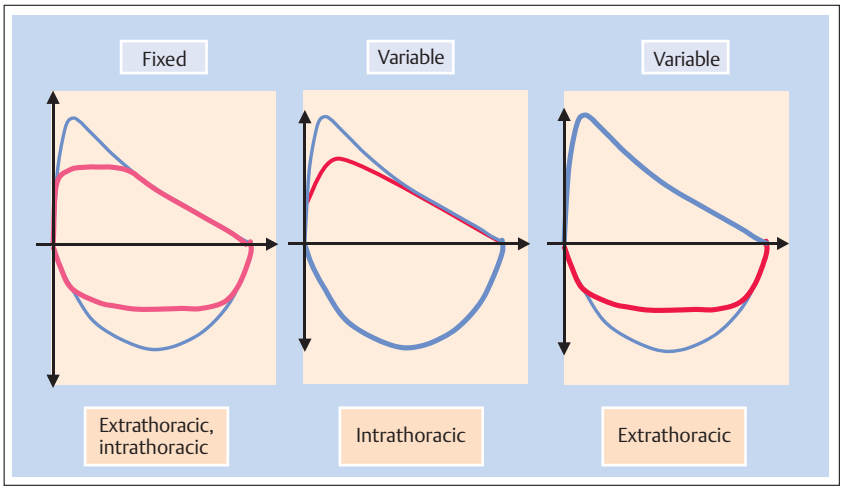
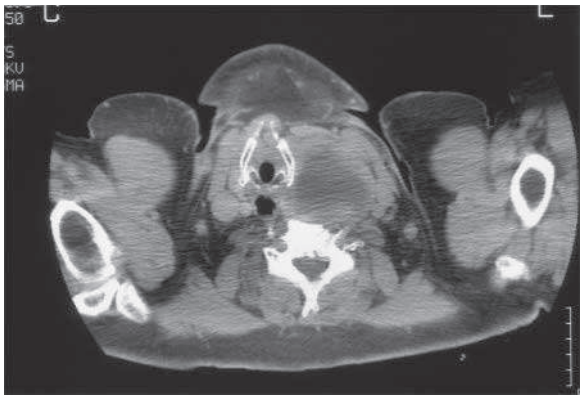


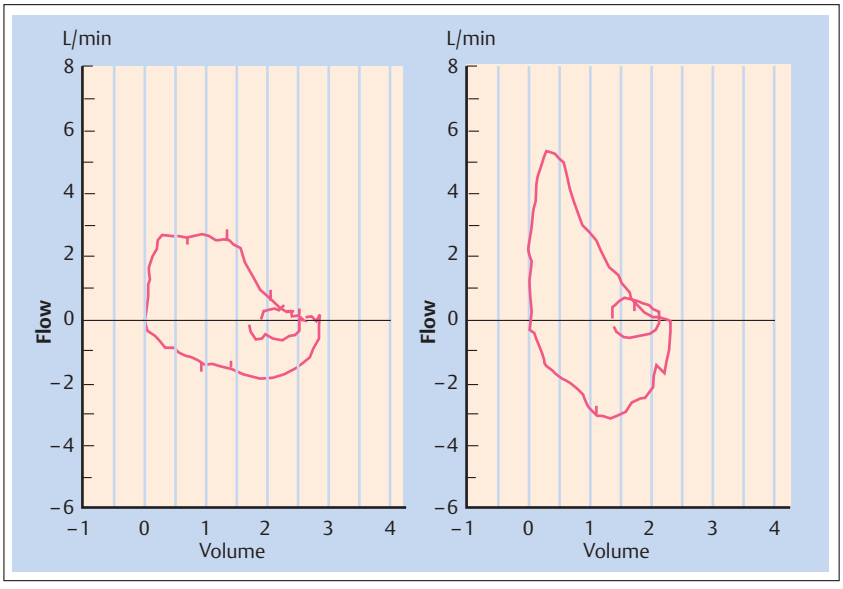
Fig. 17.**2** Upper airway stenosis. The inspiratory and expiratory flows are limited both during inspiration and expiration to the same degree if the stenosis is fixed, independent of its localization. If the stenosis is variable and localized outside the thorax, only the inspiratory flow is limited. If the variable stenosis is localized inside the thorax, only the expiratory flow becomes limited.



a

b

Fig. 17.**3** Goiter encroaching on the trachea:
a extrathoracic component of the goiter at the level of the larynx
b retrosternal part of the goiter, encroaching on and shifting the trachea.



a **b**

Fig. 17.**4** Flow–volume curve before and after surgical resection of the goiter:
a before resection, inspiratory and expiratory impairment of airflow is present: fixed obstruction
b after resection, inspiratory and expiratory airflow is no longer limited.

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Physical findings such as auscultation and percussion are paramount for the diagnosis. The differential diagnosis is discussed according to the principles discussed in Chapter 18.

To distinguish obstructive and ventilatory defects, clinical and radiological findings may be diagnostic but often have to be supplemented by pulmonary function tests.

Pulmonary Dyspnea

The following disease categories are causes of pulmonary dyspnea:

Obstructive Ventilatory Defects. These diseases are characterized by an increase in the *inspiratory or expiratory resistance* to airflow (e. g., upper airway stenosis, bronchial asthma, and COPD).

Restrictive Ventilatory Defects. In restrictive pulmonary disorders the compliance of the lung is decreased by an inflammatory or fibrotic pathology (pneumonia, lung fibrosis), by an increased water content of the lung (pulmonary edema), or by a tumor or atelectasis. The excursion of the lung may be restricted by its surrounding structures, e. g.: chest cage (e. g., kyphoscoliosis), pleural effusion or pleural thickening, neuromuscular diseases characterized by a decreased force of the inspiratory and expiratory muscles (e. g., muscle dystrophy, amyotrophic lateral sclerosis). These extrapulmonary causes of restrictive ventilatory defects will be discussed in the section of extrapulmonary etiologies of dyspnea.

Vascular Lung Diseases. These disorders affect primarily the pulmonary vessels e. g., pulmonary emboli, primary and secondary pulmonary arterial hypertension (anorectic drugs, associated with other diseases: HIV, scleroderma, chronic thromboembolic pulmonary hypotension).

Diagnostic Approach. Increased airflow resistance, which is characteristic for obstructive lung diseases, may be detected by wheeze noises heard over all lung fields. In contrast, auscultation may be normal in patients with restrictive lung diseases. To differentiate these two conditions *pulmonary function tests* are mandatory. In restrictive disorders the lung volumes and capacities are low, whereas in obstructive defects the dynamic lung volumes are impaired (FEV_1, FEV_1/FVC, PEF).

Pulmonary dyspnea is usually aggravated by exercise but not by changes in body position. Platypnea with orthostatic hypoxemia is a rare exception and consists of shortness of breath accompanied by arterial hypoxemia, which is more pronounced in the upright position than when lying. The *platypnea–orthodeoxia syndrome* may occur in heart defects with a right–left shunt, intrapulmonary shunts (AV malformations), and after pneumonectomy. In pneumonectomy platypnea–orthodeoxia is due to an open foramen ovale causing a right–left shunt, which increases in the upright position.

Extrapulmonary Dyspnea

Cardiac Dyspnea

Etiology and Pathogenesis. This form of shortness of breath is mainly due to *left-sided heart failure*, caused by coronary artery heart disease, hypertensive or valvular heart disease, or cardiomyopathy. Pulmonary venous hypertension is a consequence of an impeded venous blood flow to the left heart. As a consequence, pulmonary capillary pressure increases and the blood content in the pulmonary vascular bed is augmented. Lung compliance decreases, total lung capacity and vital capacity decrease, but resistance to airflow increases. *Acute interstitial and alveolar edema* with transudation in the alveolar space decreases lung compliance, and hypoxemia due to ventilation–perfusion imbalance ensues.

In the supine body position pulmonary congestion is aggravated by the redistribution of blood from the lower extremities and the splanchnic circulation into the thorax. The right ventricle increases its output, which cannot be matched by the impaired left ventricle. This increases pulmonary congestion. This mechanism causes orthopnea and nocturnal cardiac asthma.

Clinical Findings. Corresponding to the different etiologies, cardiac dyspnea manifests in *various ways* and may resemble pulmonary dyspnea. In both forms shortness of breath occurs at the onset, preferentially or exclusively *during exercise* (exercise dyspnea). Cardiac dyspnea occurs mainly in the supine position (orthopnea) or during the night after falling asleep. Dyspnea during the night may also occur in obstructive lung diseases (see below).

The breathing pattern of cardiac dyspnea is characterized by *rapid, shallow breathing* (irritation of juxta-

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capillary J-receptors by interstitial pulmonary edema) and is not different from the breathing pattern in lung diseases. Periodic breathing (Cheyne–Stokes respiration) is a characteristic feature of severe congestive heart failure and is often either asymptomatic or a cause of intermittent dyspnea. Cheyne–Stokes respiration is a bad prognostic sign (see Disturbed Control of Breathing, p. 503).

Lung auscultation reveals *rales* (discontinuous breath sounds), particularly during inspiration and over the basilar lung regions. Pulmonary congestion may also cause edema of the bronchial mucous membranes, which leads to prolonged expiration and wheezing (continuous breath sounds), a phenomenon which is called "cardiac asthma."

Diagnosis and Differential Diagnosis

Auscultatory Findings. In contrast to pulmonary etiologies, cardiac dyspnea is accompanied by fine rales at the end of inspiration over the dependent lung region. However, fine rales may also be heard in certain lung diseases, particularly in lung fibrosis. Occasionally pleural effusion is present, more commonly on the right than on the left side. An accentuated pulmonary sound (P II) due to elevated pulmonary vascular pressure may be present. Cardiac auscultation is crucial and may provide hints for the presence of cardiac failure (third and forth heart sound, gallops). Mitral stenosis, which can be silent for a long time, should not be missed. The typical auscultatory findings may only be present during exercise.

Chest Radiograph. The chest radiograph shows increased hilar and perihilar markings and often frank pulmonary edema. A typical *radiologic finding* is redistribution of the lung circulation, i. e., the cranially located pulmonary vessels become clearly visible since they have the same diameter as those located in the basal portions of the lungs (see Fig. 19.**1**). In heart diseases with a dilatation of the heart chambers, the heart silhouette becomes enlarged (cardio–thoracic ratio > 0.5).

Sputum. Sputum is not viscous but thin or frothy, and mixed with tiny amounts of blood (pulmonary edema). In chronic left ventricular failure the sputum color may become rust-brown ("heart failure cells").

Pulmonary Function. In left ventricular failure vital capacity is decreased due to lung congestion. Most commonly the FEV_1 is decreased proportionally. In certain cases the FEV_1/FVC ratio becomes lower then normal, i. e., combined obstructive–restrictive ventilatory disorder.

Laboratory Findings. Brain natriuretic peptide (BNP) serum levels are elevated in almost all cases, a finding that may be helpful in the differential diagnosis of dyspnea. Due to the high sensitivity of this test a normal serum level of BNP suggests a noncardiac cause of shortness of breath. However, BNP may be mildly elevated in severe lung diseases accompanied by pulmonary hypertension.

Diagnostics Involving Apparatus. The radiologic, electrocardiographic, and echocardiographic features in heart failure are discussed further in Chapter 20.

No diagnostic problems arise in pure forms of cardiac or pulmonary failure. In particular cases difficulties may arise due to a combination of heart and lung disease.

Right-sided heart failure may be accompanied by shortness of breath that is caused by an underlying lung disease. In such a situation the lung may be the leading organ, and the right heart failure is due to pulmonary arterial hypertension.

Low O_2 Content in the Ambient Air

Hypobaric hypoxia occurs at an altitude of around 3000 m (9800 ft) above sea level (inspiratory O_2 partial pressure is 100 mmHg, arterial Po_2 60 mmHg) and induces mild alveolar hyperventilation, which, however, is not able to completely compensate for hypoxemia. Moderate hypoxemia at rest occurs at an altitude of 3500 m (11 500 ft) and severe hypoxemia is observed above 5500 m (18 000 ft). Acclimatization to altitude occurs within hours to days and may partially offset shortness of breath.

Anemia

Acute bleeding causes volume depletion leading to hypovolemic shock, which is accompanied by arterial hypotension, mental impairment, and oliguria or anuria. In individuals with a healthy cardiovascular system and healthy lungs, chronic anemia is surprisingly well tolerated. Only strenuous exercise causes shortness of breath under such circumstances.

Metabolic Acidosis

Metabolic acidosis induces deep breathing by direct stimulation of the brain stem resulting in alveolar hyperventilation. Deep and often frequent breathing is therefore suggestive of acidosis. The most common causes of metabolic acidosis are ketoacidosis in diabetes, acidosis in renal insufficiency, and intoxication

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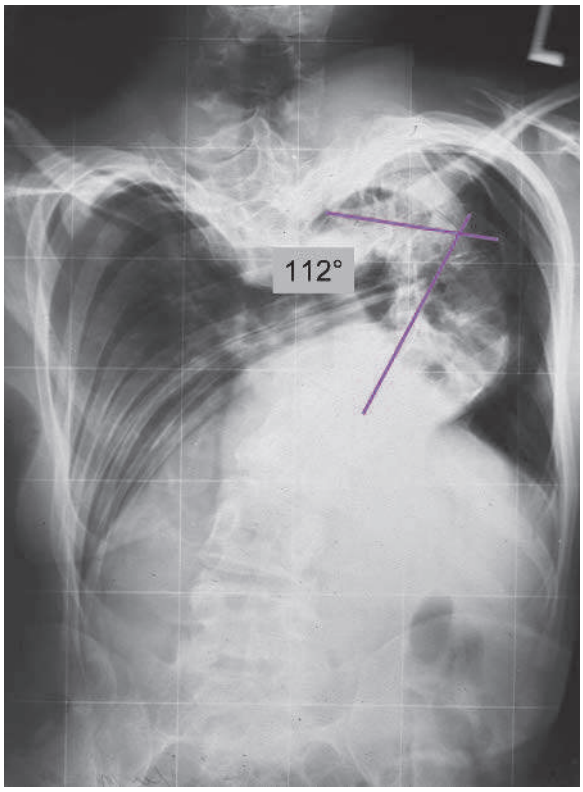

Fig. 17.**5** Advanced idiopathic kyphoscoliosis in a 23-year-old man causing a moderately severe, restrictive ventilatory defect.

(e. g., overdose of salicylate, ethylene oxide in antifreeze liquids).

Panic Reaction (Hyperventilation)

Panic reactions or panic attacks are often accompanied by chest pain, a feeling of oppression, shortness of breath, a sensation of being unable to take enough deep breaths, and dizziness. Panic attacks are common in younger individuals and occur preferentially during psychic stress. Panic attacks are occasionally accompanied by hyperventilation, i. e., inappropriate ventilation in relation to the individual metabolism, and cause symptoms of acute respiratory alkalosis, which consists of paresthesia at the fingertips and around the mouth. In severe cases tetanic cramps may occur.

Diseases Characterized by Extrapulmonary Restriction

Extrapulmonary restriction may be caused by pleural effusions, pleural thickening, tumors (e. g., mesothelioma), deformities of the thorax, or a weakness of the diaphragm.

Kyphoscoliosis. Idiopathic forms of kyphoscoliosis (Fig. 17.**5**) and deformities of the vertebral column secondary to neuromuscular diseases (e. g., postpolio) or after thoracic surgical interventions in childhood may be followed by deformation and stiffening of the thoracic cage. In such situations the respiratory muscles work uneconomically for geometric reasons and the respiratory reserve is reduced. In advanced kyphoscoliosis the strength of the respiratory pump is too low and is not capable of maintaining adequate ventilation. As a consequence, alveolar hypoventilation occurs initially during sleep and exercise, later on also during rest and mild daily activities. The resulting symptoms consist of dyspnea, fatigue, headache, and right-sided heart failure complicated by edema of the lower extremities.

Diaphragmatic Paralysis and Neuromuscular Respiratory Failure. Acute *bilateral diaphragmatic paralysis* causes severe dyspnea and, occasionally, life-threatening ventilatory impairment. Chronic forms of diaphragmatic paralysis are usually better tolerated. *Unilateral diaphragmatic paralysis* often remains asymptomatic and causes shortness of breath only during exercise. The clinical findings in diaphragmatic paralysis are characterized by a paradoxical breathing pattern, i. e., during inspiration the abdomen moves inward in contrast to a normal outward displacement. The elevation of the air-containing lung borders may be detected by percussion and the breath sounds over the lower lung fields are diminished. The vital capacity is typically lower when measured in the prone position then when the patient is seated or upright. Airway pressure during the sniff maneuver (i. e., "sniff nasal pressure") or inspiratory pressures against a blocked mouth piece (i. e., maximal inspiratory airway pressure) are reduced. Paradoxical movements of the diaphragm can be documented by ultrasonography or by radiography.

Various muscle or nerve diseases such as muscular dystrophy, spinal muscle atrophy, motoneuron diseases (e. g., amyotrophic lateral sclerosis), poliomyelitis, and polyradiculitis may be causes of *bilateral weakness or paralysis of the diaphragm* and the auxiliary breathing muscles. Another reason for paralysis of the breathing muscles is a traumatic lesion of the cervical spine. In rapidly progressive neurologic diseases, e. g., Guillain–Barré polyradiculitis, shortness of breath becomes a cardinal symptom. In slowly progressive diseases, e. g., in muscular dystrophy or in postpolio syndrome, the patients have enough time to adapt their physical activity to the ventilatory reserve. These patients often do not suffer from shortness of breath for quite a long time

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but complain of headache, difficulty with concentration and sleep disturbances, and may show signs of cor pulmonale.

Unilateral diaphragmatic paralysis is most frequently due to a lesion of the phrenic nerve, caused by lung cancer, other intrathoracic tumors or inflammation, or by iatrogenic injuries during an operative procedure (e. g., heart surgery). Quite often no cause is determined. Cryptogenic or idiopathic diaphragmatic paralysis occurs and the right diaphragm is more often affected than the left.

> The most common etiology of unilateral diaphragmatic paralysis is metastatic lung cancer.

Diaphragmatic Relaxation. Unilateral diaphragmatic paralysis must be distinguished from diaphragmatic relaxation, congenital problem. In theses cases the muscles are very thin and the diaphragm may be elevated considerably. The phrenic nerve is not injured. During inspiration the diaphragm may move paradoxically. The resulting complaints are uncharacteristic and minor.

Respiratory Dysregulation

During wakefulness, breathing is automatically controlled by the autonomous nervous system according to metabolic demands. In addition, ventilation is influenced by cortical and sensory inputs including voluntar breathing and emotions (behavioral control). During sleep, the behavioral stimuli are absent and breathing is solely under metabolic control. Compared to wakefulness, hypercapnic as well as hypoxic ventilatory drives are reduced during sleep. Consequently, sleep is a vulnerable phase for disturbed breathing regulation and an impaired control of breathing may occur preferentially or exclusively during sleep. Diseases accompanying advanced pulmonary or extrapulmonary respiratory impairment (e. g., COPD, neuromuscular diseases) or the ingestion of sedative or narcotic drugs (e. g., benzodiazepines, morphine derivates) may impair breathing regulation *secondarily*. This is usually followed by alveolar hypoventilation. The term *primary* disturbance of breathing regulation is reserved for situations without any underlying lung diseases. Examples for such conditions are sleep apnea syndrome and the rare congenital, genetically determined or acquired, idiopathic primary alveolar hypoventilation syndrome.

Sleep Apnea Syndrome. A distinction is made between *obstructive* sleep apnea syndrome with a prevalence of 4% in men and 2% in women and *central* sleep apnea syndrome, which is less common. Both are characterized by repetitive apnea during sleep, which disturbs the sleep architecture, and leads to excessive daytime somnolence. Since the breathing pattern is usually normal during daytime, the breathing disturbance cannot be recognized in the awake patient. The diagnosis may be suspected based on the patients history and is confirmed by cardiorespiratory and neurophysiologic monitoring (i. e., by polysomnography) during sleep. Clinical manifestation, diagnosis, and therapy of obstructive sleep apnea syndrome will be discussed below.

Central sleep apnea syndrome occurs usually in patients with heart failure (Cheyne–Stokes breathing), after a stroke, suffering from another neurological disease, or without obvious underlying disease (idiopathic central sleep apnea syndrome). Disturbed nocturnal breathing may impede the sleep quality (difficulty to fall asleep or maintain sleep) and hence be followed by daytime somnolence or may cause intermittent episodes of shortness of breath during the night. Quite often the symptoms are mild. Therapy consists, if possible, of treatment of the underlying disease. Therapies that may be used with variable effects consist of theophylline, acetazolamide, and oxygen or nocturnal positive pressure ventilation via a nasal or face mask.

Cheyne–Stokes Breathing. This type of respiratory disturbance may be observed in patients with severe heart failure during sleep or wakefulness. Cheyne–Stokes breathing is characterized by periodic waxing and waning of ventilation with phases of hyperventilation and central apnea or hypopnea (Fig. 17.**6**). The underlying pathophysiologic mechanisms are not entirely clear. Increased responsiveness of the respiratory control center for carbon dioxide resulting in hyperventilation, prolonged circulation time, and disturbed mechanics of breathing due to pulmonary congestion are suspected causes. Cheyne–Stokes breathing is a harbinger of poor prognosis. If pharmacologic treatment is optimized and heart transplantation is not an option yet, the patient may be treated by noninvasive nocturnal positive pressure ventilation.

Obesity–Hypoventilation Syndrome. This syndrome consists of excessive obesity and alveolar hypoventilation with obstructive sleep apnea. The term Pickwick syndrome originates from the excellent portrayal of the fat boy Joe in Charles Dickens' *Pickwick Papers*, who suffered from excessive daytime sleepiness. Chronic hypoventilation causes pulmonary hypertension with cor pulmonale. The treatment consists of weight reduction, which is difficult to attain and maintain without bariatric surgery. Nocturnal positive pressure ventilation promptly improves the symptoms of hypoventilation and sleep apnea.

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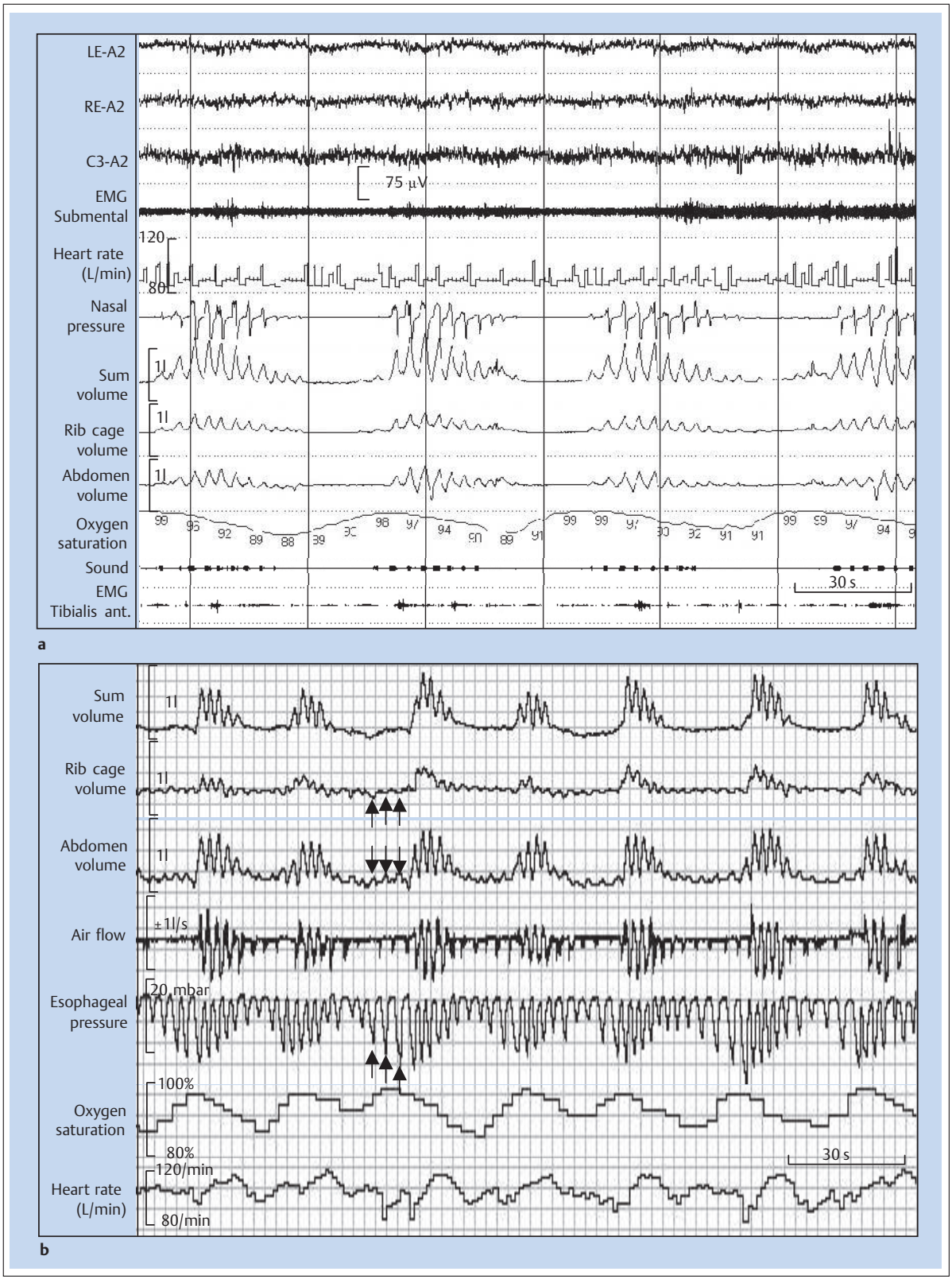

Fig. 17.**6** Polysomnography

a Recording in a patient with Cheyne–Stokes breathing due to severe heart failure. The cyclic increase and decrease of the ventilation with repetitive central apnea is traced by the registration of the pressure curve at the nostrils (nasal pressure) and with sensors of a respiratory inductive plethysmograph (thoracic volume, abdominal volumes, sum). Cyclic oxygen desaturations occur with a time delay after the ap- ▷

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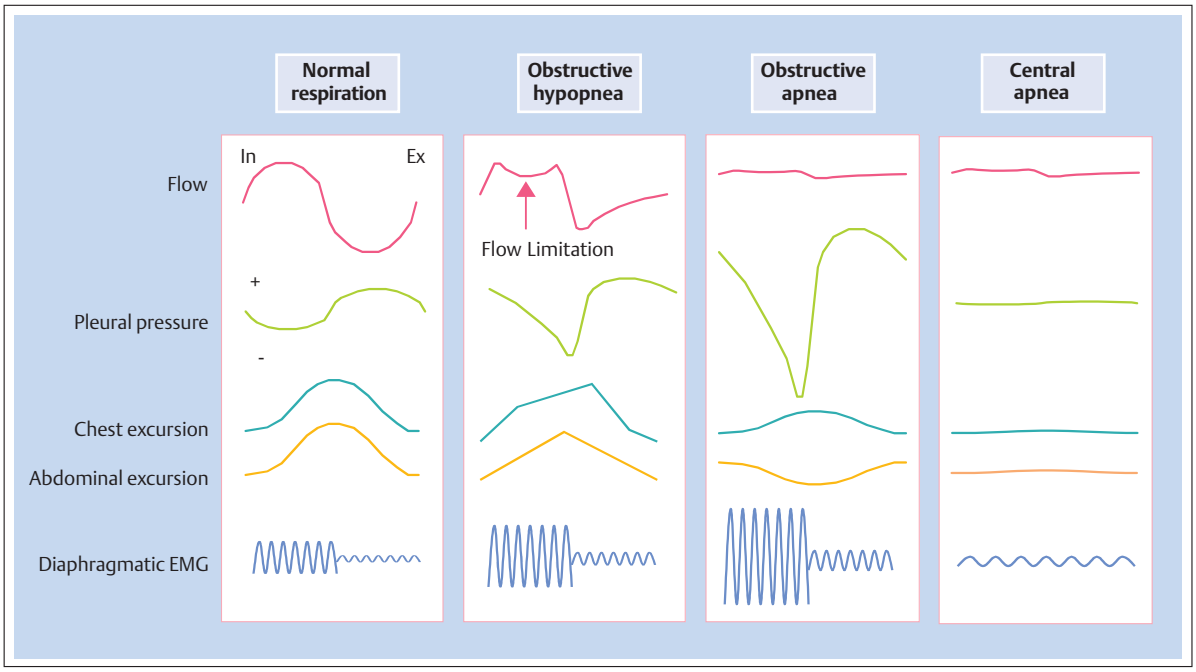

Fig. 17.**7** Apnea or hypopnea is defined as a cessation or reduction of airflow for 10 seconds or longer. In obstructive apnea/hypopnea, which is due to a partial or complete obstruction of the upper airway, the effort of the breathing muscles is maintained or even increased. Accordingly, the amplitude of the diaphragmatic EMG is augmented and the pleural pressure swings become marked. The typical paradoxical thoracoabdominal breathing excursions occur. In contrast, in central apnea neither diaphragmatic EMG activity nor pleural pressure swings can be observed.

Polysomnography

Measurement Methods. Polysomnography traces various neurophysiologic parameters, such as the electroencephalogram, electromyogram, electrooculogram, and cardiorespiratory variables during sleep. (Fig. 17.**6**). The ventilation is registered using sensors for pressure or temperature at the nose, chest and abdomen sensors, which record respiratory excursions, and pulse oximetry. In addition, the ECG, body position, and supplementary variables can be recorded according to diagnostic needs. These studies are performed in a sleep laboratory and allow evaluating the relationship between sleep–wake stages, ventilation, and other physiologic functions. Polysomnography is the basis for assessing sleep-related breathing disorders and other sleep disturbances. Simplified recordings can be performed with portable devices in outpatients who have a high pretest probability for a sleep apnea syndrome.

Assessment of Breathing Disorders. In adults, episodes of breathing cessation lasting longer then 10 seconds are called apneas. If ventilation is transiently reduced for longer than 10 seconds and by more than 50 % hypopnea is diagnosed. *Apnea and hypopnea* have similar physiologic consequences, which comprise episodes of oxygen desaturation, an increase in the partial pressure of carbon dioxide in the blood, and variation of the heart rate and the blood pressure. According to the type of apnea/hypopnea and individual sensitivity, waking occurs.

Obstructive apnea/hypopnea is caused by total or partial upper airway obstruction and can be recognized based on the persistent paradoxical movements of the chest and abdomen during the cessation of oronasal airflow. In central apnea/hypopnea the breathing effort stops or is considerably reduced intermittently (Fig. 17.**7**).

The degree of sleep-disordered breathing is assessed based on the average number of apnea and hypopnea per hour of sleep, i. e., the *apnea/hypopnea index*, the number of episodes of arterial desaturation of more than 3–4 % and further indices. The diagnosis of sleep-associated hypoventilation requires the measurement of the Pco_2 by arterial blood gas analysis or by transcutaneous measurement.

neas, and each apnea is followed by an arousal detectable by the EEG, EMG, and EOG.

b Polygraphic tracing in obstructive sleep apnea. During each obstructive episode accompanied by cessation of airflow, increasing pleural pressure swings occur (arrows). The heart rate slows during apneas and increases excessively during arousals. The arterial saturation shows cyclic alterations.

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Diseases

Diseases of the Larynx and Trachea

Larynx. *Inflammatory changes* of the laryngeal structures (epiglottitis, allergic edema) and *functional disturbances of the vocal cords* are the cause of important disorders. *Unilateral vocal cord paralysis*, most often due to an injury of the recurrent nerve, usually causes hoarseness. In contrast, *bilateral vocal cord palsy* is the cause of considerable dyspnea and stridorous breath sounds, already evident with a slight increase in ventilation as a consequence of exercise or emotions (see Fig. 17.**3**).

Shortness of breath is a complaint of otherwise healthy persons who complain of asthmalike attacks due to abnormal movement of their vocal cords as a manifestation of panic attacks. This disorder, called vocal cord dysfunction is poorly understood. Its diagnosis may be confirmed by flow–volume curves documenting variable flows or by laryngoscopy showing abnormal vocal cord movements during breathing maneuvers, e. g., adduction of the vocal cords during inspiration.

Trachea. The following pathologies are potential causes of upper airway obstruction:

- compression of the trachea by a goiter
- scars in the trachea secondary to a prior tracheal intubation
- malignancies (squamous cell carcinoma, adenoid cystic carcinoma)
- tracheobronchial papillomatosis or relapsing polychondritis.

Quite often such uncommon disorders may be misdiagnosed as bronchial asthma for many years. A characteristic diagnostic hallmark is stridorous breathing observed by the patient or the physician.

Bronchial Asthma

Bronchial asthma is a common disease. Its prevalence in adults is between five and 10%.

Definition. Bronchial asthma is an inflammatory airway disorder characterized by the following features:

- *variable airway obstruction*, which reverses either spontaneously or as a consequence of treatment
- *bronchial hyperreactivity* induced by various chemical or physical stimuli.

The essential pathophysiologic aspect of this definition is reversibility or variability of airway obstruction. Airway obstruction is due to *inflammatory swelling* of the bronchial mucosa, *bronchospasm*, and tenacious mucous containing exfoliated inflammatory cells ("eosinophilic bronchitis").

In allergic forms of bronchial asthma these features may be reproduced under laboratory conditions by the inhalation of a specific antigen. Minutes after the inhalation of the antigen bronchial obstruction occurs, which wanes spontaneously or is reversed by the inhalation of a beta-adrenergic drug (early phase reaction: bronchospasm). A few hours later obstruction to airflow recurs and persists much longer, e. g., up to 12 hours (late phase). This type of reaction can only be blocked by pretreatment with an anti-inflammatory drug, e. g., corticosteroids, leukotriene antagonist).

Forms of Bronchial Asthma and Pathogenesis

The following forms of bronchial asthma may be distinguished (Tab. 17.**2**):

- allergic ("extrinsic") bronchial asthma
- nonallergic ("intrinsic") bronchial asthma
- mixed forms of bronchial asthma.

Allergic bronchial asthma occurs in the context of atopy, i. e., the propensity of the patient to react with an exaggerated production of IgE antibodies. This type of bronchial asthma occurs preferentially, but not exclusively, in children and young adults. It is often preceded by allergic rhinoconjunctivitis and rhinosinusitis (hay fever) for many years. Mast cells carrying IgE antibodies on their surface degranulate when the antigen comes into contact with these antibodies and release histamine, leukotrienes C4, D4, E4, and other mediators, which cause bronchospasm and an inflammatory reaction of the bronchi with hypersecretion.

Nonallergic Bronchial Asthma. Much less clear is the pathogenesis of nonallergic bronchial asthma. Patients with nonallergic bronchial asthma do not react to specific antigens. They often suffer from nonallergic rhinosinusitis with polyposis nasi, and quite often they also have aspirin intolerance ("Samter triad").

Mixed Forms. A common form is mixed bronchial asthma. In these cases allergic as well as nonallergic mechanisms play a role.

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Table 17.**2** Bronchial asthma: clinical differential diagnosis of the two most common forms

Features	Extrinsic (exogen-allergic) asthma	Intrinsic (endogenous) asthma
Begin	Mainly in childhood and young adulthhood	Mainly in childhood and after age 30
Allergy in family history	Frequent	Rare
Atopy (rhinitis, neurodermitis)	Frequent	Rare
Trigger	Inhalational allergens (mites, pollen)	Viral infections (HRS virus, adenovirus, rhinovirus)
Duration of symptoms	Acute, minutes to hours (asthmatic attack), rarely over days, hardly ever persistent	Commonly periodic or persistent asthma, severe, relentless, later on unremitting
Infections of the sinuses	Rare, nasal polyps: uncommon	Frequent, nasal polyps, impaired sense of smell
Blood and sputum eosinophilia	Frequent	Frequent (marked!)
Drug hypersensitivity (aspirin and other NSAID)	Rare	Frequent (approximately 10%–20%!)
Type of reaction (immunologic)	I and/or III	I, IV (?)
Antibodies	IgE (or IgG) elevated	Absent or within normal range
Total IgE	Frequently elevated	Normal, rarely elevated
Skin test with allergen extracts (intracutaneous, prick test)	Positive after approximately 15 minutes; edema after 6–12 hours (Arthus type)	Negative
Inhalation provocation test with allergens	Positive	Negative or nonspecific reaction for solvents
Desensitization or allergen avoidance	Possible, effective	Noneffective, small effects

Epidemiology. Bronchial asthma is the most common chronic disease in childhood. However, frequently bronchial asthma also occurs in adults. Asthma in children is most often of allergic origin, whereas in adults both forms of bronchial asthma, i. e., allergic and nonallergic asthma may be observed. In smokers bronchial asthma may concur with chronic bronchitis. A distinction between these two airway diseases is not always possible.

Diagnosis and Clinical Findings

History. For the diagnosis of bronchial asthma the medical history plays an essential role. Quite often the patient becomes symptomatic and develops typical asthmatic symptoms when he/she is exposed to certain environmental factors (e. g., pollen, bedding dust, flour dust, etc.): attacks of shortness of breath, cough, wheeze breathing noises, and expectoration. An asthmatic attack may develop during the night or may manifest only as *paroxysmal cough* ("cough variant asthma").

Clinical Findings. In severe forms of asthma clinical examination reveals tachypnea. Pulmonary hyperinflation as a consequence of bronchial obstruction to airflow is diagnosed based on hyperresonance on percussion and low lung borders. On auscultation expiration is prolonged and abnormal breath sounds, e. g., wheezing, may be heard. In severe forms of bronchial asthma breath sounds become diminished and eventually disappear completely ("silent chest"). In such situations mucus plugging is a prominent feature. If the patient uses his/her auxiliary breathing muscles (e. g., sternocleidomastoidei and scaleni muscles) the forced expiratory volume in one second is usually lower then 1 L. The presence of pulsus paradoxus signifies a very severe asthmatic attack.

> The condition of a severe persistent asthma attack that does not respond to therapy is called status asthmaticus.

Spirometry. Lung function shows a reduction in VC and the FEV_1, as well as a decreased FEV_1/FVC ratio (Fig. 17.**8**). Total lung capacity and residual volumes are increased. Arterial blood gases reveal hypoxemia and hypocapnia (alveolar hyperventilation). When obstruction to airflow increases, Pco_2 becomes normal and eventually increases (respiratory failure type II).

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	Before inhalation		After inhalation		Change	
FVC	3.02 L	86%	3.44 L	91 %	+0.42 L	+14%
FEV_1	2.07 L	70%	2.85 L	71 %	+0.78 L	+38%
FEV_1/FVC	69%		83%			
PEF	4.95 L/s	75%	6.55 L/s	99%		+32%

Fig. 17.**8** Flow–volume curve and spirometric values before and after inhalation of an beta-adrenergic drug. The increase of the FEV_1 and an almost normalized flow–volume curve are characteristic.

Chest Radiograph. Low lung borders and horizontally oriented ribs are present as signs of pulmonary hyperinflation. In severe cases of bronchial asthma the chest radiograph serves to rule out complications such as pneumothorax and mucus plugs with atelectasis.

Sputum. *Microscopic cytological examination* of the sputum reveals abundant eosinophils, Charcot–Leyden crystals, and possibly Curschmann spirals. Macroscopically the sputum in bronchitic patients is similar to sputum of asthmatics, i. e., sputum in asthma may appear purulent (due to eosinophilic leucocytes) in the absence of bacterial or viral infection.

Laboratory Findings. *Eosinophilia* may be present in allergic as well as nonallergic forms of bronchial asthma. If the number of eosinophils is considerably increased, i. e., to several thousand per microliter, Churg–Strauss vasculitis or allergic bronchopulmonary aspergillosis may also be present.

Allergy Tests. The measurement of total IgE is not helpful, since a distinction between allergic and nonallergic forms of bronchial asthma is not possible. Skin tests (prick) with various antigens are performed and interpreted in light of a thorough history for causative triggers. Positive skin tests are diagnostic for atopy, and hence allergic asthma is possible in the clinical context. In certain situations it is useful to measure specific serum IgE (i. e., radioallergo-sorbent test, RAST).

In addition to allergens and nonspecific irritants, viral infections play a major role as triggers of exacerbation. In contrast to COPD, bacterial infection is rarely a trigger for asthma exacerbation.

Specific Forms of Bronchial Asthma

- exercise-induced asthma
- occupational asthma
- asthma induced by physical or chemical irritants
- aspirin-induced asthma
- asthma induced by gastroesophageal reflux
- asthma presenting solely with cough (cough variant asthma).

Exercise-Induced Asthma. Exercise may elicit bronchial obstruction in allergic as well as in nonallergic forms of bronchial asthma. Changes in temperature and osmolality of the bronchial tree are responsible mechanisms. Exercise-induced asthma is not a pathophysiologically, distinct form of asthma. Obstruction to airflow occurs

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with a latency of approximately five minutes after exercise, peaks at around 10 minutes, and reverses after 30–60 minutes. In children this manifestation of asthma occurs more frequently than in sedentary adults.

Occupational Asthma and Asthma Induced by Physical or Chemical Irritants. Occupational asthma is triggered by industrial dust, vapors, and gases. Approximately 2–15% of asthmatics suffer from occupational asthma. In certain cases asthma is mediated by IgE antibodies (flour [baker asthma], proteases, platinum salts, epoxy resin, formaldehyde, isocyanate, etc.), whereas in other forms there is unspecific irritation of the bronchial mucosa by physical or chemical stimuli (heat, cold, inert dusts, chlorine compounds, SO_2, naphthochinone, vanadium pentoxide, etc.).

Asthma and Gastroesophageal Reflux. Pathogenetically two mechanisms are discussed: aspiration of small amounts of stomach content causes bronchospasm, or bronchoconstriction resulting from a reflex mediated through the irritation of afferent vagal fibers in the distal esophagus by gastric acid. There is no scientifically sound study proving either of these hypotheses. However, clinical observations support the assumption that in certain asthma patients, gastroesophageal reflux may trigger or maintain asthma. A therapeutic trial may be warranted.

Psychological Aspects of Asthma

Despite extensive literature, there is no evidence that psychological mechanisms play a major role in the pathogenesis of asthma. Asthmatics do not differ from persons without asthma in their personality structure or in their behavior. However, in those suffering from asthma, emotions may influence the course of the disease (e.g., anxiety → hyperventilation → decrease of Pco_2 and/or cooling of the bronchial mucosa → release of mast cell mediators → bronchospasm.

Bronchitis

Bronchitis and asthma are different diseases and must be differentiated. The following further distinctions are made: acute and chronic bronchitis with two chronic forms—simple chronic bronchitis and chronic obstructive pulmonary disease (COPD). COPD is differentiated from simple chronic bronchitis by obstruction to airflow, which is diagnosed by spirometry.

Acute Bronchitis

Definition. Acute bronchitis is characterized by an acute inflammation of the airways, usually caused by viruses, e.g., myxovirus (i.e., influenza A, B, C, parainfluenza, HRS virus), adenoviruses, and picorna viruses (e.g., rhinoviruses). Acute bronchitis is differentiated from an acute exacerbation of COPD (see below) by the patient's history.

Clinical Findings. Acute bronchitis is often a feature of the so-called common cold, which is most commonly accompanied by rhinosinusitis, a sore throat, and cough. Acute bronchitis usually occurs endemically, most frequently during winter. Acute rhinosinusitis needs to be differentiated from allergic rhinosinusitis and inflammation by industrial toxins, as well as from rhinitis vasomotorica.

Chronic Bronchitis and Chronic Obstructive Pulmonary Disease (COPD)

Chronic bronchitis is an airway disease, characterized by cough and sputum production lasting for 3 months per year during at least two consecutive years (WHO, 1961).

The aforementioned definition of chronic bronchitis is used worldwide, not only in epidemiology but also in clinical practice. The differentiation between simple and obstructive chronic bronchitis is relevant with respect to prognosis. A diagnosis of COPD is made if chronic irreversible obstruction to airflow ($FEV_1/FVC < 0.7$) is present (Tab. 17.**3**).

Table 17.**3** Chronic obstructive pulmonary disease (COPD). Severity degree according to GOLD (*)

Stage I	mild	$FEV_1/FVC < 0.7$	$FEV_1\% \geq 80\%$ predicted
Stage II	moderate	$FEV_1/FVC < 0.7$	$50\% \leq FEV_1\% < 80\%$ predicted
Stage III	severe	$FEV_1/FVC < 0.7$	$30\% \leq FEV_1\% < 50\%$ predicted
Stage IV	very severe	$FEV_1/FVC < 0.7$	$30\% < FEV_1\%$ predicted or $FEV_1 < 50\%$ predicted accompanied by respiratory failure

* GOLD: **Glo**bal initiative for chronic obstructive **l**ung **d**isease: www.goldcopd.com

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Etiology and Pathogenesis. Epidemiologic studies show that tobacco smoking is the most important, albeit not the sole cause of chronic bronchitis. The start and duration of chronic bronchitis is influenced by exogenous as well as by endogenous factors; multiple factors play a role in its etiology. Exogenous factors besides tobacco smoking are air pollutants (SO_2, NO_x, O_3, dust, soot particles), occupational exposure to toxic substances, as well as viral and bacterial infections. In addition, the circumstances of occupation, social background, place of residence, and family size play a role. Endogenous causes, only partially known, are age and sex as well as genetic factors.

Clinical Findings. Diagnostic clinical criteria are:

- *history*: cough, sputum, occasional episodes of shortness of breath, usually during the night
- *auscultation*: prolonged expiration, adventitious continuous and discontinuous expiratory breath sounds, characteristic for obstruction to airflow.

Spirometry. Pulmonary function tests are characteristic for bronchial obstruction. The forced expiratory volume in the first second, i. e., FEV_1 is decreased even more than the vital capacity resulting in a low FEV_1/FVC ratio.

Chest Radiograph. *Radiologic findings* are often within normal limits. Pathologic findings consist of increased lung markings ("dirty chest"), rarefication of the pulmonary vasculature and hyperinflation (emphysema!).

Exacerbation. A typical feature of chronic bronchitis is recurrent deterioration. Exacerbations are caused by viral or bacterial infections or by environmental influences. In more than one-third of exacerbations the cause remains unknown. The patient's quality of life deteriorates due to exacerbations. In patients with impaired pulmonary reserve exacerbations are accompanied by shortness of breath during mild exercise or even at rest. Severe exacerbations may cause respiratory failure and even death.

Even careful sputum examination does not always allow confirmation of a bacterial etiology of exacerbation. Even between exacerbations the lower airways of patients with COPD are often colonized with bacteria such as *Pneumococci*, *Hemophilus influenzae*, or *Branhamella catarrhalis*. During an exacerbation the number of bacteria increases and the sputum becomes purulent. In patients suffering from advanced COPD, Gram-negative bacteria such as *Pseudomonas aeruginosa* may play a role. In such cases sputum cultures during an exacerbation may serve as a basis for choosing the appropriate antibiotic.

Chronic bronchitis may be attributed to chronic dust exposure, e. g., in stonemasons (silica exposure) and other professions with heavy dust exposure. Farmers, who are frequently exposed to large quantities of organic fine dust particles, are 9 times more likely to develop COPD than people with other occupations.

Small Airway Diseases (Bronchioles)

Bronchioles are small (< 2 mm inner diameter), peripheral airways with walls not containing cartilage. Small airways are involved in various lung diseases. In adults they contribute less to total airway resistance than in children. Nevertheless, if the small airways are inflamed, even in adults, a considerable airflow obstruction may develop. The term small airway disease, commonly used in former years, does not represent a disease entity.

Classification. Diseases of small airways may be distinguished clinically, etiologically, and pathologically. A distinction is made between *primary diseases of the bronchioli*, preferentially involving these peripheral airways (e. g., acute bronchiolitis, constrictive bronchiolitis, diffuse panbronchiolitis, and respiratory bronchiolitis) and *interstitial lung diseases with involvement of the bronchioli* (e. g., bronchiolitis in hypersensitivity pneumonitis, bronchiolitis associated with desquamative interstitial pneumonitis in smokers).

Acute Bronchiolitis. This type of bronchiolitis occurs preferentially in children younger than two years of age and is most commonly due to infections caused by the respiratory syncytial virus (HRSV), but also by influenza and parainfluenza viruses and other viruses, as well as by *Mycoplasma* and *Chlamydia*. The symptoms consist of cough, wheezing, tachypnea, and prolonged expiration. A distinct late consequence of bronchiolitis is the so-called MacLeod syndrome (unilateral lobar emphysema).

In adults symptomatic acute bronchiolitis is relatively rare. It may also be caused by airway infections by viruses or *Mycoplasma* or by the inhalation of irritant toxic gases.

Constrictive Bronchiolitis. It is characterized by a concentric obstruction of membranous and respiratory bronchioli by peribronchiolar inflammatory cellular infiltrates, leading eventually to complete scarring obstruction. The lung function is characterized by irreversible bronchial obstruction, eventually combined with mild pulmonary restriction and impaired gas exchange. The chest radiograph is often normal. In contrast, the computed tomogram of the lung (particularly when taken during expiration) shows circumscribed areas of variable attenuation (mosaic pattern).

Constrictive bronchiolitis occurs in *collagen–vascular diseases* (chronic polyarthritis, Sjögren syndrome) but also after viral infections, after the inhalation of toxic gases (NO_2, SO_2, O_3, phosgene, aromatic diisocyanates), after treatment with penicillamine and gold, after bone marrow transplantation (as manifestation of graft-versus-host reaction, GVH), and after lung transplantation (in acute or chronic rejection). In certain cases the etiology is unknown, i. e., idiopathic form of constrictive bronchiolitis. Constrictive bronchiolitis often has a re-

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lentless course, eventually causing shortness of breath and respiratory failure.

Diffuse Panbronchiolitis. This type of bronchiolitis occurs preferentially in Japanese people with certain HLA types. The patients have symptoms of chronic bronchitis and recurrent rhinosinusitis, and eventually experience respiratory failure. The differential diagnosis includes bronchiectasis due to primary ciliary dyskinesia or cystic fibrosis. Its course may be improved by a long-term antibiotic treatment with macrolide.

Respiratory Bronchiolitis. Certain smokers develop this particular form of bronchiolitis characterized by an accumulation of pigmented macrophages in the lumen of the respiratory bronchioli. The CT scan shows micronodules in the lung parenchyma. Respiratory bronchiolitis (RB) may concur with an interstitial pneumopathy (respiratory bronchiolitis–interstitial lung disease: RB–ILD) and with desquamative types of interstitial pneumonitis (desquamative interstitial pneumonitis: DIP). In all these forms symptoms consist of cough, sputum, and shortness of breath during exercise. The auscultation reveals inspiratory crackles. If the patient is able to abstain from smoking DIP may resolve almost completely.

Cryptogenic Organizing Pneumonia. In this type of lung disease, which is also called idiopathic bronchiolitis obliterans organizing pneumonia (idiopathic BOOP or chronic organizing pneumonia), the bronchioli as well as the lung parenchyma are affected. The histologic features consist of intraluminal polyps of proliferative fibroblasts and myofibroblasts, which obstruct the bronchioles, the alveolar ducts, and eventually the alveoli. The pathology is preferentially localized in the lumen and not around the small airways. Although this pattern is characteristic, it is not specific.

Secondary forms of cryptogenic organizing pneumonia can be observed in collagen–vascular diseases (e. g., rheumatoid arthritis), infections, drugs (e. g., amiodarone), after aspiration, and after radiotherapy of lung or breast cancer.

By definition, none of these known etiologies are found in *idiopathic forms*. This type occurs preferentially in elderly persons. The symptoms consist of nonproductive cough, shortness of breath, fever, loss of appetite, and weight loss. On auscultation inspiratory crackles may be heard. The chest radiograph shows bilateral, patchy infiltrates or areas of consolidation with changing localizations in the evolution of the disease. For diagnosis of BOOP known etiologies, particularly infections, must be excluded (by bronchoalveolar lavage) and usually lung biopsy is performed. BOOP usually responds to systemic corticosteroids prescribed for several months.

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) and other interstitial and infiltrative lung diseases may be accompanied by bronchiolitis and are discussed in Chapter 18.

Pulmonary Emphysema

Definition. Pulmonary emphysema, a component of COPD, is defined *anatomically*: permanent dilatation and destruction of various parts of the pulmonary acinus, the morphologic unit of the lung where the gas exchange takes place. Intra vitam, pulmonary emphysema may be suspected based on a synopsis of clinical and functional findings, and the diagnosis is supported by radiologic findings (high-resolution CT). Characteristic functional features of advanced emphysema are increased lung compliance leading to pulmonary hyperinflation, increased airflow resistance particularly during expiration due to airway collapse, and impairment of diffusion (Fig. 17.**9**).

Types of Emphysema

According to the preferentially involved part of the pulmonary acinus the following types of emphysema may be distinguished:

- centrilobular or centriacinar emphysema: involves the proximal acinus and the bronchioli respiratorii
- panlobular or panacinar emphysema involves the entire acinus
- paraseptal or periacinar emphysema involves the distal acinus.

This histologic discrimination is of limited clinical value. *Centriacinar emphysema* is mainly found in smokers and preferentially involves the upper lung regions. In contrast, *panlobular emphysema* involves mainly the lower lung fields and is typical for severe alpha$_1$-antitrypsin deficiency.

The CT scan of the chest allows the distinction between bullous, heterogeneous, intermediate, and homogeneous types of emphysema. Such morphological aspects are important for lung volume resection, a surgical therapy for emphysema (Figs. 17.**10**–17.**12**). A bulla is defined as a zone of emphysematous lung destruction measuring more than 3–5 cm and which is not surrounded by a distinct membrane.

Clinical Findings. Pulmonary emphysema, chronic bronchitis, and bronchiolitis are the pathologic–anatomic substrate of COPD. The contribution of these components differs in individual patients. In severe cases of COPD, emphysema is a major component.

Most patients suffering from advanced emphysema present as so-called *pink puffers*. These patients have an asthenic constitution, are underweight, and shortness of breath is their main complaint. Hypoxemia is either mild or absent and the arterial Pco_2 is increased except

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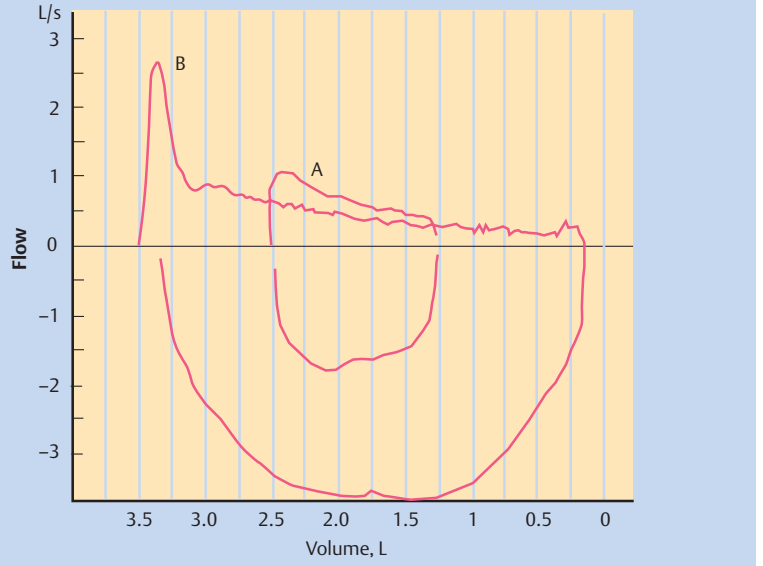

	Before inhalation		After inhalation	
FVC	3.38 L	88%	3.37 L	86 %
FEV_1	1.04 L	35%	1.19 L	42%
FEV_1/FVC	0.37%		0.42%	
TLC	8.52L	126%		
RV	5.10 L	199%		
CO diffusion	44 %			

Fig. 17.**9** Flow–volume curve and spirometric values in advanced chronic obstructive lung disease accompanied by lung emphysema. The flow–volume curve shows severe expiratory flow limitation (expiratory collapse). Spirometry quantifies the severe airflow obstruction, not changing relevantly after inhalation. Hyperinflation and a decreased CO diffusing capacity are also present. A: tidal breathing flow–volume curve. B: forced expiratory and inspiratory flow–volume curve.

Fig. 17.**10** High resolution CT scan in a smoker with markedly heterogeneous pulmonary emphysema. Alongside almost normal lung regions, other parts of the lung are almost completely destroyed.

in advanced cases (respiratory failure type II). The Po_2 drops during exercise and pulmonary artery pressure increases. As a consequence of the lung hyperinflation, the flat diaphragm is rendered inefficient as the respiratory pump. Clinical examination reveals marked activation of the auxiliary inspiratory muscles (sternocleidomastoidei and scaleni muscles). The chest and abdominal compartment move in asynchrony (i. e., paradoxic breathing pattern). The percussion of the chest becomes hyperresonant, the lung borders are low, and the dullness of heart and liver is absent.

The so-called *blue bloater* is a much rarer phenotype. Blue bloaters are overweight and do not complain about shortness of breath, even when their lung function is severely impaired. The pathophysiological hallmark consists of respiratory failure type II. As a consequence polyglobulia develops and the clinical diagnosis of hypoxemia becomes apparent. Pulmonary hypertension is present and the diagnosis of cor pulmonale may be straightforward if ankle edema, ascites, and enlarged neck veins are visible. Hypoxemia during sleep occurs frequently. Moreover, due to the obesity, obstructive sleep apnea is often also present. Since ventilation in blue bloaters depends on hypoxemia, oxygen therapy is

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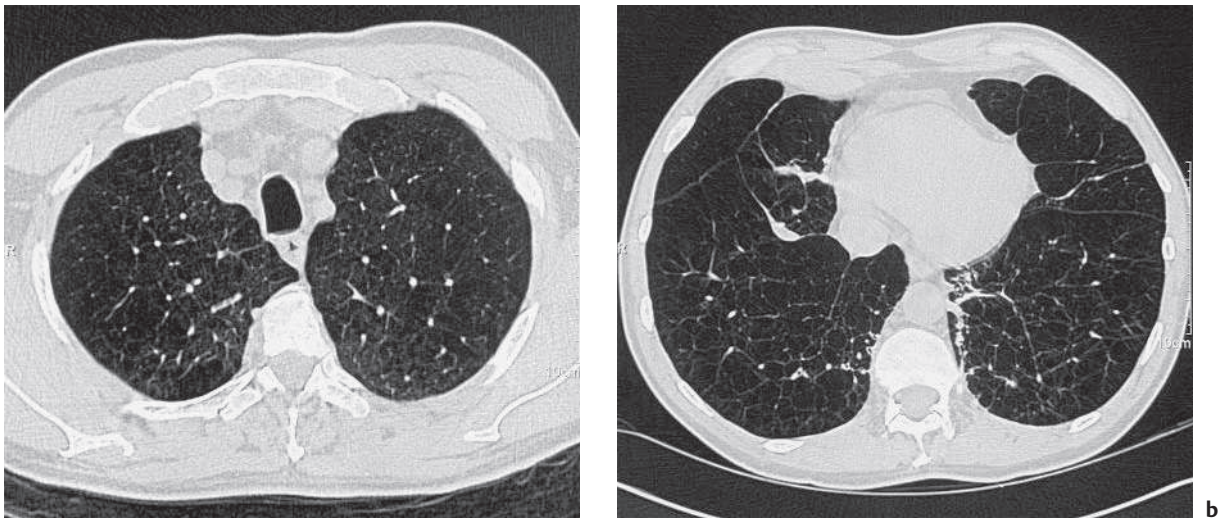

Fig. 17.**11** Pulmonary emphysema in a patient with alpha$_1$-antitrypsin deficiency.
a The apical lung regions are relatively well preserved.
b The lung structure of the lower lung regions are almost completely destroyed.

not allowed except under close monitoring of the patient and the arterial blood gases (Pco_2 and pH).

Diagnosis. Only moderately advanced and severe forms of pulmonary emphysema can be diagnosed based on clinical features and a conventional chest radiograph. A *decreased diffusing capacity* for CO is a sensitive functional parameter. In patients with advanced disease irreversible pulmonary hyperinflation is present (body plethysmography). The most sensitive and specific method for diagnosis is high resolution CT.

Etiology. As with chronic bronchitis, cigarette smoking is the most prominent risk factor for the development of emphysema. Additional toxic inhalants, particularly at the workplace, may play an additional role. The severe form of alpha$_1$-antitrypsin deficiency, mainly homozygous PiZZ, is the only well-characterized genetic risk factor for the development of pulmonary emphysema in smokers. Low serum levels of the protective antiproteinase shifts the balance in favor of proteinases (e. g., elastase, collagenase), which destroy the lung parenchyma. The proteinases are a product of decaying neutrophils, which are sequestered in the lungs of smokers (neutrophil alveolitis). Smokers with severe alpha$_1$-antitrypsin deficiency become severely impaired at an age of 40 to 50 years. Nonsmokers with the same genetic defect develop emphysema but at an advanced age and they have a normal life expectancy (Fig. 17.**13**).

Pulmonary emphysema is an essential component of advanced chronic obstructive pulmonary disease (COPD). Since in an individual case the contribution of the single pathologies (bronchitis, bronchiolitis, and emphysema) can not be precisely appreciated, the more general term COPD is used. COPD is defined by irreversible obstruction to airflow based on spirometry.

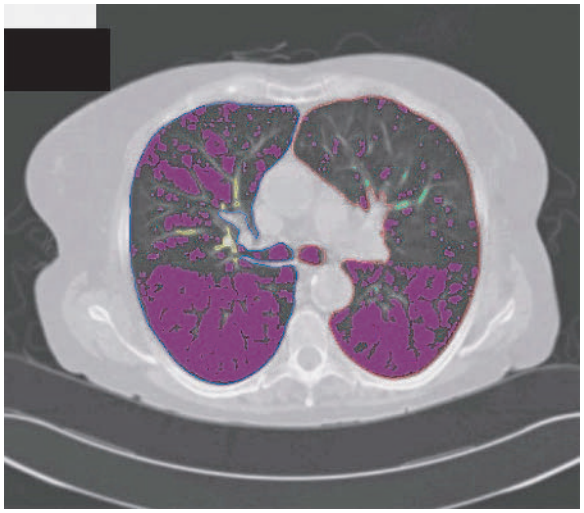

Fig. 17.**12** Color coded CT in a patient with severe emphysema. Attenuation values below -910 HU are marked in purple.

Localized Bullous Emphysema. In this rare disease, which is not caused by smoking, space-occupying bullae, preferentially localized in the upper lobes, may compress adjacent normal lung tissue.

Bronchiectasis

Definition. Bronchiectases are rare but important chronic airway diseases. Bronchiectases are characterized by a lack of tapering and irreversible dilatation of the airways. Typical symptoms are chronic cough, usually accompanied by sputum production.

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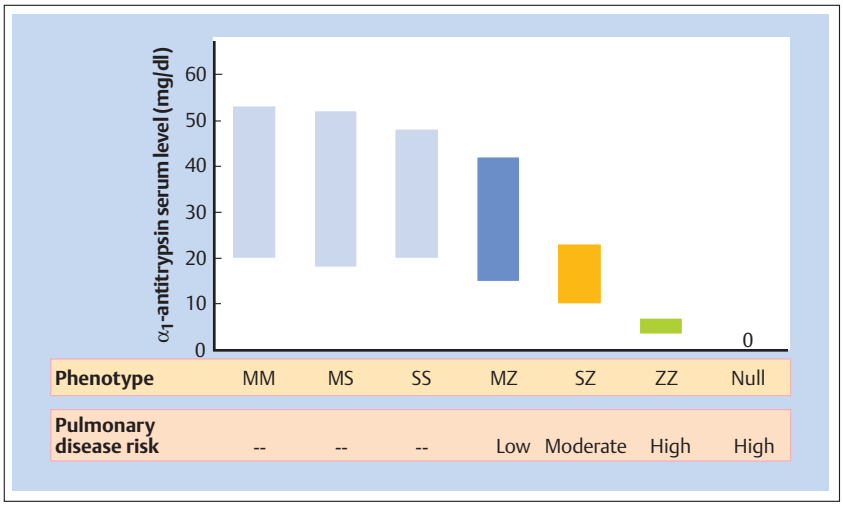

Fig. 17.**13** Alpha$_1$-antitrypsin serum level corresponding to various alpha$_1$-antitrypsin phenotypes. In terms of clinical relevance, the homozygous form ZZ (PiZZ) and the heterozygous variant SZ (PiSZ) are most important.

Etiology and Pathogenesis. A distinction is made between localized and diffuse bronchiectasis. Localized forms involve one or several lung lobes and are mainly caused by a childhood infection. If diffuse bronchiectasis is present, an underlying systemic disease should be sought. In this type of bronchiectasis the upper airways are usually also involved (chronic rhinosinusitis).

- cystic fibrosis (mucoviscidosis)
- primary ciliary dyskinesia (particular form: Kartagener syndrome)
- common variable immunodeficiency syndrome (CVID)
- bronchiectasis after bronchiolitis and bronchitis (e. g., rheumatoid arthritis), allergic bronchopulmonary aspergillosis (APBA), ulcerative colitis, celiac disease (sprue), yellow nail syndrome.

Diagnosis. The leading symptoms are chronic cough and sputum. Copious amounts of sputum, particularly in the morning, are typical for severe forms. If no sputum is produced bronchiectasis is not excluded. Major hemoptysis is a feared complication, which is caused by a ruptured bronchial artery.

On *auscultation* coarse rales are a typical finding, particularly if localized. If the small airways are involved by the underlying inflammation an obstructive ventilatory defect may cause symptoms and can be diagnosed by spirometry. In advanced cases, the surrounding lung parenchyma is involved by chronic inflammation and causes a restrictive component.

The *sputum* contains a mixed flora consisting of *Hemophilus influenzae*, *Diplococcus pneumoniae*, or *Staphylococcus aureus*. In chronic bronchiectasis, *Pseudomonas aeruginosa* or other Gram-negative bacteria (e. g., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Achromobacter xylosoxidans*) may be present. Mycobacteria, particularly *Mycobacterium avium-intracellulare* (MAI) need to be looked for at regular intervals.

In most cases the *chest radiograph* shows increased linear markings, tubular structures ("tram lines"), or cystic formations suggestive for the presence of bronchiectasis. Localized bronchiectasis is most commonly found in the posterior segments of both lower lobes, in the middle lobe, and in the lingula. Diffuse bronchiectasis is usually more prominent in the upper than in the lower lobes. A normal chest radiograph does not exclude mild, usually tubular, bronchiectasis! Bronchography has been replaced by high-resolution CT (Fig. 17.**14**). A bronchus is called bronchiectatic if its outer diameter is larger then the diameter of the accompanying pulmonary artery. The bronchial wall is usually thickened. The lack of tapering may be clearly visible if the bronchus runs in the plane of the CT slice.

Cystic Fibrosis (Mucoviscidosis)

Prevalence and Pathogenesis. Cystic fibrosis (CF) is one oft the most common autosomal-recessive genetic disorder with an incidence of about one in 2000–3000 live births. The mutation, particularly the Δ508 mutation on chromosome 7, leads to a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is part of a complex chloride channel that is present in all exocrine tissues. The impaired transport of chloride and water is not only responsible for an increased salt content of sweat but the cause of viscous secretions in the lungs, pancreas, liver, intestines, and reproductive tract. The *sweat test* demonstrating a high sodium chloride concentration remains a valuable first diagnostic tool. Additional diagnostic tests comprise genetic analysis and the measurement of the transepithelial electrical potential of the nasal mucosa. Early diagnosis and modern treatment concepts, which include prompt antibiotic therapy of bronchopulmonary infections, are responsible for the prolongation of CF patients' life expectancy beyond 30 years.

Clinical Findings. The lung pathology consisting of bronchiectasis, bronchiolitis, recurrent bronchial infec-

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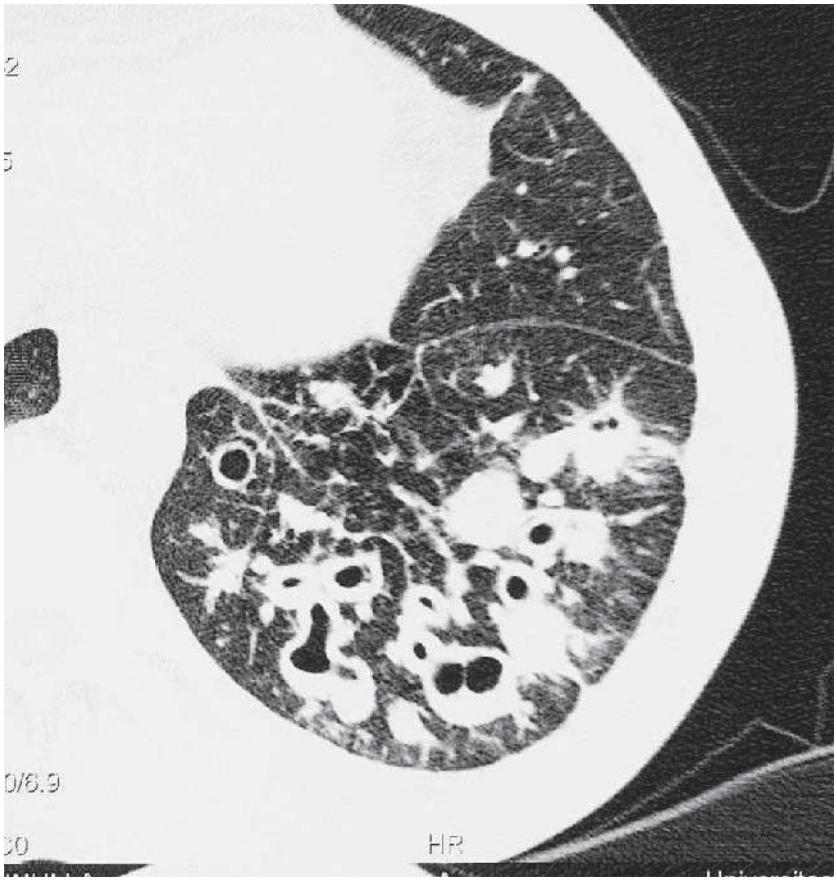

Fig. 17.**14** Advanced bronchiectases in the lower lobe, partially filled with secretion.

tions, and progressive deterioration of the lung function is a key feature in adult CF patients. The exocrine and endocrine *pancreatic insufficiency* (diabetes) cause fewer therapeutic problems. The bronchial tree, as well as the sinuses, are colonized with *P. aeruginosa* in most adult CF patients. The concentration of *P. aeruginosa* may be decreased but it cannot be eradicated by intravenous antibiotics. The patients complain of chronic cough and sputum.

Patients develop shortness of breath with disease progression. CF patients are usually underweight despite substitution with pancreas enzymes. In progressed stages the lung is hyperinflated and breath sounds on auscultation are characteristic for obstruction to airflow and bronchiectasis. In almost all patients clubbing and hourglass nails are present. Pain in the extremity bones adjacent to the joints is suggestive for hypertrophic osteoarthropathy (Marie–Bamberger syndrome). Clubbing is also found in patients with advanced bronchiectasis of other etiologies and is typical for cyanotic heart defects and as a paraneoplastic manifestation of non-small cell lung cancer.

Primary Ciliary Dyskinesia

Kartagener was the first to describe patients with chronic rhinosinusitis, bronchiectasis, and situs inversus. This constellation is called Kartagener syndrome and is due to a congenital defect in the ciliary structure and function (immotile or dysmotile ciliary syndrome). Primary ciliary dyskinesia is an autosomal-recessive inherited disorder, occurring equally in men and women with a prevalence of one in 20 000–30 000 and is accompanied by situs inversus in about one-half of the cases. The underlying defect consists of various ultrastructural or functional ciliary deficiencies leading to impaired ciliary beating. As a consequence most men with the disorder are infertile due to immotile sperm and only about one-half of the women may become pregnant and give birth to a living child. The impaired mucociliary clearance predisposes to chronic upper and lower airway infections, which usually manifest in adults as bronchiectasis.

A distinction has to be made between primary ciliary dyskinesia and cystic fibrosis, diseases that may be accompanied by infertility and Young syndrome, which occurs only in men. Young syndrome is characterized by chronic sinupulmonary infections with cough and sputum production as well as infertility. Infections are

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predisposed by bronchiectasis or chronic bronchitis, infertility is due to obstructive azoospermia. The ultrastructure of the cilia does not show the defects that are characteristic for ciliary dyskinesia (lack of dynein arms, transposition of microtubules, etc.) but rather nonspecific defects secondary to infection.

Common Variable Immunodeficiency Syndrome (CVID)

The clinical features vary in this deficiency, which is due to a heterogeneous immunologic defect characterized by hypogammaglobulinemia and recurrent infections of the upper and lower airways. Additional manifestations consist of malabsorption with diarrhea associated with an increased occurrence of gastrointestinal lymphomas. The underlying pathophysiology is not well understood but is mainly characterized by an impaired differentiation of B cells accompanying a reduced secretion of immunoglobulins. Typical for CVID is a low serum level for IgG, almost always associated with absent or low IgA level.

Allergic Bronchopulmonary Aspergillosis (APBA)

This disease should be suspected in patients with difficult-to-treat asthma. The underlying defect consists of an enhanced production of IgE against aspergilli. Typical features are: blood eosinophilia, markedly elevated IgE serum levels, as well as specific IgE and IgG (precipitating antibodies) against aspergilli. The patients may cough up rubberlike bronchial casts containing aspergilli. In the chest radiograph fingerlike structures may be visible and the CT scan shows central bronchiectasis which is typical for APBA.

Additional rare diseases of the bronchial tree are: *tracheobronchomegaly* (Mounier–Kuhn syndrome) and *William–Campell syndrome* (absent cartilages). Other rare causes of recurrent bronchial infections are relapsing *polychondritis* and *tracheobronchial papillomatosis*.

Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) does not cause cough, sputum, or shortness of breath. OSAS is the most common sleep-related breathing disorder and has a prevalence of 4% in men and 2% in women. It occurs preferentially in habitual snorers and causes hypopnea and apnea accompanied by periodic desaturation by intermittently collapsed upper airways. As a consequence, repetitive waking occurs, which impairs the restorative effect of sleep. In addition, increased activity of the sympathetic nervous system may have adverse cardiovascular effects. During wakefulness breathing is normal. The following factors increase the risk for sleep apnea: male gender, familial disposition, obesity, large neck circumference, and anatomical narrowing of the upper airway, such as enlarged tonsils and adenoids (particularly in children). OSAS may also occur in hypothyroidism or acromegaly.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?
This refers to your usual way of life in recent weeks. Even if you have not done some of these things recently, try to imagine how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing
(Please check the appropriate circle)

Sitting and reading	○0	○1	○2	○3
Watching TV	○0	○1	○2	○3
Sitting, inactive in a public place (e.g., theater or meeting)	○0	○1	○2	○3
As a passenger in a car for an hour without a break	○0	○1	○2	○3
Lying down to rest in the afternoon, when circumstances permit	○0	○1	○2	○3
Sitting and talking to someone	○0	○1	○2	○3
Sitting quietly after a lunch, without alcohol	○0	○1	○2	○3
In a car, while stopped for a few minutes in traffic	○0	○1	○2	○3

Fig. 17.**15** Epworth questionnaire for the evaluation of sleepiness.

Clinical Findings. Patients complain about daytime sleepiness, difficulties with concentration, nonrestorative sleep, a dry mouth in the morning, and headache. Occasionally nocturnal choking attacks occur. The bed partner reports cyclic snoring and repetitive apnea. Quality of life is impaired by hypersomnolence and cognitive impairment. A well-known complication of OSAS is the tendency to fall asleep while driving a car. OSAS is also a risk factor for arterial hypertension and possibly for other cardiovascular diseases such as myocardial infarction and stroke.

Diagnosis. A diagnosis may be suspected based on the typical history (Fig. 17.**15**) and is supported by recordings during sleep (polysomnography or respiratory polygraphy). The differential diagnosis comprises simple snoring not associated with breathing or sleep abnormalities, central sleep apnea, and nocturnal hypoventilation (see above), as well as other causes of hypersomnolence. These are sleep deprivation, a variety of internal diseases (e. g., nocturnal dyspnea due to obstructive airway diseases or congestive heart failure),

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neurologic diseases (Parkinson syndrome), psychiatric diseases (depression), and narcolepsy. Narcolepsy is characterized by sleep attacks, cataplexia (sudden loss of muscle tone), hypnagogic hallucinations (i. e., vivid dreamlike sensations while falling asleep or waking up), and sleep paralysis.

Therapy. The most effective treatment is nocturnal positive pressure breathing (i. e., continuous positive airway pressure, CPAP). This pneumatic splint normalizes the nocturnal breathing and usually brings about rapid improvement in sleep quality and hypersomnolence. If CPAP is not tolerated or accepted, a removable oral appliance during the night is an option. This device is snapped onto the dental arches at night and keeps the jaw in an advanced position thereby preventing the collapse of the upper airways. Surgical interventions (e. g., adenoidectomy and tonsillectomy, uvulopalatopharyngoplasty, and maxillary surgical interventions) are indicated only in selected cases.

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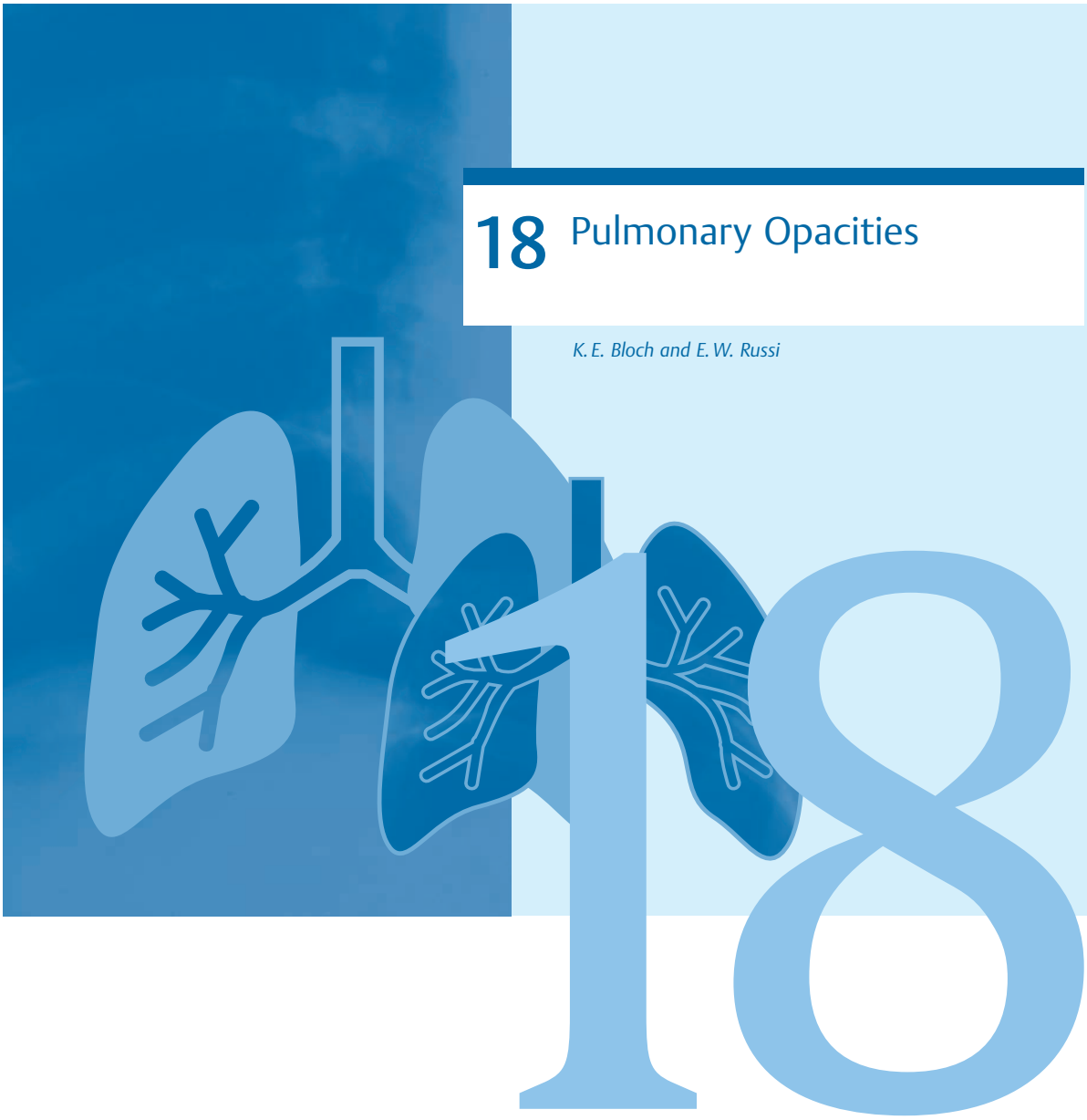

18 Pulmonary Opacities

K. E. Bloch and E. W. Russi

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Radiologic Morphology of Pulmonary Opacities

By definition, the diagnosis of pulmonary opacities requires a radiographic examination. Although the presence of opacities may be suspected on clinical grounds, chest percussion and auscultation are often normal or equivocal. Opacities of the lung parenchyma may be related to extravascular fluid accumulation (exudate, transudate) and to infiltration of inflammatory, fibrotic, or neoplastic cells. The following discussion refers to conventional chest radiography. A larger amount of anatomical information, and a significantly higher spatial resolution, can be obtained by a computed tomography (CT) scan of the chest including spiral acquisition in thin slices and visualization in high-resolution techniques, with and without application of a contrast agent. However, a CT scan is generally not performed as the initial radiologic examination due to its higher costs and radiation exposure. For the description of CT images a specialized nomenclature, different from that used to describe conventional chest radiography, is applied.
Pulmonary opacities are characterized by their size, distribution, and pattern.

Size. Based on their size and extension, *localized* opacities (such as those found in lobar pneumonia or tuberculoma) are differentiated from *diffuse* opacities (such as those found in fibrosing alveolitis, or pneumoconiosis).

Pattern of Infiltrates. Inflammatory or neoplastic infiltrates are typically associated with opacities that preserve the lung structure. Infiltrates may occur with an *acinar* or *interstitial* pattern:

- *Acinar Infiltrates.* Diseases that affect the pulmonary acini (e. g., pneumoconioses) have the following characteristics:
  - homogeneous density
  - tendency for confluence
  - air bronchograms
  - absence of lung volume loss.
- *Interstitial Infiltrates.* Diseases that predominantly affect the pulmonary interstitium (e. g., fibrosing alveolitis) have the following characteristics:
  - ground-glass opacity
  - inhomogeneous density
  - linear and reticular densities (Kerley A, B, and C lines)
  - noduli
  - "honeycombing"
  - loss of lung volume.

Consolidation. This term refers to a dense opacity that conceals the structure of the affected lung parenchyma. Consolidation is seen in pneumonia, lung cancer, or metastasis.

Mass Lesions. A typical characteristic of a pulmonary mass is its tendency to encroach upon adjacent lung parenchyma and other structures. This is not only seen in neoplasia but also in inflammatory diseases (pulmonary abscess).

Nodules. A nodule is defined as a rounded, clearly delineated opacity of less than 3 cm in diameter. Solitary or multiple pulmonary nodules may be related to cancer, infection, or organic and inorganic dust exposure (such as found in silicosis).

Opacities with Central Hypodensity. These opacities occur due to necrotic destruction such as found in an abscess (bacterial abscess, cavity due to infection with *Mycobacterium tuberculosis*), pulmonary infarct, neoplasia, or vasculitis (Wegener granulomatosis).

Mixed Patterns of Pulmonary Opacities. The simultaneous occurrence of various types of opacities is common.

Additional Diagnostic Criteria. Certain lung diseases are associated with a distinct distribution and pattern of radiologic opacities. The high-resolution CT scan may be diagnostic in some of these diseases (e. g., Langerhans cell histiocytosis, lymphangioleiomyomatosis, or aspergilloma). In contrast, other diseases occur with variable, nonspecific findings that preclude a definitive diagnosis by chest radiography or even by CT scan (e. g., sarcoidosis, or amiodarone pneumopathy).

18.1 Infectious Pulmonary Infiltrates (Pneumonias)

Infectious pulmonary infiltrates result from an inflammatory response to the infection caused by microorganisms. The clinical manifestation is determined by the type of the infectious agent (bacteria, viruses, fungi, or parasites) and the immunologic response of the host. The following discussion is arranged according to the infectious agent (Tab. 18.**1**).

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Table 18.1 Classification of inflammatory infiltrates

Infectious pneumonia

Bacterial pneumonia
- due to Gram-positive organisms
  - *Streptococcus pneumoniae* (pneumococci type 1–90)
  - *Streptococcus*
  - *Staphylococcus*
  - *Actinomyces*
  - *Nocardia*
- due to Gram-negative organisms and organism not identifiable by light-microscopy
  - *Haemophilus influenzae*
  - *Klebsiella*
  - *Branhamella (Moraxella) catarrhalis*
  - *Escherichia coli*
  - *Proteus*
  - *Pseudomonas*
  - *Serratia*
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*
  - *Chlamydia psittaci* (ornithosis)
  - *Brucella* (Bang pneumonia)
  - *Legionella pneumophila*
  - *Rickettsia* (Q-fever)
  - *Bacillus anthracis*
- due to Gram-positive and Gram-negative anerobic organisms (*Bacteroides*, *Fusobacterium*)
- due to *Mycobacterium tuberculosis* complex
  - *M. tuberculosis*
  - *M. bovis*
  - *M. africanum*
- due to atypical mycobacteria
  - *M. avium-intracelluare* complex
  - *M. kansasii*
  - *M. fortuitum*, *M. abscessus*, and *M. chelonei*

Viral pneumonia
- Influenza virus
- Adenovirus
- *Coronavirus* (SARS)
- *Hantavirus*
- pneumonia due to virus not primarily affecting the lungs (measles, Epstein–Barr virus)

Fungal pneumonia
- fungal infection in the immunocompromised host
  - candidiasis (moniliasis)
  - aspergillosis
  - *Pneumocystis carinii*
  - *Mucor* mycosis (geotrichosis)
  - cryptococcosis (torulosis)
- endemic fungal infections
  - blastomycosis
  - histoplasmosis
  - coccidioidomycosis

Pneumonia due to parasites
- *Toxoplasma gondii*

Noninfectious pneumonia

Physical–chemical pneumonia

Pneumonia with eosinophilia (see Eosinophilic Pulmonary Infiltrates p. 546)

Inflammatory pulmonary infiltrates in collagen vascular disease (see Diffuse Parenchymal Lung Disease/Pulmonary Fibrosis p. 548)

Due to circulatory failure
- cardiogenic pulmonary edema
- infarction pneumonia

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Prognostic Factors in Community-Acquired Pneumonia

In a patient with community-acquired pneumonia, the severity of the illness and the need for hospital care have to be assessed. The following factors may aid in this assessment:

- age > 50 years
- co-morbidity such as a neoplasia, congestive heart failure, chronic obstructive lung disease, or renal and hepatic diseases
- altered consciousness
- tachycardia > 125 beats/min.
- respiratory rate > 30/min.
- systolic blood pressure < 90 mmHg
- body temperature < 35 °C or > 40 °C.

If none of the above-mentioned risk factors is present, the clinical course is generally favorable and treatment of the pneumonia may be performed at home.

The following findings represent additional risk factors:

- acidosis: arterial pH < 7.35
- serum urea ≥ 30 mg/dL (11 mmol/L)
- serum sodium < 130 mmol/L
- serum glucose ≥ 250 mg/dL (14 mmol/L)
- hematocrit < 30 %
- leukocyte count < 4000 × 10^6/L or > 20 000 10^6/L
- arterial oxygen partial pressure: Po_2 < 60 mmHg
- multilobar pulmonary infiltrates
- pleural effusion.

Bacterial Pneumonia

Bacterial pneumonias are still among the leading causes of death due to infectious diseases despite the widespread use of antibiotics. The organisms responsible vary according to where the infection is acquired (at home, in the hospital or another institution, in the intensive care unit), host factors such as the age of the patient, co-morbidities, and the individual immune response. *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, Gram-negative enteric bacilli, *Staphylococcus aureus*, and *Legionella pneumophila* are the most common causes of bacterial pneumonia. Together with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and the respiratory viruses, they account for the majority of community-acquired pneumonias. In contrast, hospital-acquired pneumonias are more commonly caused by Gram-negative organisms.

Classification

According to Where the Infection Was Acquired and the Host Defense. One of the major determinants of the type of microorganism and course of the pneumonia is whether it has been acquired in the community ("*community-acquired pneumonia*") or in a special setting such as in a hospital ("*hospital-acquired pneumonia*"), nursing home, prison, or in other institutions where many people live closely together.

Another major determinant of the susceptibility to certain infections, and of particular clinical presentations, is the ability of a patient to create an *effective immune response*. In nonimmunocompromised patients, bacterial pneumonias generally occur with an acute course (with high fever, cough, and production of putrid sputum), whereas bacterial pneumonias may initially have a less dramatic course in the immunocompromised host. Nevertheless, neither the clinical presentation, laboratory tests, nor the radiographic appearance allows a reliable diagnosis of the infectious agent of pneumonia. Thus, the term *atypical pneumonia* is inappropriate and, at best, of historical interest. Originally, atypical pneumonias were thought to be caused by microorganisms other than *Streptococcus pneumoniae*. The first recognized "atypical agents" were *Mycoplasma pneumoniae*; subsequently *Chlamydia pneumoniae* and *Legionella pneumophila* were identified. Since pneumonia caused by *Streptococcus pneumoniae* and other bacteria may have a clinical and radiologic presentation similar to infections by the "atypical agents," the distinction between typical and atypical pneumonia is clinically useless.

According to the Infectious Agent. Another classification of pneumonia is based on the microorganism. However, the identification of the agents responsible is often not feasible or successful. Even in patients hospitalized for treatment of pneumonia, the microorganism is identified in less than half of cases.

Other Classifications. These are based on the mode of transmission of the infection and the *radiologic appearance*. These classifications may help to identify the potential spectrum of microorganisms responsible: for example, community-acquired aspiration pneumonia is generally caused by a mixed flora of anaerobic and aerobic bacteria. In contrast, in hospital-acquired aspiration pneumonia, Gram-negative bacteria are often involved. Hematogeneous pneumonias are often caused by *Staphylococcus* spp. Special conditions predispose the patient to certain infections. Examples are HIV infection (*Pneumocystis carinii*, *Mycobacterium tuberculosis*, and *mycobacteria* other than *tuberculosis*), chemotherapy-induced agranulocytosis (bacterial pneumonias, invasive fungal infections), prolonged corticosteroid therapy (*Pneumocystis carinii*), and immunoglobulin deficiency (infections by capsulated microorganisms).

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Although often used, the radiologic classification based on the extension and pattern of infiltrates is clinically of minor relevance. The following patterns may be identified: localized or diffuse forms, unilateral or bilateral, and lobar or segmental pneumonic infiltrates. If the opacities are confluent and show an air bronchogram the pattern is called acinar. If the infiltrates are ill-defined of linear, reticular, or nodular shape, and if there is no air bronchogram, the pattern is called interstitial. A solitary abscess is a typical complication of aspiration pneumonia. Multiple pulmonary abscesses suggest a hematogenic spread, such as occurs in staphylococcal infection. Pulmonary infarction may occur as a consequence of an invasive *Aspergillus* infection or may occur in *Pseudomonas aeruginosa* pneumonia.

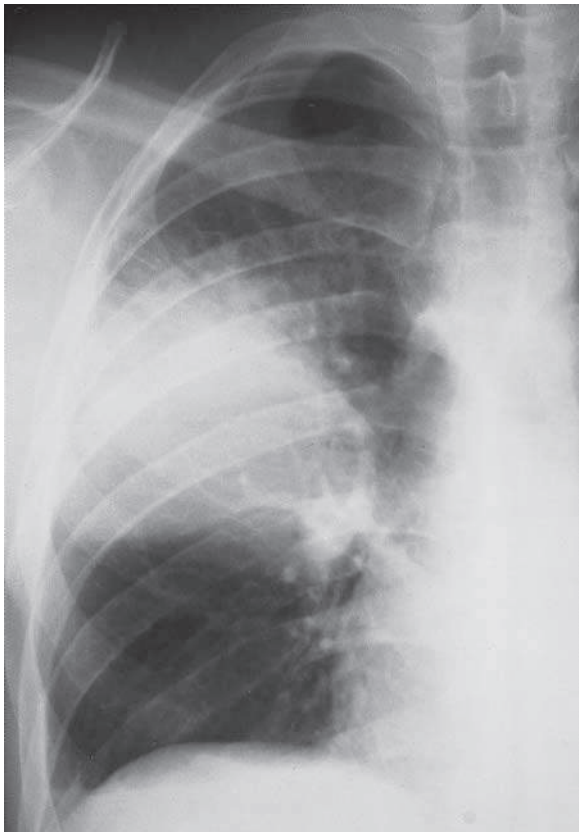
Clinical Presentation of Bacterial Pneumonias

Pneumonias Due to Gram-Positive Microorganisms

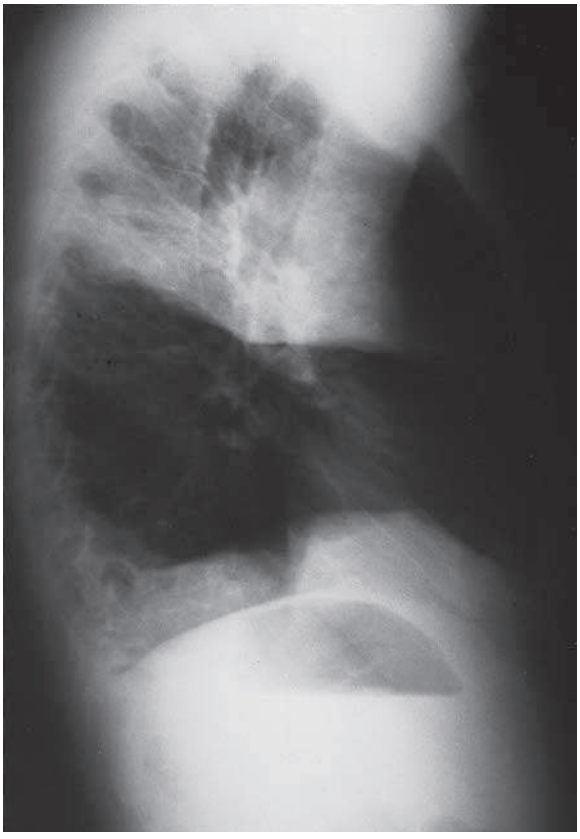
As already observed by Hans Gram in 1884, the majority of bacterial pneumonias are caused by Gram-positive bacteria, namely *Streptococcus pneumoniae*, *staphylococci*, and *streptococci*. *Peptococci* and *peptostreptococci*, *Actinomyces israelii*, *Nocardia asteroides*, *Bacillus anthracis*, and *Mycobacterium tuberculosis* are also positive for staining.

Pneumococcus Pneumonia. Currently, 20–60% of community-acquired bacterial pneumonias are caused by *Streptococcus pneumoniae*, and 5% of patients with this infection still die as a consequence. Patients with a compromised immune defense system, immunoglobulin deficiency, hemoglobinopathies, or following splenectomy are at particular risk.

The *clinical presentation* of *Pneumococcal pneumonia* classically starts with sudden onset, high fever, chills, and pleuritic chest pain. Untreated, the fever remains at



a



b

Fig. 18.**1** *Pneumococcal* pneumonia. Homogeneous confluent infiltrate of the right upper lobe (lobar pneumonia) in a 32-year-old man.

a Posterio-anterior view.
b Lateral view.

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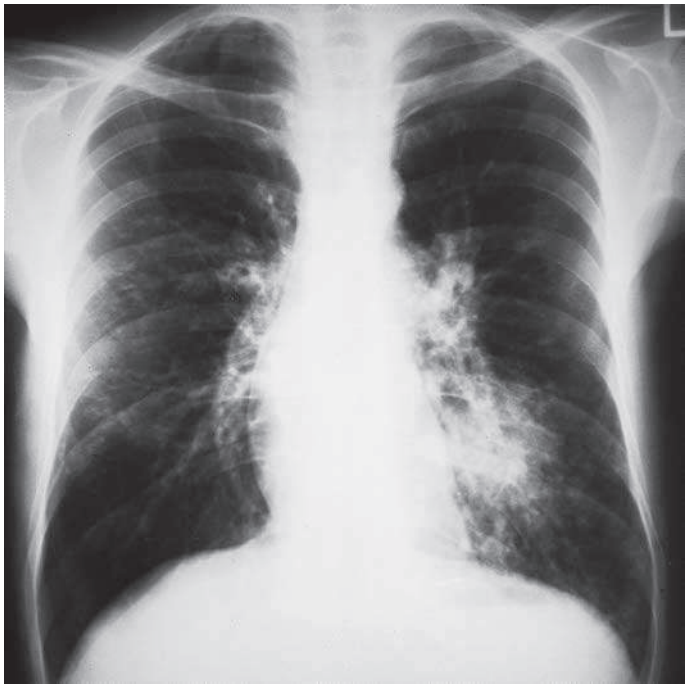

Fig. 18.**2** *Staphylococcus* pneumonia with focal and confluent infiltrates in the middle and lower lobes in a patient with Hodgkin lymphoma (lobular pneumonia or bronchopneumonia) in a 33-year-old man.

temperatures up to 39–40 °C. The pulse rate is also elevated.

The following findings can occur:

- *Chest percussion*: dullness, increased fremitus.
- *Auscultation*: bronchial breath sounds, end-inspiratory rales, often perioral herpes infection, leukocytosis up to 30 000/μL (30×10^9/L) with pronounced left shift, toxic granulations, and lymphopenia.
- *Radiologic*: in the chest radiograph the infiltrates are dense, homogeneous, and clearly delineated with air bronchograms. They may extend to entire lobes (lobar pneumonia) (Fig. 18.**1**) or consist in one, or more rarely, in multiple ill-defined infiltrates.
- *Sputum*: microscopic examination of the frothy sputum reveals Gram-positive diplococci. Abundant amounts of Gram-positive diplococci identified in putrid sputum are diagnostic for *Streptococcus pneumoniae*. Since pneumococci are normal saprophytes of the oropharyngeal mucosa (carrier rate 5–70%), only moderate or minor amounts of Gram-positive diplococci do not allow a definitive identification of *Streptococcus pneumoniae*.
- *Blood cultures*: in hospitalized patients blood cultures are positive in one-fourth to one-third of cases.

The *resorption* of infiltrates takes place within four to eight weeks. Delayed resorption of infiltrates may indicate another diagnosis (tuberculosis, neoplasia) or a complication, and may occur in patients in a reduced general condition, such as from alcohol abuse, diabetes, or chronic obstructive airway disease.

Complications of *Pneumococcal pneumonia* include atelectasis, pleural empyema, parapneumonic effusion, delayed resorption, pulmonary abscess formation (in approximately 2% of cases), and pericarditis. Minor effusions are common (60%), major effusions are rare (5%). Metastatic spread of the infection leading to septic arthritis, endocarditis, meningitis, or peritonitis is mainly seen in immunocompromised patients or after splenectomy.

Streptococcal and Staphylococcal Pneumonia. While streptococcal pneumonias are relatively rare in adults, staphylococcal infection accounts for 3–5% of bacterial pneumonias in outpatients, and for 6–24% in hospitalized patients. Streptococcal and staphylococcal pneumonias may occur as a complication of influenza viral infection. In addition, streptococcal pneumonia may result from a spread of an upper airway infection to the lungs. Streptococcal and staphylococcal pneumonias generally have an acute course with severe febrile illness. The chest radiograph shows multiple patchy infiltrates spreading over one or several lobes (bronchopneumonia; Fig. 18.**2**). Abscess formation is a common complication that typically occurs in staphylococcal pneumonia. The diagnosis is confirmed by blood cultures, which are positive in approximately 20% of staphylococcal pneumonias.

Pulmonary Actinomycosis and Nocardiosis. Pulmonary actinomycosis has a prolonged course with fever, phlegm, pleural pain, and leukocytosis. It is commonly associated with manifestation of the infection at other sites, in particular in the oral cavity and the jaw. The

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Fig. 18.**3** Combined *Pneumocystis carinii* and *Nocardia asteroides* pneumonia in a in a 50-year-old male patient receiving chemotherapy.

typical radiologic manifestation includes pleural-based infiltrates that may extend beyond the visceral pleura to the chest wall or to adjacent lobes. The microscopical identification of *Actinomyces* in the sputum or bronchial washings suggests the diagnosis (yellow sulfur granula corresponding to *Actinomyces israeli* colonies). The definitive cultural diagnosis may require several weeks.

Pulmonary infection by the mandatory aerobic and weakly acid-fast staining *Nocardia* spp. (*Nocardia asteroides*, *Nocardia brasiliensis*) predominantly occurs in the immunocompromised host or in patients with preexisting chronic lung diseases, e. g., pulmonary alveolar proteinosis (Fig. 18.**3**).

Pneumonias Due to Gram-Negative Bacteria and Microorganisms not Identifiable under Light Microscopy

This includes pneumonias due to *Haemophilus influenzae*, Gram-negative *Enterobacteriaceae* (*Klebsiella pneumoniae*, *Escherichia coli*, *Proteus*, *Enterobacter*, and *Serratia*), *Pseudomonas aeruginosa*, and *Branhamella (Moraxella) catarrhalis*. Legionnaires disease, Q-fever, and Bang disease are also caused by Gram-negative bacteria (i. e., *Legionella pneumophila*, *Rickettsia*, and *Brucella*, respectively). *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are both common causes of community-acquired pneumonias. These microorganisms cannot be visualized by light microscopy due to their small size. It has been estimated that 9–20% of community-acquired pneumonias and more than 40% of hospital-acquired pneumonias are due to Gram-negative bacteria.

***Haemophilus influenzae* Pneumonia.** *Haemophilus influenzae* in its capsulated or uncapsulated form is thought to cause 3–10% of community-acquired pneumonias. It commonly occurs in patients with chronic lung disease, such as chronic obstructive pulmonary disease (COPD) or bronchiectasis, who are also susceptible to *Klebsiella* infection.

Pneumonias Due to Gram-Negative Enterobacteria. *Klebsiella* spp. along with *Haemophilus influenzae* are the most common Gram-negative microorganisms causing community-acquired pneumonia. Alcoholics, diabetics, and patients with chronic airway disease are most susceptible. The clinical presentation is similar to that of other bacterial pneumonias such as caused by *Streptococcus pneumoniae*. The diagnosis is made by identification of *Klebsiella pneumoniae* (Gram-negative, capsulated diplobacillus) in the sputum or blood culture (50–70% of blood cultures are positive).

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***Pseudomonas aeruginosa* Pneumonia.** This predominantly occurs in severely ill, hospitalized patients, and in patients with bronchiectasis. More than 40% of hospital-acquired pneumonias are due to *Pseudomonas* and other Gram-negative bacteria. These nosocomial pneumonias may be related to long-term antibiotic therapy, immunosuppression, cytotoxic chemotherapy, or mechanical ventilation. Bacteriemic *Pseudomonas aeruginosa* pneumonia is associated with a high mortality rate (i. e., 60–70%) despite appropriate antibiotic treatment.

***Mycoplasma* Pneumonia.** *Mycoplasma pneumoniae* are estimated to be the causative agent in 3–35% of community-acquired pneumonias. The microorganisms are spread to close contacts by aerosol formation during coughing. *Mycoplasma* pneumonias are therefore commonly observed in preschools and schools, and among military personnel. The incubation period is approximately three weeks. Following the infection, lifelong immunity develops.

Mycoplasma pneumoniae infections may pass without apparent symptoms, but more severe infections, with fever, bronchitis, and pneumonia, may also occur. The disease usually starts with headaches, malaise, and fever. The cough is usually nonproductive. Less than 10% of patients present clinically with a typical pneumonia. Pulmonary auscultation may be normal. Associated symptoms may include pharyngitis, rhinosinusitis, and otitis (sometimes with protracted hemorrhagic, bullous myringitis).

The chest radiograph in *Mycoplasma* pneumonia shows nonspecific alterations, usually consisting in bronchopneumonic infiltrates. *Mycoplasma* infections may be associated with extrapulmonary manifestations such as hemolysis (cold agglutinins), a rash, and arthritis.

This small microorganism cannot be seen under light microscopy. A cultural identification may take several weeks and is therefore clinically not useful. Instead, a serologic examination (complement fixation) may suggest a *Mycoplasma* infection by an increase in IgM and, subsequently, in IgG antibodies. A four-fold increase in antibody titers over the course of the disease or an individual titer of $> 1:32$ are suggestive of the diagnosis. An increase in antibodies may be expected within seven to nine days after infection with a maximal response after three to four weeks.

***Chlamydia* Pneumonia.** *Chlamydia* are mandatory intracellular microorganisms. Worldwide, their main manifestation consists of genitourinary and ophthalmic infections (*Chlamydia trachomatis*). Pulmonary infections are due to *Chlamydia pneumoniae* and, less frequently, *Chlamydia psittaci*.

The clinical presentation of *Chlamydia pneumoniae* is nonspecific. Symptoms may start acutely with pharyngitis and a hoarse voice. Pulmonary infiltrates may occur as ground-glass opacities and be unilatral or bilateral.

A serologic diagnosis is not feasible, since immunization without previous clinical manifestation is common.

***Legionella* Pneumonia (Legionnaires disease).** *Legionella* are ubiquitous organisms that are commonly found in water from sprinklers, air conditioners, and humidification systems. The infection occurs by inhalation of aerosol of water containing *Legionella*. It is not always associated with clinical disease; 1.5–20% of healthy subjects have circulating antibodies.

Legionella pneumonia may be acquired in the community and in the hospital and its *prevalence* varies largely, i. e., 1–22.5%. Men are more commonly affected than women and there is a seasonal predilection in the period from June through November.

Symptoms at the beginning of the disease include fatigue, malaise, joint pain, and headache. One to two days after infection, the disease manifests fever, nonproductive cough, pleuritic chest pain, nausea, vomiting, diarrhea, abdominal pain, and abnormal neurologic signs. A laboratory examination may reveal a moderate leukocytosis, proteinuria hematuria, and hypophosphatemia.

Radiologically, diffuse, patchy, and homogeneous confluent infiltrates are found (Fig. 18.**4**). Pleural effusion is present in 50% of patients, but abscess formation is rare. The diagnosis of *Legionella* infection is based on culture, serologic, and immunologic testing. In clinical practice, identification of *Legionella* antigen in the urine is most useful, as it provides a rapid diagnosis within hours, whereas the cell culture diagnosis takes several days.

***Rickettsia* Pneumonia.** This is caused by *Coxiella burnetii*, a Gram-negative coccus, which presents clinically as Q-Fever. Although Q-fever was first described in Queensland the letter Q stands for query, alluding to the unknown etiology of the disease at that time. As *Coxiella* is found in animal milk and secretions, farmers, animal dealers, and veterinarians are exposed to the infection. It can present as a flulike disease with fever, cough, myalgia, and headaches. During physical examination splenomegaly, enlarged and tender cervical lymph nodes, and bradycardia may be found. *Rickettsia* pneumonia cannot be distinguished clinically, radiologically, or histologically from pneumonia due to *Mycoplasma pneumoniae*. The chest radiograph may show segmental consolidation of lower lobes, patchy infiltrates, and ground-glass opacities.

The *differential diagnosis* includes infectious mononucleosis. Additional information on Q-fever is provided in Chapter 4.

***Brucella* Pneumonia.** Pulmonary infiltrates in Bang disease are rare and have no typical appearance. Infiltrates may appear in the perihilar area. Diagnosis is made serologically. Clinical presentation is described in Chapter 4.

***Branhamella catarrhalis* Pneumonia.** *Branhamella* or *Moraxella catarrhalis*, a Gram-negative diplococcus, may cause bronchopneumonia in patients with COPD or with immunosuppression.

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Fig. 18.**4** *Legionella* pneumonia in a 51-year-old woman.
a In the postero-anterior chest radiograph the paracardial infiltrate is clearly delineated from the border of the heart (negative silhouette phenomenon). It therefore has to be posterior to the heart.
b This is confirmed in the lateral view.

Psittacosis–Ornithosis. This disease is caused by *Chlamydia psittaci* and occurs in veterinarians, zoo personnel, and bird fanciers. As *Chlamydia psittaci* is not only found in parakeets and budgerigars, but in other birds such as chickens and pigeons, the disease has been named ornithosis.

If transmitted by parakeets, the clinical course may be particularly severe. After an incubation period of 10–14 days, severe headaches, epistaxis (in 25 % of patients), and fever with a temperature of up to 39 °C occur. The chest radiograph shows dense, irregular infiltrates. After an initial moderate leukocytosis with pronounced left shift, leukopenia develops.

The diagnosis relies on a history of exposure to birds and a positive serologic test (complement fixation titer 1:16 or higher). However, the test becomes positive only 10–14 days after onset of the disease. Asymptomatic infection or a mild form of the disease (with cough, flulike illness, and with a positive antibody reaction) are common, in particular in persons with repetitive or chronic exposure.

Anthrax Pneumonia. *Bacillus anthracis* is transmitted by contact with sheep, goat, and cattle, or with their hair or wool, or by contaminated meat. The most common form is cutaneous infection. Gastrointestinal manifestations include abdominal pain, diarrhea, and life-threatening gastrointestinal hemorrhage. Recently, anthrax has gained renewed interest since it has been used in biological warfare and bioterrorism. Inhalation of even small amounts of anthrax spores may cause a severe, lethal pneumonia that is unresponsive to treatment.

Pneumonia Due to Multiple Gram-Positive and Gram-Negative Organisms ("Mixed Flora")

Anaerobic and Aspiration Pneumonia. Pneumonia with anaerobic organisms such as *Fusobacteriae* and *Bacteroides* spp. is most commonly due to oropharyngeal aspiration. Rarely, it may result from hematogeneous spread from an intra-abdominal abscess. Elderly persons and patients with impaired upper airway reflexes (due to neurologic disease or after upper airway surgery [such as tonsillectomy]), alcoholics, and

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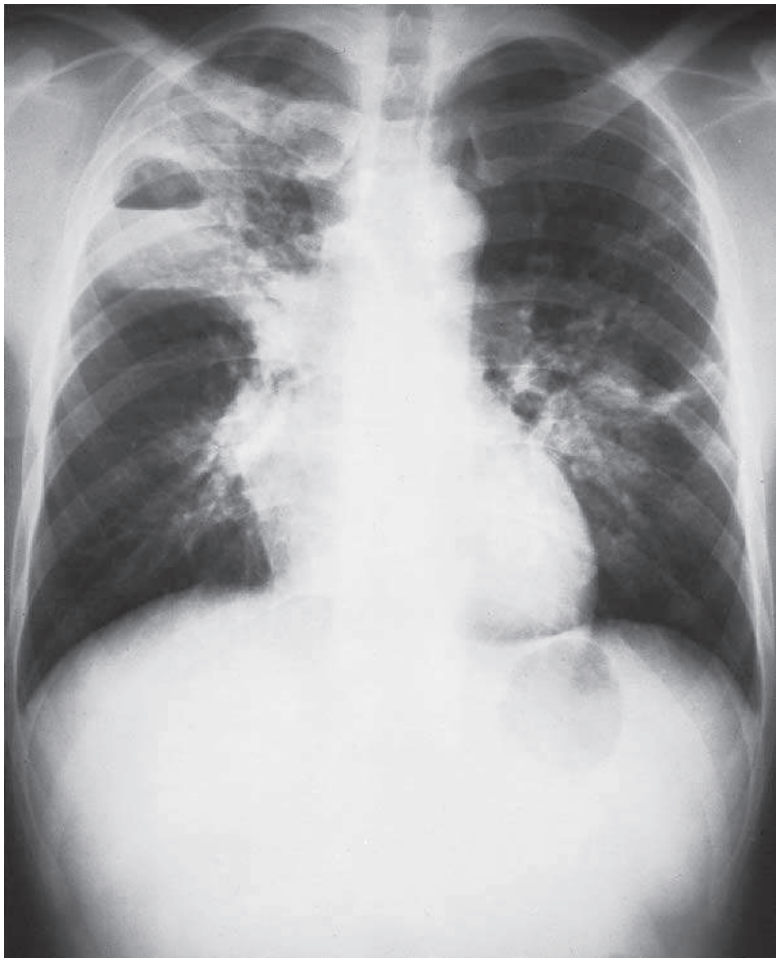

Fig. 18.**5** Pulmonary abscess in the right upper lung field in a 25-year-old man.

those with reduced general health are at particular risk of aspiration pneumonia.

Depending on body position, aspiration occurs into the posterior segments of upper and lower lobes (in supine patients) or into the basal lower lobe segments, in particular on the right side (in sitting patients).

Accordingly, infiltrates are seen at these locations in the chest *radiograph*. There is a tendency for abscess formation and for empyema (Fig. 18.**5**). The differential diagnosis of aspiration pneumonia related to infection with anaerobic organisms includes *massive aspiration of acidic gastric content*, which may cause an acute respiratory distress syndrome (ARDS) by chemical irritation. The radiologic findings include varying diffuse, patchy, or confluent infiltrates and consolidation (Fig. 18.**6**).

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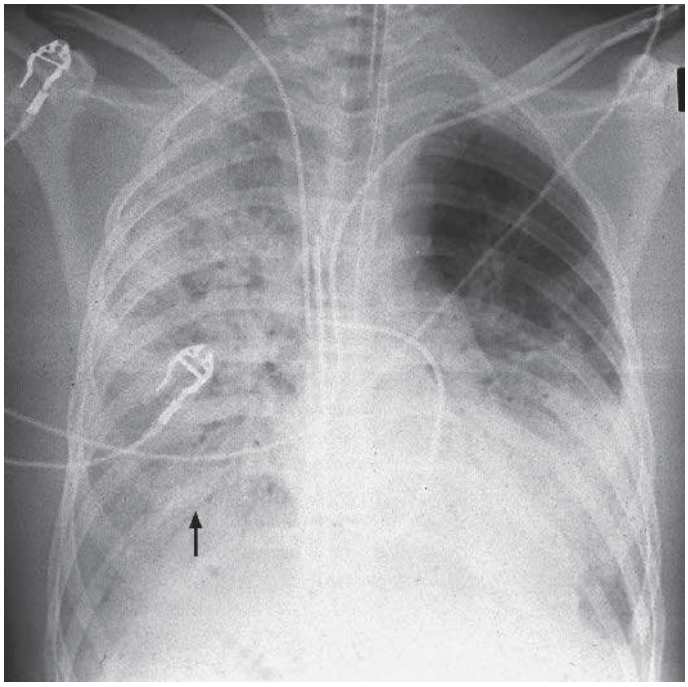

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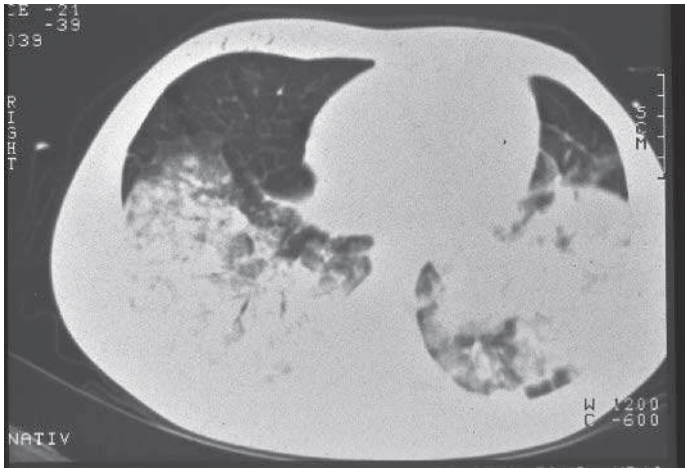

b

Fig. 18.**6** Acute respiratory distress syndrome (ARDS) due to staphylococcal sepsis.
a Bilateral infiltrates with an air bronchogram (arrow), endotracheal tube.
b CT scan with consolidations in the dorsal, dependent lung zones.

Pulmonary Tuberculosis

Diagnosis of Tuberculosis. The proof of a tuberculous origin of pulmonary infiltrates is the identification of *Mycobacterium tuberculosis* in the sputum, bronchial secretions, or bronchial lavage (smear and culture). Sputum examination has to be performed at least three times and should be followed, if appropriate, by bronchoscopy with bronchial washings or lavage.

The diagnosis of tuberculosis requires cell culture identification of *M. tuberculosis* complex (in particular *M. tuberculosis* and *M. bovis*). The distinction between *M. tuberculosis* and mycobacteria other than tuberculosis (MOTT) is generally not feasible by microscopic examination alone, but requires cultural and molecular biologic testing (e. g., by PCR = polymerase chain reaction or MTD = gene probe amplified *Mycobacterium tuberculosis* direct test). A negative PCR from a smear positive for acid-fast bacilli makes the diagnosis of tuberculosis highly unlikely. A positive PCR alone, however, does not differentiate between active and inactive tuberculosis.

> There is no criterion for the definitive diagnosis of tuberculosis infection other than a positive culture.

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The *general clinical manifestations* of pulmonary tuberculosis are nonspecific. They include night sweats, low-grade fever, weight loss, and chronic cough. Similar symptoms are also caused by other diseases. A positive skin reaction to tuberculin (i. e., a positive Mantoux test) suggests infection with tuberculosis (or previous BCG vaccination!) but does not allow the identification of patients with active disease. In addition, immunosuppressed patients may have a negative skin reaction despite *M. tuberculosis* infection. Detecting *Mycobacterium tuberculosis*-specific gamma interferon-producing T cells in blood samples from patients with suspected tuberculosis has promise as a novel diagnostic test, but its role in various settings has yet to be determined.

Classification. A distinction is made between primary and postprimary tuberculosis, which can be associated with acute and chronic pulmonary infiltrates.

The American Thoracic Society recommends the following classification of persons exposed to contacts with tuberculosis or who have tuberculosis disease:

- stage 0: not exposed, not infected
- stage 1: exposed, infected (tuberculin skin test negative)
- stage 2: exposed, infected (tuberculin skin test positive)
- stage 3: tuberculosis disease.

Primary Tuberculosis

Clinical Features. Primary tuberculosis may occur at any age in areas of low prevalence, whereas it affects mainly children in areas of high prevalence. The presentation is nonspecific with low-grade fever (usually no more than 38 °C). Therefore, diagnosis is often missed.

Laboratory Tests. The differential blood count reveals moderate left shift and monocytosis in nearly 50 % of the cases, but there is generally no lymphocytosis or lymphopenia. The erythrocyte sedimentation rate is moderately elevated as is the C-reactive protein (CRP).

Tuberculin Reaction. The tuberculin skin test is generally strongly positive. Conversion occurs four to six weeks after the infection.

Chest Radiograph. There is a peripheral infiltrate with hilar adenopathy (Ghon primary complex).

Course. Primary tuberculosis extends over several weeks to months but usually passes unnoticed. A small calcified nodule (Ghon lesion) may be evident later. The following complications may occur: necrotic cavity formation in the area of the pulmonary infiltrate (primary phthysis), bronchial compression and obstruction, or perforation of a lymph node into the bronchial lumen with bronchogenic spread, resulting in bronchial tuberculosis and caseous pneumonia. A hematogenic spread may lead to miliary tuberculosis. Exsudative pleuritis is also a manifestation of primary tuberculosis. In general, primary tuberculosis heals without leaving residua or results in the formation of calcified scars or tuberculomata.

Postprimary Pulmonary Tuberculosis

Definition. The term postprimary tuberculosis (reactivation) refers to the manifestation of disease in a host who has been previously infected with tuberculosis and has acquired cellular immunity.

Pathogenesis. Postprimary tuberculosis represents an *endogenous reactivation* of (radiologically often not apparent) preexisting foci. The direct progression from primary to postprimary tuberculosis is rare. However, postprimary tuberculosis may also result from *exogenous reinfection*.

Clinical Features. Typical manifestation includes a chronic cough, subfebrile temperature, poor appetite, and weight loss for several weeks. In addition to pulmonary tuberculosis, the infection may be reactivated in other organs (tuberculous lymphadenitis, urogenital tuberculosis, vertebral spine meningitis). A distinction is made according to the following forms of the disease:

- *localized manifestations*: (exsudative pulmonary tuberculosis, tuberculous cavity)
- *generalized manifestation*: (miliary tuberculosis)
- *chronic*: fibroproliferative lesions.

Exudative Pulmonary Tuberculosis

This term reflects extensive infection of the pulmonary parenchyma with tubercle bacilli. The foci of infection contain *exudative* inflammation and *liquefied* necrotic areas with cavities (Figs. 18.**7**, 18.**8**). The caseous necrosis and the subsequent cavitary destruction are thought to reflect a pronounced hypersensitivity reaction to the tuberculous antigen. Typically, the apical and posterior segments of the upper lobes and the apical regions of the lower lobes are involved. In the immunosuppressed patient (e. g., with HIV infection), the chest radiograph may not show the typical location of infiltrates and they may involve lower lobes and may not cavitate.

Tuberculous Cavity

The cavity represents a typical manifestation of postprimary tuberculosis (Fig. 18.**8**). It is a thick-walled cavity, mostly in the apical and posterior segments of the upper lobes and in the apical segments of the lower lobes.

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a

b

Fig. 18.**7** Exudative pulmonary tuberculosis with patchy and partly confluent infiltrates in a 39-year-old woman. Before (**a**) and after (**b**) chemotherapy.

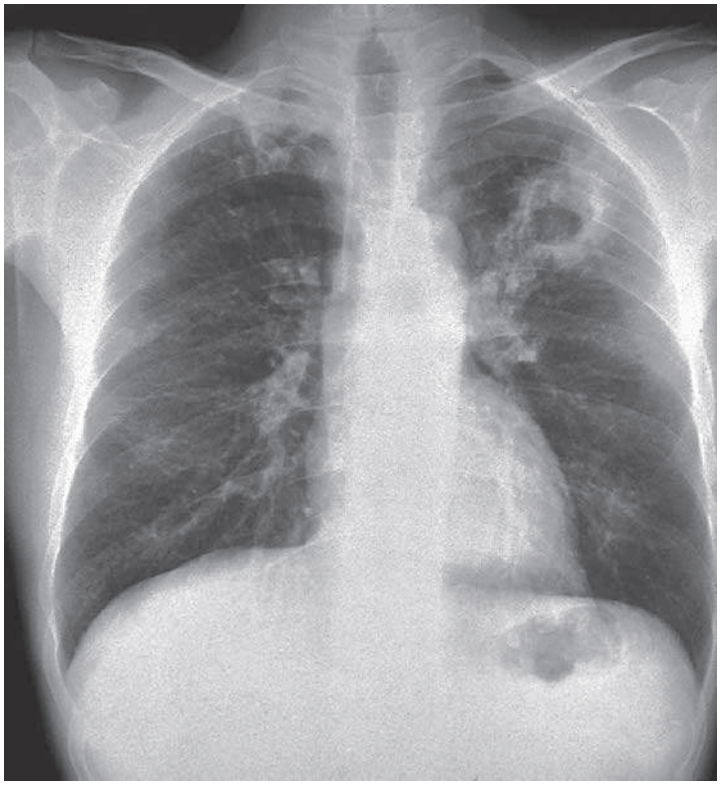

Fig. 18.**8** Tuberculous cavity in the left upper lobe in a 43-year-old man.

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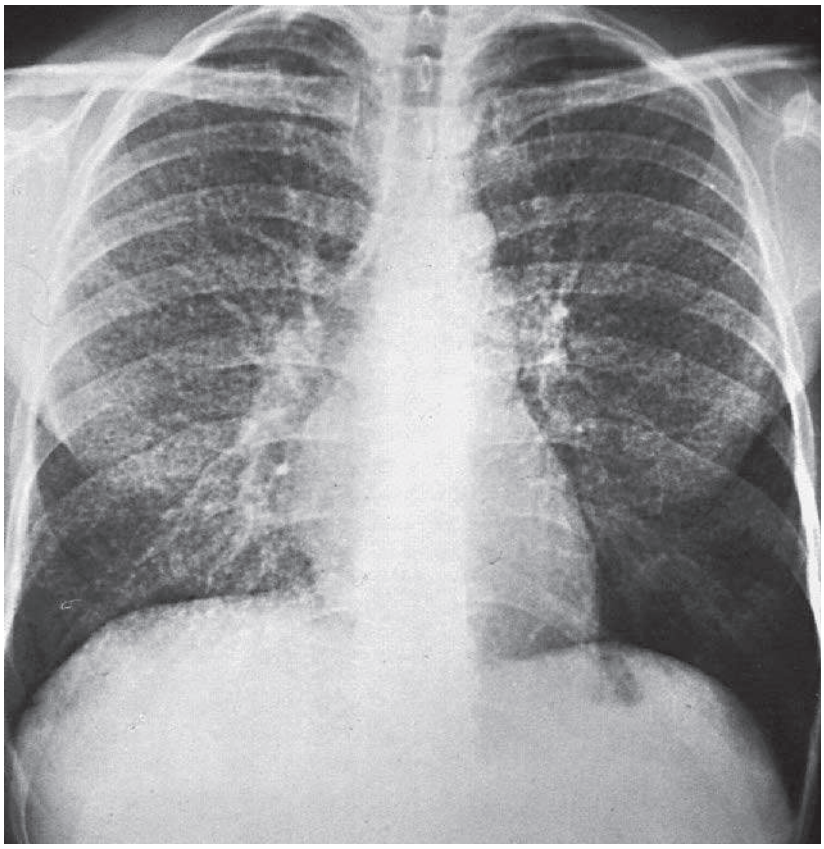

Fig. 18.**9** Miliary tuberculosis. The patient has miliary noduli that are evenly distributed over their entire lungs.

Chest Radiograph. The differential diagnosis of a tuberculous cavity includes an abscess (with an air–liquid level), aspergilloma (i. e., a fungus ball in a preformed cavity), and squamous cell carcinoma with central necrosis. If a cavity is not visible in the conventional chest radiograph, it may show up in a CT scan of the chest.

Microbiologic Diagnosis. If a cavity exists, the sputum is usually positive for acid-fast bacilli. A repeated negative sputum examination makes the diagnosis of a tuberculous cavity unlikely. If the sputum is negative in the direct microscopic inspection, cultural identification of the tubercle bacilli is still possible. Alternatively, bronchial secretions or postbronchoscopic sputum may reveal the organisms.

Miliary Tuberculosis

See also Chapter 4.

Pathogenesis. Miliary tuberculosis represents a hematogeneous spread of tubercle bacilli. In children, miliary tuberculosis may occur as a primary infection. In adults it is more likely to be a reactivation triggered by a *reduced cellular immune defense* (poor nutrition, alcoholism, diabetes, HIV infection, or advanced age). Miliary tuberculosis may have an acute or chronic course with only mild symptoms. This may occur in elderly persons in whom the diagnosis may only be made postmortem.

Chest Radiograph. *Radiographically*, miliary tuberculosis has typical features. They consist of multiple *nodules*, 1–3 mm in diameter, evenly distributed over the entire lung parenchyma (Fig. 18.**9**). With initiation of antituberculous therapy, the miliary foci generally disappear after several weeks to months without remaining residua. Exceptionally, a patient may succumb to the infection even without the miliary nodules seen in the chest radiograph if the nodules are very small (< 1 mm in diameter).

Differential Diagnosis. The following diseases have to be considered in the differential diagnosis of miliary tuberculosis:

- sarcoidosis
- silicosis
- exogen allergic alveolitis
- histiocytosis X (Langerhans cell histiocytosis)
- hematogeneous spread of a neoplasm
- microlithiasis alveolaris.

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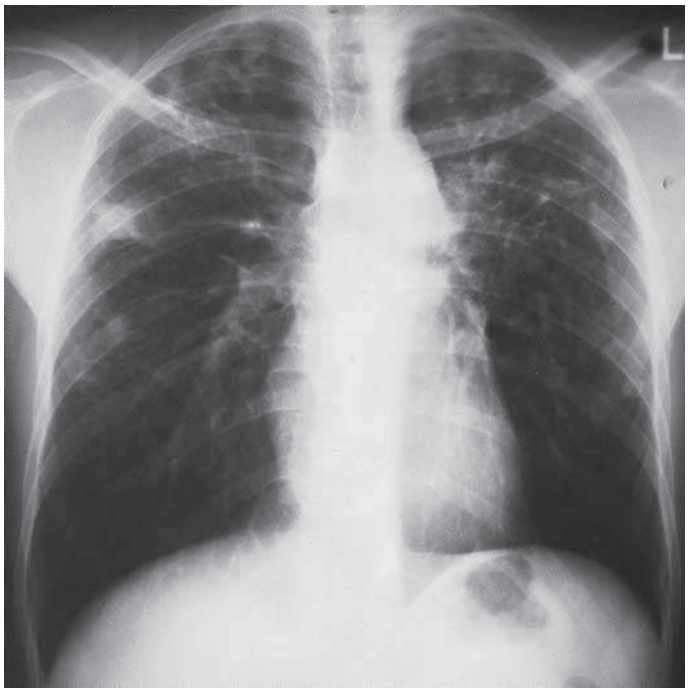

Fig. 18.**10** Fibroproductive pulmonary tuberculosis with multiple foci in both apical and middle lung fields. The hilum is apically displaced in a 31-year-old man.

Fig. 18.**11** Calcified tuberculoma in a 74-year-old woman.

Fibroproliferative Tuberculosis

In contrast to acute forms of tuberculosis, fibroproliferative tuberculosis does not show patchy infiltrates but linear, partly calcified, densities with signs of traction and distortion of the lung structure, mostly in the upper lobes (Fig. 18.**10**). The identification of tubercle bacilli may be difficult.

Tuberculoma

A special manifestation of tuberculosis is tuberculoma. It is identified in the chest radiograph as a rounded, moderately dense opacity of up to 5 cm in diameter (Fig. 18.**11**), sometimes with lobulation or calcification.

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Disease Due to Mycobacteria Other Than Tuberculosis (MOTT)

Mycobacteria other than tuberculosis (MOTT), also called atypical mycobacteria, may present clinically in a similar way as *M. tuberculosis* complex.

Diagnosis. *Radiologically*, multiple noduli and infiltrates are seen. If there are cavities, they tend to be rather thin-walled with less extension of the inflammation to the adjacent parenchyma. Suspicion of infection with atypical mycobacteria arises if pulmonary disease does not respond to the standard antituberculous therapy patients with a history of previous tuberculosis, chronic lung disease (bronchiectasis), or HIV.

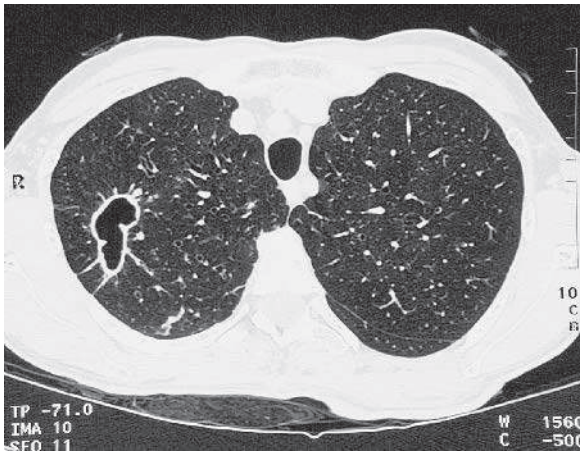
The diagnosis of disease due to MOTT requires the repeated, *cell culture identification* of the organism (at least three times) in sputum specimens, other secretions, or biopsy material.

Causitive Agent Characteristics. Atypical mycobacteria differ from the mandatory human pathogen *M. tuberculosis* in that they are ubiquitous saprophytes that survive in soil and water and rarely cause infection and disease. Some MOTT grow more rapidly in culture (*M. fortuitum* and *M. chelonei*) than the slow-growing tubercle bacilli. *M. avium-intracellulare*, *M. kansasii*, *M. scrofulaceum*, *M. xenopi*, and *M. szulgai* are also slow-growing MOTT, some of them forming pigments (*M. kansasii* and *M. scrofulaceum*).

Manifestations. *M. kansasii* and *M. avium-intracellulare* may cause pulmonary disease. Rarely, *M. scrofulaceum*, *M. szulgai*, *M. simiae*, and *M. fortuitum-chelonei*, as well as *M. abscessus,* may represent the cause of pulmonary abscess formation.

A rare, but fairly characteristic, disease is observed with *M. avium-intracellulare* (MAI) pulmonary infection in patients (mostly women) suffering from bronchiectasis. The main symptom is chronic cough, usually non-productive. The high-resolution chest CT (HRCT) scan shows bronchiectasis with peribronchial infiltrates and so-called "tree in bud" alterations (Fig. 18.**12**), corresponding to peribronchial infection and inflammation.

Additional manifestations of infection with MOTT may include lymphadenitis (*M. scrofulaceum*), soft tissue abscesses, and wound infection (*M. fortuitum-chelonei*).



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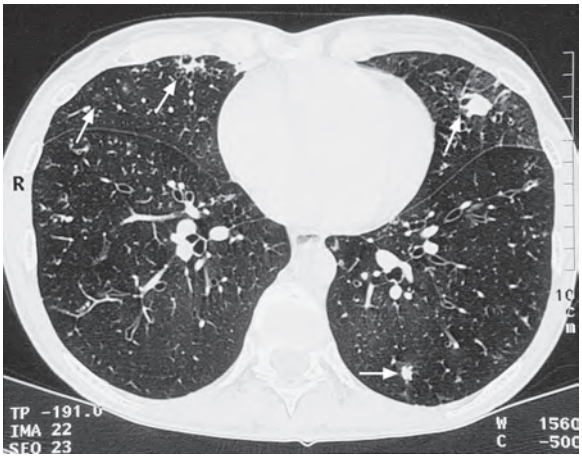

b

Fig. 18.**12** *Mycobacterium avium-intracellurare* infection.
a CT scan with a cavitary lesion in the right upper lobe.
b Several nodular and patchy infiltrates in the middle lobe, the lingula, and in the left lower lobe (arrows).

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Viral Pneumonia

Influenza Pneumonia

Influenza pneumonia is fairly common and has been described as an acutely progressive and fatal disease during influenza epidemics. Although influenza pneumonias without other pathogens have been observed, secondary infection with bacteria such as pneumococci, streptococci, and in particular staphylococci, are also common.

Pneumonia due to paramyxoviruses (parainfluenza, mumps, measles, and respiratory syncitial viruses) are common in children, but rarely occur in adults. Reoviruses also rarely cause pneumonia in adults and usually occur as "common cold infections."

Adenovirus Pneumonia

Adenovirus infection is associated with pulmonary infiltrates in 10–20% of infections. The general symptoms of adenovirus infection may give a hint that this organism is causing pneumonia. In military recruits adenovirus is common, as approximately 50% of the military personnel in training camps acquire adenovirus infection.

Acute fever with a temperature up to 39 °C, cough, headaches, nausea, vomiting, meningitis, pharyngitis, conjunctivitis, and lymphadenopathy precede the pneumonia. Leukocytosis of approximately 10000/μl (10×10^9/L) may be found. The duration of fever is two to three days. The diagnosis relies on complement fixation with a rise in antibody titers. The virus may also be identified in sputum and stool samples. Pulmonary infiltrates are hazy and not very dense (Fig. 18.**13**). Pulmonary auscultation is unremarkable.

Severe Acute Respiratory Syndrome (SARS)

On March 15 2003, patients with an acutely progressive respiratory disease were found in the Chinese province of Guangdong, and in Hong Kong, Vietnam, Singapore, and Canada and this finding gained worldwide interest. The World Health Organization (WHO) coined the term "severe acute respiratory syndrome" (SARS), and has coordinated the efforts of identification of cases and modes of transmission. Thanks to major scientific efforts, the cause of the disease, a hitherto unknown *Coronavirus*, was identified and techniques for diagnosis and treatment guidelines were established.

Clinical Features. The disease comprises two phases beginning with fever (> 38 °C), malaise, myalgia, and headaches. Three to seven days later cough, dyspnea, and subsequently respiratory failure develop. The chest radiograph shows bilateral infiltrates and, in severe cases, white lungs with a clinical picture of ARDS occur (see Fig. 18.**6**).

Diagnosis. Evidently, SARS can not be clinically differentiated from other potentially severe respiratory infections such as influenza pneumonia. The diagnosis is made in the appropriate clinical setting (prior residence in an endemic or epidemic SARS area). Identification of the SARS pathogen requires special laboratory tests. The treatment is supportive as causative therapy is currently not available. Mortality rate depends on age and is from 10% in young patients to 40% in patients aged over 60 years.

Hantavirus Pneumonia

In 1993, patients with an acute febrile illness were observed in the Southwest USA. They suffered from progressive respiratory failure and fatal shock within a few days. Mortality rate was 50–70%. Subsequent investigations revealed that the syndrome was due to an RNA virus, belonging to the *Bunyaviridae* family, the so-called *Hantavirus*. The reservoirs of this virus are mice and rats. The infection is acquired by inhalation of aerosolized animal excretions. Human-to-human transmission has not been observed.

The *diagnosis* relies on the serologic identification of IgM antibodies or a four-fold increase in IgG antibody titers. The *differential diagnosis* includes mainly other virus diseases such as influenza.

Pneumonia Due to Nonpneumotropic Viruses

Viruses that are not primarily pneumotropic may still cause pneumonia. This is the case in *measles pneumonia* (see Fig. 18.**13**). The typical exanthema is the clue to the diagnosis. More difficult is the diagnosis of pneumonia related to Epstein–Barr virus infection (*mononucleosis infectiosa*), *erythema exsudativum multiforme*, *hepatitis epidemica*, and *choriomeningitis*. In immunosuppressed patients the *varicella-zoster virus*, and *cytomegaloviruses* may also cause pneumonia. In varicella-zoster pneumonia, multiple miliary nodules with calcifications typically occur.

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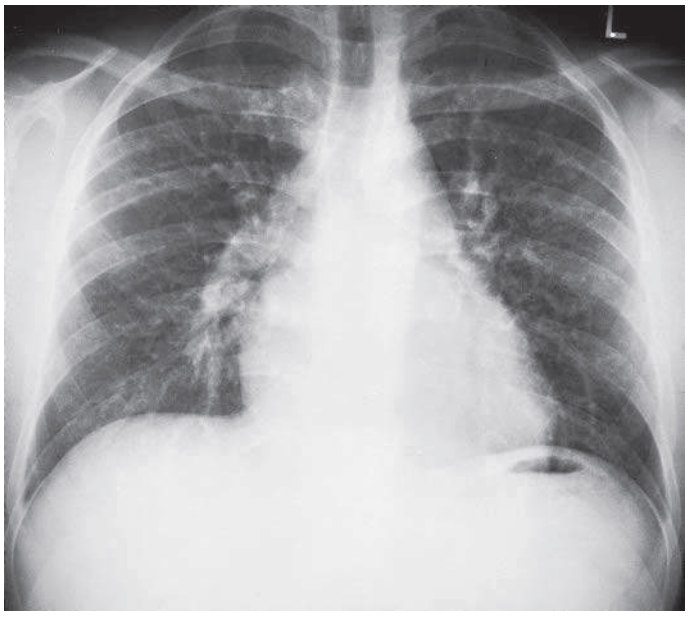

Fig. 18.**13** Viral pneumonia; bilateral ground-glass opacities of middle and lower lung fields. Multiple fine reticulonodular opacities. Histologically, a giant cell interstitial pneumonia typical for measles pneumonia was found in this patient.

Fungal Pneumonia

It is crucial to distinguish pulmonary fungal infections affecting predominantly or exclusively *immunocompromised* patients from those also observed in immunocompetent patients. Conditions associated with impaired immune response that predispose to fungal infections include agranulocytosis, neutropenia, corticosteroid treatment, and AIDS. In contrast, *endemic* fungal infections occur in immunocompetent residents of certain areas. Bronchopulmonary disease may also be related to an *immunologic reaction* to fungal antigens without invasive or only semi-invasive growth in the bronchial tree (allergic bronchopulmonary aspergillosis).

Fungus Infection in Immunocompromised Patients

Pneumonia Due to Yeasts and Molds

The most important agents are the yeasts *Candida* and *Cryptococcus*, and the molds *Aspergillus* and *Mucor*. All are found worldwide.

Diagnosis. These fungal infections are associated with variable chest radiographic manifestations (Fig. 18.**14**), sometimes mimicking bronchopneumonia, chronic tuberculous infection, interstitial pneumonitis, or lung cancer. The fungi are ubiquitous, and therefore their identification in the sputum does not necessarily signify a pulmonary infection. Invasive growth of the fungus has to be suspected from the clinical presentation in the particular setting of a patient. The definitive diagnosis requires a histological proof of invasive growth along with the cultural identification of the fungus.

Candidiasis and Aspergillosis. *Candidiasis (moniliasis)* and *aspergillosis* are seen most commonly. As mentioned above, infections with the causative fungi occur nearly exclusively in patients with immune deficiency. Empirical treatment is generally initiated without delay to prevent life-threatening progression of the infection in severely ill patients. CT images in invasive aspergillosis typically reveal multiple opacities, at times with central necrosis. Pulmonary infiltrates in a patient with positive blood cultures for *Candida albicans* are suggestive of a generalized fungal infection with pulmonary involvement.

Pneumocystis carinii Pneumonia

Pneumocystis carinii pneumonia is mainly observed in patients with cancer who are receiving chemotherapy, and as a complication of AIDS (see Fig. 18.**3**). Rapidly progressive dyspnea associated with ground-glass opacities, micronodular or homogeneous confluent infiltrates in the chest radiograph are consistent with *Pneumocystis* pneumonia in the immunocompromised host. The direct identification of the fungus in alveolar macrophages may be made in spontaneous sputum or

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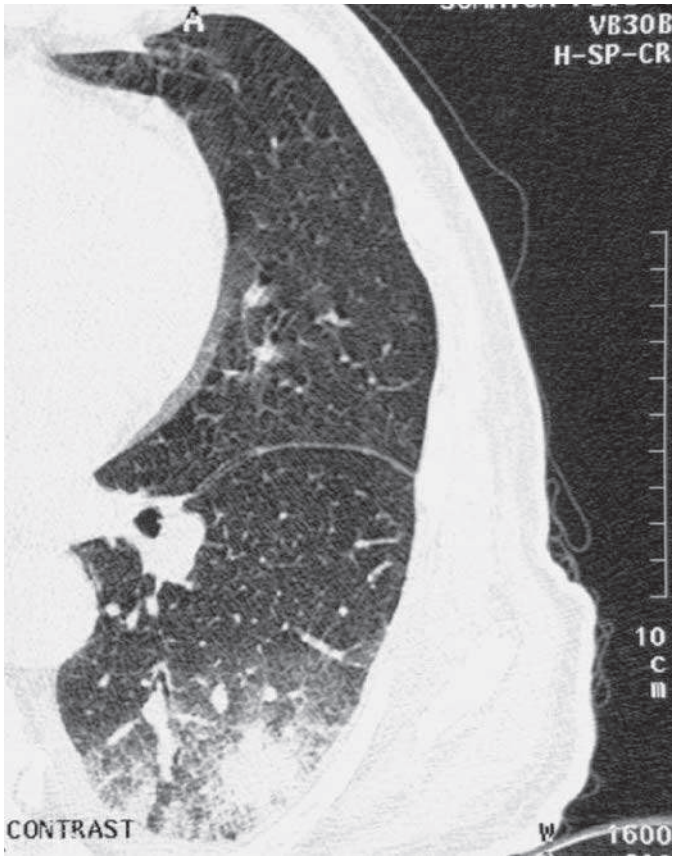

b

Fig. 18.**14** Invasive aspergillosis of the lung in a patient with ill-defined pneumonic infiltrates in both lower lobes.
a Right lower lobe.
b Left lower lobe.

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a b

Fig. 18.**15** Inactive disseminated histoplasmosis. Typically, there are multiple calcified nodules in both lungs and calcified hilar lymph nodes.
a Postero-anterior view.
b Close view of the right hilum.

after sputum provocation by inhalation of 2–5 % sodium chloride solution. The most sensitive diagnostic means are bronchial lavage and transbronchial lung biopsies.

Endemic Fungal Infection

These infections are caused by dimorphic fungi (*Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*), which are mainly found in North and South America. In the USA histoplasmosis and coccidioidomycosis are common. *Histoplasma* spp. infection may pass unnoticed or manifest itself as an acute disease resulting in multiple, partly calcified pulmonary nodules (Fig. 18.**15**). The differential diagnosis includes tuberculous granuloma and nodules after varicella pneumonia. The diagnosis of histoplasmosis is supported by the typical clinical presentation and serologic tests.

Allergic Bronchopulmonary Aspergillosis and Mycetoma

Endobronchial growth of *Aspergillus fumigatus* may induce immunologic type I and III reactions. Clinically, this corresponds to bronchial asthma and allergic bronchopulmonary aspergillosis, respectively (see below). The endobronchial fungi are usually noninvasive, but semi-invasive growth may occur. Bronchopulmonary aspergillosis is found in combination with atopy in patients with bronchial asthma or cystic fibrosis. The diagnostic criteria include: bronchial asthma, bronchiectasis, variable pulmonary infiltrates, increased total IgE, specific anti-*Aspergillus* IgE, precipitins, a positive skin reaction to *Aspergillus*, identification of *Aspergillus* in the sputum, and blood eosinophilia. Radiologically characteristic are digit-like opacities and central bronchiectasis.

Aspergillomas (or mycetomas, fungus balls) develop when *Aspergillus* grows as a clump in a preformed pulmonary cavity, in particular in a inactive tuberculous cavity. The radiologic documentation of a cavity with a rounded central opacity in the dependent part is typical (Fig. 18.**16**). The differential diagnosis includes pulmonary abscess formation, a partly necrotic bronchial cancer, and an *Echinococcus* cyst.

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Fig. 18.**16** Aspergilloma of the lung. A rim of air surrounds the fungus ball within a tuberculous cavity seen here in a 28-year-old man.

Pulmonary Parasitosis

Various parasites may cause pulmonary disease. *Helminths* (*Ascaris*, *Ancylostoma*, *Strongyloides*, and *Filaria*) are associated with transient or chronic eosinophilic lung infiltrates, echinococci cause pulmonary cysts, and protozoans, such as *Toxoplasma gondii*, cause interstitial pneumonia in immunocompromised patients.

Differential Diagnosis of Pulmonary Infiltrates in HIV Infection

The following diseases should be considered in patients with HIV infection and pulmonary infiltrates:

- tuberculosis
- atypical mycobacteriosis
- opportunistic infections (*Pneumocystis carinii*, *Cytomegalovirus*, Epstein–Barr virus, toxoplasmosis, fungi)
- Kaposi sarcoma (p. 561).
- noninfectious lymphocytic interstitial pneumonitis
- lymphocytic granulomatosis.

18.2 Noninfectious Pulmonary Infiltrates

See Tab. 18.**1**.

Physical or Chemical Pneumonitis

If an infection cannot be identified as the cause of a pneumonia; noninfectious physical and chemical injuries of the lungs have to be considered. For example, *ionizing radiation* (Fig. 18.**17**), *metal fumes* (manganese, cadmium, mercury, iron, aluminum), and *gases* (nitric oxide [silo fillers disease, p. 557], sulfur oxide, ozone, ammonia, phosgene, or chlorine) may damage bronchioli and alveoli. Depending on the extent and the type of the exposure *bronchiolitis*, *pulmonary edema*, *pneumonitis*, and finally *fibrosis* may occur.

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Fig. 18.**17** Radiation pneumonitis in the right middle and lower lung field in a 54-year-old woman who had received radiation therapy for breast cancer.

Radiation Pneumonitis

Pulmonary radiation injury often goes unnoticed. It occurs after radiation therapy of cancers of the breast, lungs, esophagus, and mediastinum (thymoma, Hodgkin and non-Hodgkin lymphoma). The incidence of radiation pneumonitis varies depending on the extent and protocol of application, and it has significantly decreased with technical improvements. Radiation therapy of breast or lung cancer leads to alterations in the chest radiograph in about one-third of patients, and in 10% of patients it causes clinical symptoms.

Clinical Features. Radiation pneumonitis is observed between one and six months after the end of treatment. It is associated with a slowly progressive cough, fever, and dyspnea, but it often does not cause any symptoms. After a duration of up to one month, spontaneous restitution usually occurs.

> Rarely, radiation pneumonitis results in fibrosis, sometimes even without clinically apparent acute manifestation.

Diagnosis. Pulmonary function tests reveal a restrictive ventilatory defect and a reduced diffusing capacity. Accordingly, the chest radiograph shows a reduced lung volume and focal or confluent, patchy or reticular infiltrates (see Fig. 18.**17**). Radiation therapy of breast cancer may cause bronchiolitis obliterans organizing pneumonia (BOOP), a syndrome associated with dyspnea, fatigue, and varying unilateral and bilateral infiltrates.

Lipoid Pneumonia

Chronic repeated inhalation of oily substances such as nose drops into the bronchi may cause pulmonary infiltrates, predominantly in the lower lobes. The diagnosis relies on the *typical history* and *fat droplets in the sputum*, which may be found even weeks after discontinuation of the application of nose drops.

Infiltrates Due to Chronic Congestive Heart Failure

Chest Radiography. Chronic congestive heart failure may lead to *localized unilateral* or *bilateral* reticular infiltrates due to *pulmonary interstitial edema* (Fig. 18.**18**). Associated radiologic signs are cardiomegaly, redistribution of pulmonary circulation from predominantly lower zones to lower and upper zones, increased caliber of pulmonary veins, Kerley A and B lines, and pleural effusions. Exclusively left-sided infiltrates are rarely due to congestive heart failure. A localized interlobar effusion may mimic a pulmonary mass (tumor) (Fig. 18.**19**), which disappears after treatment of heart failure ("vanishing tumor").

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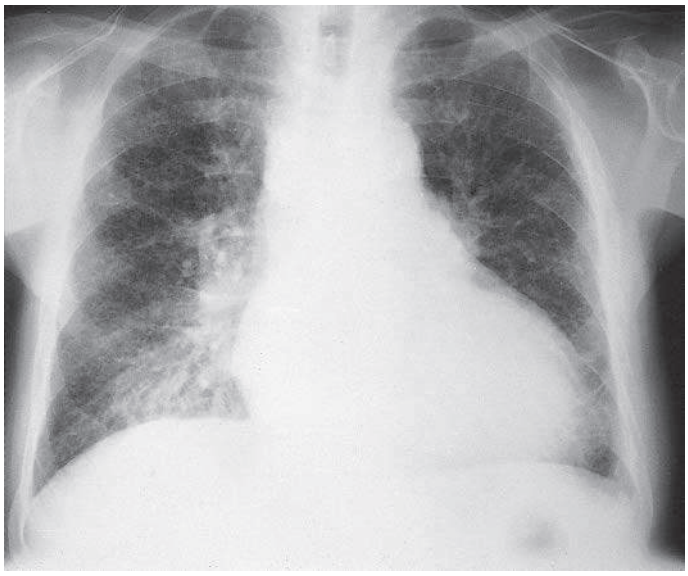
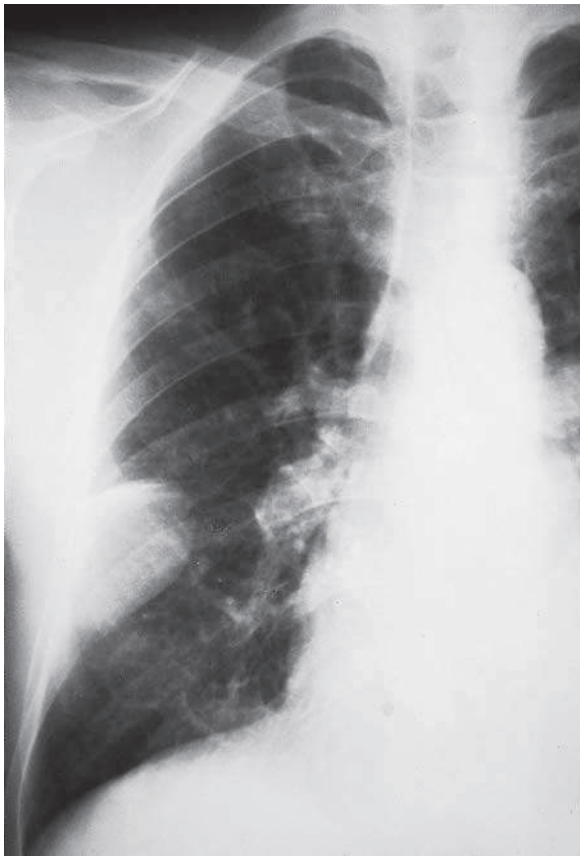


Fig. 18.**18** Interstitial pulmonary infiltrates in a patient with congestive heart failure.



a

b

Fig. 18.**19** Right-sided interlobar effusion (vanishing tumor). in a 46-year-old man.

Before (**a**) and after (**b**) treatment.

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Fig. 18.**20** Pulmonary infarct with triangular opacity in the right middle and lower lung fields, elevation of the diaphragm, and possibly pleural effusion.

Auscultation. This reveals predominantly basal pulmonary rales. Sputum examination with Berlin blue staining reveals hemosiderine-containing macrophages.

Pulmonary Infarction–Infarction Pneumonia

Definition. Infarction pneumonia corresponds to secondary infection of a pulmonary infarction. The diagnosis is difficult, since the clinical manifestation is similar to pulmonary infarction alone (see below).

Pathogenesis. Pulmonary infarction is a rare complication of pulmonary thromboembolism (Figs. 18.**20**, 18.**21**). As the lungs have a pulmonary and a bronchial circulation, tissue hypoxia with necrosis is rare. Pulmonary infarction may be more common if congestive heart failure coexists. The cause of pulmonary embolization, including the source of the emboli (e. g., deep vein thrombosis in the lower extremities), should always be considered. If no thrombosis is found, then a right atrial tumor (myxoma) may be the cause (rarely) of pulmonary embolization with infarction.

Clinical Features. The following signs are consistent with infarction pneumonia:

- rapid deterioration of general condition
- persisting fever and tachycardia
- progressive leukocytosis > 20 000/μL (> 20 × 10^9/L) (uncomplicated pulmonary embolism may be associated with leukocytosis of up to 20 000/μL (20 × 10^9/L)!)
- yellow, putrid sputum
- a cavitation of the pulmonary infiltrate (see Fig. 18.**20**).

Pleural pain may not be pronounced with major pulmonary infarction. As the chest wall excursions on the corresponding side may be reduced, the classical signs of rales and pleural rub may not be pronounced or appear only later in the course of the disease.

The predominant symptoms include sudden dyspnea associated with a feeling of oppression, tachycardia, accentuated second pulmonary heart sounds, and gallop. Extensive pulmonary emboli may cause hypotension and cyanosis.

Diagnosis. Risk factors for thrombosis and typical symptoms, including *minor hemoptysis*, suggest the diagnosis of pulmonary emboli with infarction. A typical, wedge-shaped infiltrate extending from the hilum to the chest wall is not always seen and the infiltrates may be difficult to differentiate from a bronchopneumonia of another origin. However, spiral-angio-CT demonstrates the intravascular emboli and confirms the diagnosis.

Major pulmonary infarction is usually recognized clinically while minor infarction is often missed. Risk factors for thrombosis (immobility, recent surgery), pleural pain, dyspnea, pulmonary infiltrates, effusion, tachycardia, and fever may all suggest the diagnosis. In major pulmonary infarctions the levels of bilirubin, lactate dehydrogenase (LDH), and liver enzymes may be elevated. These result, in part, from right-sided heart failure with congestion of the liver. Pulmonary function tests reveal a restrictive ventilatory defect and a reduced diffusing capacity. Arterial blood gas analysis

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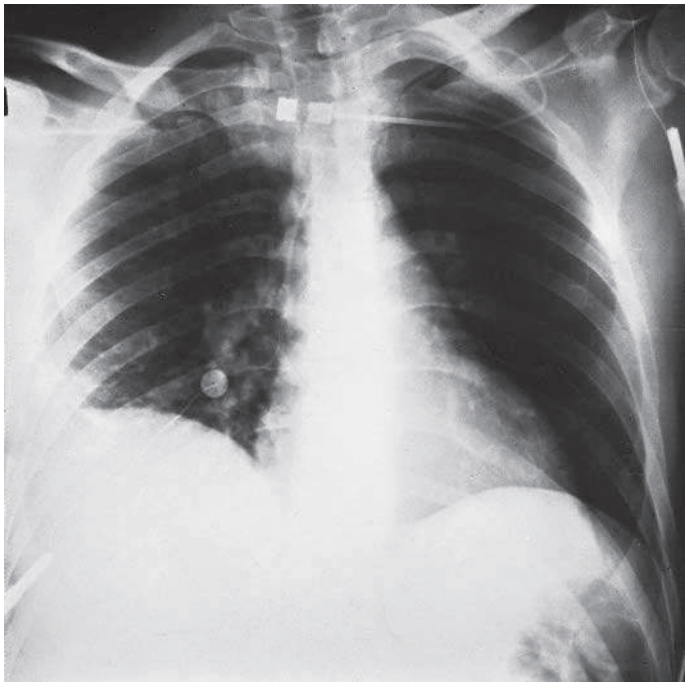
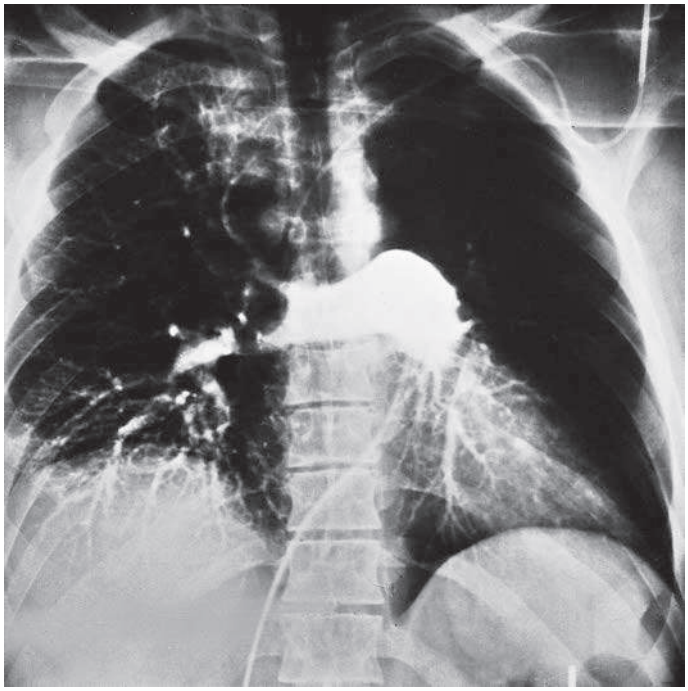


a



b

Fig. 18.**21** Central pulmonary emboli
a In the conventional chest radiograph pulmonary circulation on the right side is absent, resulting in increased transparency of this side. The diaphragm is elevated and an effusion (or hematoma) cannot be ruled out.
b The pulmonalis angiogram reveals occlusion of several branches of the left pulmonary artery and a subtotal occlusion of the right-sided branches.

Fig. 18.**21 c** ▷

may show hypoxemia and respiratory alkalosis (hyperventilation).

Differential Diagnosis. The differential diagnosis of infarction pneumonia includes *pulmonary hemorrhage* associated with embolization, *atelectasis*, *uncomplicated pulmonary infarction* without secondary infection, and *bronchopneumonia*. In pericarditis and myocardial infarction, the character of chest pain is not pleural, i. e., it is not influenced by respiration and dyspnea is not the main symptom. In pulmonary edema, the sputum may be frothy but frank hemoptysis does not occur.

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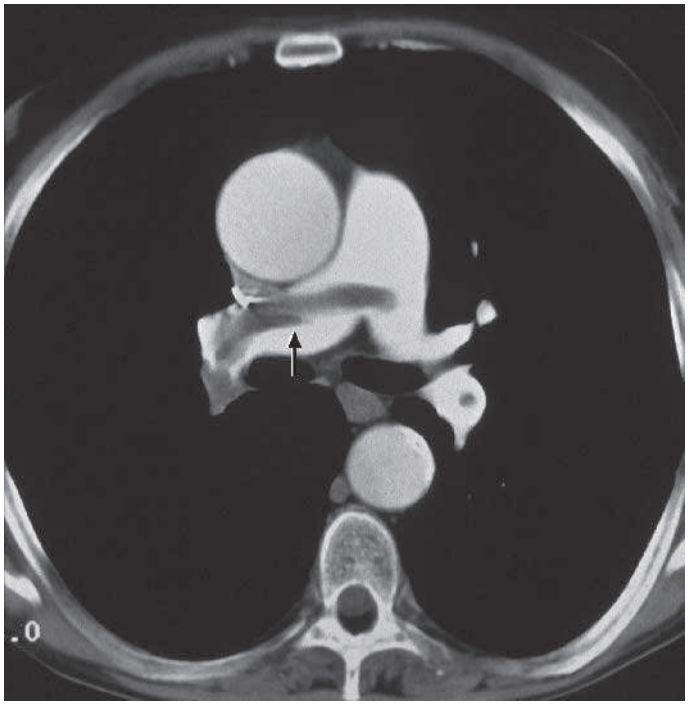

c

Fig. 18.**21**
c A spiral-angio-CT scan performed in another patient shows several central pulmonary emboli (arrow = floating embolus in the pulmonary artery main stem and in the right pulmonary artery).

Pneumonia Associated with Bronchiectasis

This type of pneumonia is characterized by recurring infiltrates at the same location. The patients may report chronic purulent sputum production. Auscultation may reveal rales and the chest radiograph shows predominantly linear shadowing or patchy infiltrates. A chest CT scan confirms the diagnosis.

Pneumonia Due to Bacterial Superinfection

Bacterial pneumonia may also represent *superinfection* of an other underlying lung disease, such as malignancies, collagen vascular diseases (see below), or may occur with immunosuppressive or cytotoxic therapy (see Fig. 18.**3**). Pulmonary infiltrates due to superinfection are common in influenza infection, typhoid fever, infection with *Salmonella* spp., measles, brucellosis, general sepsis, and malaria.

Chronic Pneumonia

Bacterial pneumonia may sometimes have a prolonged course extending over more than eight weeks. Rarely, carnification may result in shrinking of the lung parenchyma with restrictive ventilatory defect. The protracted course is not generally due to a special type of microorganism but rather it is caused by a particular response of the host. This may be the case in elderly patients, or patients with COPD, diabetes, alcoholism, but also with associated tuberculosis or malignancy and bronchiectasis. An extended course of pneumonia should prompt the evaluation for potential complications, such as a parapneummonic effusion and empyema, repeated aspiration, and gastroesophageal reflux.

Other Noninfectious Pulmonary Infiltrates

Eosinophilic pulmonary infiltrates, collagen vascular disease, sarcoidosis, organic and inorganic dust exposure are discussed below.

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18.3 Eosinophilic Pulmonary Infiltrates

Definition and Classification. These infiltrates are due to a heterogeneous group of diseases that have in common a pulmonary infiltration with eosinophilic granulocytes. The diagnosis is made if radiologic infiltrates and blood eosinophilia coexist or if a bronchial lavage or lung biopsy reveals a predominance of eosinophilic granulocytes. Thus, blood eosinophilia is not always present. The classification of eosinophilic pulmonary infiltrates is shown in Tab. 18.**2**.

Transient Eosinophilic Pulmonary Infiltrates (Löffler)

Transient eosinophilic pulmonary infiltrates may be due to larvae of three types of worms passing the pulmonary vascular bed on their way to the gastrointestinal tract: *Ascaris lumbricoides* (originally described by Wilhelm Löffler), *hook worms,* and *Strongyloides stercoralis*.

Clinical Features. Patients complain of nonproductive cough and an unspecific malaise. The eosinophilic infiltrates are typically transient and disappear over the course of approximately two weeks.

Blood eosinophilia varies between 7–70%. The total leukocyte count is not significantly elevated. Maximal eosinophilia lags a few days behind the pulmonary infiltrates.

As transient pulmonary infiltrates are most commonly caused by *Ascaris* infection, these eggs may be identified in stools, however not at the time of the pulmonary infiltrates but about two months later.

Pulmonary Eosinophilia with Parasitosis and Tropical Pulmonary Eosinophilia

Certain parasites (see Tab. 18.**2**) are associated with hematogeneous spread, eosinophilia, and pulmonary infiltrates. Tropical pulmonary eosinophilia is due to an immunologic reaction to microfilaria of *Wuchereria bancrofti*.

Allergic Bronchopulmonary Aspergillosis (ABPA)

Pathogenesis. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to mucosal growth of *Aspergillus* in patients with asthma. Central bronchiectasis and fibrotic scarring of the lung parenchyma may occur, due to recurrent bronchial obstruction, inflammation, and mucus plugging ("mucoid impaction").

Clinical Features. As a rule, allergic bronchopulmonary aspergillosis occurs in patients with chronic asthma, cystic fibrosis, or bronchiectasis of other etiology. Patients suffer from asthmatic attacks, nonspecific malaise, and cough up mucus plugs.

Diagnostic Criteria. Major criteria are:

- history of asthma
- positive immediate type skin reaction to *Aspergillus* antigen
- precipitating serum antibodies against *Aspergillus fumigatus*
- total serum IgE > 1000 ng/mL (1 U/mL = 2.4 ng/mL)
- blood eosinophilia
- pulmonary infiltrates
- central bronchiectasis
- specific IgE and IgG against *Aspergillus fumigatus*.

Table 18.**2** Eosinophilic pulmonary infiltrates

- Drug related
  - nitrofurantoin, L-tryptophan, phenytoin
- Helminths
  - transient pulmonary infiltrates (Löffler infiltrates) during pulmonary passage of larvae
  - parasites with direct infiltration of the lung parenchyma and massive spreading: *paragonimus, echinococcosis, cysticercosis, schistosomiasis*, disseminated *strongyloidiasis, trichinosis*, hook worms (e.g., *ancylostomiasis*)
  - tropical eosinophilia: *Wuchereria bancrofti* and others.
- Fungi (*Aspergillus*)
  - allergic bronchopulmonary aspergillosis
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Bronchial asthma
- Churg–Strauss syndrome
- Others
  - hypereosinophilic syndrome
  - neoplasia-associated eosinophilia

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If the first three criteria are met in the absence of bronchiectasis the term seropositive ABPA may be used. Minimal criteria for bronchiectatic forms of ABPA include: asthma, positive skin reaction to *Aspergillus* antigen, elevated IgE, and central bronchiectasis.

A skin prick test for *Aspergillus* is the first step in the diagnostic evaluation of ABPA. A negative result makes the diagnosis unlikely. In case of a positive test, serum IgE and precipitating antibodies should be determined. ABPA is unlikely if the total IgE concentration is below 1000 ng/mL or if there are no precipitating antibodies.

The *chest radiograph* may be normal or there are varying infiltrates with finger-shaped opacities ("plugs") and ateletatic lung zones. Bronchiectasis is visualized by CT scan.

Drug-Induced Pulmonary Eosinophilia

Eosinophilic pulmonary infiltrates have been described with the use of various drugs, most commonly with nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics, L-tryptophan, and recombinant granulocyte–macrophage colony stimulating factor (GM-CSF).

Acute Eosinophilic Pneumonia

Clinical Features. Symptoms include fever, nonproductive cough, dyspnea, and respiratory failure.

Diagnosis. Auscultation reveals rales. *Radiologically*, bilateral acinar and interstitial infiltrates are noted, sometimes accompanied by pleural effusion. Blood eosinophilia is absent or not pronounced, although eosinophils are predominant in the bronchial lavage. Pulmonary function studies show a restrictive ventilatory defect and impaired diffusion. The etiology of acute eosinophilic pneumonia is unknown. Systemic corticosteroid treatment provides rapid relief.

Chronic Eosinophilic Pneumonia

Clinical Features. The disease has a subacute or chronic course with fever, night sweats, weight loss, nonproductive cough, and dyspnea.

Diagnosis. The chest radiograph shows nonsegmental, peripheral infiltrates ("bat-wing infiltrates" resembling a negative depiction of a pulmonary edema; Fig. 18.**22**). Functional evaluation shows restriction and hypoxemia. Histological examination reveals infiltration of the alveoli and the interstitium with eosinophilic granulocytes. The peripheral blood shows eosinophilia. Treatment with systemic corticosteroids provides rapid improvement of symptoms, pulmonary function, and pulmonary infiltrates. Typically, infiltrates may flare up at the same location after discontinuation of treatment.

Eosinophilic Infiltrates with Asthma

Clinical Features. Eosinophilic pulmonary infiltrates may occur in patients with chronic asthma. In addition to asthma symptoms (cough, dyspnea), fever, malaise, and pleuritic chest pain may occur.

Diagnosis. There is blood eosinophilia. *Radiologically*, recurrent bilateral apical infiltrates are seen. The etiology is unknown. The differential diagnoses of allergic bronchopulmonary aspergillosis and Churg–Strauss syndrome have to be considered.

Allergic Granulomatosis and Angiitis (Churg–Strauss Syndrome)

Churg–Strauss syndrome is a vasculitis occurring in patients with chronic severe asthma. It is associated with rhinitis and blood eosinophilia. The vasculitis may also affect the nervous system (mononeuritis multiplex), the skin, the heart, the gastrointestinal tract, but rarely the kidneys. The chest radiograph shows varying nonspecific infiltrates.

Diagnosis. There are no specific laboratory findings. Eosinophilia is pronounced (several thousands/μL). In addition, there are signs of inflammation such as elevated erythrocyte sedimentation rate, C-reactive protein (CRP), and anemia. Certain patients have positive p-ANCA blood titers.

The disease is rare, but the diagnosis should not be missed since it may be aggressive and even lethal. Corticosteroid therapy is effective but there may be recurrence after discontinuation of treatment.

Hypereosinophilic Syndrome

This severe, eventually fatal, disease is characterized by eosinophilic infiltrates in various organs.

Diagnostic Criteria:

- blood eosinophilia: > 1500/μL for more than three months
- symptoms and signs of organ dysfunction
- exclusion of other cases of eosinophilia.

The etiology of the disease is unknown but may be related to a hematological malignancy. Endomyocardial fibrosis may develop.

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Fig. 18.**22** Chronic eosinophilic pneumonia; Typically, the infiltrates are located in the periphery and they have no segmental distribution shown here in a 61-year-old woman.

18.4 Diffuse Parenchymal Lung Disease (DPLD)/Pulmonary Fibrosis

Definition. Diffuse parenchymal lung diseases (DPLD) are a heterogeneous group of diseases that share common clinical, functional, radiologic and histopathologic features.

Clinical Features and Classification. Most patients suffer from *dyspnea*. They have *diffuse pulmonary infiltrates* and lung function tests reveal a *restrictive ventilatory defect*. Interstitial lung disease may be due to a variety of causes. Many forms are quite rare. Most common are interstitial pneumonitis due to inhalation of organic and inorganic dust, and sarcoidosis. Cryptogenic forms may occur secondary to collagen vascular diseases and granulomatosis.

Diffuse parenchymal lung diseases (DPLD or interstitial pneumonias) can be classified according to whether the etiology is *known* or *unknown* (cryptogenic) (Fig. 18.**23**). DPLD of unknown etiology may be part of the manifestation of sarcoidosis, collagen vascular disease, angiitis, or it may occur without other systemic manifestation as cryptogenic fibrosis alveolitis.

Pathogenesis. Independent of the etiology of the DPLD, their pathogenesis is similar. Initially, the alveolar epithelium and the capillary endothelium are damaged directly by toxic substances such as oxygen radicals, cytotoxic drugs (bleomycin), or indirectly by immunologic mechanisms that results in release of mediators from inflammatory cells. Subsequent to the injury to epithelial and endothelial cells, inflammatory cells migrate into the interstitium and the alveoli; alveolitis develops, i. e., the first common manifestation of any interstitial pneumonitis (sarcoidosis, cryptogenic fibrosing and allergic alveolitis, asbestosis, collagen vascular disease).

Depending on the type of the disease, there is local infiltration of neutrophilic granulocytes (fibrosing alveolitis), T lymphocytes (sarcoidosis), or eosinophilic granulocytes (chronic eosinophilic pneumonia). Without therapy, alveolitis progresses and fibrosis develops, finally resulting in honeycombing.

Fibrosis and honeycombing are the common result and end stage of alveolitis in any type of interstitial pneumonia.

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Idiopathic Interstitial Pneumonia

Etiology and Classification. The etiology of idiopathic interstitial pneumonias is, by definition, not known as it does not occur as a manifestation of systemic disease. There are several different forms that differ in regard to clinical presentation, radiology, and histopathology. These diseases include, in order of decreasing prevalence (Fig. 18.**23**):

- idiopathic pulmonary fibrosis (IPF)
- nonspecific interstitial pneumonia (NSIP)
- cryptogenic organizing pneumonia (COP)
- acute interstitial pneumonia (AIP)
- respiratory bronchiolitis-associated interstitial pneumonia (RB-ILD)
- desquamative interstitial pneumonia (DIP)
- lymphocytic interstitial pneumonia (LIP).

The nomenclature of these entities has undergone several changes over the last few years but has been adapted according to international consensus (Fig. 18.**23**). Idiopathic interstitial pneumonias are rare (prevalence 60–80 per 100 000, incidence 25–32 per 100 000). The prevalence of idiopathic pulmonary fibrosis has been estimated at 6–16 per 100 000. The nonspecific interstitial pneumonia and the other forms listed above are even rarer.

The most important differential diagnoses are protracted pulmonary infection, such as *Pneumocystis carinii* pneumonia, exogen allergic alveolitis, collagen vascular disease, and certain work-related diseases.

Differential Diagnosis. The clinical presentation of the various forms of interstitial pneumonias is described below:

- Bacteriologic, virologic, and serologic examinations of sputum, bronchial secretion lung biopsy and puncture, and blood tests may reveal the infectious origin of the disease.
- A detailed history of professional exposures are of paramount importance for the diagnosis of interstitial pneumonias due to inhalation of dusts that cause allergic alveolitis (farmer lung, humidifier lung) and pneumoconiosis (silicosis, asbestosis).

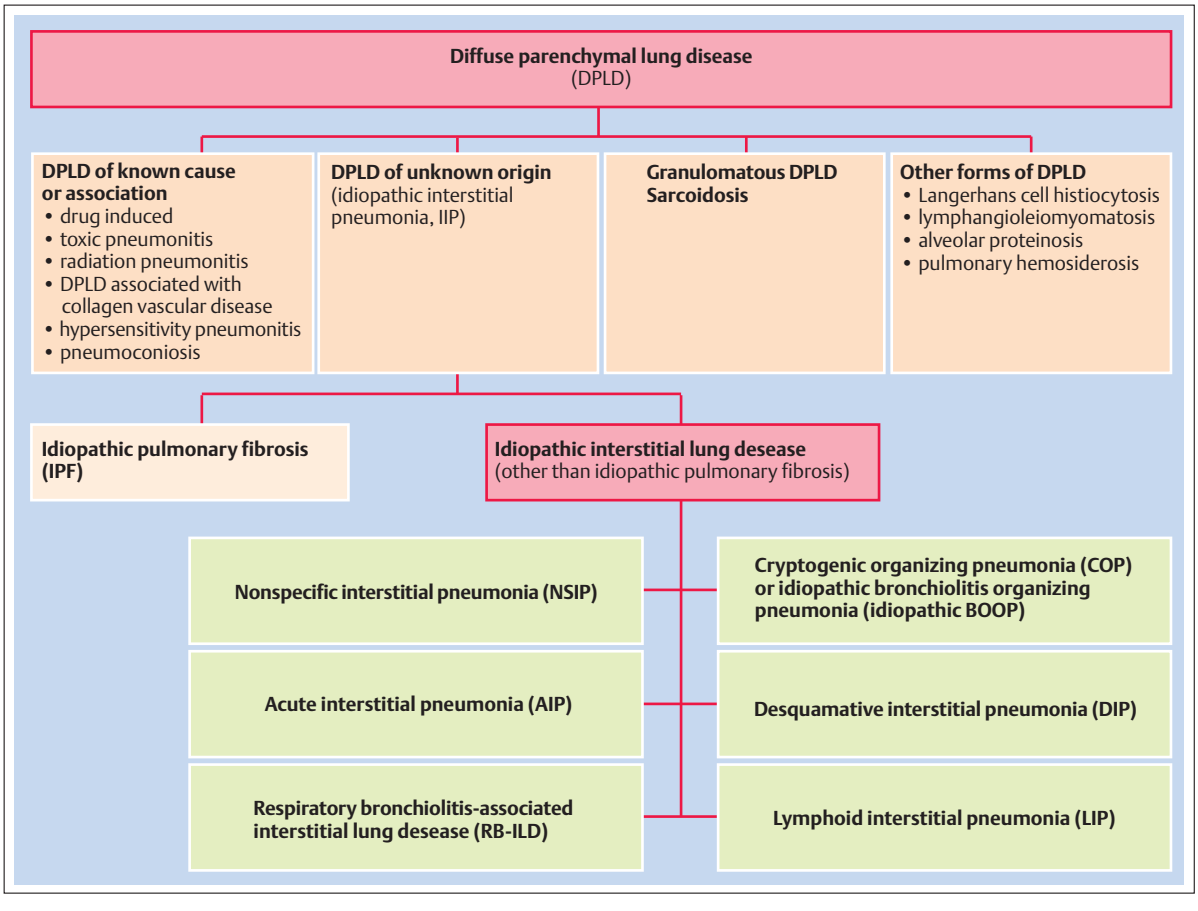

Fig. 18.**23** International classification of diffuse parenchymal (or interstitial) lung diseases (DPLD).

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Fig. 18.**24** Drug-induced pulmonary fibrosis due to busulfan in a 46-year-old man.

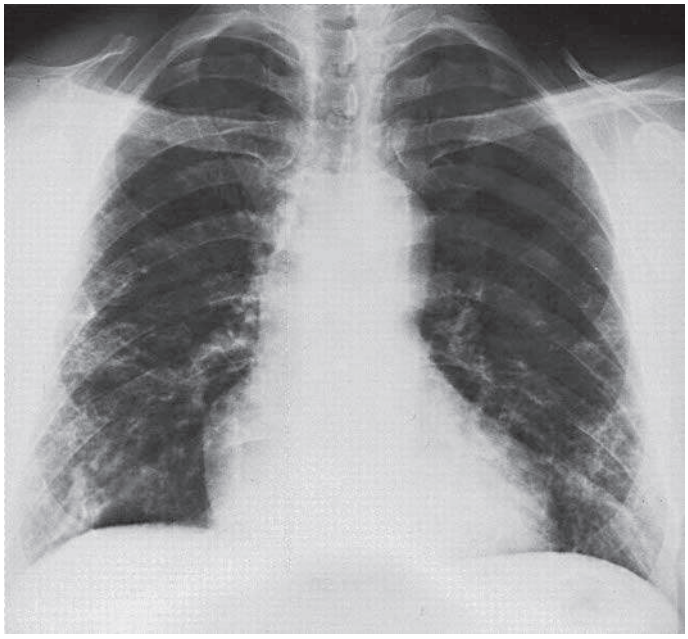

Fig. 18.**25** Amiodarone lung. There are reticulonodular infiltrates in both lower lung fields, which are partly confluent, found in a 53-year-old man.

- In exogen allergic alveolitis, the history is often suggestive.
- A detailed history may also reveal exposure to pneumotoxic drugs and radiation (Figs. 18.**24**, 18.**25**, and see Fig. 18.**17**).

Idiopathic Pulmonary Fibrosis (IPF)

Clinical Features. At initial presentation patients are usually older than 50 years. The first complaints are dyspnea and nonproductive cough. Rarely, weight loss, malaise, fatigue, subfebrile temperature, and arthralgias

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also may be present. Clubbing is observed in 25–50% of cases. Lung auscultation reveals typical "velcro crackels." In advanced stages, cyanosis and signs of right-sided heart failure appear. The median survival is only 2.5–3.5 years.

Pulmonary Function Studies. At the early stages of the disease diffusing capacity is reduced; progressive loss of lung volumes is observed later. The vital capacity is reduced more than forced expiratory volume in one second, i. e., the FEV_1/FVC ratio is increased, which is characteristic for restrictive lung disease. Marked hypoxemia is common and Po_2 drops during exercise. With progressive disease, dyspnea worsens and is present even at rest. Combined hypoxemia and hypercapnia is observed in the final stages of the disease.

Chest Radiograph. There are bilateral reticular infiltrates, initially most pronounced in basal and peripheral zones associated with reduced lung volumes and sometimes with cysts (Fig. 18.**26**). The high-resolution chest CT scan confirms reticular infiltrates with predominance in the basal and peripheral lung zones, and only little ground-glass opacity. Lung architecture is distorted and destroyed and there may be traction bronchiectasis. The end-stage of these alterations is the honeycomb lung (Fig. 18.**26b, c**).

Laboratory Tests. There are nonspecific signs of inflammation with elevation of the erythrocyte sedimentation rate and the CRP. Autoantibodies may also be demonstrated: in 37–45% of patients antinuclear antibodies, in 13% antimitochondrial antibodies, and in 10% antimyocyte antibodies appear. There is elevation of gamma globulins, and, at times, of cryoglobulins.

Histology. There is a pattern of "usual interstitial pneumonia" (UIP) with destruction of the lung architecture, honeycombing, and fibrosis with irregular fibroblast buds, often with subpleural and paraseptal distribution. Typically lesions of various stages of destruction are found simultaneously. Interstitial inflammation is not marked, and there are no granulomata or Langerhans cells.

Diagnosis. The bronchial lavage reveals a predominance of neutrophil granulocytes but eosinophils are also seen; however, there is no, or only a mild, increase of lymphocytes. The diagnosis is suspected on clinical grounds. At times, the CT radiologic findings are so typical that no histological proof of the diagnosis is required. In other cases, lung biopsy by video-assisted thoracoscopy is performed in at least two areas of the lungs that show different degrees of destruction.

Nonspecific Interstitial Pneumonia (NSIP)

Clinical Features. Patients suffering from nonspecific interstitial pneumonia (NSIP) are generally younger (40–50 years of age) than those with idiopathic pulmonary fibrosis (IPF). The onset is insidious with cough and dyspnea. The later course may extend over several years and stabilization, or even improvement, has been observed. Survival in NSIP is significantly better than in IPF. At auscultation there are fine crackles. Pulmonary function testing reveals a restrictive pattern and impaired diffusing capacity, and there is hypoxemia.

Chest Radiograph. The radiograph shows bilateral interstitial and sometimes patchy infiltrates with basal predominance. The high-resolution CT scan shows ground-glass opacity and reticular interstitial markings with basal predominance, but rarely cysts or honeycombing. The architecture of the lung parenchyma is preserved (Fig. 18.**27**).

Histopathology. Interstitial lymphocytic and plasmacellular infiltrates are found in NSIP. The lung structure is generally intact and fibrosis is not pronounced. In later stages, there is regeneration of alveolar epithelium and appearance of fibroblasts and collagen fibers in the interstitium and alveoli. The lesions are similarly advanced in various lung regions, which is in contrast to the heterogeneity of UIP, the histologic correlate of IPF.

Cryptogenic Organizing Pneumonia (Idiopathic Bronchiolitis Obliterans Organizing Pneumonia [BOOP])

Epler and coworkers described the clinical, functional, and radiologic characteristics of idiopathic interstitial pneumonias associated with bronchiolitis. They termed the disease "bronchiolitis obliterans organizing pneumonia" (BOOP). Today the term "cryptogenic organizing pneumonia" (COP), rather than idiopathic BOOP, is preferred to clearly differentiate from constrictive bronchiolitis.

Clinical Features. Major symptoms are cough, sputum production, and dyspnea associated with fever, night sweats, myalgia, and weight loss developing over the course of one to three months. There are rales at auscultation. Clubbing is not a feature of COP. Lung function testing shows a restrictive ventilatory defect with impaired diffusion. Airflow obstruction is not present despite the bronchiolitis. There is rapid improvement with corticosteroid therapy. Discontinuation of treatment may result in a recurrence.

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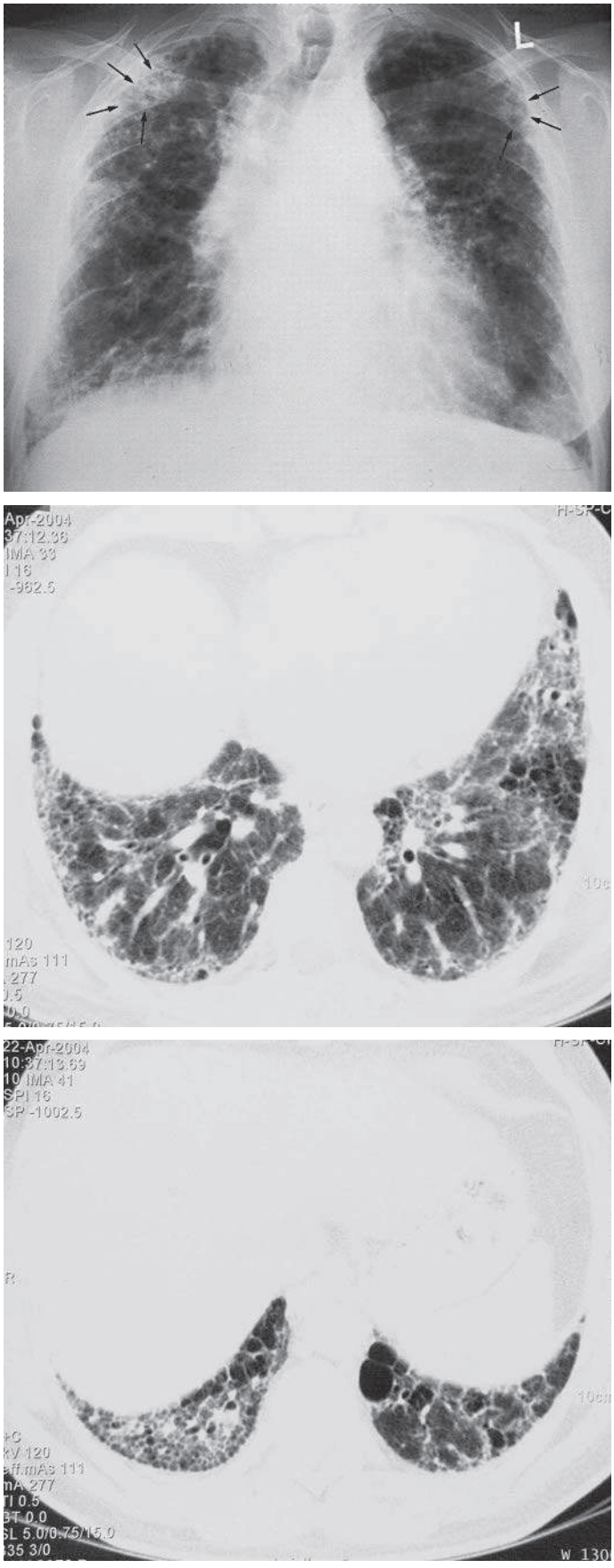

Fig. 18.**26** Idiopathic pulmonary fibrosis. The distribution and stage of the alterations are non-uniform.

a Bilateral reticulonodular opacities and loss of lung volume in the conventional chest radiograph.

b High-resolution CT scan shows thickened interlobular septa, patchy infiltrates.

c Honeycombing.

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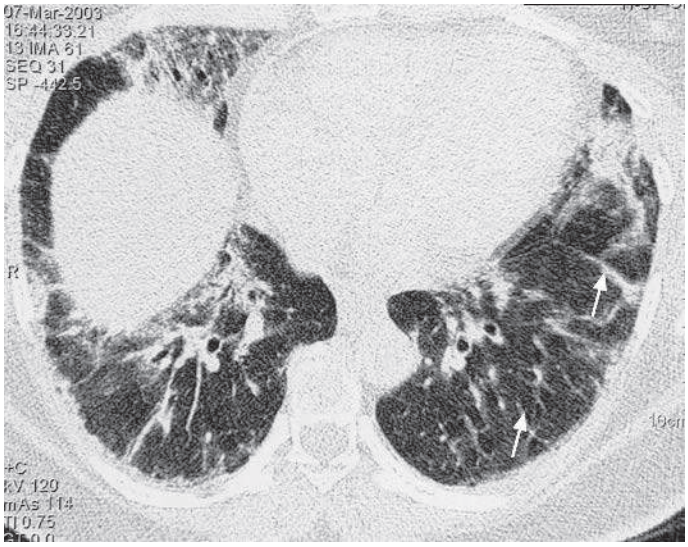
a



b

Fig. 18.**27** Nonspecific interstitial pneumonia (NSIP). There are multiple ill-defined infiltrates, thickened interlobular septa (arrow), and ground glass opacities in both lungs. However, there is no honeycombing.
a Level of the middle lobe, lingula an lower lobe.
b Basal level.

Diagnosis. There is an elevated erythrocyte sedimentation rate, elevated CRP, and leukocytosis. The chest radiograph typically shows patchy infiltrates with a tendency for consolidation. These may appear as rounded opacities and pleural effusion. Histologically, infiltrates in the interstitium and in the peribronchiolar region are seen, and there are intrabronchiolar buds. The lung architecture is preserved.

Differential Diagnosis. Differentiation from infectious pneumonia is important. The diagnosis is sometimes made only after unsuccessful antibiotic therapy. There are secondary forms of BOOP which occur in association with collagen vascular disease, such as in rheumatoid arthritis, lupus erythematodes, colitis ulcerosa, infectious diseases (HIV-associated infections, malaria, viral diseases), as graft-versus-host-reaction after organ transplantation, in myelodysplastic syndromes, cryoglobulinemia, after inhalation of toxic fumes, and as a side effect of drugs (amiodarone, cephalosporins, bleomycin, L-tryptophan, sulfasalazine, barbiturates, D-penicillamine, gold salts, etc.).

Acute Interstitial Pneumonia (AIP, Hamman–Rich Syndrome)

The disease described by Hamman and Rich in 1935 begins acutely with a viral syndrome including cough, sputum production, and rapidly progressive dyspnea. Despite intensive treatment consisting in corticosteroids, about one-half of patients succumb to the disease within one to two months. Clinically and radiologically, acute interstitial pneumonia (AIP) resembles an "acute respiratory distress syndrome" (ARDS). The Po_2/FIO_2 is sometimes less than 200 mmHg and bilateral infiltrates are extensive. Histologically there is

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diffuse alveolar damage (DAD) with thickened alveolar walls, organization of alveolar spaces, and inflammation with hyaline membranes. The differential diagnosis includes acute forms of interstitial pneumonia in sepsis and ARDS (see Fig. 18.**6**), shock, and toxic pulmonary drug effects.

Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD)

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) usually has a benign course and predominantly affects male smokers, less commonly women. Cough and dyspnea are the main symptoms. If smoking is stopped improvement is observed, progression to advanced fibrosis does not occur. The chest radiograph reveals thickening of bronchial markings due to infiltration of central and peripheral airways, ground-glass opacity and other nonspecific alterations: "dirty chest." In the chest CT scan, centrilobular noduli, ground-glass opacities, and a mosaic pattern with zones of varying densities are typical. Histologically, alveolar macrophages and inflammation of small airways are observed.

Desquamative Interstitial Pneumonia (DIP)

Desquamative interstitial lung disease (DIP) is nearly exclusively seen in smokers (as is RB-ILD). The symptoms are dyspnea and cough. Interestingly, approximately one-half of the patients develop clubbing. The prognosis is good. After discontinuation of smoking and corticosteroid therapy there is gradual improvement. The radiograph reveals ground-glass opacities in the lower lobes, and sometimes a few cysts are found. In the bronchial lavage and in lung biopsies brownish macrophages are typical.

Lymphoid Interstitial Pneumonia (LIP)

Lymphoid (or lymphocytic) interstitial pneumonia (LIP) is more common in women than in men. It starts with a slowly progressive course over several months. Patients complain of cough and dyspnea. In the chest radiograph ground-glass opacities and cysts appear. Histologically, there are lymphocytic and plasmocytic interstitial infiltrates. Autoimmune diseases such as Hashimoto thyroiditis, Sjögren syndrome, hemolytic anemia, or collagen vascular diseases (rheumatoid arthritis, lupus) or AIDS, in particular in children, are associated with LIP.

Interstitial Pneumonia in Association with Collagen Vascular Disease

The lungs are involved in many collagen vascular diseases.

Pathogenesis and Histology. One has to distinguish the (primary) alterations of the lung that occur as a direct manifestation of collagen vascular disease and the (secondary) alterations due to infectious complications and drug therapy.

Lung histopathology of the primary changes is indistinguishable from idiopathic forms of interstitial pneumonia. Interstitial pneumonitis is seen in association with chronic polyarthitis, dermatomyositis, and lupus erythematodes. There is vasculitis. Necrosis, granuloma formation, and fibrosis may occur. A typical consequence of vascular involvement in these diseases is pulmonary hypertension. Alveolar hemorrhage may develop secondary to capillaritis. Pulmonary hemorrhage is observed in Wegener granulomatosis, systemic lupus erythematodes, and cryoglobulinemia.

Secondary alterations are often of infectious origin. They may result from aspiration of gastric content (aspiration pneumonia in scleroderma) or from immunosuppressive therapy (bacterial infection, *Pneumocystis carinii* pneumonia). Methotrexate and gold are typical examples of drugs that may cause lung disease.

Chest Radiograph. The radiographic pattern provides certain clues to the diagnosis. If the collagen vascular disease has resulted in hemorrhage, ground-glass opacities and diffuse micronodular infiltrates are seen. If there is pulmonary fibrosis, lung volumes are reduced and there is honeycombing in the basal zones (Fig. 18.**28**). Vasculitis results in formation of ill-defined granuloma of variable sizes, which are diffusely scattered, sometimes with necrotic destruction and cavity formation (see p. 570).

Extrapulmonary Manifestation. *Clinically*, *extrapulmonary manifestations* of collagen vascular disease (skin, joint, heart, esophageal involvement) provide clues to the etiology, e. g., dysphagia is associated with scleroderma or a butterfly-shaped exanthema of the face suggests lupus erythematodes. Chapter 4 discusses serologic and immunologic aspects of collagen vascular diseases.

Differential Diagnosis. Extrapulmonary manifestations and immunologic or serologic examinations assist in the differentiation of collagen vascular disease-associated *interstitial pneumonia* from *idiopathic pulmonary fibrosis*. The differentiation of sarcoidosis is easy in the early

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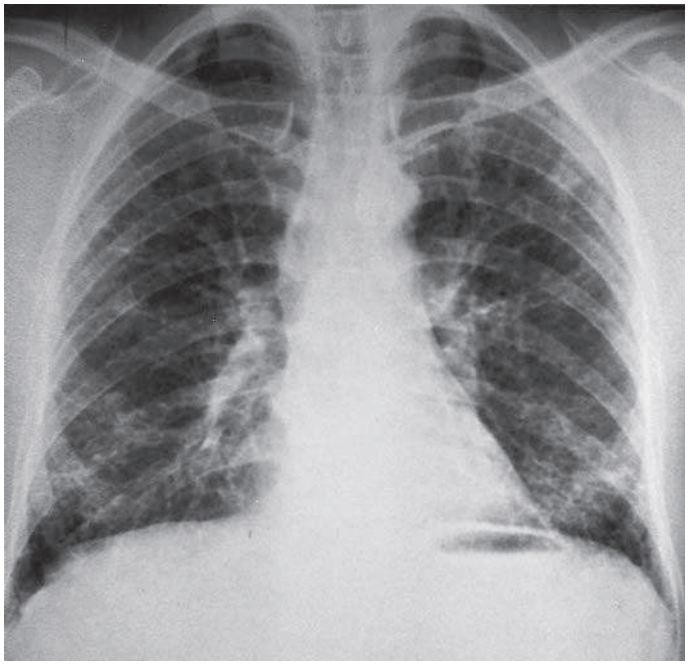

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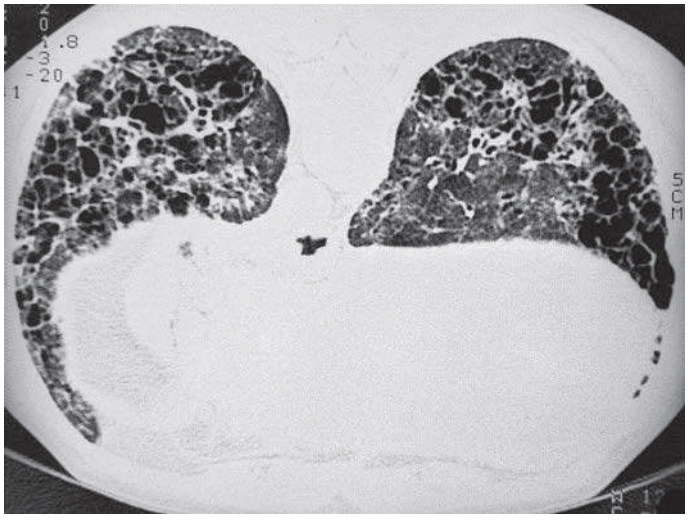

b

Fig. 18.**28** Scleroderma lung in a 46-year-old man.
a Reticulonodular infiltrates in both lungs.
b The CT scan shows honeycombing.

stages but may be impossible in advanced stages when there is extensive fibrosis and honeycombing. The following rare diseases have to be considered in the differential diagnosis:

- Wegener granulomatosis
- idiopathic pulmonary hemosiderosis
- Goodpasture syndrome
- alveolar proteinosis
- lymphangioleiomyomatosis
- microlithiasis alveolaris.

In addition to the clinical findings, the microbiologic evaluation, bronchoalveolar lavage, and histology of lung biopsies may help in the differential diagnosis. Diffusely infiltrating malignancies, lymphangiosis carcinomatosa, lymphoma, and leukemia should also be considered.

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Toxic and Drug-Induced Interstitial Pneumonia

This type of pneumonia is observed after treatment with certain drugs and inhalation of toxic fumes and gases (see also Noninfectious Pulmonary Infiltrates, above).

Drug-Induced Pulmonary Fibrosis

There are a large number of drugs that may induce pulmonary fibrosis:

- most cytotoxic drugs (for example: bleomycin, busulfane, cyclophosphamide, methotrexate)
- antibiotics (furadantine, salazopyrine)
- ganglion-blocking agents (hexamethonium)
- diphenylhydantoin, methysergide, practolol, ergotamine, and gold
- amiodarone.

The injuries may represent dose-dependent toxic effects (oxygen, cytotoxic drugs) or immulogic reactions (furadantine).

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

Pathogenesis. Hypersensitivity reactions to inhaled organic dust may result in diffuse parenchymatous lung disease of known origin. It is not known why certain persons respond to organic allergic dust with an asthmatic reaction of their airways or with alveolitis, and why this does not occur in others despite similar exposure.

More than 100 different causes of extrinsic allergic alveolitis have been described. The resulting diseases have been named according to the type of exposure or work. The following list is incomplete but includes commonly observed examples of hypersensitivity pneumonitis:

- bird fancier lung: proteins contained in feces of parakeets and budgeriars
- pigeon breeder lung: feces from pigeons
- farmer lung: thermophilic actinomyces species (*Micropolyspora faeni*, *Micromonospora vulgaris*)
- humidifier lung and humidifier fever
- mushroom worker lung (mushroom spores, thermophilic actinomyes)
- cheese washer lung (moldy cheese): *Aspergillus fumigatus* and *A. clavatus*: allergic bronchopulmonary aspergillosis, *Penicillium casei*
- wood dust pneumonitis, sequoiosis, wood trimmer disease
- suberosis: moldy cork dust.

In many patients, the clinical presentation is suggestive of hypersensitivity pneumonitis but none of the known allergens can be clearly identified as the responsible agent. In this case, humid and fungus-containing rooms may be the cause.

Clinical Features. There are acute, subacute, and chronic forms. The main symptom is *progressive dyspnea*. In acute and subacute forms, there is often a clear temporal relationship among exposure and appearance of symptoms (e.g., less symptoms on weekends in work-related hypersensitivity pneumonitis). There are also symptoms of systemic inflammation such as fever, malaise, arthritis, and weight loss. Auscultation reveals fine crackles or it may be normal.

Diagnosis. There may be leukocytosis but without eosinophilia. Impaired gas exchange is an early sign that can be detected with pulse oximetry during walking or with arterial blood gas analysis and measurement of diffusing capacity. Pulmonary function tests may show a restrictive pattern.

The chest radiograph is normal in early stages and may show diffuse nodular infiltrates. The high-resolution CT scan is quite often characteristic with the following elements: ground-glass opacity (alveolitis), diffusely distributed centroacinar noduli (bronchiolitis). In more advanced stages, there is fibrosis that cannot be differentiated radiologically from other types of fibrosis.

The diagnosis is based on a *typical history* with appropriate exposure and, if feasible, demonstration of symptomatic and functional improvement with avoidance of the exposure. In acute and subacute forms, the bronchoalveolar lavage shows marked lymphocytosis (> 60%) with a predominance of CD8 lymphcytes (i. e., a reduced CD4/CD8 ratio, suppressor cell alveolitis). It may also reveal a moderate eosinophilia (up to 20%) and some mast cells.

> The combination of typical clinical, functional, and CT radiographic findings is suggestive for hypersensitivity pneumonitis. The diagnosis is confirmed with consistent findings in the bronchoalveolar lavage.

Transbronchial or surgical lung biopsies may be necessary to confirm the diagnosis in certain atypical cases. Histological features include bronchiolitis, granuloma, inflammatory alveolar infiltrates, and in chronic forms, pulmonary fibrosis.

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Since the sensitivity and specificity of precipitating antibodies against suspected allergens is rather low, the role of serologic tests in the diagnosis of hypersensitivity pneumonitis is minor.

Differential Diagnosis. In farmers, the following differential diagnoses have to be considered: bronchial asthma, COPD due to inhalation of organic dust, silo filler disease, and acute organic dust toxic syndrome (ODTS). ODTS has a similar clinical presentation as farmer lung with a flulike illness starting after massive inhalation of organic dust. The symptoms appear four to eight hours after exposure with fever, chills, headache, malaise, myalgia, cough, and dyspnea are found. The chest radiograph is normal. Even after repeated exposure, no structural alterations of the lungs are visible. The cause of this syndrome is a reaction to bacterial endotoxins (*Enterobacter agglomerans* and others). The disease is self-limiting and shares common characteristics with the metal fume fever.

In patients with dyspnea, normal physical findings, normal spirometry but reduced diffusing capacity pulmonary, and arterial hypertension have to be considered as a differential diagnoses, which should be evaluated with echocardiography.

Pneumoconiosis

Silicosis

Pathogenesis. The diagnosis of silicosis requires a history of exposure to silicon dioxide, silica in crystalline form as quartz, and less commonly in other forms. Industries and occupations at risk are:

- tunnel mining
- underground excavation
- quarrying: sandstone, granite, sand
- stone work: granite sheds, monumental masonry, tombstones
- ceramic industry: manufacture of pottery, stoneware, bricks for ovens
- sandblasting.

In Western countries and the USA, new cases of silicosis are rare due to prophylactic measures in the industry. The quartz dust (SiO_2) causes irritation resulting in alveolitis, granuloma formation, and fibrosis. In miners and sandblasters, pulmonary alterations may be observed already after two to four years with rapid progression thereafter. In other professions, the first manifestations of silicosis usually appear only after more than five years.

Generally, silicosis has a protracted course over many years. Acute forms leading to early death have been described after massive exposure to high concentrations of quartz dust. The pneumoconiosis occurring in foundries is usually caused by an exposure to mixed dust including silica, coal, and iron (sidero–silico anthracosis; Figs. 18.**29**, 18.**30**). The prognosis is much better than in pure silicosis and the exposure may be more than 30 years.

Clinical Features. Chronic forms of silicosis may occur with chronic bronchitis with cough, sputum production, dyspnea, and wheezing. Spirometry often reveals airflow obstruction.

Radiologic Classification of Silicosis

Classification. Radiologically, silicosis is divided into four grades:

- Silicosis grade 0–I: (beginning silicosis): linear or reticular markings, with or without hilar adenopathy, barely recognizable noduli up to 1.5 mm in diameter.
- Silicosis grade I: increased and dense hili, fine nodular and reticular shadows (2–4 mm in diameter) in the periphery of middle and upper lung fields (Fig. 18.**29**).
- Silicosis grade II: dense nodular opacities (4–6 mm in diameter) in the periphery and intermediary zones of upper and middle lung fields (Fig. 18.**30**).
- Silicosis grade III: confluent, homogeneous opacities, linear shadows, noduli, scarring and traction with zones of traction, emphysema, pleural adhesions, consolidation (Fig. 18.**31**).

ILO Classification. The International Labor Organization (ILO) has created an international classification system applicable to all types of pneumoconiosis (ILO 1970/1972).

The type of opacification is described with letters p, q, r, s, t, and u:

p = micronodular up to 1.5 mm in diameter
q = miliary up to 3 mm in diameter
r = nodular up to 10 mm in diameter
s = fine
t = medium
u = large.

The density of nodules and linear shadows is described as 1–3:

1 = low density of nodules
2 = relatively even distribution over all lung fields
3 = highly dense nodular shadowing that prevents clear identification of the lung structure.

Noduli may conglomerate. The conglomerates and scars are graded according to their size as A, B, or C:

A = conglomerate of < 5 cm in diameter
B = in between A and C
C = conglomerate of a size of more than one-third of the lung.

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Fig. 18.**29** Mild silicosis (grade I) with fine nodule and reticular markings in the peripheral zones of the middle lung fields in a 56-year-old man.

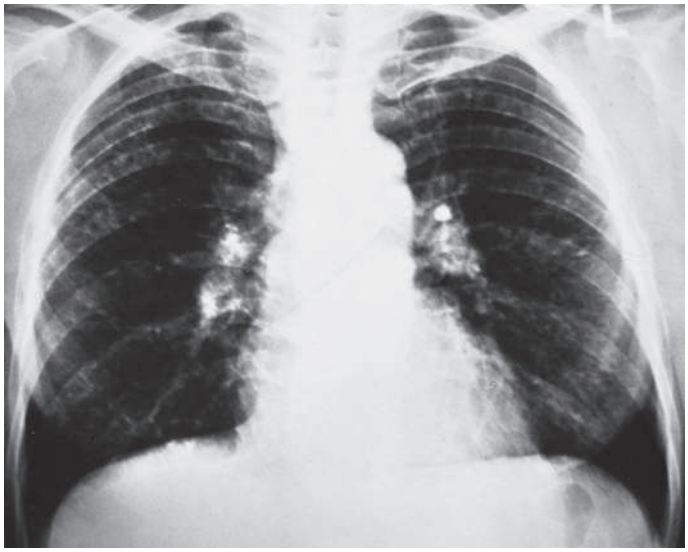

Fig. 18.**30** Moderate silicosis (grade II). Multiple, peripheral fine nodular densities. Calcified hila; as seen in a 60-year-old man.

The diagnosis of silicosis is based on the history of exposure and the appropriate radiographic alterations.

If the diagnosis is unclear, lung biopsy may be performed. Quartz crystals are identified within granulomas by polarization microscopy.

Differential Diagnosis. An important differential diagnosis in patients with silicosis is the coexistence of pulmonary tuberculosis. Massive conglomerates and cavities should raise the suspicion of tuberculosis (Fig. 18.**31**). The identification of tubercle bacilli in the sputum or bronchial secretions is essential.

Caplan Syndrome. In 1953, Caplan described coarse nodular alterations of the lungs in coal miners with chronic polyarthritis. In contrast to pneumoconiosis, the solitary or multiple nodules of 0.5–5 cm in size developed much more rapidly. Histopathologic examination demonstrated that the noduli were due to the rheumatoid arthritis rather than to the dust exposure. The prevalence of Caplan syndrome is approximately 30% in patients with pneumoconiosis and chronic polyarthritis.

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Fig. 18.**31** Severe silicosis (grade III) with conglomerates in the apical lung zones in a 45-year-old man.

Fig. 18.**32** Pneumoconiosis due to thorium in a 67-year-old man.

Silicatosis and Other Pneumoconioses

These diseases are caused by silicate-like and other dusts and include the following:

- asbestosis
- kaolin pneumoconiosis (porcelain worker)
- mica pneumoconiosis
- talc pneumoconiosis
- aluminium lung
- berylliosis.

Talc pneumoconiosis is observed in rubber industry workers. *Siderosis* is caused by inhalation of iron welding fumes or in iron mines. Baritosis, related to barium or barite inhalation, and stannosis, associated with the tin industry, are pneumoconioses in which the lung reaction is relatively minor despite heavy dust loads (Fig. 18.**32**).

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Fig. 18.**33** Asbestosis. Reticular markings in the middle lung zones. Calcified pleural plaques on the diaphragm of a 69-year-old man.

Hard metal lung results from inhalation of metal alloys that include tungsten carbide, cobalt, titanium, tantalum, and others used for the manufacture of tools, jet engines, and ferromagnets.

Several silicatoses are not distinguishable clinically and radiologically from silicosis.

Asbestosis. As asbestosis does not induce granuloma formation but pulmonary fibrosis, it is radiologically characterized by diffuse reticular opacities predominantly in the lower lung fields (Fig. 18.**33**).

> In contrast to other pneumoconiosis, asbestosis does not predispose to tuberculosis. However, it is associated with a high risk of bronchial cancer, pleural and peritoneal mesothelioma, and gastrointestinal cancers.

In addition to pulmonary fibrosis, asbestos exposure may cause benign pleural effusions and calcified pleural plaques, which are typically located on the diaphragmatic surface of the pleura, but also occur on other parts of the pleura as well (Fig. 18.**33**).

The sputum of patients with asbestosis may reveal "*asbestos bodies* or *ferruginous bodies*" that correlate with the time and load of exposure. These particles are asbestos fibers associated with ferritin, which makes them stainable with iron stains. Ferruginous bodies are not only observed in asbestosis but also in other pneumoconiosis.

Berylliosis. Berylliosis shares several radiologic and clinical characteristics with sarcoidosis. The disease has mostly affected workers in the fluorescent light industry. There are *acute* and *chronic* forms. Acute berylliosis causes an interstitial organizing pneumonia similar to a viral pneumonia. Chronic berylliosis is characterized by disseminated granuloma formation in the lungs, liver, spleen, and lymph nodes.

Differential Diagnosis of Pneumoconioses. Pneumoconioses have to be differentiated from other lung diseases that cause micronodular and patchy infiltrates:

- tuberculosis, in particular miliary tuberculosis (see Fig. 18.**9**)
- sarcoidosis, in particular miliary forms of sarcoidosis (see Fig. 19.**4**)
- extrinsic allergic alveolitis
- viral pneumonias (see Fig. 18.**13**)
- bronchopneumonias (see Fig. 18.**2**)
- histoplasmosis (see Fig. 18.**15**)
- congestive heart failure (see Fig. 19.**1**)
- lymphangiosis carcinomatosa (see Fig. 18.**35**)
- alveolar cell carcinoma (see Fig. 18.**34**)
- Kaposi sarcoma of the lung (see Fig. 18.**36**)
- lymphoma and leukemia
- bronchiectasis
- cystic fibrosis (see Fig. 18.**38**)
- collagen vascular disease, granulomatosis (Wegener disease; see Fig. 18.**46**)
- hemosiderosis in mitral stenosis and idiopathic pulmonary hemosiderosis
- aymloidosis
- lipid-storing diseases (Gaucher disease, Niemann–Pick disease)
- Langerhans cell histiocytosis.

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Diffuse Granulomatous Pulmonary Diseases

The most important form is sarcoidosis. As it is nearly always associated with hilar adenopathy it is discussed in Chapter 19.

Other Diffuse Parenchymal Lung Diseases and Orphan Lung Diseases

Alveolar Cell Carcinoma, Bronchoalveolar Cell Carcinoma, and Pulmonary Adenomatosis

Clinical Features. Bronchoalveolar carcinoma is a relatively rare lung cancer (2–6% of all lung cancers). It has to be considered in long-standing pulmonary infiltrates of unknown origin. In early stages, bronchoalveolar carcinoma may occur as a solitary peripheral pulmonary nodule found during a routine examination. Even in advanced, diffusely infiltrative stages the course may extend over several months. Despite extensive pulmonary infiltration and consolidation, the clinical symptoms may initially be moderate. Subsequently, dyspnea and cough due to *abundant secretion* develops. Up to more than 1 L of sputum may be expectorated each day. On the other hand, some patients have a nonproductive cough.

Diagnosis. Tumor cells may be found in the sputum or bronchial secretions. Bronchoalveolar cancer cells can not be cytologically differentiated from adenocarcionoma cells of other origin (gastrointestinal cancer of the colon or pancreas). The chest radiograph is not characteristic. Depending on whether the alveolar cell carcinoma is *localized* or *diffuse*, the chest radiograph shows a solitary pulmonary nodule or a localized infiltrate, or multiple noduli and consolidation (Fig. 18.**34**). In advanced stages there are large, ill-defined infiltrations with consolidation in one or both lungs.

Lymphangiosis Carcinomatosa

Lymphagiosis carcinomatosis produces reticular or micronodular opacities irregularly distributed over the lungs (Fig. 18.**35**). The differential diagnosis of lymphangiosis carcinomatosis includes *miliary tuberculosis*, *pneumoconiosis*, *bronchopneumonia*, and *congestive heart failure*.

Kaposi Sarcoma

Kaposi sarcoma is associated with human herpes virus 8 (HHV-8) infection and occurs in AIDS and other conditions with impaired immune defense such as in patients with organ transplants.

Clinical Features. The clinical and radiological findings are similar to opportunistic pneumonias. Symptoms include *dyspnea*, *dry cough*, *hemoptysis*, fevers, malaise, and weight loss. The chest radiograph shows nonspecific diffuse reticular infiltrates (Fig. 18.**36**). Hilar adenopathy occurs in about 25% of cases, and hemorrhagic pleural effusions in around 40%. However, the chest radiograph may be normal. Infiltration of the bronchial mucosa by the sarcoma may be seen in bronchoscopy as multiple reddish areas.

Differential Diagnosis. This includes opportunistic infections, tuberculosis, and atypical mycobacteriosis.

Pulmonary Hemosiderosis

There are primary and secondary forms of pulmonary hemosiderosis. *Primary idiopathic pulmonary hemosiderosis* is a rare disease, predominantly of children but also of adults. The course is intermittent with hemoptysis, pulmonary infiltrates, and hypochromic anemia. *Secondary pulmonary hemosiderosis* occurs in congestive heart failure (mitral stenosis), Goodpasture syndrome, rapidly progressive glomerulitis, collagen vascular disease (lupus erythematodes, Wegener disease, Churg–Strauss vasculitis, antiphospholipoid syndrome), and after inhalation of certain toxic substances (such as trimellitic anhydride, isocyanate, D-penicillamine).

Goodpasture Syndrome

Pathogenesis. Goodpasture syndrome is an autoimmune disease. There is a type II hypersensitivity reaction with circulating cytotoxic antibodies (IgG, IgM) against the basal membrane of lungs and kidneys. There is an association with the HLA-DRw2 antigen, influenza A_2 virus infection, and there seems to be a familial predisposition. Men around 20 years of age are most commonly affected.

Clinical Features. The most common symptom is *hemoptysis*, which indicates diffuse pulmonary hemorrhage. As a consequence, there is severe anemia and

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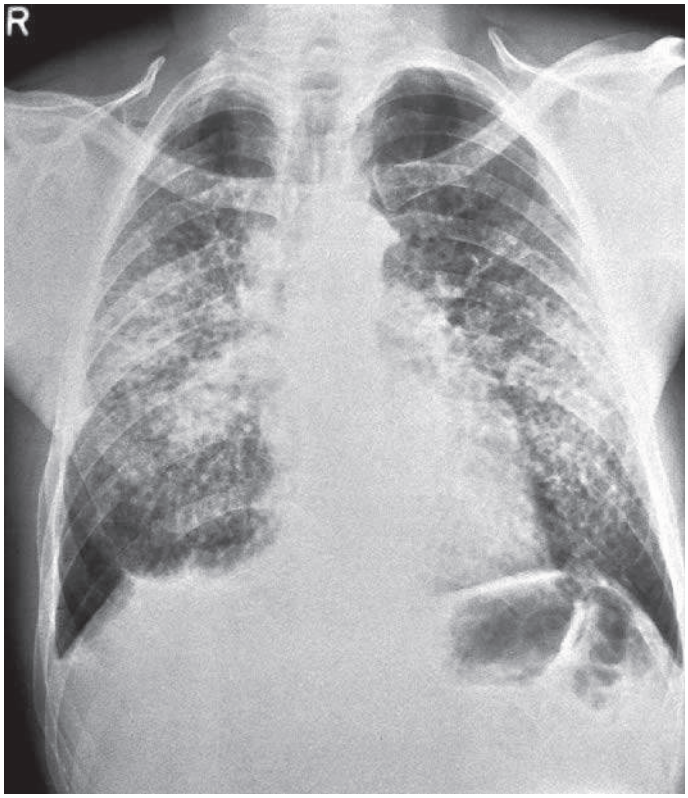

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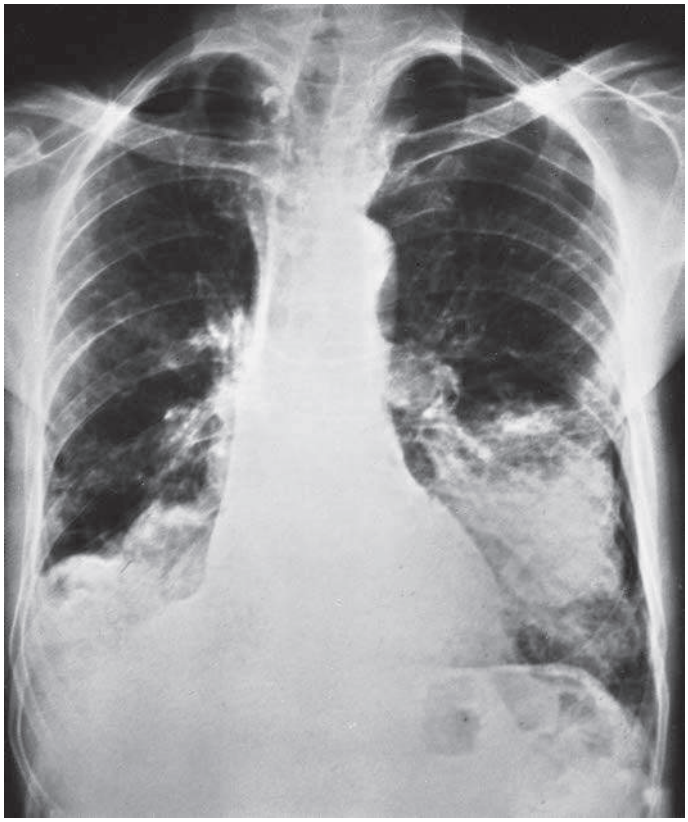

b

Fig. 18.**34** Alveolar cell cancer
a Diffuse type.
b Localized type.

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Fig. 18.**35** Lymphangiosis carcinomatosa predominantly on the right side (breast cancer) in a 62-year-old woman.

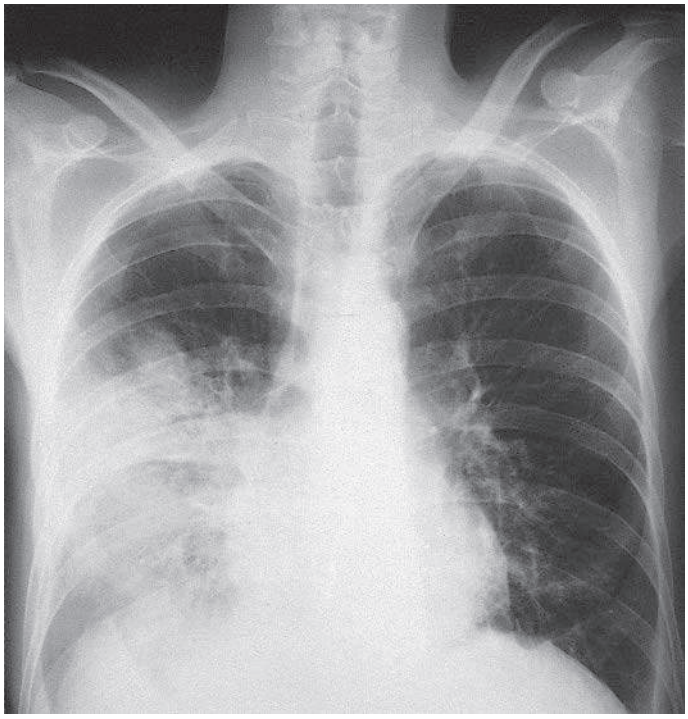

Fig. 18.**36** Kaposi sarcoma of the right lung. Fine nodular partly confluent infiltrate in the middle lung zones. The lower zones are partly opacified by pleural effusion in a 34-year-old man.

hyposiderinemia. *Proteniuria and hematuria* may start weeks to months later.

Diagnosis. At the time of pulmonary hemorrhage there are diffuse, ill-defined patchy infiltrates in the *chest radiograph*. Pulmonary function testing shows a restrictive ventilatory defect. Diffusing capacity may be elevated due to carbon monoxide binding by the alveolar blood. Hemosiderin containing macrophages may be seen in the sputum. The *differential diagnosis* includes other diseases associated with pulmonary hemorrhage, such as collagen vascular disease (lupus erythematodes, Wegener granulomatosis, allergic granulomatosis, angiitis, antiphospholipid syndrome, Schönlein–Henoch purpura, cryoglobulinemia, Behçet syndrome) and idiopathic pulmonary hemosiderosis.

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Antiphospholipid Syndrome

In patients with antiphospholipid syndrome, the lungs may be affected by thromboembolic disease secondary to the coagulopathy, pulmonary artery hypertension, and diffuse pulmonary hemorrhage due to pulmonary capillaritis.

Pulmonary Alveolar Proteinosis (PAP)

Pulmonary alveolar proteinosis (PAP) is a diffuse disease of the lung parenchyma due to accumulation of amorphic Periodic Acid Schiff (PAS)-positive staining materials. There is virtually no inflammation and the lung architecture is maintained. The material consists predominantly of phospholipid and apoprotein components of the surfactant. The cause of the *primary form* of the disease is a dysfunction of the alveolar macrophages and of their interaction with GM-CSF. There are also *secondary forms* associated with certain pulmonary and hematologic diseases.

Clinical Features. Symptoms consist of slowly progressive *dyspnea*, *cough*, and expectoration of gelatinous material. Clinical examination is often normal or rales may be present. PAP predisposes to opportunistic infections, such as nocardiosis and atypical mycobacteriosis.

Diagnosis. The *chest radiograph* shows bilateral acinar infiltrates extending to the periphery of the lower and middle lung fields. The high-resolution CT scan shows ground-glass opacities in combination with thickened interlobular septa in a polygonal pattern ("crazy paving").

The diagnosis relies on bronchial lavage and *lung biopsy*. The bronchial lavage typically shows an opalescent aspect ("egg shampoo"). The alveolar macrophages are full of PAS-positive material.

Microlithiasis Alveolaris

The rare *microlithiasis alveolaris miliaris pulmonum* has a familial predisposition and is characterized by microlithes (calcium-containing stones) in up to 80% of the alveoli. The microlithes may be found in the sputum. The main symptoms are *dyspnea* and *cyanosis*. There is a restrictive ventilatory defect. In the final stages, cor pulmonale may develop after several years (the youngest described patient was 25, and the oldest 72 years old).

Langerhans Cell Histiocytosis

Nomenclature. Langerhans cells have a central role in the pathogenesis of this disease. The disease should therefore no longer be called histocytosis X, Abt–Letterer–Siwe, or Hand–Schuller–Christian disease. It is crucial to know whether one or several organs are involved, since this determines the prognosis and treatment.

Pathogenesis. Langerhans cell histiocytosis of the lung is a rare interstitial lung disease predominantly occurring in young smokers (20–40 years of age). Smoking seems to be an important etiologic factor. Langerhans cells are differentiated cells of the monocyte–macrophage line. They may be identified by electron microscopy by the so-called *Birbeck granules* (X-bodies) and immunohistochemically by identification of the *S100 proteins*.

Clinical Features and Diagnosis. The disease may occur initially as *pneumothorax*. Symptoms consist of a *cough* and *dyspnea*. The clinical examination is usually normal, and in early stages only the *diffusing capacity* is decreased. The *radiologic findings* are typical, consisting of reticulonodular infiltrates, small nodules with central necrosis, and cyst formation, but without lung volume loss. The basolateral costophrenic angles are usually not affected. A high-resolution CT scan is usually diagnostic. The most common *extrapulmonary manifestations* are eosinophilic granulomata of the bone (cystic bone lesions, 4–20%), and diabetes insipidus (15%).

Lymphangioleiomyomatosis (LAM)

Epidemiology. LAM is a rare disease of unknown origin. It occurs exclusively in women of child-bearing age.

Pathogenesis. There is accumulation of atypical smooth muscle cells in the bronchovascular bundle and in the interstitium. Another typical feature is cystic dilation of the terminal bronchioli.

Clinical Presentation. These alterations explain the clinical presentation and the complications:

- progressive dyspnea and airflow obstruction
- recurrent pneumothoraces due to rupture of cysts
- chylothorax due to lymph leakage into the pleural space.

Diagnosis. The *radiologic findings* in high-resolution CT are usually diagnostic (Fig. 18.**37**). In the *histology*, LAM cells stain with monoclonal antibody HMB-45.

Commonly, there are renal, retroperitoneal, or intra-abdominal angioleiomyomata.

The *differential diagnosis* includes: idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, Langerhans cell histiocytosis, cystic forms of sarcoidosis, and pulmo-

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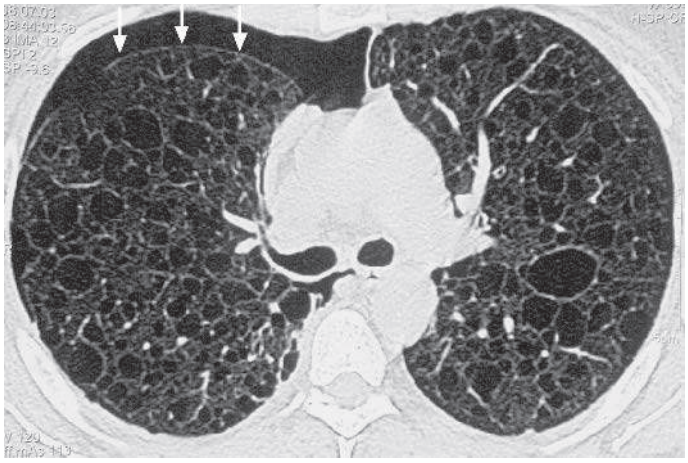

Fig. 18.**37** Lymphangioleiomyomatosis with multiple cysts and pneumothorax (arrows).

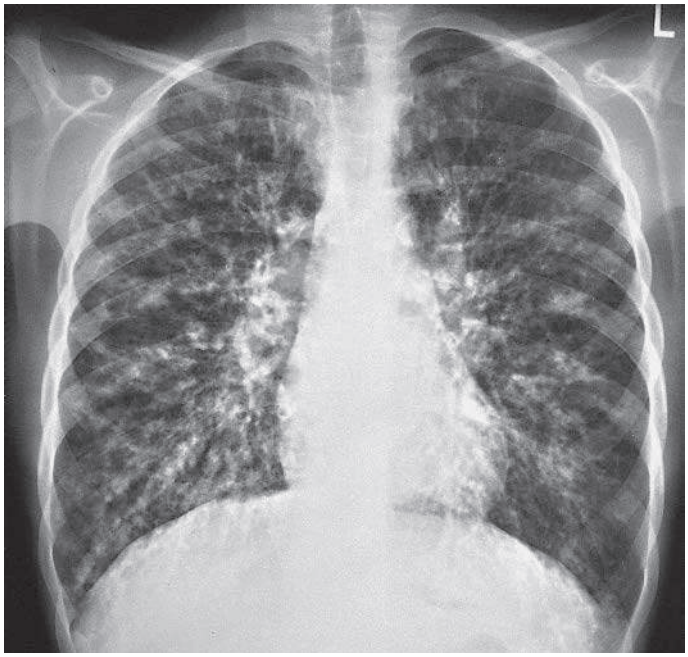

Fig. 18.**38** Cystic fibrosis. Hyperinflated chest. The lungs show multiple nodules and reticular opacities. Enlarged hila (cor pulmonale!). Several cystic lesions in a 21-year-old man.

nary emphysema. The autosomal dominant-inherited tuberous sclerosis causes an identical lung disease.

The disease has a progressive course. The median survival is less than 10 years.

Formation of Cysts and Honeycombing

In a honeycombing lung, the parenchyma is replaced by multiple cysts and fibrosis. Most cysts are congenital but they also develop due to infection associated with mucus plugging, bronchiolitis, and localized hyperinflation (see also p. 574).

The diagnosis of honeycomb lung is based on *radiologic examination* showing multiple cysts (see Fig. 18.**26**). The etiology can often not be determined, since honeycombing occurs in the end stages of various diseases such as the various forms of diffuse parenchymatous lung disease, *chronic bronchiolitis*, *cystic fibrosis*, and *lymphangioleiomyomatosis* (Fig. 18.**38**).

Honeycombs and Cysts

The terms honeycombs and cysts correspond to thin-walled lesions of one to several millimeters in diameter.

A honeycomb lung is the end stage of many different lung diseases.

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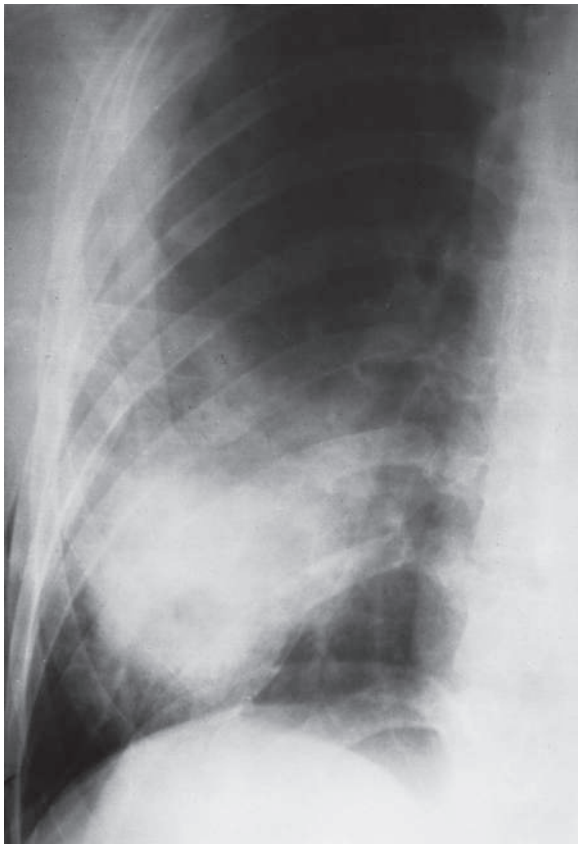
18.5 Pulmonary Nodules

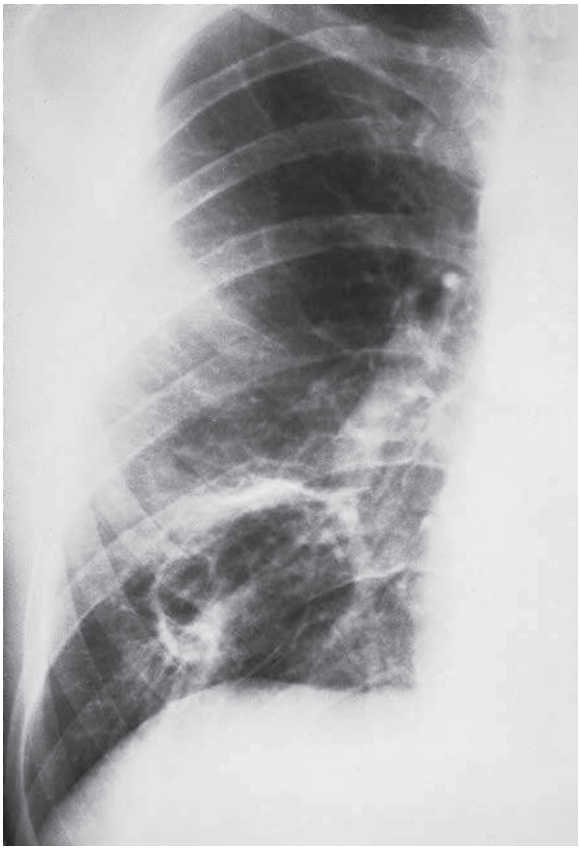
Definition. A pulmonary nodule is defined as a rounded, clearly delineated opacity in the lung parenchyma of up to 3 cm in diameter that is not adjacent to the chest wall, hilum, or mediastinum. An opacity of greater than 3 cm in diameter is termed a pulmonary mass that has a different differential diagnosis than a nodule. The probability of neoplastic origin increases with the size of a nodule or mass, respectively. Pulmonary nodules are rarely causing symptoms and are often detected in a routine chest radiograph.

Diagnosis. The *major question* is whether the lesion is *benign* or *malignant*. If the patient is young, i. e., < 30 years, the nodule is likely to be benign. It may represent a malformation (bronchogenic cyst, arteriovenous malformation), a benign neoplasia (dermoid, hamartoma), infection (tuberculoma, histoplasmoma, echinococcosis, pulmonary abscess), or rarely, a hematoma (Fig. 18.**39**). In patients older than 40 years, pulmonary nodules are generally neoplasms: bronchial cancer, metastasis, non-Hodgkin lymphoma, etc.

The *radiologic characteristics* of a nodule (i. e., solitary, multiple, density, calcification, or central necrosis) may narrow the differential diagnosis somewhat. For example, calcifications are typical for a tuberculoma but some bronchial cancers may also have *calcifications*. *Prior chest radiographs* are helpful in the determination of changes in the size of a nodule and in assessment of the likelihood of malignancy: a nodule that doubles in size in less than seven days or more than 465 days suggests a benign etiology. The diagnosis is confirmed by biopsy (either transbronchial or by thoracoscopy or thoracotomy) or by direct resection and histologic examination. Depending on the number of lesions, one can differentiate solitary from multiple pulmonary nodules.



a



b

Fig. 18.**39** Traumatic hematoma of the lung.
a Before resorption
b After resorption, a pseudocyst has developed.

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Solitary Pulmonary Nodules

Etiology. The following considerations apply to a solitary pulmonary nodule (up to 3 cm in size). The differential diagnosis varies with age, smoking history, residence or geographic origin of the patient, radiologic characteristics, and other factors: malignoma, granuloma, hamartoma, and other benign lesions of various etiology. The probability that a solitary pulmonary nodule represents a bronchial cancer in a 60-year-old heavy smoker is very high. Conversely, malignancy is unlikely in a young nonsmoker.

Diagnosis. Evaluation depends on the suspected diagnosis and differential diagnosis, the general condition of the patient, comorbidities, pulmonary functional reserves, and other aspects. If malignancy is likely, direct surgical biopsy or resection with immediate histologic examination is performed. Depending on the histologic findings, resection is completed or extended if cancer is confirmed. The problem of bronchoscopic or transthoracic biopsy lies in the high rate of nondiagnostic results and in the low chance of making a definitive diagnosis of nonmalignant disease (such as granuloma or hamartoma). As video-assisted thoracoscopic resection of a nodule generally has a low complication rate, it is commonly used in the evaluation of solitary pulmonary nodules. If a neoplasia is judged to be an unlikely etiology of a pulmonary nodule, volumetric CT evaluation may be performed initially and later in the course to reliably document absence of growth of the lesion and to rule out malignancy.

Malignant Neoplasms

Bronchial Cancer. Bronchial cancer is by far the most common malignant neoplasia of the lungs. Diagnostically relevant information comprises the smoking history, current and previous chest radiographs, findings that suggest metastasis to the lymph nodes, liver, or bones, bronchoscopic findings, and the histology or cytology of the neoplasm. Certain lung cancers are very slowly progressive and bronchoscopy may be negative in a patient with a peripheral solitary nodule. Some malignant nodules have an irregular circumference and calcifications (in 2–10%, in particular, squamous cell cancers, Fig. 18.**40**). *Carcinoma* and *tuberculosis* may coexist (scar cancer!).

Pancoast Tumor. Neoplasms of the superior sulcus, so-called pancoast tumors, lead to typical symptoms: shoulder pain, paresis of the arm or hand with muscular atrophy, and Horner syndrome. Lesions of the ribs are common (Fig. 18.**41**). Histologically, pancoast tumors may be squamous-cell carcinoma, adenocarcinoma, or large-cell and small-cell cancers.

Pulmonary Metastasis. Metastasis of distinct tumors (3–5% of all solitary pulmonary nodules), bronchoalveolar carcinoma, Hodgkin and non-Hodgkin lymphoma, and multiple myeloma (Fig. 18.**42**) are additional neoplasms that may occur with solitary nodules.

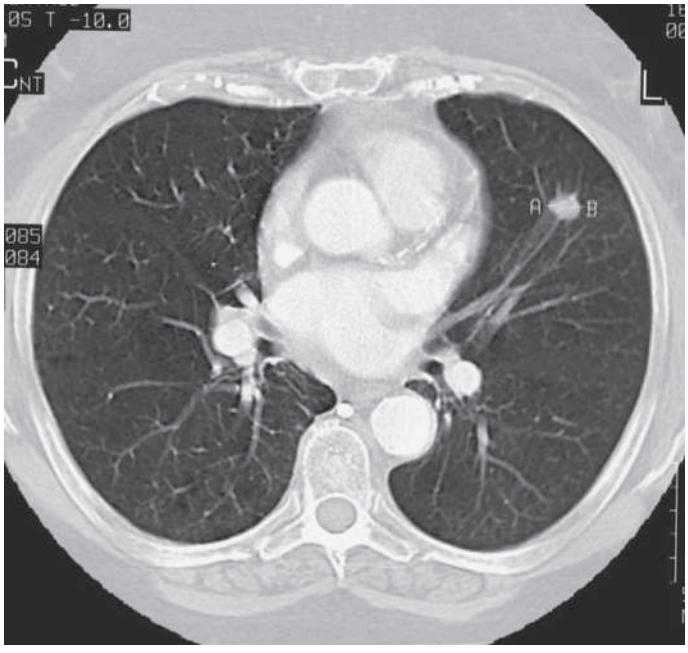

Fig. 18.**40** Solitary nodule in the lingula.

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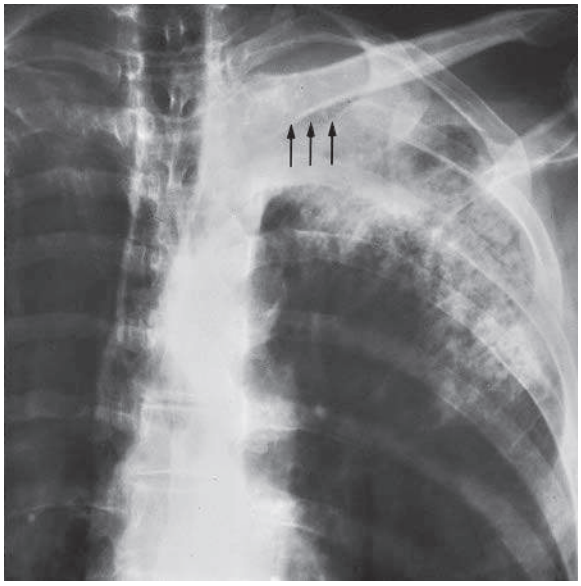

Fig. 18.**41** Pancoast tumor. Peripheral bronchial cancer in the left apex with destruction of the third rib. Perifocal infiltrates indicate pneumonia.

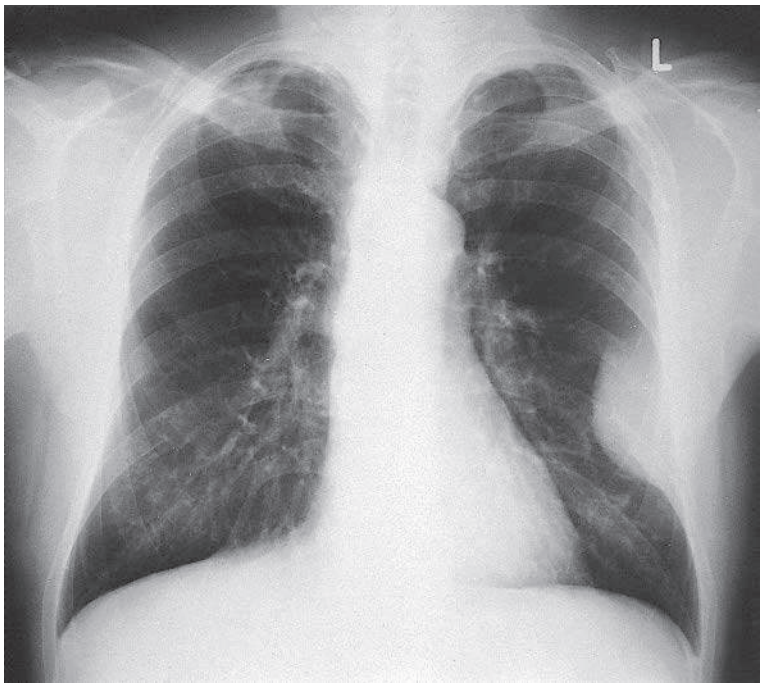

Fig. 18.**42** Multiple myeloma in the left lung in a 56-year-old man.

Hodgkin Lymphoma. *Hodgkin lymphoma* may be associated with pulmonary infiltrates or nodules: solitary or multiple nodules, large confluent infiltrates that may be similar in appearance to a tuberculous infiltrate, a bronchial cancer, or pneumonia. The diagnosis is facilitated by the fact that the lungs are rarely the only manifestation of the disease. The clinical presentation of Hodgkin disease is described in Chapter 14.

Malignant Lymphoma. The isolated malignant lymphoma of the lung is rare. The *differential diagnosis* includes *bronchial cancer* and *chronic pneumonia*. The diagnosis requires a histologic examination. Differentiation between small-cell cancer and lymphoma is sometimes difficult.

Predominant symptoms include cough, pain, chest tightness, poor appetite, and weight loss. In the radiologic evaluation the lymphoma is most commonly a mass within the lung parenchyma that is *not* adjacent to the hilum.

Primary malignant lymphoma belongs, along with the pseudolymphoma, *lymphoid interstital pneumonia*, *lymphoid granulomatosis*, and *plasma cell granuloma*, to the lymphoproliferative diseases of the lung. Whereas plasma cell granuloma is a benign disease, the other cited diseases may develop into a malignant lymphoma.

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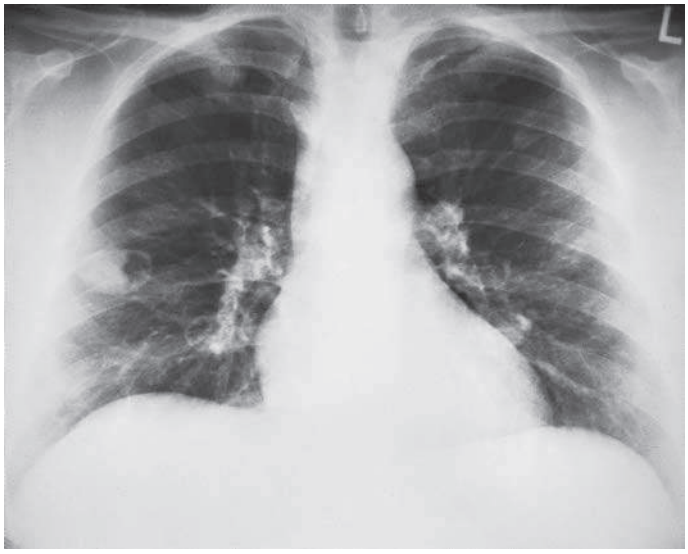

Fig. 18.**43** Pulmonary echinococcosis. There are at least three cysts (two on the right, one on the left). The left sided cyst has an air–fluid level shown in a 42-year-old man.

Clinically, the different forms of these diseases cannot easily be distinguished, and diagnosis requires a biopsy and histological evaluation.

Benign Tumors

These generally have an *asymptomatic course* and are detected during a chest radiographic examination performed for other reasons. *Fibromas*, *lipomas*, *chondromas*, *osteomas*, and *hamartomas* are characterized by clearly delineated opacities. Their growth is extremely slow, over several years, and they may calcify. Their location is usually in the lung periphery, whereas *neurinomas* originate from the posterior mediastinum. *Dermoids* and *teratomas* are located in the anterior mediastinum. The absence of growth, an unaffected general health, and the lack of any humoral changes are suggestive of a benign tumor. However, the type of tumor may only be suspected.

Certain *benign* or *semimalignant lung tumors* have an *endobronchial* growth that is associated with cough, atelectasis, and pneumonia. Rarely, these tumors may induce endocrine alterations, such as carcinoid syndrome with bronchial carcinoid, and hypoglycemia with intrathoracic mesodermal tumors.

Inflammatory Pulmonary Nodules

Inflammatory nodules occur either as a consequence of *infection* or as an *immunologic reaction*.

Immunologic Causes. Inflammatory immunologic nodules are observed in *granulomatosis* and *angiitis* (Wegener granulomatosis) and in collagen vascular diseases. In chronic polyarthritis, the *necrobiotic nodule* (rheumatic nodule) may also be located in the lung parenchyma, close to the pleura, mostly in the lower lobes. There may be multiple nodules associated with a pleural effusion.

Infectious Causes. Potential causes of a solitary inflammatory nodule are:

- bacterial infections (tuberculosis, *Klebsiella* pneumonia, aspiration pneumonia, actinomycosis)
- fungal infections (aspergillosis, histoplasmosis, nocardiosis, coccidioidomycosis, blastomycosis, and cryptococcosis)
- parasitosis (echinococcosis, filiariosis)
- tuberculoma.

Tuberculoma

Depending on the geographic area of residence of a patient, up to 90% of inflammatory pulmonary nodules are due to tuberculosis or histoplasmosis.

The diagnosis of a tuberculoma is based on the location in the upper lobe, central necrosis, calcification (see Fig. 18.**11**), and "satellite lesions," i. e., small perifocal infiltrates (found in 80% of cases). As a rule, a tuberculoma does not grow. The tuberculin skin test is positive. The larger the tuberculoma, the higher is the risk of residual activity.

Echinococcosis

Rounded and clearly delineated nodules, either solitary or multiple, may represent echinococcosis (Fig. 18.**43**), particularly, if the patient is from an endemic area and suffers from cough and pleural pain.

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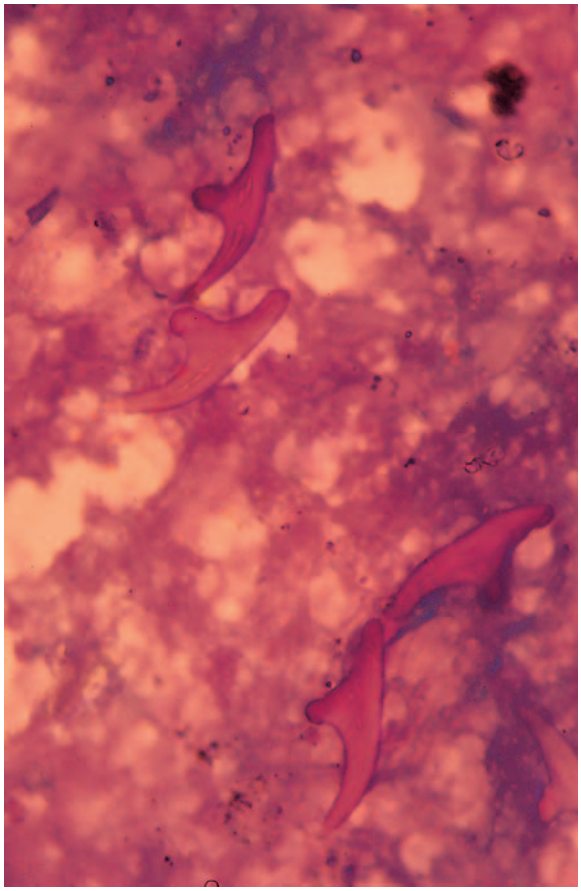

Fig. 18.**44** Expectorated scolices in the sputum in a 45-year-old woman.

Diagnosis. Consistent with echinococcosis are: eosinophilia (in 20–25%) and positive indirect immunofluorescence tests. If a rounded, air-filled space appears after expectoration of the content of a cyst, echinococcosis is likely. Secondary to cyst rupture, a severe anaphylactic reaction may occur with pronounced blood eosinophilia (caution: this risk is also associated with puncture!). The diagnosis of echinococcosis is confirmed by the identification of scolices with two rows of hooks in the sputum (Fig. 18.**44**), but this is rarely successful.

Depending on the findings in the chest radiograph, the differential diagnosis includes *benign tumors* and *lung cancer* or *metastasis*. If the lesions are calcified, tuberculosis should also be considered.

Pulmonary Nodules of Various Etiology

Interlobar effusion, in particular situated between the middle and upper or lower lobe (see Fig. 18.**19**), and *intrapulmonary hematomas* may also appear as pulmonary nodules. These are termed *vanishing tumors* or *phantom tumors* since they disappear with treatment. Rarely, a pulmonary nodule is caused by inhalation of oily nose drops (*lipoid pneumonia*) or by *amyloidosis*. Malformations may also occur as nodules. *Bronchogenic cysts*, *lung sequestration*, *arteriovenous malformations*, and *varicosis of pulmonary veins* are other causes of nodular opacities in the chest radiograph.

Multiple Pulmonary Nodules

The etiology of multiple pulmonary nodules is similar to those of solitary pulmonary nodules with exception of bronchial cancer, which is rarely multicentric. The differential diagnosis includes *malignancies*, i. e., metastases, *infectious diseases* (tuberculoma, septic metastasis *Staphylococcus* infection, echinococcosis, histoplasmosis), *immunologic diseases* (Wegener granulomatosis, chronic polyarthritis, sarcoidosis), *pneumoconiosis* (silicosis), and malformations (bronchogenic cysts, arteriovenous malformations).

Metastasis

Multiple noncalcified pulmonary nodules are likely to be metastases of a neoplasm (Fig. 18.**45**). The predominant symptoms are usually determined by the primary tumor and not by the pulmonary metastasis. Metastasis of the lungs are common in:

- colon and gastric cancer
- renal cell cancer
- cancer of the testis
- sarcoma
- breast cancer
- prostatic cancer
- thyroid cancer
- pancreatic cancer.

Wegener Granulomatosis

In Wegener disease there are necrotizing granuloma of the upper respiratory tract (90% of patients), usually multiple pulmonary nodules (in 90% of patients), which are up to 9 cm in diameter with central necrosis, and renal symptoms (in 80% of patients). Lung diseases due to Wegener disease may present clinically as pneumonia (Fig. 18.**46**). Fever is common.

The *diagnosis* is confirmed by circulating c-ANCA (sensitivity 96%; specifity > 90% in active disease) and biopsy of affected organs (nasal mucosa), which shows necrotizing granuloma and inflammation of small vessels (arteries, veins, capillaries).

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Fig. 18.**45** Multiple pulmonary metastasis of a renal cancer in a 54-year-old man.

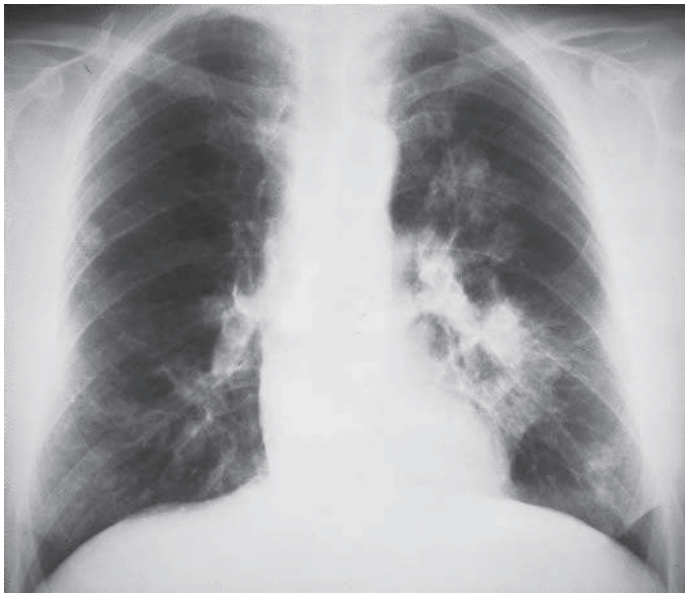

Fig. 18.**46** Wegener granulomatosis with multiple ill-defined nodules in the left lung and a solitary nodule on the right in a 63-year-old man.

Other Pulmonary Granulomatosis

In addition to the classical Wegener granulomatosis, there are four other types of granulomatosis:

- The limited form of Wegner disease that is not associated with upper airway disease or with focal glomerulonephritis.
- Lymphomatoid granulomatosis, a T-cell lymphoma, is characterized by pronounced lymphoreticular proliferation in the lungs, kidneys, skin, and central nervous system.
- Necrotizing sarcoidlike granulomatosis and bronchocentric granulomatosis affect only the lungs.
- Bronchocentric granulomatosis is associated with allergic bronchopulmonary aspergillosis.

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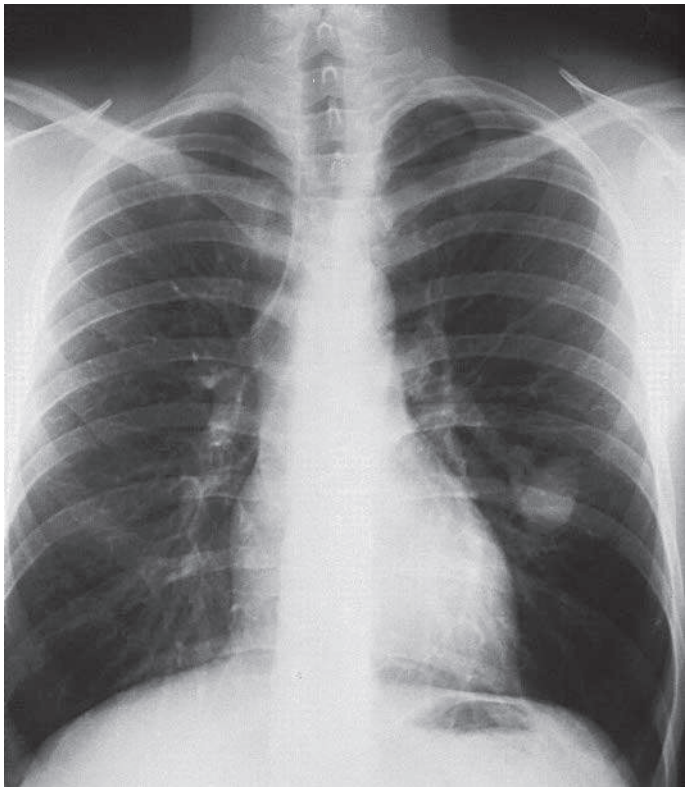

Fig. 18.**47** Solitary arteriovenous aneurysm in the left lung in a 20-year-old man.

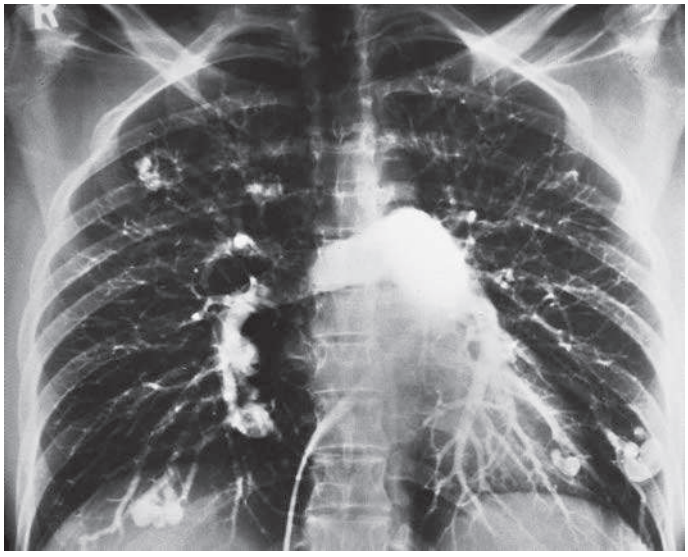

Fig. 18.**48** Multiple arteriovenous aneurysms of the lung in hereditary teleangiectasis (Rendu–Osler–Weber disease). The pulmonary angiogram confirms that the nodules are aneurysms in a 27-year-old woman.

Arteriovenous Aneurysms

Arteriovenous (AV) aneurysms are rare causes of pulmonary nodules. The main symptoms are cyanosis, polyglobulia, clubbing, dyspnea, and hemoptysis. The degree of cyanosis depends on the amount of hypoxemia, i. e., the fraction of right–left shunt, which is determined by the size and number of AV aneurysms. They may present radiologically as individual nodules (Fig. 18.**47**) or as multiple fine alterations. In general, high-resolution CT scans or, in certain cases, angiography is diagnostic (Fig. 18.**48**). Angiography may allow the occlusion of aneurysms by insertion of coils or particles.

In about one-third of patients with pulmonary arteriovenous (AV) aneurysms there are AV malformations in other organs. They also suffer from *hereditary teleangiectasis* (Rendu–Osler–Weber disease). Conversely, only 20% of patients with Rendu–Osler–Weber disease have pulmonary aneurysms. Notorious complications include hemoptysis, stroke, and brain abscess.

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18.6 Cavernous and Cystic Lung Diseases

Definition. A *cavernous lesion* usually results from central necrosis of a pulmonary infiltrate or nodule. The necrotic debris is expectorated. A *cyst* or *bulla* is an air-filled, thin-walled, nonvascularized cavity, which may be congenital or acquired.

Pathogenesis. Cavernous lesions may be solitary or multiple. The solitary lesions may represent cavernous tuberculosis (see Fig. 18.**8**), necrotizing bronchial cancer (there is cavity formation in 2–10% bronchial cancers), or a nonspecific, nontuberculous pulmonary abscess (see Fig. 18.**5**). Multiple cavernous lesions may be due to septic emboli with abscess formation, Wegener disease, or metastasis of a neoplasm (about 4% of pulmonary metastases have central necrosis).

Clinical Features. Cystic lesions may also correspond to bronchogenic cysts or cystic bronchiectasis. Multiple cysts are present in the honeycomb lung which is the end stage of various lung diseases. Emphysematous bullae, an inactive pulmonary abscess, or tuberculosis, as well as *Echinococcus* may also appear as cysts if the content of the lesion has been expectorated. The distinction between a cavitary lesion and a cyst may be difficult or impossible, particularly if the lesion corresponds to a late stage tuberculous cavitary lesion.

Tuberculous Cavitary Lesion

See p. 531.

Pulmonary Abscess

Etiology. Abscess formation may occur as a complication of pneumonia or may be due to hematogenic spread of an infection at another primary location. Principally, abscess formation may occur in any pneumonia but the incidence differs according to the microorganism. Typically, cavitation occurs in aspiration pneumonia due to anaerobic bacteria. These abscesses are nearly always solitary. Abscesses due to hematogeneous spread are multiple and bilateral. Typically multiple abscesses are observed in right-sided endocarditis with *Staphylococcus aureus*.

Clinical Presentation. A *solitary pulmonary abscess* occurs with *cough* and *sputum*, which may have a foul smell. Body temperature is only slightly elevated. The laboratory signs of inflammation are not different than in other infections. The sputum Gram stain reveals multiple Gram-positive and Gram-negative rods and cocci.

Patients with a *hematogenic pulmonary abscess* complain of pleural pain or may not have pulmonary symptoms. They have fever associated with the systemic inflammation, chills, and, in tricuspid endocarditis, they may have abdominal pain and edema of the lower extremities due to the elevated central venous pressure.

Diagnosis. The physical signs are not pronounced. The diagnosis is based on the clinical presentation and the radiograph. In multiple septic pulmonary abscesses the blood cultures may be positive.

The *chest radiograph* shows a cavity with a central hypodense area, thick walls, and an air–fluid level (see Fig. 18.**5**). Hematogenic lung abscesses rarely have an air–fluid level.

Differential Diagnosis. A pulmonary abscess can be differentiated from a *tuberculous cavitary lesion* by the identification of microorganisms. In contrast to an abscess, the tuberculous cavitary lesion has a thicker wall and no air–fluid level. Other differential diagnoses include: bronchial cancer, in particular squamous-cell cancer, aspergilloma, a bronchopulmonary sequestration, an infected emphysematous bulla, and a bronchogenic cyst that communicates with the bronchial tree through a fistula.

Pulmonary Abscess Due to Aspiration

(See also Aspiration Pneumonia p. 528.)

Typical risks for aspiration of saliva or oral and gastric content with ensuing pulmonary abscess are disturbances of swallowing, such as those occuring in neurologic disease, alcohol intoxication, disturbed consciousness, and epileptic seizure. Commonly prominent paradontosis is found. A foreign-body aspiration should also be considered.

> The localization of these abscesses is characteristic. If the aspiration occurs in supine position, the abscess forms in the posterior segments of the upper and the apical segments of the lower lobes; if the aspiration occurs in the sitting position, the abscess forms in the basal segments of the lower lobe.

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The organisms causing the abscess belong to the normal flora. of the oral cavity: Gram-negative bacilli such as *Bacteroides fragilis*, *B. oralis*, *B. corrodens*, and *B. melaninogenicus* and *Fusobacterium nucleatum*; Gram-positive cocci such as peptostreptococci or peptococci and Gram-positive bacilli such as *Propioni bacterium* species, or *Eubacterium* species.

Pulmonary Abscess Formation as a Complication of Bacterial Pneumonia

This is common in *Staphylococcus* and anaerobic pneumonia but relatively rare in pneumococcal pneumonia.

Metastatic Lung Abscess

Multiple abscesses due to hematogeneous spread are typical. Examples are metastatic abscesses in infected lower extremity, thrombosis, and right-sided (tricuspid valve) endocarditis.

Amoebic Abscess. A special form of lung abscess is the amoebic abscess. It is located in 95% of the cases in the right lower and middle lobe and develops by penetration of a liver abscess due to *Entamoeba histolytica* into the pleural cavity and lungs.

The diagnosis may be made by microscopic identification of the trophozoites or cysts. If there is a fistula to the liver abscess the patient expectorates brownish material.

Lung Cysts

Uncomplicated solitary or multiple cysts are generally asymptomatic and detected during a routine examination. They are very thin-walled and have no perifocal infiltrate. If a cyst forms after an infection it is described as a *pneumatocele*.

It is important to consider the rare bronchogenic cyst in the differential diagnosis. It is located adjacent to the hilum. Complications include superinfection.

Cavernous and Cystic Lesions of Various Etiologies

The following etiologies of cavernous and cystic lesions have to be considered in the differential diagnosis:

- bronchiectasis
- pulmonary sequestration
- echinococcosis with hydatid cyst
- actinomycosis
- nocardiosis
- endemic fungus diseases (histoplasmosis, coccidioidomycosis, cryptococcosis)
- opportunistic fungal infection (invasive aspergillosis)
- Wegener granulomatosis
- chronic polyarthritis (necrobiotic rheumatoid nodule)
- rarely: sarcoidosis, Hodgkin and non-Hodgkin lymphoma, hematogeneous metastasis.

Cysts may also appear as a consequence of thorax trauma or ARDS. These *cysts* are thin-walled and may be termed pneumatocele.

Aspergilloma. In cavitary lesions *Aspergillus* colonies may grow and form a fungus ball (aspergilloma), which consists of fungal mycelia, cellular debris, fibrin, and mucus.

The radiologic appearance is typical (see Fig. 18.**16**): within a cavity, located mostly in the upper lobes, there is a rounded opacity surrounded in the upper aspect by air. Aspergilloma are often found by chance, since they are asymptomatic. A dangerous complication is hemoptysis due to rupture of a vessel in the wall of the cavity containing the aspergilloma. The diagnosis of aspergilloma is made by CT. The identification of fungi in the sputum or serologically is not diagnostic in this context.

18.7 Atelectasis

Atelectasis is defined as lung parenchyma not containing air. Atelectasis may be classified according to the location and pathogenesis.

Pathogenesis. If resorption of air from lung parenchyma takes place distal to an obstruction, the atelectasis is termed *obstructive*. The rate of absorption depends on the amount of collateral ventilation. The obstruction of a lobar bronchus is more likely to result in atelectasis than that of a segmental bronchus since lung segments have more collateral ventilation than lobes. Nonobstructive atelectasis may occur in pneumothorax, effusion, compression (tumor), loss of structural stability due to lack of surfactant (preterm birth, ARDS), and scarring with retraction. A special form is the rounded atelectasis, which is observed after asbestos exposure.

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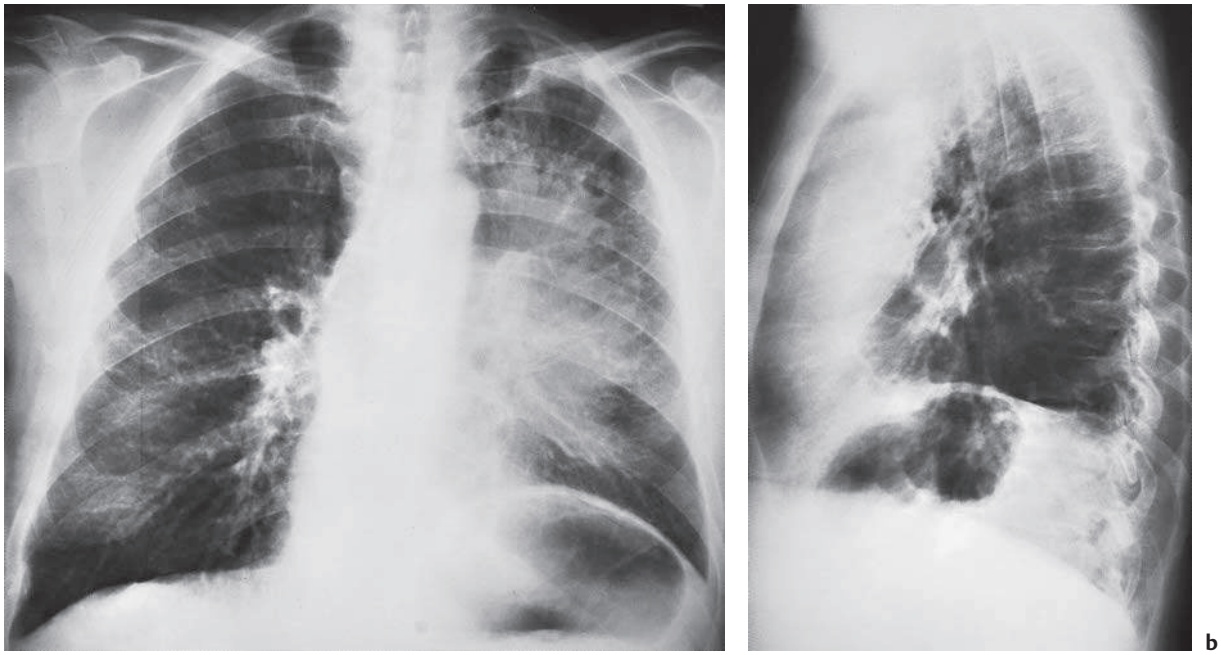

Fig. 18.**49** Left upper lobe atelectasis due to a central bronchial cancer. Elevated diaphragm on the left. 70-year-old man.
a In the PA radiograph, the left cardiac border is not clearly delineated (positive silhouette sign).
b In the lateral view, the lobar boundary is displaced ventrally. No air bronchogram.

Obstructive atelectasis may be due to:
- Bronchial tumors (most commonly bronchial cancer [Figs. 18.**49**, 18.**50**], carcinoid tumor [p. 569]). The symptoms associated with atelectasis are generally not caused by the atelectasis but by the underlying disease such as bronchial cancer. They may consist of cough or hemoptysis.
- Obstruction of a bronchus by mucus, i. e., mucoid impaction (p. 546).
- Obstruction of a bronchus by a foreign body. This should always be considered, in particular in children and elderly persons. As the aspirated material is often not radioopaque, the foreign body may not be detected in the chest radiograph. Foreign bodies are more often aspirated into the right- than into the left-sided bronchi.

Non-obstructive atelectasis is caused by:
- Loss of contact among visceral and parietal pleura, such as in pleural effusion or pneumothorax.
- Compression atelectasis is usually not a major diagnostic problem since the clinical presentation is dominated by underlying disease (pleural effusion, mass).
- Loss of alveolar stability. This may occur in premature neonates due to lack of surfactant or in ARDS.
- Scarring.

The most common atelectasis are plate-like atelectasis. They may occur as a consequence of
- reduced diaphragmatic motility, in particular after upper abdominal surgery
- pulmonary embolism.

Rounded atelectasis are a special type of atelectasis with a rounded appearance, often in contact to the visecral pleura and with a tail. They may occur in subjects exposed to asbestos.

Diagnosis. *Physical examination* allows detection of relatively large atelectases.

Radiologically, the extent of atelectasis (e. g., upper lobe collapse) and the potential causes (lung cancer) are analyzed. The most important radiologic characteristics are:
- localized opacity
- displacement of a fissure
- volume loss.

Additional signs are:
- elevation of the diaphragm
- displacement of the mediastinum including the trachea
- displacement of the hilum
- reduced intercostal space
- absence of air bronchograms.

Assessment of atelectasis requires detailed anatomic knowledge. Massive atelectasis appears as homogeneous opacities that can not be differentiated radiologically from other causes.

Microatelectasis may cause ventilation–perfusion inhomogeneity with disturbance of gas exchange but may not be visible in the radiograph.

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Fig. 18.**50** Atelectasis of the right upper lobe due to a central bronchial cancer. The fissure between the middle and upper lobe is displaced apically. No air bronchogramm, seen in a 69-year-old man.

Fig. 18.**51** Platelike atelectasis in the left and right lower lung fields with elevated diaphragm as seen in a 67-year-old woman.

18.8 Middle Lobe Syndrome

Definition. The middle lobe syndrome presents as recurrent illness with cough, repeated infection, and radiologically detectable infiltrates or reduced aeration of the middle lobe because of decreased collateral ventilation of this lobe.

Pathogenesis. The middle lobe accounts for about 10% of lung volume. Compared to other lobes, the middle lobe has a greater tendency for collapse. This may be explained by anatomic characteristics:

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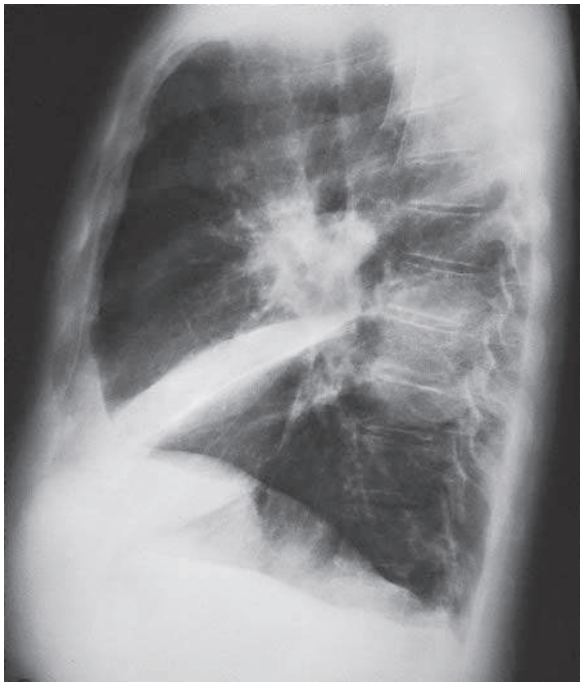
- The middle lobe has, as a rule, no collateral ventilation since it is separated from the upper and lower lobes of the right lung by a complete fissure.
- The middle lobe bronchus is relatively long and surrounded at its departure from the intermediary lobe by lymph nodes that may swell.

Causes. Opacification of the middle lobe may be due to shrinking or atelectasis (Fig. 18.**52**). Swelling of peribronchial lymph nodes due to tuberculosis is currently rare and compression of the bronchus by a tumor is more common. However, the middle lobe bronchus may also be open. There may be recurrent infection with scarring and tubular bronchiectasis, which may be seen as linear middle lobe infiltrates in the chest radiograph.

a



b

Fig. 18.**52** Middle lobe atelectasis due to bronchial cancer shown in a 66-year-old man.
a The atelectatic middle lobe blures the boundary of the heart in the PA view (positive silhouette sign).
b The lateral view confirms that there is middle lobe atelectasis.

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18.9 Opacities in the Cardiophrenic Angle

Causes. Opacities in the right-sided and left-sided cardiophrenic angles may be related to a diseased medial segment of the middle lobe, anterior segment of the left lower lobe, or inferior segment of the lingula. Linear densities should raise the suspicion of bronchiectasis. A blurred border of the left ventricle may also be due to pleuro–pericardial adhesions.

If there is a homogeneous, clearly delineated opacity, a neoplasia of the lungs, bronchi, mediastinum, pericardium, pleura, or diaphragm has to be considered and differentiated from cystic lesions, diaphragmatic hernia, or rupture.

Cysts and Hernias

Mesothelial Cyst (Pericard Cyst). These round or oval, thin-walled cysts with a size of several millimeters contain yellowish liquid. They are located in the cardiophrenic angle (mostly on the right side). The cysts are asymptomatic and detected by chance (see Fig. 19.**21**).

Hernias and Ruptures. Herniation of abdominal or retroperitoneal structures into the thorax may be congenital or result from trauma.

The most common nontraumatic hernia is the *hiatal hernia* of the esophagus. In adults, the usually asymptomatic *Bochdalek hernia*, consisting of fat tissue may be found. The opacity is situated posteromedially and should be differentiated from other paravertebral lesions. Even rarer is the *Morgagni hernia*, which is located in the retroperitoneum or parasternally and results from increased intra-abdominal pressure (abdominal obesity, trauma). This hernia may contain omentum, liver, and parts of the intestine.

Diaphragmatic Relaxation. The common but harmless *localized diaphragmatic relaxation* may mimic other diseases.

Lung Sequestration

If there is a history of recurrent bronchopulmonary infections with infiltrates in the posterobasal thorax, which occur repeatedly at the same location, then a pulmonary sequestration has to be considered. This is a malformation of the lungs resulting in a nonfunctional part of the lung. It has no connection to the bronchial tree and is fed by the systemic circulation.

There is *intralobar sequestration* (75%) in which the sequestrated lung zone is within the parenchyma of a normal lobe and not covered by pleura. In contrast, an *extralobar sequestration* (25%) has its own visceral pleura. The most important differential diagnosis is postinfectious bronchiectasis, which is also often located in the posterolateral lung zones.

The *diagnosis* of a sequestration is performed by CT, which may sometimes show the feeding vessel departing from the aorta.

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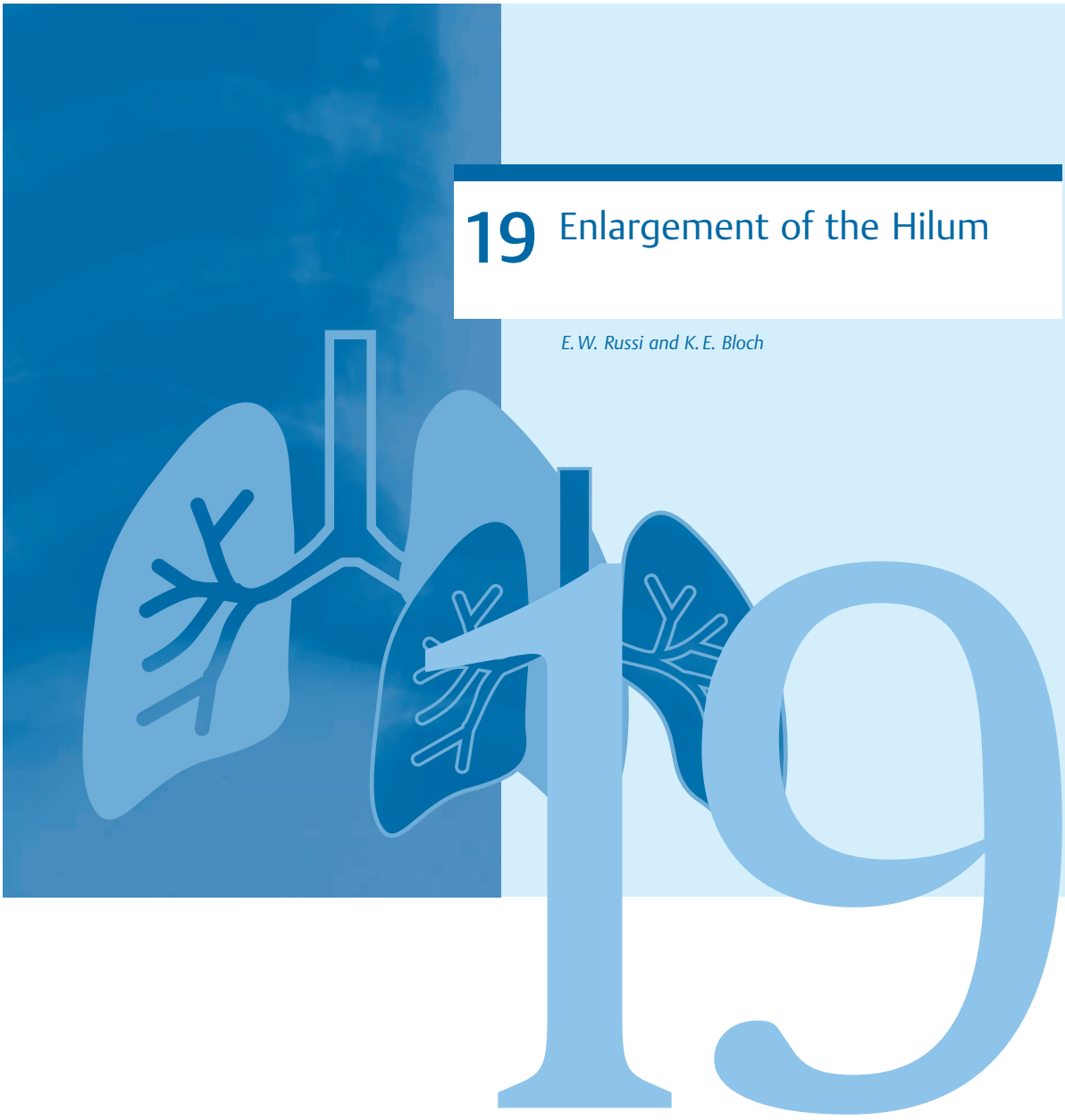

19 Enlargement of the Hilum

E. W. Russi and K. E. Bloch

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General Remarks

The hilum is formed by *lymph nodes*, *blood vessels*, and *bronchi*. Therefore, an enlargement of the hilum may be due to alterations of these structures.

Clinical Features. An enlargement of the hilum does not cause any specific symptoms and is not detectable by physical examination except when size and bulk means that percussion over the anterior chest wall becomes dull. Symptoms and signs are caused by the underlying disease (e. g., infection, lung cancer, vascular abnormalities). If enlargement of the hilum is accompanied by bronchial obstruction or infiltration of the lung, auscultation may become abnormal: *bronchial breath sounds*, *adventitious discontinuous sounds* (*rales*) over the involved region of the lung, *abnormal cardiac* or *vascular sounds*. Eventually, extrathoracic lymph nodes, which are enlarged due to the underlying disease, may become palpable.

Diagnosis. An enlargement of the hilum is diagnosed *radiologically* and additional *differentiation* is often possible considering clinical findings (Tab. 19.**1**). It is frequently difficult to decide, based on a plain chest radiograph, if the hilum has a normal configuration. The right hilum is usually more prominent then the left hilum, which is partly obliterated by the heart. *Computed tomography* (CT), with intravenous contrast, is the most appropriate method for assessing hilar structures.

Differential Diagnosis. It may be useful to distinguish between *unilateral* and *bilateral* hilar pathology, although various diseases may cause both.

Table 19.**1** Differential diagnosis of the most common causes of hilar enlargement

	Sarcoidosis	Tuberculosis	Hodgkin lymphoma	Non-Hodgkin lymphoma
Age	young age	young age	young age	any age
Hilar adenopathy	symmetrical	asymmetrical	asymmetrical	asymmetrical
Involvement of the lung	diffuse, small infiltrates	occasionally, circumscribed	15–40 %, coarse infiltrates, nodules	up to 50 %
Involvement of the mediastinum	frequent	rare	frequent (up to 61 %)	frequent
Fever	rare (only in Löfgren syndrome)	subfebrile	subfebrile to high fever (Pel–Ebstein)	occasionally
General symptoms	minor	minor	minor up to severe	may vary
Other lymph nodes	28–73 %	rare	30–50 %	95 %
Splenomegaly	10–18 %	rare	12–48 %	30 %
Blood sedimentation rate	normal or moderately elevated (in Löfgren syndrome)	normal or moderately elevated	moderately to markedly elevated	moderately to markedly elevated
C-reactive protein (CRP)	normal	elevated	normal	normal
Blood smear	normal or leukopenia	normal or left–shift, monocytosis	lymphopenia eosinophilia	not characteristic
Tuberculin skin test	negative, rarely positive	strikingly positive	usually positive (healed tuberculosis), later negative due to impaired cellular immunity	

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19.1 Bilateral Hilar Enlargement

Pulmonary Congestion

Hilar congestion (Fig. 19.**1**) is due to dilated pulmonary veins, which branch out from the hilum to the periphery of the lung. The boundaries between hilar structures and lung parenchyma are blurred and help to rule out a tumor as underlying pathology. The density decreases toward the periphery of the lung and both sides are equally involved. Hilar congestion normally accompanies pulmonary congestion, which can be detected during *auscultation* by fine endinspiratory rales over both lungs, preferentially over the basal regions. The diagnosis is supported if other features of heart disease are present: symptoms of heart failure, dilatation and abnormal configuration of the heart silhouette, abnormal findings on auscultation such as a third or fourth heart sound (gallop).

Etiology. Pulmonary congestion is due to *left ventricular failure* caused by hypertensive or ischemic heart disease, cardiomyopathy, or aortic or mitral valve disease. Rarer causes for pulmonary venous congestions are myxoma of the left atrium or "veno-occlusive disease" of the lung.

Hilar Enlargement Caused by Dilated Pulmonary Arteries

(see also Congenital Heart Diseases, Chapter 21)

An enlargement of the hilum with distinct contours caused by dilated pulmonary arteries may be observed:

- in heart diseases with an increased pulmonary flow due to a left–right shunt (atrial septal defect, ventricular septal defect)
- elevated pulmonary pressure (pulmonary hypertension; Fig. 19.**2**)
- Eisenmenger complex (Chapter 29; see Fig. 20.**19**)
- aneurysm of the pulmonary artery.

The likelihood for the presence of a congenital heart disease as the pertinent pathology decreases with advanced age.

Sarcoidosis (Boeck Disease)

Bilateral hilar lymph node enlargement in an asymptomatic person is suggestive for sarcoidosis.

Fig. 19.**1** Bilateral congested hila due to mitral stenosis and regurgitation. The lung vessels are prominent in the upper lung fields, a phenomenon called "redistribution." Shown here in a 65-year-old woman.

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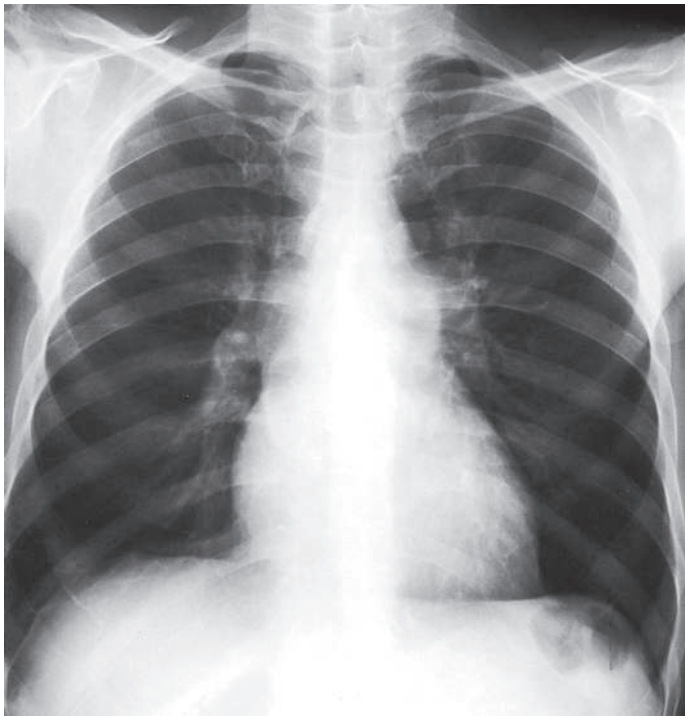

Fig. 19.**2** Primary pulmonary hypertension. Both hila are enlarged due to dilated branches of the pulmonary artery (diameter of the right descending pulmonary artery: > 16 mm). Hyperlucent lung field and pruning of the vessels. Shown here in a 54-year-old man.

The most common cause for bilateral hilar enlargement in an asymptomatic person (incidental radiologic finding) is sarcoidosis.

Etiology. The etiology of sarcoidosis remains enigmatic. In former years it was speculated that sarcoidosis might be due to a particular immune response in certain patients suffering from tuberculosis or be caused by inhaled particles such as pine pollens. Inhalational exposure to beryllium may cause a disease that is indistinguishable from sarcoidosis. Currently, sarcoidosis is assumed to be due to a local excess of *hyperreactive T-helper lymphocytes*. However, the responsible stimuli are unknown and it remains unresolved if viruses (e. g., Epstein–Barr virus, herpes simplex virus, or Cytomegalovirus) play a role in the pathogenesis of the disease. Since sarcoidosis may cluster in families and has a higher prevalence in Black populations, as well as in persons with certain HLA types, it is assumed that genetic factors may play a role.

Pathogenesis. Sarcoidosis is characterized by an *immunlogic imbalance*.

In the lung, macrophages and preferentially CD4-positive T-helper lymphocytes are activated. These cells secrete interferon-γ, interleukin-2 (IL-2) and other cytokines that stimulate the proliferation of T cells. The macrophages produce tumor necrosis factor-α, IL-12, IL-15, and growth factors. The ratio between alveolar T_4/T_8 lymphocytes is increased. In bronchoalveolar lavage fluid this ratio is > 3.5 instead of about 2. An increased number of activated T lymphocytes stimulate the resident B cells, which boost their antibody production, resulting in hypergammaglobulinemia, a characteristic feature of sarcoidosis.

In contrast to the high immunologic pulmonary activity, blood lymphocyte numbers are decreased due to a diminished number of circulating T lymphocytes. These lymphocytes are less cytotoxic and the production of IL-1 and IL-2 is markedly reduced. As a consequence, cutaneous anergy develops, which is due to a decreased T-cell immune response (negative tuberculin reaction!)

Diagnosis. Typical *radiologic* features of sarcoidosis consist of a symmetric polycyclic enlargement of the hilar lymph nodes (Fig. 19.**3**). Additional butterfly-like subtle infiltrates in the middle fields of the lung are suggestive of sarcoidosis of the lungs (Fig. 19.**4**). These bilateral spotty infiltrates must be distinguished from nodular infiltrates caused by miliary tuberculosis (see Fig. 18.**9**) or silicosis (see Fig. 18.**30**).

In 75–90% of patients with sarcoidosis enlarged bilateral hilar lymph nodes are found, which are associated in about half of the cases by a radiologic involvement of the lung. In this group the probability of a complete radiologic remission is about 70–80%, although the enlargement of the hilum may remain unchanged for up to 15 years. In 16–25% of patients only the lung is involved and the hilum appears normal. If the pulmonary involvement persists for two years or more, remission of the disease is unlikely. In approximately 20% of patients pulmonary fibrosis develops (Fig. 19.**5**) and characteristically involves both upper lung lobes in a prominent manner.

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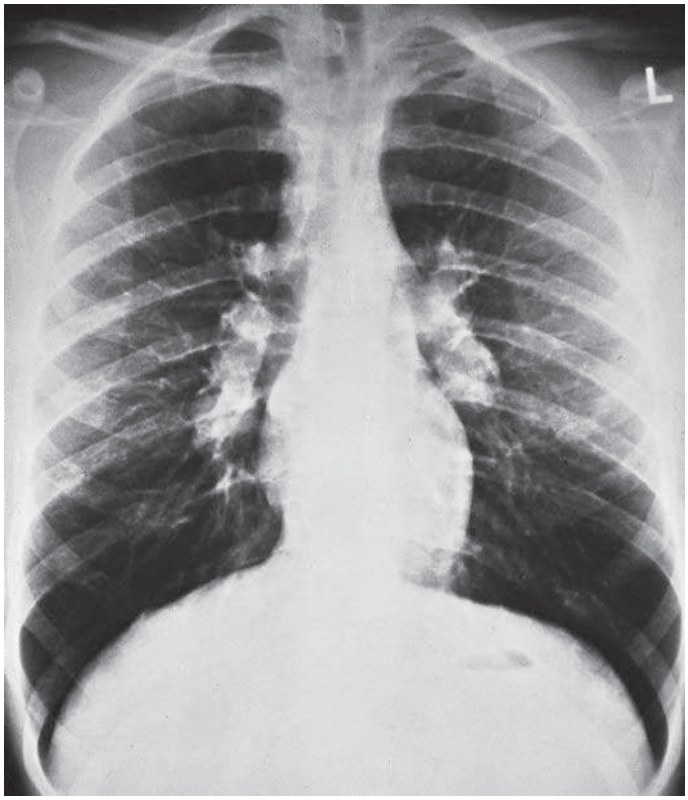

Fig. 19.**3** Sarcoidosis, stage I. Both hilar lymph nodes are noticeably enlarged. The lung structure appears normal.

Stages of Pulmonary Sarcoidosis

In *pulmonary sarcoidosis* various stages may be distinguished based on a chest radiograph. However, these stages do not necessarily reflect the pathophysiologic evolution of this systemic disease. Pathologic findings, pulmonary function tests, as well as bronchoalveolar cytology show that the lung and other organs are often already involved at an early disease stage, even if the chest radiograph is normal. Pulmonary sarcoidosis starts as a diffuse alveolitis characterized by an increased number of T-helper lymphocytes in the bronchoalveolar lavage fluid. Therefore, the classification according to radiologic stages is problematic.

Classification according to Wurm (1958) and Siltzbach (1974):

- (Stage 0: normal hilum and lungs)
- Stage I: enlarged hilar and mediastinal lymph nodes, normal lungs
- Stage II: enlarged lymph nodes and abnormal lungs
- Stage III: pulmonary fibrosis.

Classification according to Scadding (1967):

- (Group 0: normal hilum and lungs)
- Group I: enlarged hilar and mediastinal lymph nodes, normal lungs
- Group II: enlarged lymph nodes and abnormal lungs
- Group III: normal lymph nodes, abnormal lungs
- Group IV: pulmonary fibrosis (involvement of the lung > 2 years).

The *histology* of sarcoidosis is characterized by granulomas composed of epitheloid and giant cells, caseating necrosis is absent but necrosis without caseation may occur. The granulomas are not pathognomonic and may also be found as "sarcoidlike lesions" in patients with Hodgkin disease or in lymph nodes harboring tumor metastases, involved by chronic inflammation (e. g., tuberculosis, syphillis, fungal diseases, berylliosis, allergic alveolitis, cat scratch disease, primary biliary cirrhosis, ulcerative colitis, Crohn disease, infectious hepatitis, granulomatous vasculitis or lymphomatoid granulomatosis), and as a manifestation of foreign-body reaction.

Clinical Features. Sarcoidosis may manifest acutely (Löfgren syndrome), in a subacute manner, or insidiously, and may run a chronic course. In chronic courses, episodes of enhanced disease activity may occur. About one-half of the patients with sarcoidosis have no symptoms at the time of diagnosis. Patients presenting clinically with radiological stage I, but without Löfgren syndrome (see below), are asymptomatic and the sarcoidosis most commonly detected by chance on a chest radiograph.

Patients remain frequently asymptomatic even if the lung parenchyma is involved and only 20–30 % of patients complain of unproductive cough and shortness of breath, the typical symptoms of pulmonary fibrosis.

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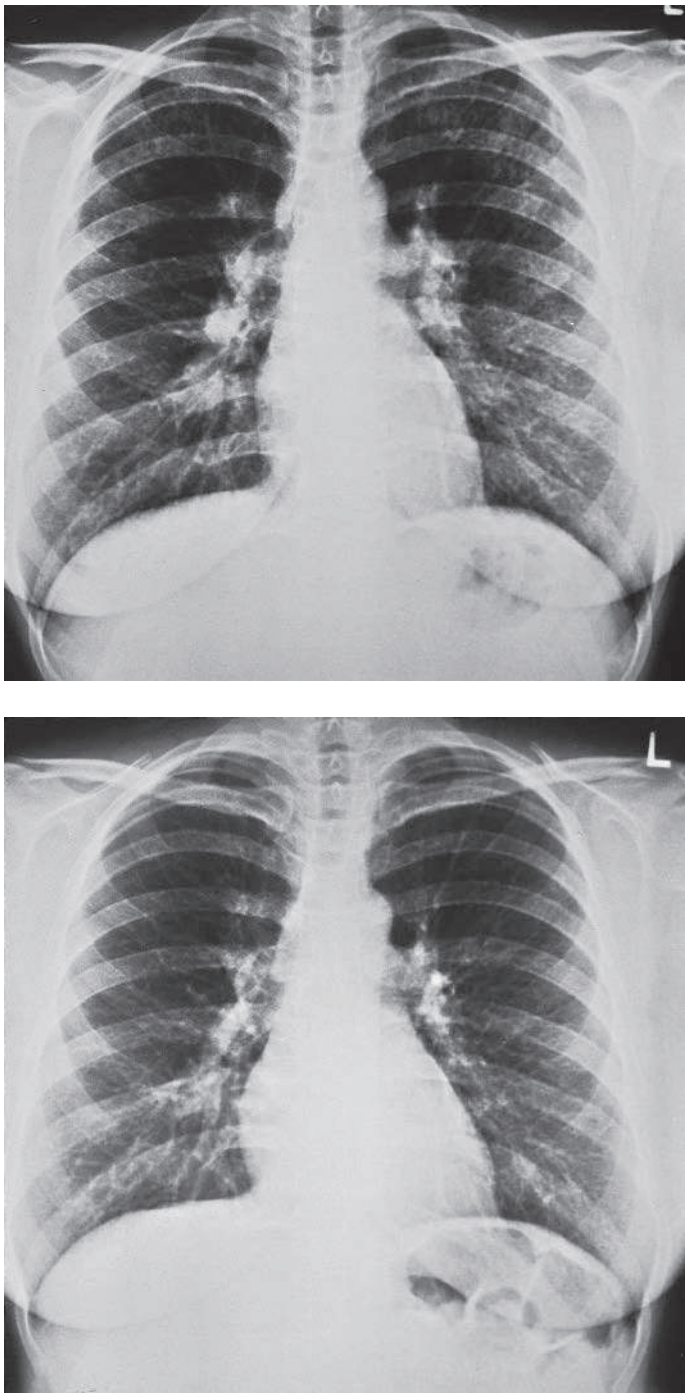

Fig. 19.**4** Stage II Sarcoidosis in a 42-year-old woman.
a Involvement of the hilar lymph nodes and the pulmonary parenchyma. Nodules (granulomas) are plainly visible in the periphery of the lung.
b After two years: resolution of the pulmonary involvement and the hilar lymph nodes without therapy.

The physical examination of the lung may be abnormal, particularly in patients with fibrotic involvement of the lung. In these cases pulmonary function is usually abnormal. Even in radiologic stage I, where the lung parenchyma appears normal, the lung diffusion capacity may be impaired. A progressive involvement of the lungs is characterized by a striking restrictive ventilatory defect. Since the inflammatory process of sarcoidosis often involves the bronchial tree, a combined obstructive–restrictive ventilatory defect is typical. In some cases, hypergammaglobulinemia and mild hypercalcemia may be found. Hypercalcinuria is common (10–60% of cases), however, nephrocalcinosis with renal failure rarely occurs.

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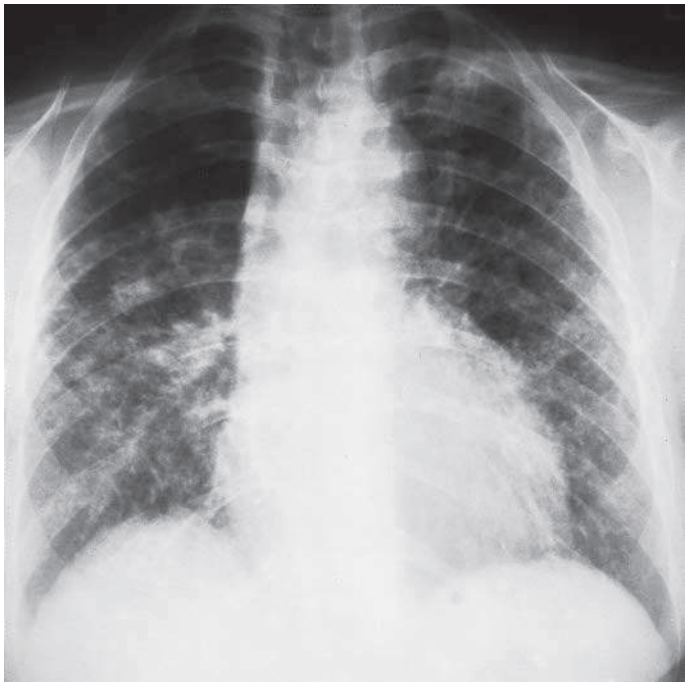

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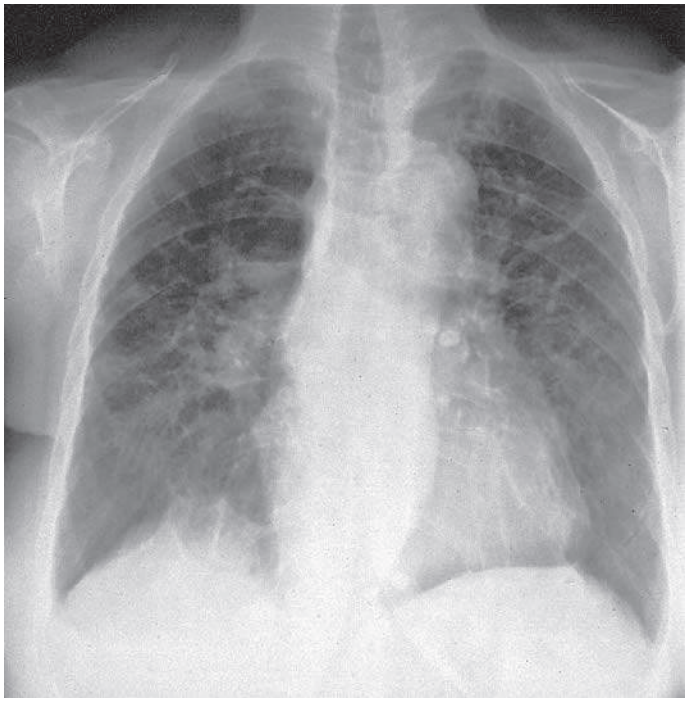

b

Fig. 19.**5** Sarcoidosis, course over 25 years in a 65-year-old woman.
a Stage III according to Scadding: involvement of the lung parenchyma without lymph node enlargement.
b Increased reticulonodular lung structure. Elevated right diaphragm due to shrinking (lung fibrosis). Calcified hilar lymph nodes.

Manifestation of Sarcoidosis in Other Organs

Sarcoidosis is a systemic disease (Fig. 19.**6**). Besides the lung, which is involved in 90% of the cases, sarcoid granulomas may be found in almost all organs: in the *liver* and *spleen* in about 70%, in the heart in up to 76%, and in the muscles in 20% of the cases.

- Involvement of the *central nervous system* (neurosarcoidosis) may cause paralysis of the nerves at the base of the brain, of the spine, and of peripheral nerves.
- I*nvolvement of the liver* is usually asymptomatic and may be accompanied by elevated liver enzymes, however portal hypertension rarely occurs.

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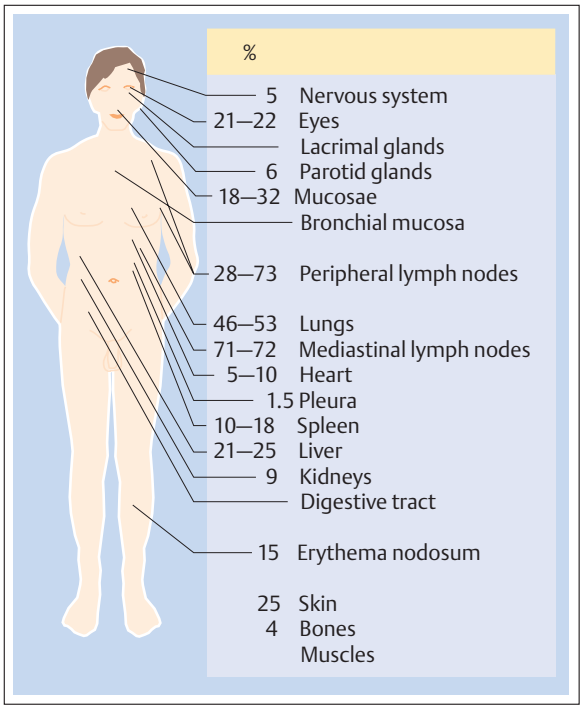

Fig. 19.**6** Organ involvement in sarcoidosis. Clinical involvement in % (according to Mayock, Silzbach, and Newman).

Fig. 19.**7** Sarcoidosis of the skin.

- *Involvement of the heart* may cause tachycardic or bradycardic rhythmic disturbances, conduction abnormalities, or eventually cardiomyopathy.
- In certain cases the *skin is involved*. A rare manifestation is the subcutaneous Darier–Roussy sarcoid (Fig. 19.**7**). Lupus pernio, a manifestation of chronic sarcoidosis, designates faint indurated plaques on the nose, cheeks, lips, and ears. In contrast, erythema nodosum is a manifestation of acute sarcoidosis (see Löfgren syndrome).
- The so-called Heerfordt syndrome or febris uveoparotidea (parotitis with facial nerve palsy and eye symptoms) suggests an involvement of these organs.
- A typical, but rare, manifestation is the so-called ostitis multiplex cystoides (Jüngling). In advanced cases, clinical examination may reveal swelling of the digits resembling "spina ventosa." The radiologic manifestation is characterized by localized cystic hyperlucencies of the bone.

Acute Sarcoidosis (Löfgren Syndrome)

Clinical Features. The acute form of sarcoidosis may manifest with fever, occasionally with high fever, and with a marked increase of the white blood cells. The erythrocyte sedimentation rate is elevated. The main symptoms consist of symmetrically swollen joints of the lower extremities and usually bilateral, rarely unilateral erythema nodosum. The bilateral hilar lymph node enlargement is obligatory (see Fig. 19.**3**) and a unilateral involvement of the hilum is rare (1–3%).

The *involvement of the joints* in sarcoidosis can manifest in various ways:

- Swelling and pain of *various joints* (arthralgias) with a duration of a few days up to two months, often accompanied by *erythema nodosum* and an *enlarged hilum*.
- *intermittent monoarticular* or *polyarticular arthritis*
- *persistent polyarticular* or rarely *monoarticular arthritis*, sometimes with deformities of the joints.

Diagnosis of Sarcoidosis

The diagnosis of sarcoidosis is based on a syndrome of well-suited symptoms, clinical and radiological findings, and the exclusion of other diseases that might occur with similar findings.

Computed Tomography (CT). Quite often a CT scan of the chest provides valuable additional information. Typical findings consist of bilaterally enlarged hilar and mediastinal lymph nodes, thickening and nodules along the bronchovascular bundle, small nodules, preferentially located in the upper lobes and along the pleura, thickened interlobular septa, and ground-glass attenuations. In advanced cases the pulmonary nodules may coalesce and parenchymal destruction, shrinking, and fibrosis occur. Conversely, the CT scan may reveal other diagnostic features such as lymph node necrosis typical for tuberculosis or infiltrative and destructive growth, a characteristic of malignancy. In cases of typical presentation, e. g., stage I characterized by asymptomatic bi-

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lateral lymph nodes or in Löfgren syndrome, histological confirmation is not mandatory.

Histology. With other presentations histological confirmation is mandatory. If lymph nodes are palpable a biopsy is straightforward. In over half of patients, transbronchial lung biopsy, in combination with biopsies of the bronchial mucosa, reveals noncaseating granuloma even in patients with radiologically normal lung parenchyma. If these examinations do not give conclusive results, surgical biopsies, i. e., by mediastinoscopy or thoracoscopy, may become necessary to make a firm diagnosis. The biopsy material should be sent for microbiological examinations to exclude an infectious etiology.

Noninvasive Tests. Noninvasive tests to support the diagnosis of sarcoidosis include *bronchoalveolar lavage* (BAL) and *gallium scintigraphy*. However, an elevated blood level of angiotensin-converting enzyme (ACE) is neither specific nor sensitive. Gallium scintigraphy, a method that is expensive and hence not routinely used, may show distinct findings consisting of tracer accumulation bilaterally in the mediastinal lymph nodes accompanied by an uptake in the parotid glands. In the BAL fluid an increase in T lymphocytes is a chracteristic finding (see above).

In former years a *negative Mantoux reaction* was considered to be of diagnostic value, but positive Mantoux reactions have been repeatedly observed in cases of histologically proven sarcoidosis. Particularly in active sarcoidosis the Mantoux test may be negative, while in chronic forms of the disease a positive reaction may be found. The Kveim reaction consists of a subcutaneous injection of sterile human spleen tissue of a person with sarcoidosis. However, since this highly sensitive and specific test is available only in a few specialized centers worldwide, it will not be discussed further.

Malignancies

Hodgkin and Non-Hodgkin Lymphomas

Hodgkin lymphoma (Fig. 19.**8**) and also non-Hodgkin lymphoma may occur with unilateral or *bilateral, but asymmetric* hilar enlargement and therefore can mimic a purely unilateral involvement on a plain chest radiograph. However, an entirely unilateral manifestation (CT scan) is rare. A diagnosis can be easily made when extrathoracic lymph nodes, accessible for biopsy, are palpable. Abnormalities of the blood are suggestive for bone marrow infiltration. Hodgkin disease is suspected if a patient suffers from intermittent fever (Pel–Ebstein; see Chapter 4), complains about itching, and if marked lymphopenia and eosinophilia are present.

> Histology is crucial for the diagnosis, classification, and prognosis of lymphoma.

If peripheral lymph nodes are not enlarged and bone marrow biopsy remains nondiagnostic, tissue for histology must be obtained by *mediastinoscopy*. A key

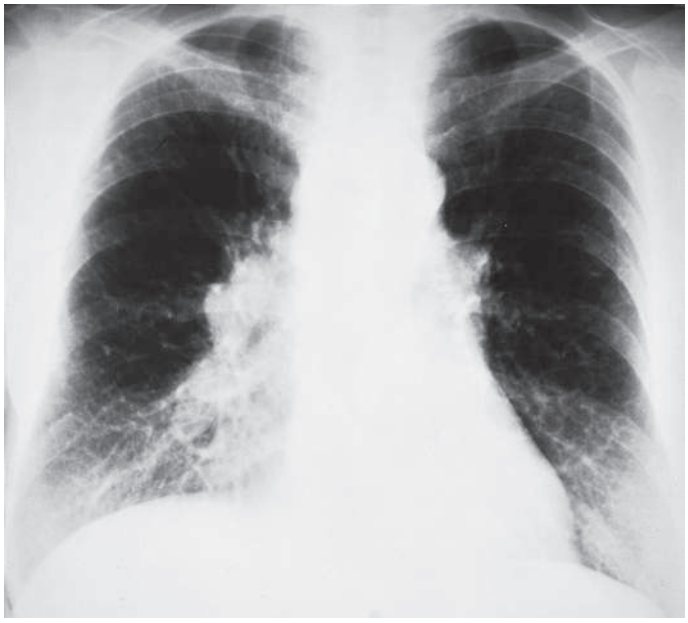

Fig. 19.**8** Hodgkin lymphoma, causing a markedly enlarged right hilum. The left hilum is also enlarged. Seen here in a 54-year-old woman.

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differential diagnosis is Castleman disease, a type of angiofollicular lymph node hyperplasia, which is a lymphoproliferative disease, which may be associated with the HIV virus and the human herpes virus 8 (HHV-8).

Leukemia

Hilar enlargement is a rarity in leukemia. The diagnosis is based on blood smears and bone marrow examination.

Hilar Lymph Node Enlargement in Other Diseases

In rare cases, particularly in younger people, enlarged hilar lymph nodes may be observed in diseases occurring with generalized lymph node swelling (mononucleosis, German measles, etc.).

19.2 Unilateral Lymph Node Enlargement

Unilateral lymph node enlargement is either caused by malignant lymphoma or even more commonly by lung cancer. Rarer causes are metastases or hilar lymph node tuberculosis.

Lung Cancer

Epidemiology. Worldwide lung cancer is the *most common cancer leading to death* in men as well as in women, and the second most common type of cancer. The most significant risk factor for lung cancer is cigarette smoking. Patients exposed to dusts and fumes (asbestos, hydrocarbons) have an additional risk.

A distinction is made between small cell lung cancer (25%) and non-small cell lung cancer (75%; squamous cell, large cell, adenocarcinoma). This distinction, based on cytological and/or histological examinations, is important for prognosis and therapy. Non-small cell lung cancer is potentially curable by surgery, if the contralateral mediastinal lymph nodes are not involved, if extrathoracic metastases are absent, and if the patient's lung function is sufficient. Small cell lung cancer causes early metastases and micrometastases, which are not detectable by existing diagnostic methods. Small cell lung cancer is treated with chemotherapy, where necessary combined with radiotherapy.

Table 19.**2** Frequency of symptoms in lung cancer (according to Hyde)

Symptoms	Initially (%)	Later (%)
Cough	29–87	48–84
Weight loss	3–69	36–42
Shortness of breath	8–58	23–42
Chest pain	30–60	28–58
Hemoptysis	6–57	9–63
Lymphadenopathy	22–23	15–20
Bone pain	7–25	–
Hepatomegaly	21–22	–
Clubbing	12–21	–
Cerebral symptoms	3–13	–
Impaired venous return	4–7	–
Hoarseness	1–18	1–4
Dysphagia	1–5	2–6
Respiratory infections	–	18–46

Prognosis. The prognosis of small cell lung cancer has changed little during the past two decades despite modern therapeutic concepts. Fewer than 15% of patients survive five years after diagnosis.

Chest Radiograph. The *radiologic* presentation of small cell lung cancer varies. Most commonly the tumor is located in the center of the lung, appears as a unilateral mass in the hilum or mediastinum, and may be accompanied by an atelectasis. A peripheral location is much less common. It either appears as solitary pulmonary nodule (< 3 cm diameter), surrounded by lung parenchyma and not abutting the pleura or the mediastinum, or as an infiltrate or a mass (> 3 cm; see Fig. 19.**9**).

> In smokers any nodule in the lung, every persisting lung infiltrate, an enlargement of the hilum, or a consolidation is suspicious for lung cancer.

An overview of the various localizations of lung cancer and common erroneous diagnoses is provided in Fig. 19.**10**.

Clinical Features. Symptoms (Tab. 19.**2**) consist of newly started and persistent (more than 6 weeks) *cough* or a change in symptoms in smokers with chronic bronchitis i. e., if the intensity or quality of the cough alters, if hemoptysis, including "minor" hemoptysis occurs, or if the patient starts to feel short of breath. The leading

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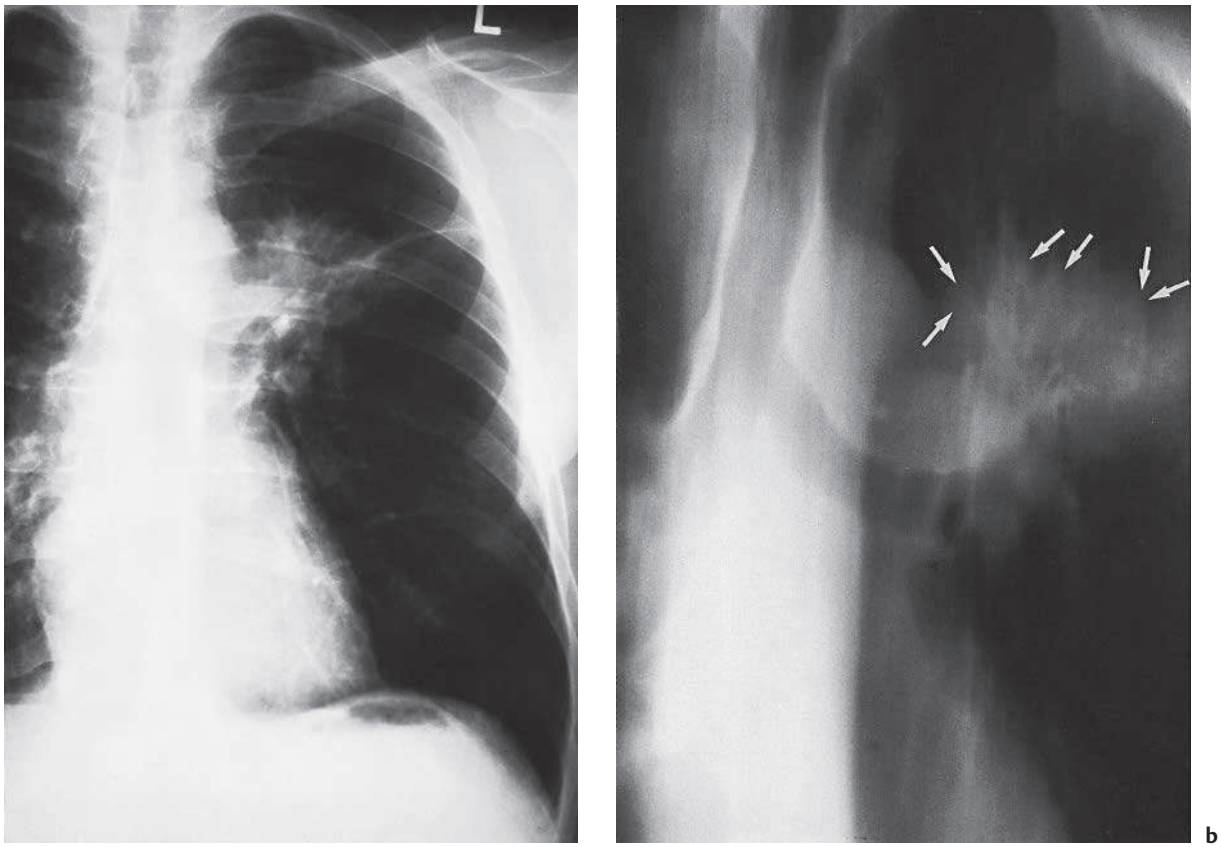

a **b**

Fig. 19.**9** Centrally located lung cancer in a 47-year-old man. **a** PA view **b** CT scan; the tumor is not sharply demarcated and seems to infiltrate the lung parenchyma.

complaints may also consist of *unspecific symptoms* such as weight loss, fatigue, local complications (e. g., pain in the chest or shoulder, impairment of the venous return, hoarseness due to recurrent nerve palsy), or symptoms due to extrathoracic metastases (e. g., enlarged lymph nodes, headache, backpain, etc). Symptoms are usually absent if the cancer occurs as a pulmonary nodule.

Diagnosis. Laboratory findings are nonspecific. Anemia, elevated alkaline phosphatase, or hypercalcemia are suspicious for metastases. In small cell lung cancer elevated lactate dehydrogenase (LDH) is suspicious for extensive metastases, particularly bone metastases. The typical presentation of small cell carcinoma consists of a bulky intrathoracic tumor whereas squamous cell carcinoma may cavitate. Typical metastases are found in the suprarenal gland, bone, brain, and liver.

In centrally localized tumors the likelihood is high that sputum cytology will reveal cancer cells. (Fig. 19.**11**). Nevertheless, bronchosopy is mandatory in most cases, particularly for staging. Flexible instruments allow a meticulous inspection under conscious sedation up to the subsegmental level. According to its localization, forceps biopsies from the tumor can be obtained under visual control or with the aid of fluoroscopy. Material for cytology is taken by brushing, washing, or transbronchial needle aspiration. In many cases

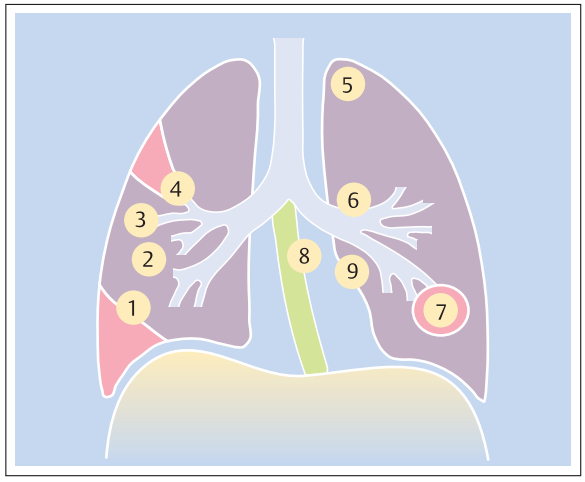

Fig. 19.**10** Various localizations of bronchial carcinomas and the characteristic misdiagnoses of lung cancer. 1. Pleural effusion (instead of peripheral lung cancer with involvement of the pleura). 2. Tuberculosis (instead of lung cancer nodule). 3. Chronic pneumonia (instead of lung cancer). 4. Atelectasis (instead of bronchial obstruction by lung cancer). 5. Neuritis (instead of Pancoast tumor). 6. Benign hilar tumor (instead of centrally located lung cancer). 7. Lung abscess (instead of necrotizing lung cancer). 8. Esophageal cancer (instead of lung cancer infiltrating the esophagus). 9. Pericarditis and myocarditis (instead of lung cancer infiltrating the pericardium and the myocardium).

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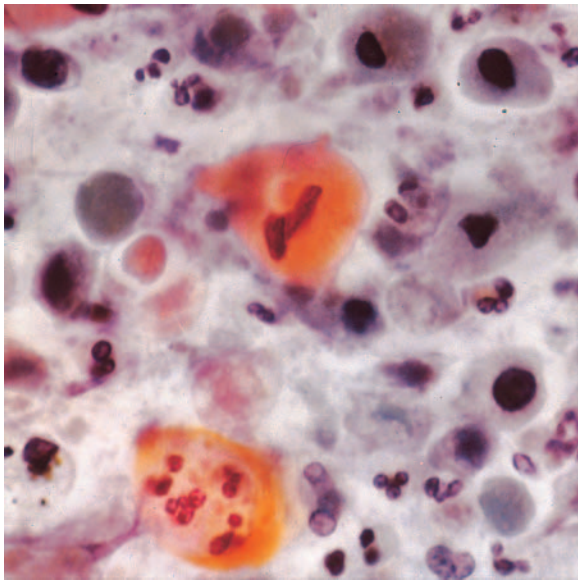

Fig. 19.**11** Sputum cancer cells: squamous lung cancer. Papanicolaou stain, magnification approximately 300x.

Fig. 19.**12** Clubbing (hypertrophic osteoarthropathy = Marie–Bamberger syndrome) in non-small cell lung cancer in a 76-year-old woman.

affected hilar or mediastinal lymph nodes may be reached by transbronchial aspiration and hence permit staging. The decision to perform needle aspiration of a peripheral pulmonary nodule for cytological diagnosis or to proceed directly to video-assisted thoracoscopic resection depends on the pretest likelihood for lung cancer and the resources of the hospital. It has to be considered that a negative needle aspiration, i. e., an aspiration not showing malignant cells, does not rule out the presence of cancer.

Histology. Histology of lung cancer shows the following distribution: squamous cell carcinoma (20–30%), adenocarcinoma (30–40%), large cell carcinoma (10%), and small cell carcinoma (20–25%). The shift in the prevalence from more centrally located squamous cell carcinomas towards peripheral adenocarcinomas is probably due to changes in cigarette smoking habits (filter cigarettes) during the past 25 years. Patients who used to be heavy cigarette smokers, to some extent also heavy drinkers, have an increased propensity to develop cancer of the upper respiratory tract (laryngeal and pharyngeal cancer) and up to 10% experience a secondary malignancy, e. g., a metasynchronous squamous cell lung cancer or a cancer of the esophagus.

Classification. The histopathologic characterization of lung cancer (grading) together with staging are the basis for therapy and prognosis (Tab. 19.**3**). Staging of lung cancer reflects the extension and eventual spread of the tumor and follows the TNM system of the International Union Against Cancer (UICC) (Tab. 19.**4**), small cell carcinoma being an exception (Tab. 19.**5**). Based on this system lung cancer is divided into stages I–IV as shown in Tab. 19.**4**.

Paraneoplastic Syndrome. Weight loss and fatigue are the most frequent paraneoplastic symptoms. Hypertrophic osteoarthropathy (Fig. 19.**12**) with clubbing is characteristic for non-small cell lung cancer. In small cell lung cancer common paraneoplastic symptoms consist of myopathy, Cushing syndrome, etc.

Carcinoid (Neuroendocrine Cancer)

Carcinoid belongs to the neuroendocrine tumors, which cover a spectrum from well-differentiated tumors with no propensity to metastasize to highly malignant small cell lung cancer. The symptoms of carcinoids are similar to the symptoms of lung cancer, since the majority arise from the main and segmental bronchi (Fig. 19.**13**). Relentless dry cough and hemoptysis are typical. Young women are more often affected than men and a diagnosis may often be made by an experienced endoscopist, based on the macroscopic aspect. Similar symptoms are caused by tumors that arise from glands of the bronchial mucosa, known as mucoepidermoid tumors, which may be benign or malignant. The most common form is adenoid cystic cancer (cylindroma), which makes up 20–30% of tracheal tumors and occurs in men and women with an equal frequency.

Benign Tumors

Benign tumors are often *asymptomatic*. On the chest radiograph they have a sharp margin and are usually detected by chance or during a check-up. These tumors

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Table 19.**3** Five-year survival based on histology and stage of the tumor 1978–1986 (according to Travis 1995)

Histology	n	All stages (%)	Local involvement (%)	Regional involvement (%)	Distant metastases (%)
All types of lung cancer	87128	13.9	39.6	14.4	1.5
Squamous cell carcinoma	26407	15.4	34.3	14.9	1.5
Adenocarcinoma	20991	16.6	49.9	16.1	1.5
Large cell carcinoma	7592	11.4	34.8	13.2	1.6
Small cell carcinoma	15656	4.6	12.3	7.5	1.4

Table 19.**4** Lung cancer stages*

Stages	
Occult cancer	T_X N0 M0
Stage 0	Tis = carcinoma in situ
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T1 N1 M0
Stage IIB	T2 N1 M0 T3 N0 M0
Stage IIIA	T3 N1 M0 T1 N2 M0 T2 N2 M0 T3 N2 M0
Stage IIIB	T4 N0 M0 T4 N1 M0 T1 N3 M0 T2 N3 M0 T3 N3 M0 T4 N3 M0
Stage IV	all T, all N, M1
Definitions	
T	**Primary tumor**
T0	no primary tumor detectable
TX	tumor detected by positive sputum cytology or positive bronchial washing
Tis	carcinoma in situ
T1	tumor with a maximal diameter of 3 cm, intrapulmonary localization
T2	tumor with a diameter > 3 cm, not less then 2 cm distal of the main carina or involving the visceral pleura, atelectasis, poststenotic pneumonia
T3	tumor > 3 cm and less then 2 cm distal of the main carina or direct involvement of the chest wall, diaphragm, mediastinal pleura, pericardium
T4	tumor of any size, infiltration the mediastinum the heart, the large vessels, the esophagus, vertebral bodies or accompanied by malignant pleural effusion
N	**Regional lymph nodes**
NX	regional lymph nodes not assessable
N0	no regional lymph node involvement
N1	peribronchial lymph node or ipsilateral hilar lymph node involved
N2	ipsilateral mediastinal lymph nodes or subcarinal lymph node involved
N3	contralateral hilar or mediastinal lymph node or ipsilateral and contralateral supraclavicular or scalenus lymph nodes involved
M	**Distant metastases**
MX	distant metastases not assessable
M0	no distant metastases
M1	distant metastases present

* Classification according to the TNM (tumor, nodes, metastases) system of the UICC, revised 1997 (Mountain).

Table 19.**5** Staging of small cell carcinoma

Limited disease
– Tumor confined to the hemithorax of origin, the mediastinum, and the supraclavicular nodes, which can be encompassed within a tolerable radiation therapy port.
– No universally accepted definition of this term is available, and patients with pleural effusion, massive pulmonary tumor, and contralateral supraclavicular nodes have been both included within and excluded from limited stage by various groups.
Extensive disease
– Tumour that is too widespread to be included within the definition of limited-stage disease above. Patients with distant metastases (M1) are always considered to have extensive-stage disease.

originate most commonly in the anterior mediastinum as teratomas (Figs. 19.**14**, Fig. 19.**20**) or from the posterior mediastinum as neurinomas of the sympathic nerve (Fig. 19.**15**). Occasionally, irregular calcifications are visible, which is characteristic of its dermoid nature.

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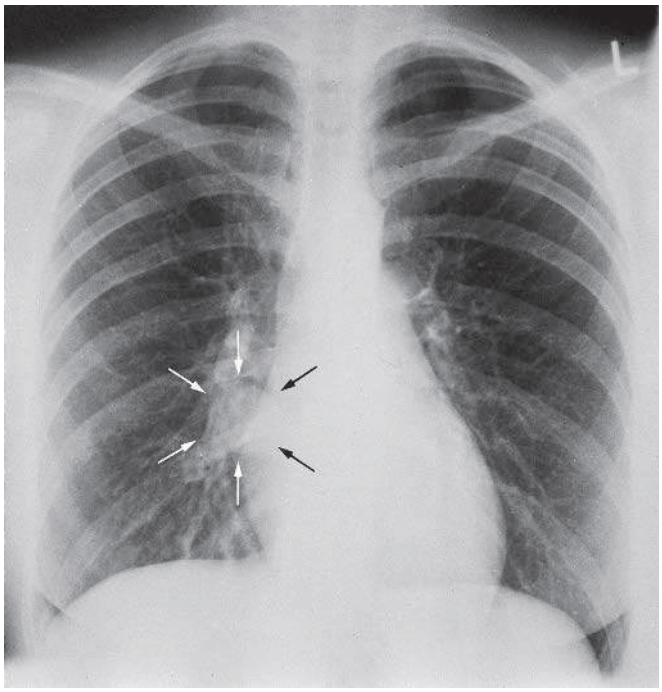

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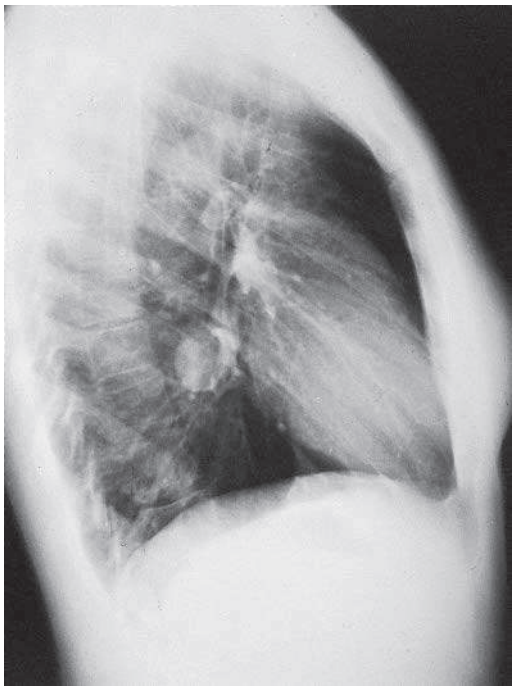

b

Fig. 19.**13** Lung cancer in a 23-year-old woman.
a The tumor is located at the lower right hilum.
b Lateral view: the tumor is clearly visible as a central rounded density.

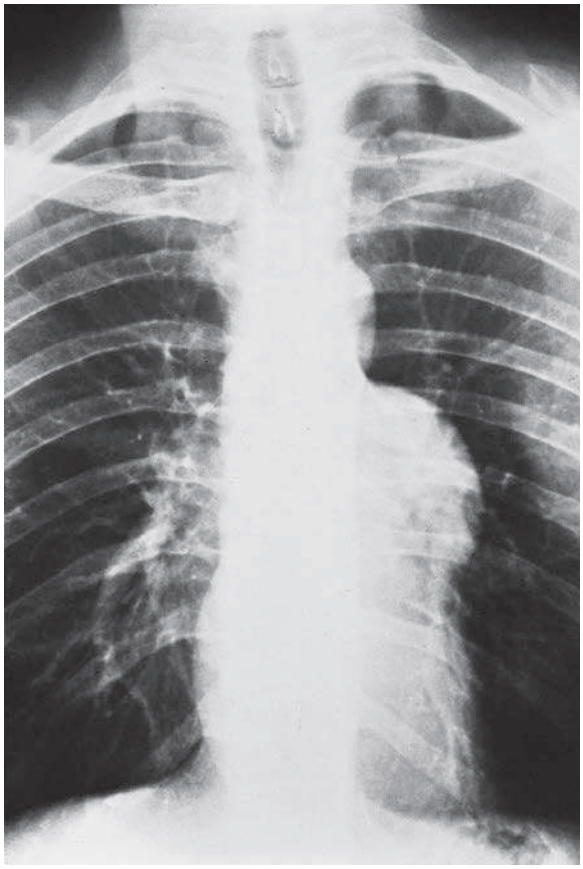

Fig. 19.**14** Dermoid cyst in the area of the right hilum in a 34-year-old man.

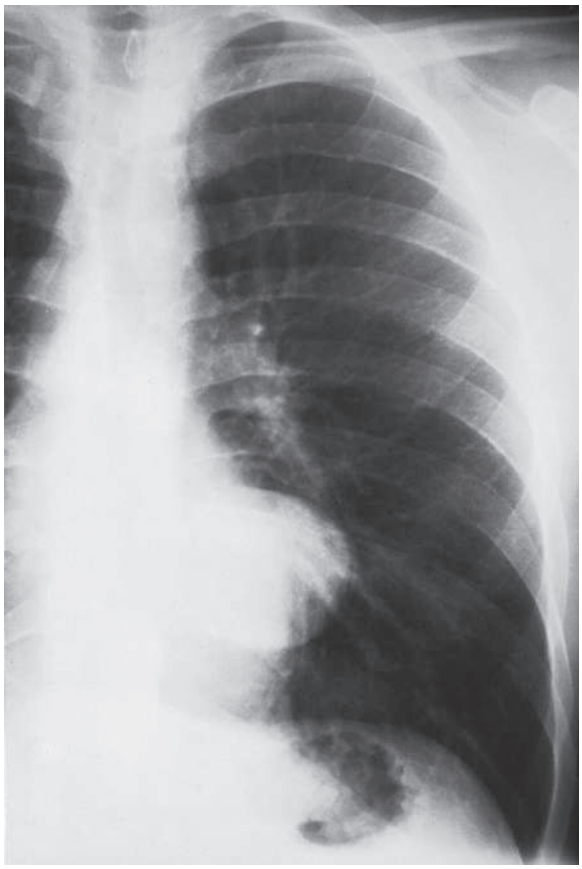

Fig. 19.**15** Neurinoma: histology after resection in a 21-year-old man.

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Fig. 19.**16** Carcinoma of the thymus. The upper and medial mediastinum are widened bilaterally and the hilar region becomes indistinct. Shown here in a 35-year-old woman.

Thymoma. It is not well known that thymomas may occur not only in the anterior mediastinum, but may also occur as hilar tumors. These may occur at any age, are more commonly unilateral but also bilateral, and have the tendency to become malignant (in approximately 25% of patients; Fig. 19.**16**). Myasthenia occurs in 10–50%, whereas a thymoma is found in only 8–10% of patients suffering from myasthenia gravis. In many patients the tumor is detected by chance; others complain of pressure in their chest, a cough, or shortness of breath. In rare cases an impairment of venous return has been reported in the literature.

Chondroma. Chondromas have a lobulated contour and are located within the lung. Echinococci are very rarely located in the hilar region.

Dermoid Cysts. Dermoid cysts (see Fig. 19.**14**) may be a challenge for differential diagnosis if no radio-opaque material (e.g., teeth) is visible and if the contour is blurred due to atelectasis and compression of the adjacent lung.

Pericardial Cysts. On the right side more commonly then on the left side, a pericardial cyst may mimic a hilar tumor. Pericardial cysts are sharply demarcated, usually located at the border of the heart, and the form may vary with respiration: it may become visible during expiration and almost completely disappear during inspiration. A CT scan allows the differentiation of cysts from blood vessels, particularly from aneurysmatic dilatations.

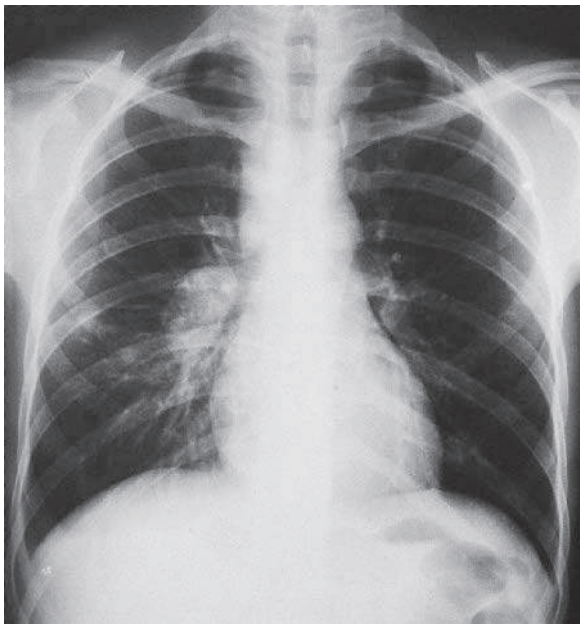

Fig. 19.**17** Hilar lymph node tuberculosis in a 30-year-old, HIV-positive man.

Hilar Lymph Node Tuberculosis

Chest Radiograph. Active hilar lymph node tuberculosis is characterized by *lobulated, sharply demarcated, hilar lymph nodes* (Fig. 19.**17**) and is usually unilateral. A

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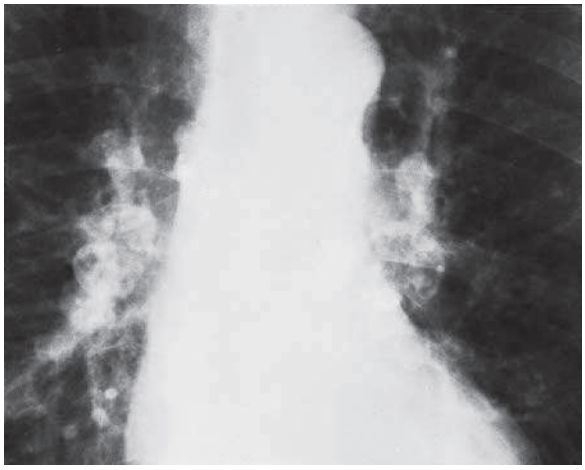

Fig. 19.**18** Calcified hilar lymph "egg shell" nodes in silicosis.

pulmonary infiltrate may be still visible. Mediastinal lymph node involvement may occur in patients with HIV infection.

Diagnosis. Mycobacteria are rarely detected in the sputum or in bronchial secretion, except when the lymph node penetrates into the bronchial tree. However, mycobacteria can be detected in lymph node puncture material microscopically, by cultures, or by polymerase chain reaction (PCR) amplification. Centrally hypodense lymph nodes seen in the CT scan are typical of tuberculosis.

Differential Diagnosis. The presence of *erythema nodosum* in patients with enlarged lymph nodes is much more common in *sarcoidosis* than in hilar lymph node tuberculosis. The *tuberculin skin test* (Mantoux reaction) is usually positive. Particular differential diagnostic problems are healed hilar tuberculosis lymph nodes. Symptoms may be absent and clinical findings are negative. In such a situation tuberculosis activity may only be judged by serial chest radiographs. Calcification is typical for tuberculosis, but may also be observed in sarcoidosis (see Fig. 19.**5b**) or *silicosis* (Fig. 19.**18**). Unilateral hilar tuberculous lymph nodes are difficult to differentiate from a unilateral hilar sarcoidosis or Hodgkin lymphoma (see Fig. 19.**8**).

19.3 Widening of the Mediastinum

The best method for a diagnostic work-up of the mediastinum is CT. A widening of the mediastinum may be caused by tumors, malformations, and by diseases of the large thoracic vessels (see Chapters 14 and 27; Fig. 19.**19**), as well as lymph node metastases in lung cancer, renal cancer, seminoma, testicular teratomas, etc.

Mediastinal Tumors

Clinical Features. In the diagnosis of mediastinal tumors the following consequences, in addition to radiological aspects and clinical symptoms, have to be considered:

- *Effect on the nervous system*: intercostal neuralgia, recurrent nerve palsy, involvement of the vagal nerve, involvement of the sympathic nerve (Horner syndrome), anisocoria, salivation, reddening of the one-half of the face. All of these symptoms are suspicious for malignancy.
- *Impairment of the venous return*: cyanosis, edema. The edematous swelling may comprise the face, the veins of the face, and the thorax, and the upper abdomen may become extremely dilated (vena cava superior syndrome). The most common causes are malignant tumors of the mediastinum (small cell lung cancer and malignant lymphoma). Much less common etiologies are aortic aneurysm, localized thrombophlebitis with thrombosis, and chronic mediastinitis of various etiologies.
- *Effect on mediastinal organs*: irritant cough, bloody sputum, shortness of breath, difficulties with swallowing, cardiac symptoms.

Diagnosis. Evaluation by *chest radiography* and *CT* scanning may provide some clues to the diagnosis but histologic confirmation is usually required:

- sharply circumscribed round lesion = benign
- irregular margin = malignant
- anterior location = teratoma (Fig. 19.**20**), thymoma, dermoid cyst, lymphoma, intrathoracic goiter, pericardial cyst
- intermediate location = lymphoma, bronchogenic or pericardial cyst, lipoma
- posterior location = neurinoma of the sympathic nerve, bronchogenic cyst, meningocele, esophageal tumor
- bone shadow or tooth in the shadow = teratoma
- moves synchronous with respiration = intrathoracic goiter
- alterations of the bone (vertebral column, ribs) = neurinomas, aortic aneurysm, or malignant tumor

> The diagnosis of a mediastinal tumor must be confirmed by a biopsy (percutaneous or by thoracoscopy, mediastinoscopy, thoracotomy).

Classification and Prevalence. Mediastinal tumors may be classified according to their *localization* (anterior, middle, posterior mediastinum) or according to their

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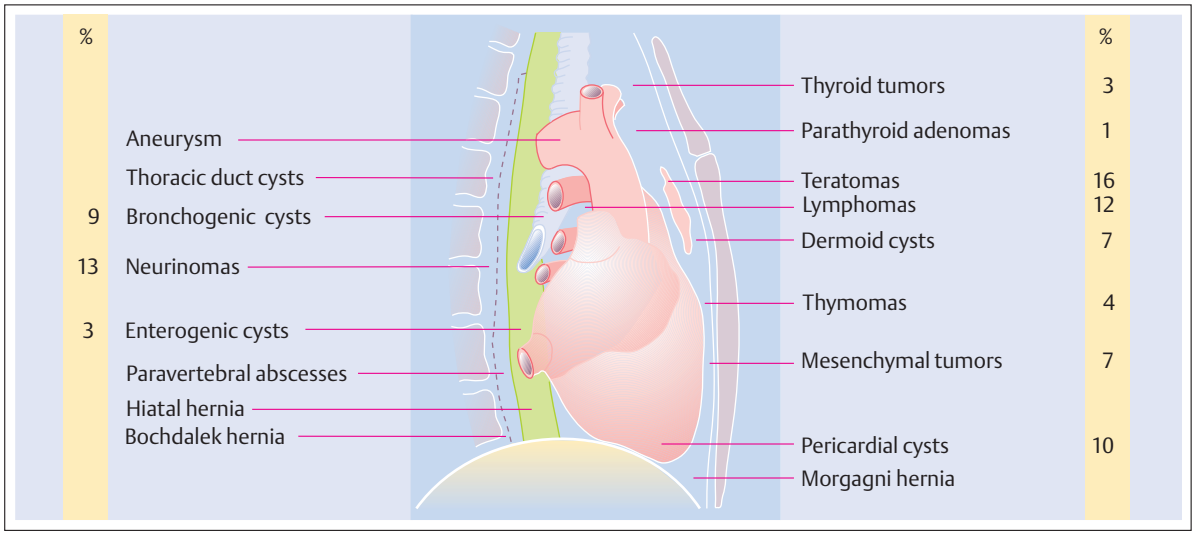

Fig. 19.**19** Localization, type, and prevalence of mediastinal masses.

embryological histogenesis. Furthermore, real tumors are differentiated from so-called pseudotumors. Real tumors originate either from the mesoblast, ectoblast, or endoblast or they are mixed tumors.

The most common *mesoblastic tumors* is lipoma followed by fibroma, lymphangioma, and myoma. Malignant forms (e. g., liposarcoma, fibrosarcoma, leiomyosarcoma) are rare. More common are lymphomas.

Among the *ectoblastic tumors*, the neurinomas (neurinoma, ganglioneuroma, neurofibroma) occur at a similar frequency as the thymomas. A persistent thymus also creates sharply demarcated, but less dense, shadows. Tumors of the thymus are accompanied by myasthenia in 10–50% of patients. Less well known is that tumors of the thymus, which are malignant in about 25% of cases, frequently cause paraneoplastic syndromes (aplastic anemia, thrombocytopenia, leukopenia, hypogammaglobulinemia, Cushing syndrome).

In leukemia, *mediastinal tumors* accompany characteristic blood pathology. Even *metastases* may mimic a mediastinal tumor.

Pseudotumors include bronchial, pulmonary, or pericardial cysts (Fig. 19.**21**), mediastinal goiter, tuberculous lymphomas, sarcoidosis, aortic aneurysm, megaesophagus, abscess, and phlegmon.

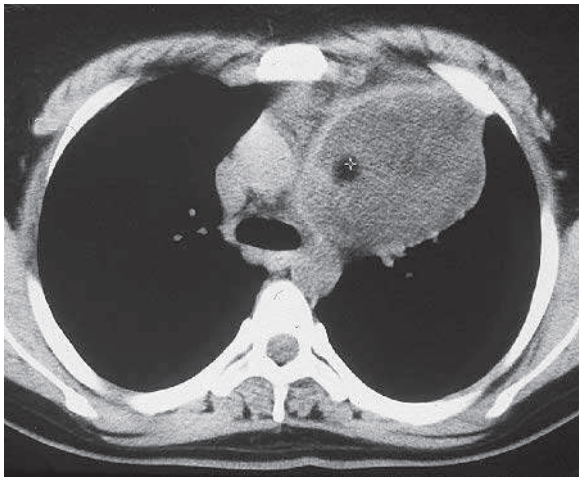

Fig. 19.**20** CT scan showing a teratoma originating from the anterior mediastinum in an 18-year-old woman.

Intrathoracic Goiter

As a rule, a connection exists with the extrathoracic part of the goiter. Displacement and narrowing of the trachea are characteristic features (Fig. 19.**22**). Nevertheless, a diagnosis based solely on the chest radiograph and the differential diagnosis to other pathologies, e. g., an aortic aneurysm of the bracheocephalic trunk, may be difficult. A key examination is scintigraphy with ^{131}I or a CT scan of the chest. Symptoms caused by an intrathoracic goiter are atypical (shortness of breath, etc.) and do not allow a distinction from other pathologies. Thyroid function usually remains normal.

Mediastinal Inflammations

Tuberculous Paravertebral Abscess, Mediastinal Phlegmon. Mediastinal tumors accompanying fever are suspicious for a tuberculous abscess or a mediastinal phlegmon.

Patients suffering from a medistinal phlegmon are very unwell (leukocytosis with toxic neutrophils). In contrast, a tuberculous abscess may be difficult to dis-

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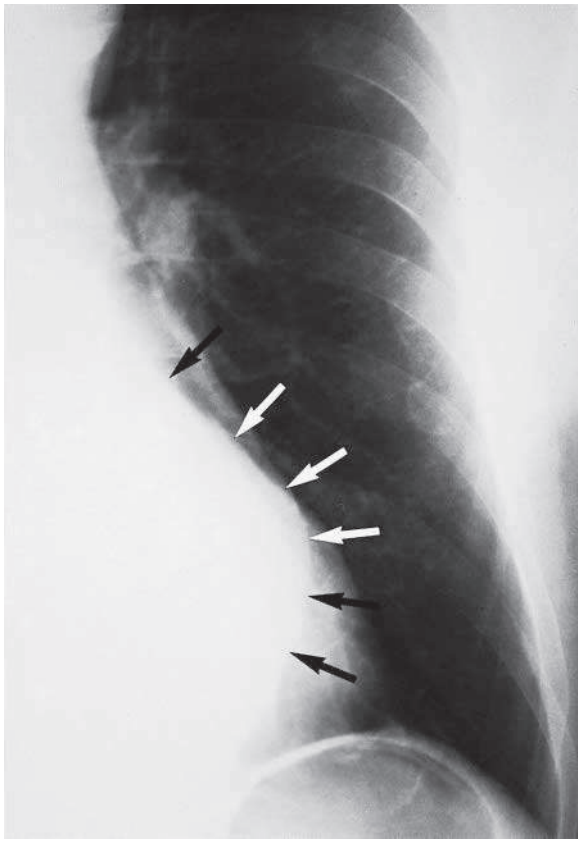

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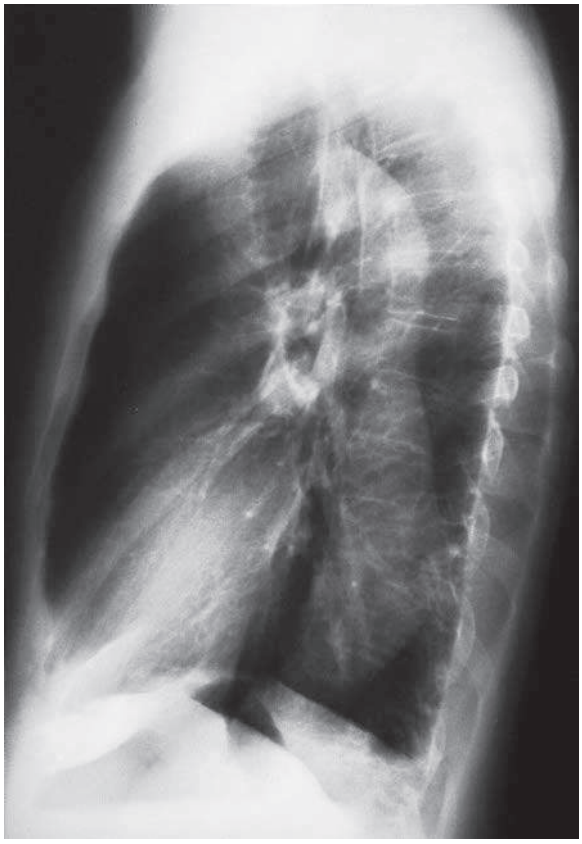
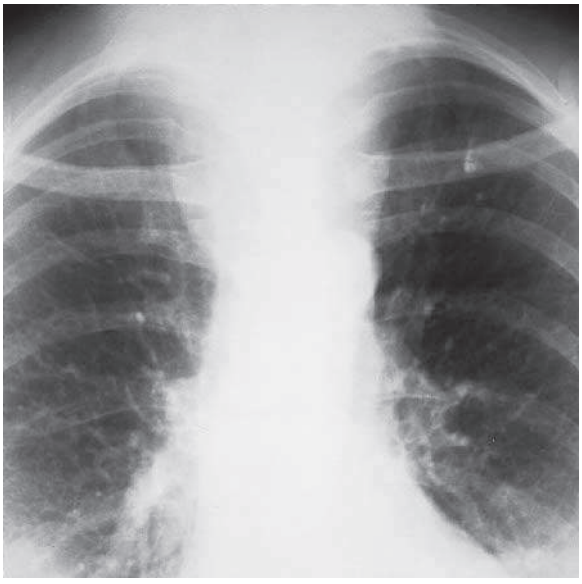


b

Fig. 19.**21** Pericardial cyst or "springwater" cyst in a 29-year-old man.

a The cyst is localized in the PA projection adjacent to the right heart silhouette.

b In the lateral projection it is recognized that the cyst is located anteriorly and abuts the chest wall.



a

b

Fig. 19.**22** Intrathoracic goiter in a 62-year-old woman.

a PA view

b The displacement of the trachea is clearly visible on the tomogram.

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tinguish from a tumor. If the vertebral column is involved, tuberculosis is the most likely diagnosis.

Lymph node tuberculosis has already been mentioned. The abscesses originate from the primary infection of hilar lymph nodes by tuberculosis and may have a prolonged course or acutely infiltrate surrounding organs.

Rare Etiologies of Mediastinal Diseases

Megaesophagus. A rare cause of a bilateral mediastinal enlargement is megaesophagus, which causes swallowing disturbances. A radiologic examination of the esophagus, a CT scan, or esophagoscopy are diagnostic.

Idiopathic mediastinal fibrosis. This is a form of idiopathic retroperitoneal fibrosis (Ormond disease) that involves the upper mediastinum. The first symptoms are caused by an obstruction of the superior vena cava. The chest radiograph shows a widened mediastinum. The diagnosis requires the exclusion of other diseases and is based on biopsies. Remission, spontaneous or as a response to systemic corticosteroids, is possible.

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Cardiac Symptoms

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Pathophysiology of Cardiac Dyspnea

Cardiac dyspnea is a cardinal symptom of heart failure. The subjective respiratory distress experienced by the patient may range from a feeling of slightly labored breathing to one of suffocation. By far the most frequent cause of cardiac dyspnea is pulmonary vascular congestion. When the pumping ability of the heart is impaired there is no longer sufficient drainage of blood from the pulmonary venous system, which leads to a rise in the pulmonary capillary pressure. The increased fluid volume in the lungs leads to swelling of the lung tissue and bronchial mucosae with a decrease in the compliance (distensibility) of the lung. As the vascular congestion builds, fluid begins to extravasate into the alveoli. This fluid infiltration may extend from the basal lung zones to the apical zones, depending on the severity of the congestion. In the most severe case of acute pulmonary edema, the alveolar air spaces fill with fluid throughout the lung, and there may be a productive cough (frothy sputum).

20.1 Differential Diagnostic Criteria

It is important to draw a distinction between *acute* and *chronic dyspnea*. Chronic cardiac dyspnea generally presents few problems of differential diagnosis. Acute dyspnea is occasionally difficult to distinguish from pulmonary dyspnea. The differential diagnosis is narrowed by taking a detailed dyspnea history and a complete cardiac and pulmonary history, looking for signs of heart failure or other cardiac diseases during the clinical examination, ordering appropriate laboratory tests, and ordering special studies such as electrocardiography (ECG), a chest radiograph, and echocardiography.

Orthopnea and paroxysmal nocturnal dyspnea suggest that the dyspnea has a cardiac cause.

Information Derived from the History and Symptoms

Both cardiac and pulmonary dyspnea are most commonly manifested as dyspnea on exertion and typically lead to rapid, shallow breathing (tachypnea). Patients may describe the respiratory distress of pulmonary dyspnea as “feeling short of breath” and “being unable to get enough air.” Cardiac patients describe their dyspnea more as an “air hunger” and a “feeling of suffocation.” Patients with poor physical conditioning describe their dyspnea simply as “labored breathing.” Unlike pulmonary dyspnea, cardiac dyspnea is aggravated by lying down (orthopnea). A history of paroxysmal nocturnal dyspnea is also a very specific sign that is virtually pathognomonic for cardiac dyspnea.

The *clinical examination* of a patient with cardiac dyspnea often reveals discontinuous moist rales confined to the base of the lung or, in more severe cases, distributed throughout the lung. They are frequently accompanied by dry rales, or wheezing – a continuous whistling sound that is loudest during expiration (cardiac asthma). Wheezing is a sign of heavy congestion and is likely to be found in patients who experience paroxysmal nocturnal dyspnea. Elements in the history that may suggest a cardiac cause of dyspnea include angina pectoris, prior myocardial infarction, hypertension, hypercholesterolemia, and diabetes. A cardiac cause should also be suspected in patients who give a history of decreased exercise tolerance with subsequent or concomitant dyspnea, accompanied by a feeling of fullness, weight gain, and nocturia. Patients with a pulmonary cause of dyspnea are more likely to give a history of obstructive lung disease, asthma, hay fever, shortness of breath, coughing, and purulent sputum. The presence of cyanosis, barrel chest, coarse rales, and an accentuated second heart sound also suggest a pulmonary etiology for the dyspnea. A cardiac cause is suggested by signs of left-sided heart failure (third heart sound, distinct cardiac murmur, moist rales over the lung fields) or right-sided heart failure (distended neck veins, positive hepatojugular reflux, peripheral edema). Hypotension and a cold periphery would also suggest a cardiac etiology.

ECG and Chest Radiograph

ECG. A normal ECG virtually excludes a significant impairment of left ventricular function. An abnormal ECG cannot prove a cardiac cause but may provide important evidence of cardiac disease. ECG abnormalities that are often seen in association with heart failure include signs of a recent or old myocardial infarction, signs of massive left or right ventricular hypertrophy, tachycardiac arrhythmias, or bradyarrhythmias such as AV block. If an angina equivalent is suspected as the cause of dyspnea, a stress ECG should be obtained.

Chest Radiograph. Cardiomegaly or signs of pulmonary congestion and edema in the chest radiograph point to a cardiac cause of dyspnea. In patients with pure diastolic

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a

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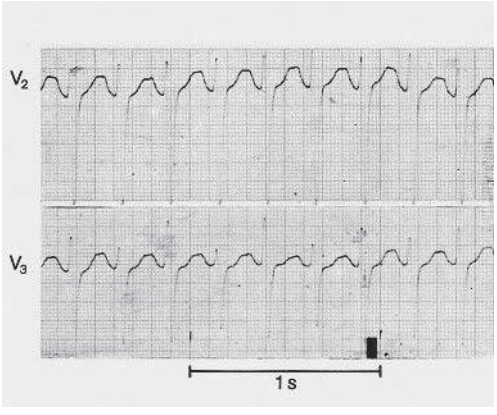

c

Fig. 20.**1** Massive pulmonary congestion without cardiac enlargement in a 52-year-old man.

a With two-day history of supraventricular tachycardia.

b Chest radiograph of the same patient two days after pharmacologic conversion of the supraventricular tachycardia to a normal sinus rhythm.

c Supraventricular tachycardia with a heart rate of 235 bpm accompanied by massive pulmonary congestion. The traces from leads V_2 and V_3 are shown. Electrical alternans is present in the V_3 lead.

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dysfunction, however, the heart may be normal or even diminished in size (concentric cardiac hypertrophy in older patients). Nevertheless, these patients will still manifest signs of pulmonary congestion and edema. Acute decompensation in patients with hypertrophic ventricles may be precipitated by events such as atrial fibrillation or other tachycardia (Fig. 20.**1**).

Laboratory Tests

BNP. Increased filling pressures in the heart, which lead to dyspnea, also lead to the production of *atrial* (ANP) and *brain natriuretic peptides* (BNP). High levels of BNP (BNP > 400 pg/mL or N-terminal BNP > 1600 pg/mL) are strongly suggestive of cardiac dyspnea, whereas normal levels (BNP < 100 pg/mL or (NT-BNP) < 300 pg/mL) exclude a cardiac cause with reasonably high confidence. The BNP level also correlates very well with the severity of heart failure, and there are few conditions besides heart failure that result in an elevated BNP. Slightly elevated BNP levels are found in patients with pulmonary hypertension, pulmonary embolism, and acute coronary syndrome. BNP levels also rise slightly in response to a general volume overload as in renal failure requiring dialysis or in liver failure due to hepatic cirrhosis. False-low BNP levels may be measured in very obese patients.

Special Tests. The BNP test may be supplemented by special laboratory tests selected in accordance with the history and clinical findings. These tests can provide additional important etiologic clues: markers for myocardial ischemia (creatine kinase, creatine kinase MB iso enzyme [CK-MB], troponin, myoglobin) in cases where myocardial ischemia is the suspected cause of dyspnea, and liver enzymes and bilirubin in patients with suspected chronic congestion. A noncardiac cause of dyspnea is more likely to be found in anemia, erythrocytosis, and in patients with an acute bacterial infection.

Blood Gases. The blood gas analysis is nearly normal in many patients with chronic cardiac dyspnea and pulmonary hypertension. Hypoxemia is a common finding in acute cardiac dyspnea. Partial or global respiratory insufficiency suggests that the dyspnea has a pulmonary cause.

Heart Failure as a Cause of Dyspnea

The most important cause of dyspnea is heart failure. Acute dyspnea may result from acute heart failure or from an acute decompensation of chronic heart failure. "Heart failure" is not a separate disease entity, but encompasses a number of diseases in which the pumping ability of the heart is impaired. This impairment may involve the systolic or diastolic function of the heart (Tab. 20.**1**).

Table 20.**1** Differential diagnosis of systolic and diastolic heart failure (modified from Givertz et al. In: Braunwald, Zipes, Libby [eds.] Heart Disease, 6th ed.)

Parameters	Systolic	Diastolic
History		
Coronary heart disease	+++	++
Hypertension	++	++++
Diabetes	++	++
Valvular heart disease	++++	+
Paroxysmal dyspnea	++	+++
Physical Findings		
Diminished heart sounds	++++	+
Third heart sound	+++	–
Fourth heart sound	+	+++
Mitral insufficiency	+++	+
Moist rales	++	+++
Distended neck veins	+++	++
Chest radiograph		
Cardiomegaly	+++	–/+
Pulmonary congestion	+	+++
Electrocardiogram		
Left ventricular hypertrophy	++	++++
Q wave	++	+
Low voltage	+++	–
Echocardiogram		
Concentric LV hypertrophy	++	++++
Left ventricular dilatation	++	+
Decreased ejection fraction	++++	–
Signs of increased LVEDP	++	++++
Abnormal LV filling	++	++++

In patients with *systolic dysfunction*, the heart is unable to contract normally, leading to exercise intolerance and decreased peripheral blood flow. *Diastolic dysfunction* is characterized by an inability of one or both ventricles to fill normally with blood. Diastolic heart failure is an important factor in the pathogenesis of cardiac dyspnea (Tab. 20.**2**).

The clinical manifestations of *left ventricular failure* differ from those of *right ventricular failure*. Left-sided heart failure or biventricular failure leads initially to pulmonary congestion and dyspnea. Right-sided heart failure causes the damming of blood back into the venous system and is manifested by increased venous filling pressures and peripheral edema (Tab. 20.**2**).

As a rule, heart failure leads to a decrease in cardiac output. This type is called *low output heart failure*. Occasionally, however, heart failure is present despite a very high cardiac output (e. g., arteriovenous fistulae). This type is called *high output heart failure*.

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Table 20.**2** Signs and symptoms of left-sided and right-sided heart failure

	Left-sided heart failure	Right-sided heart failure
Symptoms	Due mainly to diastolic dysfunction: – dyspnea – cardiac asthma – pulmonary edema – hemoptysis Due mainly to systolic dysfunction: – exercise intolerance – fatigue – decreased physical and mental performance – Cheyne–Stokes respiration – nocturia	Distended neck veins – peripheral edema – lower extremity edema – edema of hand dorsum – eyelids – anasarca nausea, vomiting upper abdominal pain nocturia
Signs	Signs of pulmonary congestion: – moist rales – wheezing – abnormal sputum cytology Fourth heart sound (presystolic gallop) Third heart sound (protodiastolic gallop) Cold extremities Oliguria	Signs of venous congestion: – increased central venous pressure – positive hepatojugular reflux – congestive hepatomegaly, cardiac cirrhosis Ascites Proteinuria Fourth heart sound
Findings in left-sided and right-sided heart failure	Tachypnea Tachycardia Peripheral exhaustion cyanosis Cardiomegaly Pleural effusion Cachexia	

20.2 Symptoms of Heart Failure and Other Cardiac Diseases

Dyspnea

Dyspnea is a primary symptom of heart disease and especially of left-sided heart failure. The severity of the dyspnea varies with that of the heart failure, and dyspnea may be manifested in various forms.

Table 20.**3** NYHA functional classification of heart failure

Class	Symptoms
I	Cardiac disease with no limitation of physical activity and no symptoms
II	Slight limitation of physical activity; moderate exertion leads to fatigue, dyspnea, or other symptoms
III	Marked limitation of physical activity; less than ordinary physical activity causes fatigue, dyspnea, or other symptoms
IV	Symptoms of heart failure are present even at rest

Dyspnea on Exertion. In chronic heart failure, dyspnea is induced by physical exertion. In the functional classification of the New York Heart Association (NYHA), the limitation of physical activity is classified into four grades of severity (Tab. 20.**3**).

Orthopnea. Lying down has the effect of increasing venous return to the heart and elevating the diaphragm. Both of these effects tend to worsen dyspnea in a patient with heart failure. This induces respiratory distress, causing the patient to wake up coughing. *Elevating the upper body* lessens the severity of the symptoms. The degree to which the patient elevates the upper body while sleeping (ask how many pillows are used!) is a good indicator of the severity of heart failure.

While orthopnea is a relatively sensitive indicator, it is not specific for heart failure. It may also occur in association with obstructive lung disease, copious ascites, and a large pleural effusion due to any cause. Lying down will cause orthopneic symptoms to appear within a few minutes, and sitting up should relieve the symptoms within minutes.

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Paroxysmal Nocturnal Dyspnea. Paroxysmal nocturnal dyspnea is caused by *intrapulmonary intra-alveolar edema* and is frequently accompanied by bronchospasms induced by congestion of the bronchial mucosa. This is often manifested clinically by *wheezing* and other features of "cardiac asthma." Concomitant cough is a typical feature of dyspnea and tends to occur after a dyspneic episode. After sleeping for two to four hours, the patient wakes from a paroxysmal nocturnal dyspneic attack, sits upright, and gasps for air. Unlike orthopnea, the dyspnea is not immediately relieved by sitting or standing, but often persists until the patient is able to cough up the excess secretions. It is not entirely clear why the paroxysmal dyspnea occurs chiefly at night, but it is reasonable to assume that nocturnal depression of the respiratory center and the low adrenergic state are contributing factors. Like Cheyne–Stokes respiration, paroxysmal nocturnal dyspnea is *very specific* for severe chronic heart failure.

Cough. Cough is also a result of pulmonary congestion and thus occurs during physical exertion or occasionally while the patient is lying down. If cough is not improved by afterload-reducing therapy or diuretic therapy, it may be caused by another pulmonary disease or may be a side effect of angiotensin-converting enzyme (ACE)-inhibitor therapy.

Speech Dyspnea and Dyspnea at Rest. Both are manifestations of severe heart failure. In the first condition, even the effort to speak is sufficient to bring on dyspnea; in the second, the patient is short of breath even while at rest.

Cardiac Asthma. Pulmonary congestion causes swelling of the bronchial mucosa, leading to bronchial asthma with a typical expiratory wheeze. Cardiac asthma is frequently associated with *dyspnea and cough*. It may be somewhat difficult to distinguish cardiac asthma from pulmonary asthma. A patient with cardiac asthma, however, often has other signs of left-sided and right-sided heart failure, such as *basal moist rales* and distended neck veins; expiratory dyspnea is less pronounced. The blood gases in cardiac asthma are frequently within normal limits, unlike pulmonary asthma, which is often associated with hypoxia, hypercapnia, and respiratory acidosis.

Signs of Venous Congestion

Abdominal Symptoms. Right-sided heart failure (see Tab. 20.**2**) is characterized by a damming of blood back into the systemic veins. While venous congestion in the neck does not produce symptoms, the reflux of blood into the liver exerts tension on the liver capsule, causing upper abdominal pain.

In chronic heart failure, the pain may disappear even though the liver remains enlarged. Chronic hepatic congestion may lead to *cardiac cirrhosis*. Swelling of the mucous membranes in the gastrointestinal tract leads to a feeling of fullness, anorexia, and occasionally nausea. The *nausea* and anorexia may be exacerbated by impaired intestinal absorption due to congestive gastritis, caused centrally by decreased cerebral blood flow, and by possible digitalis intoxication.

General Symptoms

Exercise Intolerance. After dyspnea, decreased exercise tolerance is the second most important symptom of heart failure. The pathogenesis is multifactorial, but the onset of exertional dyspnea and the inability of the heart to increase its output are the principal causal factors. Other contributing causes are loss of conditioning of the skeletal and respiratory muscles and an altered metabolism in these muscles.

Fatigue and Weakness. Fatigue and weakness are associated with a progressive loss of conditioning in heart failure. When they occur in the absence of progressive cardiac insufficiency, it is necessary to exclude other causes such as hypovolemia, hyponatremia, or a side effect of beta-blocker therapy.

Cerebral Symptoms. In patients with severe heart failure, and especially in elderly patients with cerebral atherosclerosis, the diminished cerebral blood flow may lead to a decline in mental performance. The patient may suffer concentration difficulties, sleeplessness, headache, memory loss, confusion, and anxiety. The sleeplessness caused by nocturia tends to exacerbate the cerebral symptoms.

Cheyne–Stokes Respiration. The prolonged circulation times delay the normal feedback loop between alveolar gases and the central regulation of breathing. As a result, severe heart failure gives rise to a Cheyne–Stokes pattern with periodic waxing and waning of the rate and depth of respirations.

Nocturia. During the day, blood flow to the kidneys in patients with heart failure is decreased in favor of other organs. However, renal perfusion increases when the patient is at physical rest, and the increased blood flow allows the kidney to reabsorb edema that has developed during the day. The result is an increase in nocturnal urine output.

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20.3 Clinical Examination and Findings

General Physical Examination

During the general physical examination of a heart patient, particular attention should be given to vital signs (pulse, blood pressure, respiratory rate, temperature), volume status, and perfusion status. It is also important to inspect the skin (cyanosis, clubbing, microemboli in infectious endocarditis, skin tension due to edema). Along with the medical history, symptoms, and cardiac findings, the physical examination can yield important information on the etiology and severity of the cardiac disease. The principal symptoms and findings of right- and left-sided heart failure are listed in Tab. 20.**2**.

Pulse

Pulse Quality. The character of the pulse is determined by the stroke volume and the stiffness of the artery wall. The quality of the pulse is assessed by palpating the carotid artery:

- A *weak pulse* (pulsus parvus) is noted in all conditions in which the left ventricular stroke volume is decreased or the blood pressure amplitude is small. The most important of these conditions are hypovolemia, mitral or aortic stenosis, constrictive pericarditis, and a recent myocardial infarction.
- A *slow pulse* (pulsus tardus) results from an obstruction of aortic outflow. For example, a severe calcified aortic stenosis will produce a weak and slow pulse.
- A *heaving pulse or bisferious pulse* (with two systolic peaks) is found in patients with aortic regurgitation or hypertrophic obstructive cardiomyopathy.
- A *paradoxical pulse* may occur in pericardial tamponade and other conditions (see Chapter 6).
- An *alternating pulse* is characterized by an alternation of weak and strong beats spaced at equal intervals. This pattern often follows tachycardia or extrasystoles in patients with severe decompensated hypertension, heart failure, or aortic stenosis.

Vessel Wall. The increased stiffness of the artery wall in patients with atherosclerosis (hypertensive or elderly patients) prevents damping of the pulse waves. As a result, a bisferious pulse may be noted in a patient with a normal stroke volume, or a normal pulse may be noted in a patient with a diminished stroke volume (e. g., due to aortic stenosis).

Tachycardia. Tachycardia is a common finding in patients with heart failure. At the same time, a *tachycardic arrhythmia* may be a cause of heart failure (see Fig. 20.**1**). Atrial fibrillation is particularly important in this regard. Heart diseases that are associated with significant diastolic dysfunction impose an increased volume and pressure load on the atria, which predisposes to atrial fibrillation. Atrial fibrillation is poorly tolerated in these patients, however, because the ineffectual atrial contractions cause an approximately 20% reduction of ventricular filling. This may lead to the acute decompensation of a previously asymptomatic cardiac defect (e. g., aortic stenosis, mitral stenosis, hypertrophic cardiomyopathy, or restrictive cardiomyopathy).

Volume Status

Jugular Vein Filling. Jugular vein filling is dependent on the right atrial pressure, and therefore the degree of jugular vein filling provides a means of evaluating venous congestion. The distance from the center of the right atrium to the superior border of the sternum, and thus the height of the fluid column, is almost always equal to 5 cm. If the jugular vein is collapsed at the level of the clavicle when the upper body is at a 45° angle, the central venous pressure is equal to 8 cm (5 cm + 3 cm). If the upper portion of the jugular vein is distended, the venous pressure is increased. The pressure in the right atrium can be estimated with fairly good accuracy by determining the level of venous collapse as the upper body is slowly raised to an upright position.

Jugular Vein Pulse. The pulse in the jugular vein is typically decreased during inspiration because the negative pressure in the chest causes blood to shift into the intrathoracic venous system. If the venous system is already filled, and the heart can not eject the blood volume presented to it during inspiration because its pumping ability is impaired, the jugular venous pulse will show an atypical increase on inspiration. This phenomenon, called the *Kussmaul sign*, is observed in tricuspid insufficiency, constrictive pericarditis, right-sided heart failure, right-sided myocardial infarction, and severe biventricular heart failure.

Unilateral nonpulsatile congestion of the jugular vein means that flow into the superior vena cava is obstructed (e. g., by lymphadenopathy or thrombosis). The jugular vein on the left side may be congested due to slight anatomical kinking of the brachiocephalic vein.

Changes in Venous Flow. A marked *increase in the jugular vein pulse* is noted in patients with right-sided or biventricular heart failure. It is also seen in pericardial tamponade, constrictive pericarditis, endomyocardial fibrosis, and when the right ventricle is hypertrophic due to various causes. In tricuspid insufficiency, the jugular vein gives a strong pulse and does not collapse.

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When the atrium contracts against a closed tricuspid valve, it generates an exceptionally large a wave in the venous pulse, producing a giant wave in the jugular vein called a "*cannon wave*." This can be observed with every heart beat in a patient with nodal rhythm or at irregular intervals in patients with a complete atrioventricular (AV) block or after ventricular extrasystoles.

Hepatojugular Reflux. The hepatojugular reflux can be used to detect a latent right-sided heart failure or excessive filling of the left atrium. The mechanism by which acute left-sided heart failure contributes to a positive hepatojugular reflux is not precisely known. In cases where heart failure is suspected and there is no obvious congestion of the jugular veins, the hepatojugular reflux should be tested as follows:

Continuous pressure is applied to the abdomen (liver) for one minute while the examiner observes the response of the right external jugular vein. The patient should be placed in a position that is optimal for observing venous pulsations (a 45° position is often less than optimal). In a healthy subject, the increased abdominal pressure initially evokes a rise in the jugular venous pressure, which then returns to normal within a few seconds during normal respiration. If stasis is present at the atrial level, the jugular venous pressure will remain elevated because the heart cannot expel the increased inflow of blood.

Hepatomegaly. Chronic congestive heart failure leads to enlargement of the liver. There may be an associated feeling of tension in the right upper quadrant of the abdomen. Hepatomegaly may precede the development of frank peripheral edema. The hepatic congestion may also lead to elevated bilirubin and transaminase levels, with jaundice developing in severe cases. Patients with severe long-standing right-sided heart failure and congestion may develop *cardiac cirrhosis*. Hepatomegaly with externally visible palpitations is a feature of tricuspid insufficiency (pulsating liver!).

Peripheral Pitting Edema. Early in the course of heart failure, peripheral edema develops, mainly after prolonged exertion and during the evening hours, but eventually the edema becomes constant. Generally, it shows a symmetrical distribution in both lower extremities and pits upon pressure. The edema is caused mainly by a rise of venous pressure secondary to right-sided heart failure. The extent of the edema correlates poorly, however, with the level of the systemic venous pressure. Decreased renal perfusion and an increased secretion of antidiuretic hormone activate the renin–angiotensin–aldosterone system, leading to water and salt retention and thus to edema formation. As the heart failure continues to progress, the edema becomes more pronounced. The late stage of heart failure is marked by massive generalized edema (*anasarca*).

Pleural Effusion. The pleural space drains into the systemic circulation and pulmonary circulation. Pleural effusion develops when the venous pressure becomes elevated in both systems. The effusion is frequently bilateral, but in some cases it is confined to the right side.

Ascites. A prolonged rise in the systemic venous pressure leads to an elevation of the hepatic venous pressure. This may result in the formation of ascites. Tricuspid insufficiency and constrictive pericarditis are marked by the early development of ascites, which often is not accompanied by massive peripheral edema.

Perfusion Status

The assessment of perfusion status in patients with severe advanced heart failure has proven helpful in making a prognosis and instituting treatment (Tab. 20.**4**). This simple clinical assessment provides information on the cardiac output and the pressures in the pulmonary venous system.

A *warm periphery with normal blood flow* usually signifies a normal cardiac output, while a *cold periphery* indicates poor systolic function and a decreased cardiac output. Signs of pulmonary congestion or cardiac venous congestion have been described as a "wet status."

Hypoperfusion (cold periphery) plus signs of congestion (wet status) in chronic heart failure implies a poor prognosis and requires immediate hospitalization with diuretic and vasodilator therapy.

Rales, Expiratory Wheeze

Moist inspiratory rales (fine bubbling rales, discontinuous, not consonating), heard initially over the base of the right lung and later involving all of the lung base and eventually the entire lung, are characteristic of pulmonary congestion due to left-sided heart failure. An expiratory wheeze due to congestive swelling of the bronchial mucosae or increased bronchial secretions is typical of *cardiac asthma*. The rales of *pulmonary edema* have a crackling, gurgling, hissing quality and are audible at a distance. As in cardiac asthma, they are often associated with an expiratory wheeze.

Table 20.**4** Clinical presentation of severe advanced heart failure

		Congestion at rest (WET)	
		No	**Yes**
Low Perfusion at rest (COLD)	**No**	warm and dry	warm and wet
	Yes	cold and dry	cold and wet

A *warm and dry* perfusion status with a warm periphery and no signs of pulmonary or venous congestion has a good prognosis. A cold periphery with marked congestive signs (*cold and wet* perfusion status) is an unfavorable prognostic sign.

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Table 20.**5** Valvular heart disease that may cause a palpable thrill

Time of occurrence	Possible cause of the thrill	Location of the thrill
Systole	Aortic stenosis	Suprasternal and/or second/third ICS at right sternal border
	Pulmonic stenosis	Suprasternal and/or third ICS at left sternal border
	Ventricular septal defect	Fourth ICS, left side
	Mitral insufficiency	Cardiac apex
	Tetralogy of Fallot	Left lower sternal border
Diastole	Aortic insufficiency	Right sternal border, cardiac apex

Table 20.**6** Summary of the cardiac examination

Inspection and palpation of the precordium
Precordial impulse
Apex beat (location, quality)
Thrill

Systematic auscultation
Heart sounds: S1, S2
Extra sounds: S3, S4
- early diastolic sounds
- valve opening sounds
- ejection sounds
- midsystolic click

Murmurs

Characteristics of murmurs
Timing and duration
- systolic/diastolic/systodiastolic
- early, mid, or late systolic or diastolic

Pitch
- high, medium, or low

Intensity (loudness):
- grade I: barely audible in a quiet room
- grade II: soft, but clearly audible
- grade III: intermediate loudness
- grade IV: loud, associated with a thrill
- grade V: very loud with a palpable thrill
- grade VI: very loud, audible without a stethoscope

Pattern
- crescendo, decrescendo

Quality
- harsh, grating, blowing, vibratory, musical, machinelike

Location
Radiation
- to the axilla, carotid arteries, back; possible respiratory variations

Heart failure of long duration evokes a compensatory increase in pulmonary lymphatic drainage. Often this results in the absence of audible rales despite the increased pulmonary capillary pressure and symptomatic dyspnea.

Cardiac Examination

Inspection and Palpation

The cardiac examination begins with inspection and palpation of the precordium, giving particular attention to a precordial impulse, apex beat, and palpable thrill.

Precordial Impulse. Enlargement of the right ventricle may be manifested by abnormal pulsations behind the lower sternum and in the fourth and fifth intercostal space (ICS) along the left sternal border (right ventricular heave or lift). (Late-) systolic precordial pulsations may also occur in severe mitral insufficiency. They are caused by anterior displacement of the ventricles in response to massive systolic expansion of the left atrium (left atrial lift).

Apex Beat. The cardiac apex beat is normally palpable in the fifth (or sometimes fourth) ICS on the midclavicular line. A widened (> 2 cm) and *heaving apex beat*, like that occurring with severe left ventricular hypertrophy or a postinfarction apical aneurysm, is a pathologic finding. *Downward displacement* of the apex beat (to the sixth ICS) is always abnormal, as is displacement of the apex beat outside the midclavicular line in the supine patient. A displaced apex beat is a sign of cardiomegaly, provided that the heart has normal anatomical relationships (these may be altered due to thoracic deformities such as funnel chest and kyphoscoliosis or due to an elevated right hemidiaphragm).

Palpable Thrill. A loud cardiac murmur of grade IV intensity or higher contains a large proportion of low-frequency vibrations, which induce a palpable vibration of the chest wall called a thrill. The vibration may be palpable during both systole and diastole. The most common valvular diseases that cause a thrill are listed in Tab. 20.**5**.

Systematic Auscultation

It is helpful to develop and follow a precise routine for cardiac auscultation (Tab. 20.**6**). All areas of the heart should be systematically auscultated with the patient lying supine, in left lateral decubitus, and sitting up and leaning forward. First the heart is auscultated during quiet respiration, and afterward the respiratory variability of the heart sounds is assessed. The different valve sounds are projected to different anatomical sites on the chest wall where they are most clearly audible. Five auscultatory areas are distinguished:

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1. Aortic area: second ICS along the right sternal border.
2. Pulmonic area: second ICS along the left sternal border.
3. Erb point: third ICS along the left sternal border.
4. Tricuspid area: fourth and fifth ICS along the right sternal border.
5. Mitral area: cardiac apex in the fifth ICS on the midclavicular line.

The infrascapular areas should also be auscultated while the patient is supine.

Heart Sounds. During auscultation of the heart sounds, the examiner listens for splitting of the heart sounds, assesses the intensity of the sounds, and listens for extra sounds.

Differential Diagnostic Significance of the Heart Sounds

First Heart Sound. The first heart sound results from the closure of the mitral and tricuspid valves and tightening of the valve leaflets. Normally the mitral valve closes slightly before the tricuspid valve, with the result that the first heart sound consists of two main parts, both of which are usually audible in adolescents. The splitting of the first heart sound is normally more distinct on expiration and disappears on inspiration.

Abnormal Splitting of the First Heart Sound. Further splitting of the first heart sound occurs if the tricuspid component is delayed (right bundle branch block, tricuspid stenosis). If closure of the mitral valve is delayed (left bundle branch block, mitral stenosis), the first heart sound may become louder or, in severe cases, may show reverse splitting with the mitral component occurring after the tricuspid component (Fig. 20.**2a**).
An *extra ejection sound* produced either in the aorta (aortic valve disease, dilatation and elongation of the aorta due to hypertension) or in the pulmonary artery (due to pulmonary hypertension or a congenital defect) can mimic splitting of the first heart sound.
In patients with a *prosthetic aortic valve*, a high-pitched metallic click is heard at the start of the ejection phase, produced by the impact of the ball or disk against the valve frame (Fig. 20.**3**). With a bioprosthetic valve, the ejection click is either faint or absent.

Abnormal Intensity of the First Heart Sound. Variations in the intensity of the first heart sound are clinically important. A loud, accentuated first heart sound is characteristic of a *noncalcified mitral valve stenosis*. A loud first heart sound may also be audible due to hyperthyroidism or anemia. Conversely, the first heart sound is softer than normal in patients with a heavily calcified mitral valve stenosis or left ventricular dysfunction (slow pressure rise in the left ventricle!). The intensity of the sound also varies with the PQ interval: a short PQ interval is associated with a loud first sound, a long PQ interval with a soft first sound.

Second Heart Sound. The second heart sound results from the tightening and closure of the semilunar (pulmonary and aortic) valves. Physiologically, the pulmonary valve closes slightly *after* the aortic valve. This splitting of the second sound is best appreciated during inspiration and is faint or absent during expiration. The discrimination threshold for detecting this split with a stethoscope is 0.02 seconds.

Abnormal Splitting of the Second Heart Sound. When closure of the pulmonary valve is delayed, the split between the components of the second heart sound becomes abnormally wide. Paradoxical splitting occurs when closure of the aortic valve is greatly delayed (Fig. 20.**2b**).
A *delay of pulmonary valve closure* may result from a right bundle branch block, pulmonic stenosis, or an atrial septal defect (ASD). The physiological respiratory variation is preserved in patients with a right bundle branch block. The split does not show respiratory variation in patients with a large ASD. The second heart sound is diminished in patients with pulmonic stenosis.
A *delay of aortic valve closure* leads to reverse or paradoxical splitting of the second heart sound, i. e., the split becomes paradoxically wider on expiration and narrower on inspiration. This may be audible in patients with a left bundle branch block or severe aortic stenosis.

Abnormal Intensity of the Second Heart Sound. Severe aortic stenosis results in a soft second heart sound. A normal second heart sound in a patient with presumed aortic stenosis should raise suspicion of an outflow obstruction above or below the aortic valve. The second heart sound may be exceptionally loud in systolic hypertension, especially when there is concomitant dilatation of the aortic root. A loud pulmonary component of the second heart sound is typical of pulmonary hypertension.

Extra Sounds. the split second heart sound requires differentiation from extra sounds:

- *Early diastolic extra sounds:* the most familiar extra sound in early diastole is the high-pitched opening sound of the mitral valve. Another early diastolic sound is a lower-pitched pericardial sound called the *pericardial knock* (see Fig. 20.**50**). An atrial myxoma may produce a low-pitched "tumor plop" in early diastole.
- The *mitral valve opening sound* (high-pitched sound audible in early diastole) occurs approximately 0.06–0.12 seconds after closure of the aortic valve. It is typical of a severe mitral stenosis with little calcification. A high-pitched mitral valve opening sound is also heard consistently in association with ball-type and disk-type prosthetic valves (Fig. 20.**3**). Like the ejection click of a prosthetic aortic valve, the opening sound of an artificial mitral valve is an important sign that the valve is functioning normally. An opening sound is rarely audible with a bioprosthetic mitral valve.
- The *protodiastolic gallop* is a normal third heart sound when heard in adolescents. It is *abnormal* in adults and is a typical finding in patients with left ventricular failure or mitral insufficiency. It is a sign of systolic left ventricular dysfunction.

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- Like the third heart sound, the fourth heart sound (atrial sound) leading to the *presystolic gallop* is produced by ventricular filling (Fig. 20.**4**). It occurs when the pressure wave from a strong atrial contraction impinges on a stiff ventricle. Consequently, it is considered a sign of diastolic dysfunction. It is absent in atrial fibrillation and in patients with large, poorly contracting atria. A fourth heart sound is most commonly heard in conditions where there is increased resistance to left ventricular filling caused by decreased ventricular compliance (arterial hypertension, aortic stenosis, coronary sclerosis, cardiomyopathies). A fourth heart sound may also result from an increase in ventricular stiffness due to ischemia. A fourth heart sound may be audible on the right side in patients with pulmonary hypertension or pulmonic stenosis. A fourth heart sound has also been described in conditions where there is a *chronic volume overload* but no increase in filling resistance (severe anemia, hyperthyroidism, larger peripheral arteriovenous fistulae). A fourth heart sound is always abnormal.
- When an abnormal third and fourth heart sound (protodiastolic and presystolic gallop) are both present, they are called a *summation gallop*. This finding is characteristic of severe tachycardia.
- Occasionally a short, high-pitched extra sound called a midsystolic click is audible midway between the first and second heart sounds (Fig. 20.**5**). It is relatively common for this sound to be followed by a telesystolic murmur. A *midsystolic click* is caused by sudden tension on the mitral valve apparatus (valve leaflets, chordae tendineae, or papillary muscle) due to the *systolic prolapse* of one or both mitral valve leaflets. The telesystolic murmur is caused by mitral regurgitation occurring immediately after the click. The presence of a midsystolic click without a telesystolic murmur means that the mitral valve prolapse is associated with little or no regurgitation (Fig. 20.**5**).

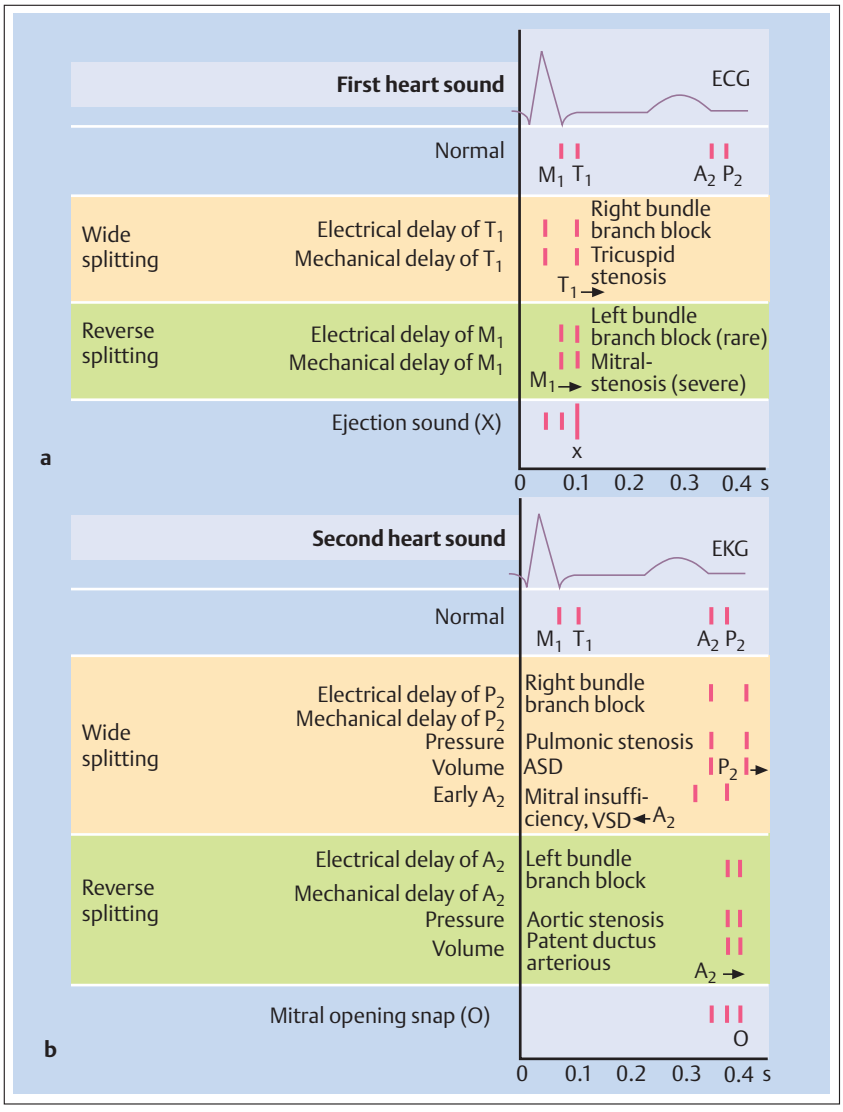

Fig. 20.**2** Schematic representation of diagnostically significant changes in the heart sounds. ASD = atrial septal defect, VSD = ventricular septal defect.
a Changes in the first heart sound.
b Changes in the second heart sound.

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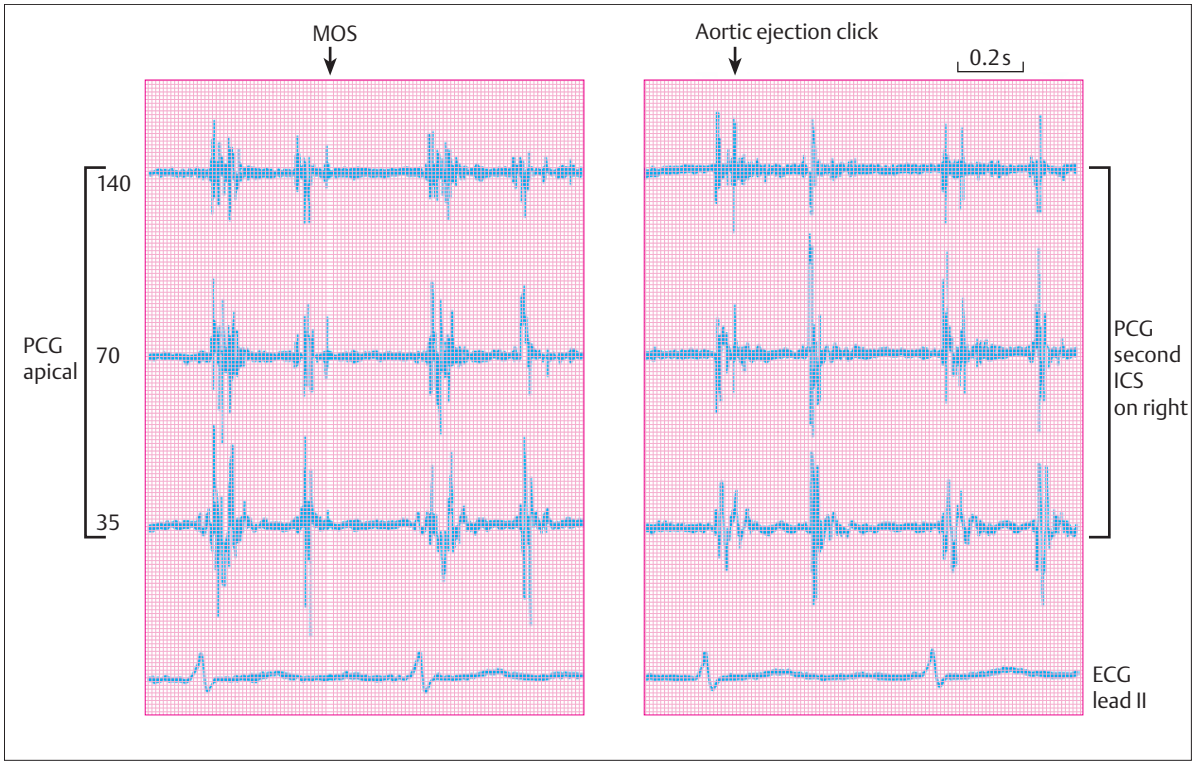

Fig. 20.**3** Phonocardiogram (PCG) at various frequencies (35, 70, 140 Hz) for Björk–Shiley valves in the mitral and aortic positions in a 55-year-old woman. The mitral valve produces a high-frequency opening snap (MOS), and the aortic valve produces an early systolic ejection click followed by a protomidsystolic ejection sound.

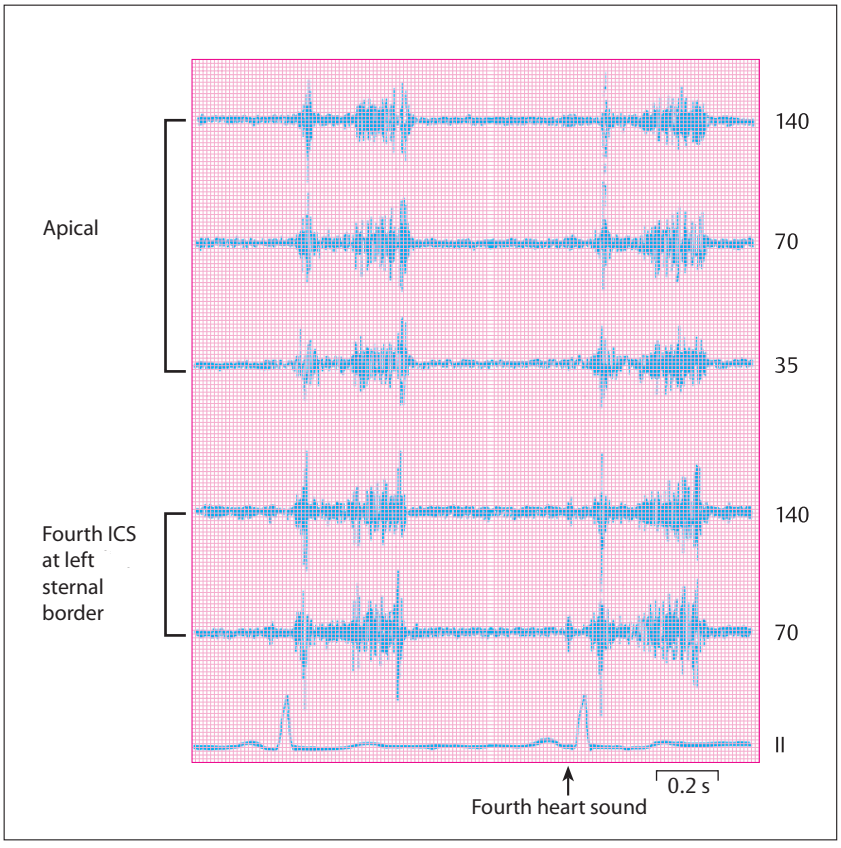

Fig. 20.**4** Phonocardiogram of telesystolic mitral insufficiency due to ischemic papillary muscle dysfunction in a 59-year-old woman with an occlusion of the right coronary artery and a high-grade stenosis of the left anterior descending (LAD) artery; moderate mitral regurgitation. A fourth heart sound is present.

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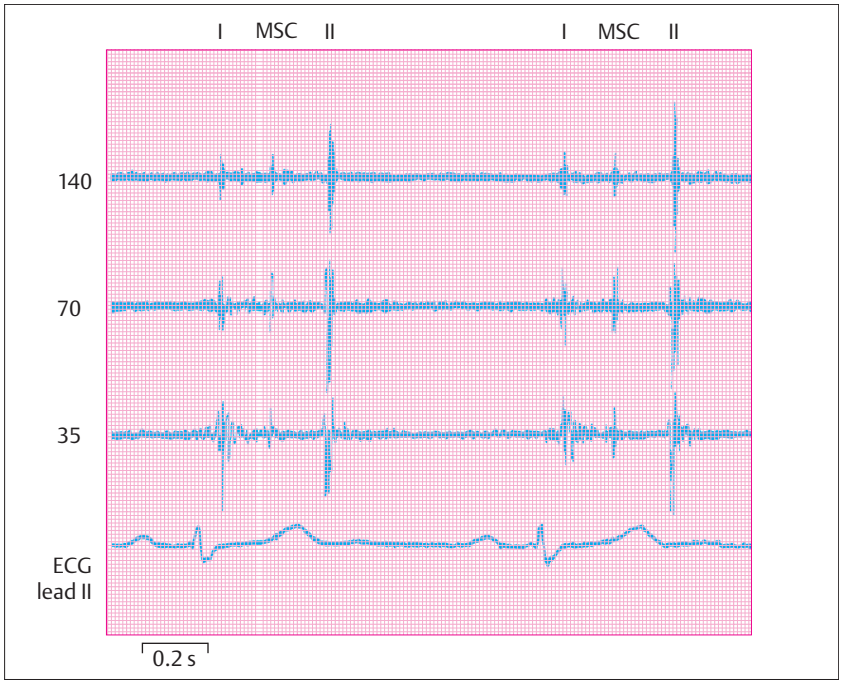

Fig. 20.**5** Midsystolic click (MSC) in a 37-year-old woman with mitral valve prolapse.

Some Guidelines for the Differential Diagnosis of Murmurs Associated with Valvular Heart Disease

Basic principles that should be noted in the evaluation of systolic and diastolic murmurs are shown schematically in Fig. 20.**6**.

Systolic Murmurs. Systolic ejection murmurs are most frequently caused by sclerosis or stenosis of the cardiac valves. In *aortic sclerosis*, an early systolic ejection murmur is audible at the base of the heart and generally does not radiate to other sites. The murmur of *aortic and pulmonic stenosis* extends almost throughout systole, but it does not begin immediately after the first heart sound and has a typical crescendo–decrescendo shape. The murmur of aortic stenosis is transmitted to the carotid arteries and radiates to the cardiac apex as a higher-pitched musical sound. A systolic ejection murmur may also result from a high ejection velocity in the left ventricular outflow tract, like that occurring in *hypertrophic cardiomyopathy* with or without obstruction. These ejection murmurs are highly variable under different hemodynamic conditions (Tab. 20.**7**). Typically the murmur of hypertrophic obstructive cardiomyopathy (HOCM) increases greatly in intensity when the patient rises from a squatting to a standing position. In HOCM, moreover, the systolic murmur may be a combination of a systolic ejection murmur in the left ventricular outflow tract and a systolic regurgitant murmur through the incompetent mitral valve. The systolic murmur associated with *coarctation of the aorta* occurs later in systole and extends slightly beyond the second aortic sound.

A benign or functional systolic murmur is most commonly heard in young patients, during pregnancy, or following athletic exertion (Tab. 20.**8**).

Table 20.**7** Differentiation of the most common systolic murmurs by simple maneuvers

Defect	Inspiration	Standing	Squatting
Mitral insufficiency	=	= or ↓	(↑)
Mitral valve prolapse	↑*	↑*	↓#
Aortic stenosis	=	↓	(↑)
Ventricular septal defect	=	=	= or ↑
Hypertrophic obstructive cardiomyopathy	=	↑ ↑	↓ ↓
Tricuspid insufficiency	↑ ↑	(↓)	(↑)

= no significant change; (↑) little or no increase; (↓) little or no decrease; ↑ increase; ↑ ↑ marked increase; ↓ decrease; ↓ ↓ marked decrease.
* Earlier click and longer murmur; # later click and shorter murmur.

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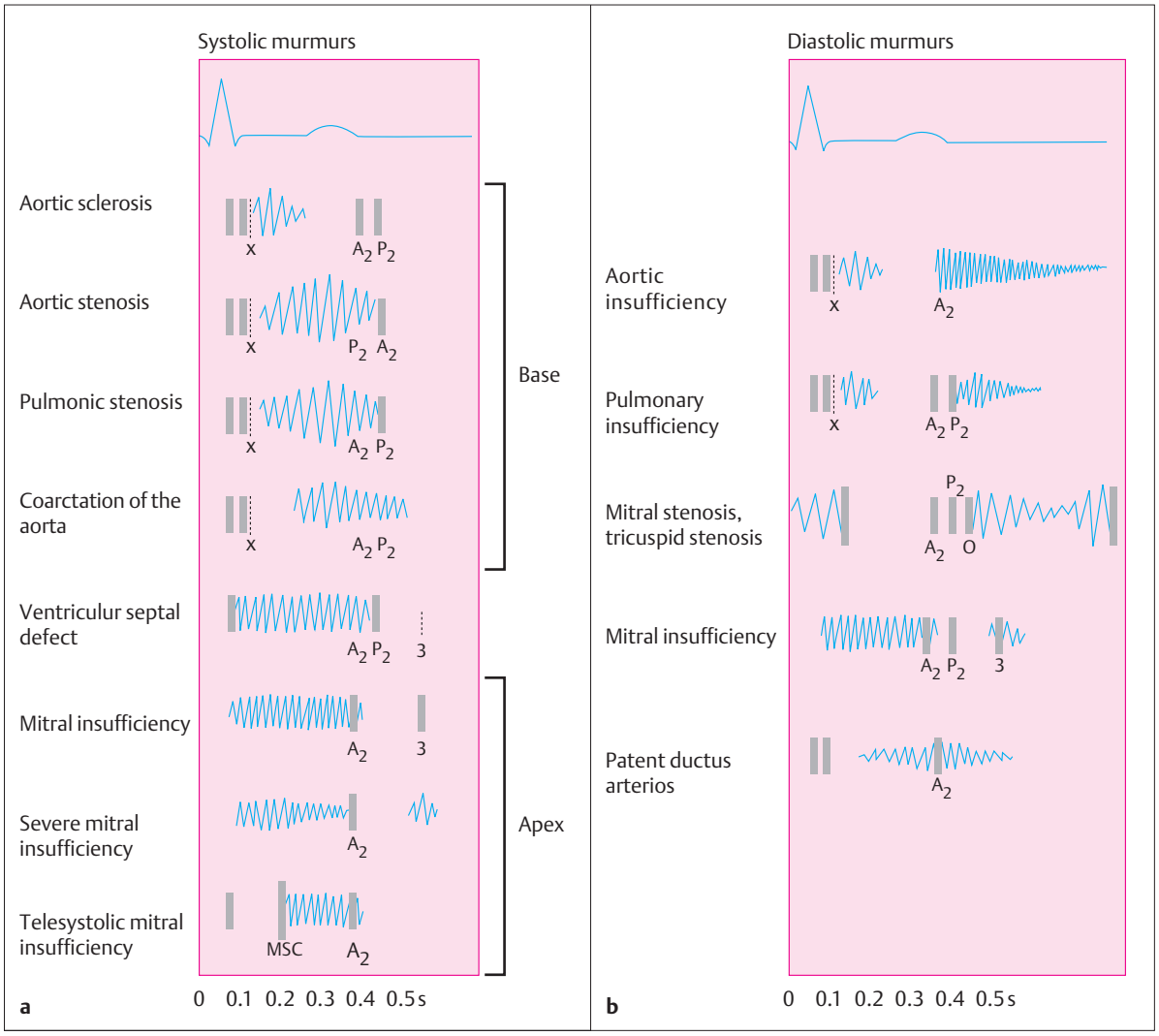

Fig. 20.**6** Schematic representation of systolic (**a**) and diastolic murmurs (**b**). X = ejection click, A_2 = aortic component, P_2 = pulmonary component, O = mitral or tricuspid opening sound, MSC = midsystolic click, 3 = third heart sound.

Table 20.**8** Characteristic features of a functional ejection murmur

- Soft
- Protomesosystolic
- Spindle shaped
- Audible at the left sternal border, faintly audible at the apex
- No radiation
- No other cardiac abnormalities

The most common systolic regurgitant murmur is that associated with *mitral insufficiency*. Typically it is holosystolic with a band-shaped pattern and masks the aortic component of the second heart sound. With very severe mitral insufficiency, the holosystolic murmur shows a distinct decrescendo–crescendo pattern. It is not unusual to find a late systolic murmur at the apex (due to mitral valve prolapse). The murmur from a *ventricular septal defect (VSD)* immediately follows the first heart sound.

Diastolic Murmurs. The diastolic decrescendo murmur in *aortic insufficiency* immediately follows the aortic component of the second heart sound (immediate murmur). In *pulmonary insufficiency* with pulmonary hypertension, the diastolic decrescendo murmur is heard immediately after the pulmonary component of the second sound. In cases of organic pulmonary insufficiency without increased pressure in the pulmonary artery, the maximum intensity of the diastolic murmur from P_2 is slightly decreased and the murmur does not show a typical decrescendo pattern; it begins with a brief crescendo followed by a decrescendo. The frequency spectrum of pulmonary insufficiency depends on the pressure in the pulmonary artery. A low-pitched murmur is heard in congenital pulmonary insufficiency (normal pressures), while a high-pitched murmur is heard in pulmonary insufficiency accompanied by pulmonary hypertension (high pressure differential).

With *mitral and tricuspid stenosis*, the diastolic murmur (rumble) is heard only after the atrioventricular valves

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have opened. A late diastolic murmur may also be caused by *atrial myxoma* and by increased flow through a nonstenosed AV valve, as in the case of a large ASD, ventricular septal defect (VSD), or severe mitral insufficiency.

Systolic–Diastolic Murmurs. A continuous systolic–diastolic murmur that is heard most clearly in the second ICS just below the left clavicle is virtually pathognomonic for a *patent ductus arteriosus*. A loud systolic–diastolic murmur in adults may also be caused by a combined aortic valve disease, coarctation of the aorta, a ruptured sinus of Valsalva aneurysm, a membranous VSD with concomitant aortic insufficiency, arteriovenous fistulae, and aortopulmonary connections. A venous hum should also be considered. This murmur characteristically disappears during a Valsalva maneuver and becomes louder after the maneuver.

Heart Murmurs. Heart murmurs are characterized by the timing and duration of their occurrence, their pitch, intensity, pattern, quality, and location. The radiation of the murmur and its respiratory variations are also evaluated (see Tab. 20.**6**). Once these characteristics have been assessed, a differential diagnosis can be made (see Fig. 20.**6**). Three principal types of heart murmur are distinguished:

- systolic murmurs
- diastolic murmurs
- continuous systolic–diastolic murmurs.

Two main types of *systolic murmurs* are distinguished: ejection murmurs and regurgitant murmurs. Systolic ejection murmurs occur during the ejection phase of ventricular contraction, i. e., they begin in early to midsystole, are generally separate from the first heart sound, and terminate before the start of the second heart sound. Systolic ejection murmurs usually have a crescendo–decrescendo (spindle-shaped) pattern. Systolic regurgitant murmurs (e. g., caused by backflow through an incompetent mitral valve) usually begin with the first heart sound and persist into the second heart sound. Typically they are band-shaped and pansystolic.

With *diastolic murmurs*, a distinction is made between early-diastolic and mid- to late-diastolic murmurs. Early diastolic murmurs are caused by blood regurgitating through an incompetent valve, most commonly the aortic valve. These regurgitant murmurs usually have a high-pitched blowing quality with a decrescendo pattern. Unlike the regurgitant murmurs in early diastole, murmurs heard in mid to late diastole are caused by forward diastolic flow through the AV valves (mitral and tricuspid valves). They begin only after the AV valve has opened and the pressure in the ventricle has fallen below the atrial pressure. They are typically low-pitched (diastolic rumble).

20.4 Diagnostic Studies

Laboratory Tests

In addition to the measurement of BNP, comprehensive blood tests should be ordered in all patients who present with a presumptive diagnosis of heart failure. The tests should include a complete blood count, electrolytes, and renal and liver values. *Anemia* may cause dyspnea (high output heart failure) or may exacerbate the symptoms of heart failure. *Polycythemia* is found in patients with a cyanotic heart disease as well as in pulmonary diseases.

Diabetes should be excluded. Creatinine and protein levels in the urine provide information on renal damage caused by decreased perfusion. Hyponatremia may be a sign of severe decompensation in heart failure. The potassium level should be known before treatment is initiated because it may be directly affected by the therapy (diuretics, ACE inhibitors). Thyroid hormones should be measured if there is evidence of thyroid dysfunction as the cause of heart failure, and the iron status (including ferritin) should be determined if there is suspicion of hemochromatosis. In cases where amyloidosis is suspected, the urine should be screened for paraproteins. Serum and urinary protein electrophoresis should also be performed, and some cases may require evaluation by myocardial biopsy or subcutaneous fat biopsy and bone marrow aspiration. Specific autoantibody tests should be ordered in patients with rheumatoid disorders.

ECG

Because heart failure is a syndrome rather than a specific entity, it is not characterized by typical ECG changes. Nevertheless, most patients with cardiac dyspnea will have an abnormal ECG based on the underlying disease (e. g., myocardial ischemia, bundle branch blocks, arrhythmias).

It is common to find signs of *left or right ventricular overload* (Tab. 20.**9**). In patients with left or right ventricular hypertrophy, the electrical axis of the heart will deviate to the left or to the right, respectively. The increase in left or right ventricular muscle mass leads to

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an increased R-wave amplitude in the leads directed to the left or right side, respectively. A reciprocal pattern is seen in the leads directed away from the hypertrophic ventricle (deep S waves).

The quantification of this amplitude increase (using the Sokolow–Lyon index or Cornell criteria) permits a rough estimate of the severity of left ventricular hypertrophy. The increase in wall thickness also leads to conduction delays and ST-segment changes. The ST segment moves downward, starting from a lowered J point, toward an asymmetrically inverted T wave. Examples of typical ECG traces recorded in left ventricular and right ventricular hypertrophy are shown in Figs. 20.**28** and 20.**22**, respectively.

Table 20.**9** Frequent ECG findings in left and right ventricular hypertrophy

ECG in left ventricular hypertrophy	ECG in right ventricular hypertrophy
left axis deviation	right axis deviation – SI–QIII type, S1–S2–S3 type
tall R waves in V_6	R in $V_1 > 0.5$ mV or R > S
positive left Sokolow–Lyon index: – S in V_1 + R in V_5 or R in $V_6 > 3.5$ mV	positive right Sokolow–Lyon index: – R in V_1 + S in $V_5 > 1.05$ mV
repolarization abnormalities in V_3 through V_6 ST-segment depression of > 0.1 mV asymmetrical T-wave inversion	repolarization abnormalities in V_1 (through V_4) ST-segment depression asymmetrical T-wave inversion
lengthening of the QRS interval (> 110 ms)	
	P pulmonale: – tall P waves in (I), II, III, avF – P wave in II > 0.25 mV – negative P wave in avL

Chest Radiograph

The chest radiograph is helpful in recognizing changes in the size and shape of the heart and detecting signs of pulmonary congestion and pleural effusion. Chest radiographs are obtained in the posteroanterior (PA) and lateral projections. In a supine chest radiograph, the cardiac silhouette appears enlarged due to the divergence of the roentgen ray beam in the anteroposterior projection.

Cardiac Size. The size of the heart is described in terms of the *cardiothoracic ratio* (Fig. 20.**7**). This is not a precise method, however, and cardiac size can be evaluated only by taking into account the overall situation (body height, body weight, position of the diaphragm). The ratio of the maximum cardiac diameter (determined by adding the right and left radii, Fig. 20.**7**) to the maximum thoracic diameter normally does not exceed 0.5. The cardiothoracic ratio has proven most useful for tracking changes of cardiac size in the same patient.

The *orientation of the heart* may cause the cardiac silhouette to appear larger in the absence of true cardiac enlargement. This is especially likely to occur with a transversely oriented heart. Scoliosis that is convex to the right also creates the impression of an enlarged left heart. A mediastinal mass, a fat pad at the cardiac apex, and a funnel chest deformity (Fig. 20.**8**) can mimic cardiomegaly. The cardiac silhouette is also enlarged in a setting of chronic pericardial effusion. Signs of pulmonary congestion are usually absent in these cases, however (Fig. 20.**9**). Occasionally cardiomegaly is found in the absence of cardiac dysfunction, as in athletes or rarely in patients with an ASD.

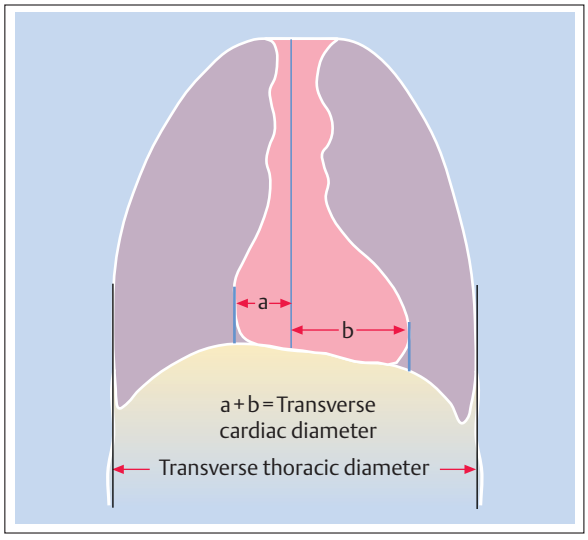

Fig. 20.**7** Measurement of the cardiothoracic ratio = transverse cardiac diameter: transverse thoracic diameter.

Please keep in mind that different causes (e.g., ventricular dilatation, ventricular aneurysm, pericardiac effusion) might contribute to cardiomegaly in the same patient.

Enlargement of Specific Cardiac Chambers. Enlargement of the *left ventricle* initially causes an enlargement of the outflow tract, especially in response to an increased pressure load on that chamber. This is characterized by downward elongation (by one ICS) and rounding of the left ventricular radiographic outline. These initial changes are followed later by dilation and widening of the heart toward the left side, deepening of the cardiac waist, and rounding of the upper outer border. The heart assumes an aortic or "duck-shaped" configuration

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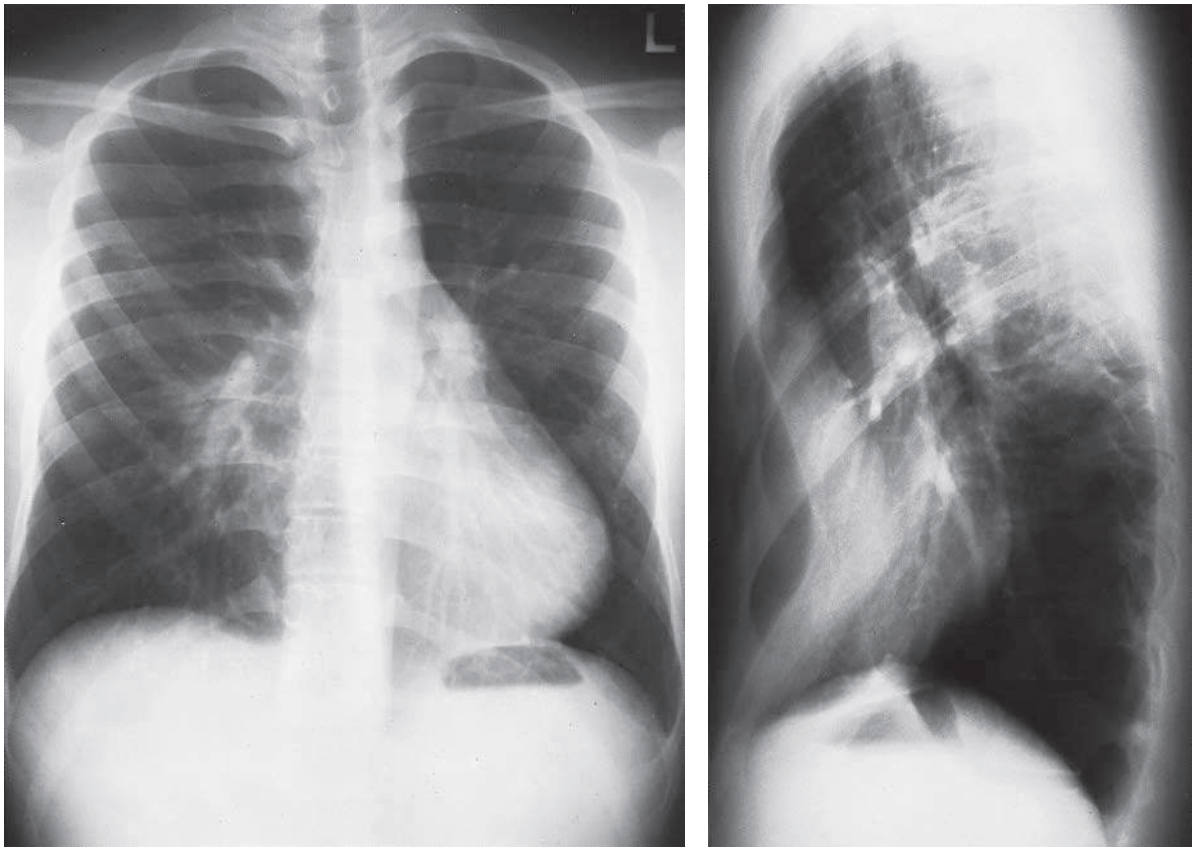

Fig. 20.**8** Funnel chest: a diagnostic pitfall in a 19-year-old man.
a PA view: displacement of the heart, due to funnel chest, which mimics an enlarged heart.
b Lateral view: conspicuous funnel chest.

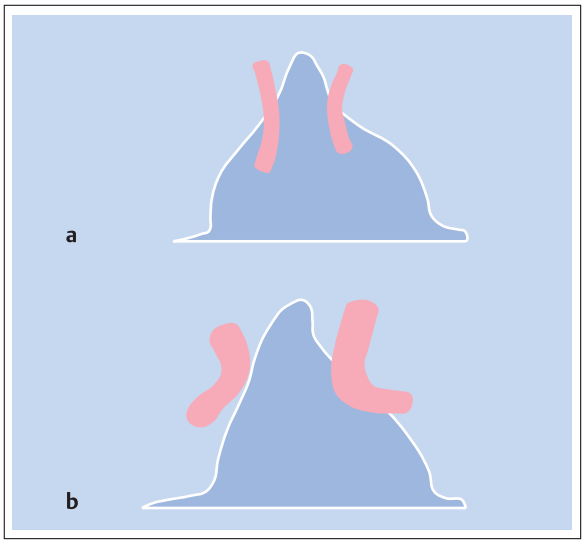

Fig. 20.**9** Differential diagnostic features in the chest radiograph; PA view.
a With a pericardial effusion the hili are obscured.
b In heart failure the hili are enlarged and laterally displaced.

(Fig. 20.**10**) reflecting eccentric hypertrophy of the left ventricle. Long-standing hypertension or decompensated aortic stenosis leads to severe enlargement of the left ventricle. The most pronounced eccentric hypertrophy, and thus the most pronounced degree of left ventricular enlargement, is seen in patients with severe chronic aortic insufficiency (see Fig. 20.**32**). Irregular protrusions of the cardiac outline in the region of the left ventricle suggest a myocardial aneurysm (Fig. 20.**11**).

Enlargement of the *left atrium* appears as a central shadow with splaying of the tracheal bifurcation (carina), an enlarged left atrial appendage that obscures the left cardiac border, and a double contour along the right atrium. In the lateral chest radiograph, the retrocardial space is indented at the atrial level (see Fig. 20.**37**).

Hypertrophy or mild enlargement of the *right ventricle* does not alter the appearance of the PA chest radiograph. However, a more pronounced degree of right ventricular dilatation is manifested by an elevation and rounding of the left cardiac border (Fig. 20.**12**). In contrast to left ventricular hypertrophy, however, the

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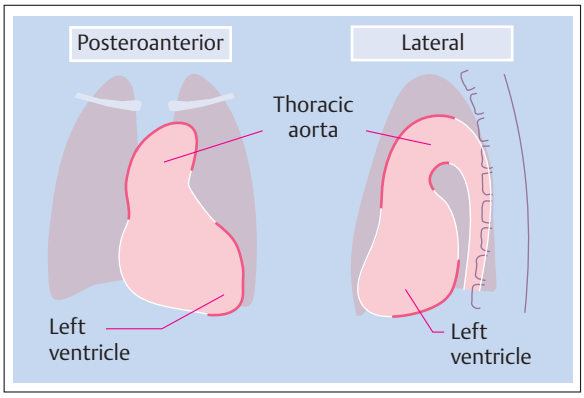

Fig. 20.**10** Aortic configuration (hypertensive heart). The left ventricle is enlarged, and the thoracic aorta is widened and elongated.

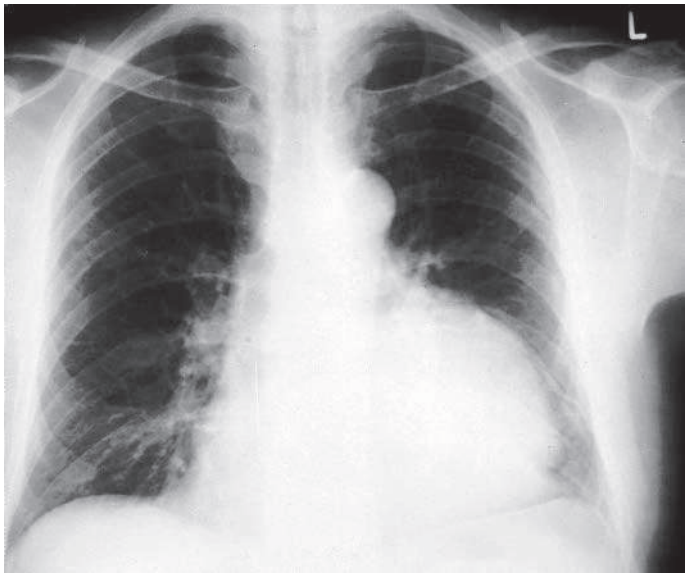

Fig. 20.**11** Myocardial aneurysm in a 65-year-old man.

apex is not elongated. The lateral radiograph shows obliteration of the retrosternal space (the triangular space between the sternum and anterior cardiac border). The PA radiograph shows fullness of the cardiac border. Usually this is accompanied by dilatation of the pulmonary artery, which forms a prominent feature on the left cardiac border (see Fig. 20.**21**).

Enlargement of the *right atrium* appears as an opacity expanding from the right side of the heart toward the right lung field.

Chronic heart failure resulting from dilatative cardiomyopathy or advanced coronary heart disease is characterized by a more or less pronounced *enlargement of all cardiac chambers* (Fig. 20.**13**).

Signs of Pulmonary Congestion. Pulmonary congestion is marked by excessive filling of the pulmonary vessels, and this is manifested by a *distension of the apical vessels* on the chest radiograph. With congenital heart defects that involve the abnormal shunting of blood (e. g., atrial septal defect), there may be hypercirculation through

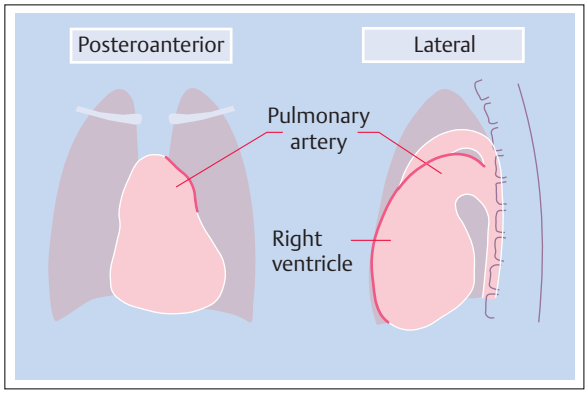

Fig. 20.**12** Configuration of the heart with an enlarged right ventricle.

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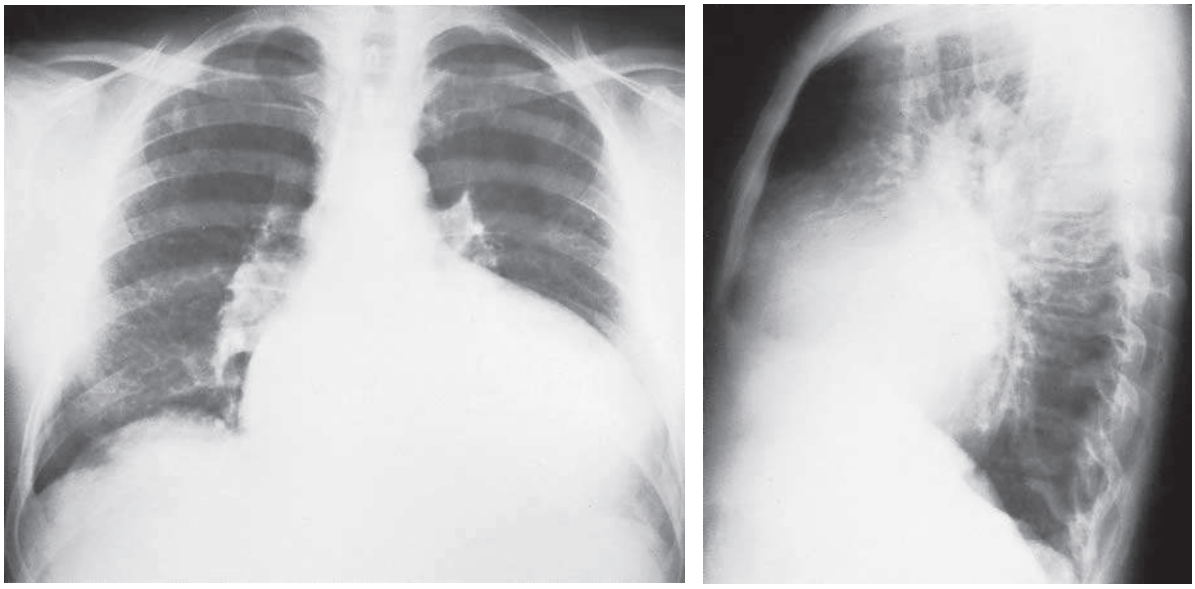

Fig. 20.**13** Massive enlargement of all cardiac chambers in a 49-year-old man with dilatative cardiomyopathy. Cardiac catheterization showed no evidence of mitral insufficiency. The coronary arteries are normal.

a PA view shows enlargement of the left ventricle and right atrium.

b Lateral view shows enlargement of the right ventricle and left atrium.

the lung with no concomitant signs of heart failure. As the pulmonary capillary pressure continues to rise, fluid is extravasated first into the interstitium and then into the alveoli, appearing on radiographs as *interstitial or alveolar edema*. In patients with chronic heart failure, there may be such a massive compensatory increase in pulmonary drainage that extravascular fluid is not increased even with heavy capillary fluid extravasation, and the radiograph shows no evidence of interstitial or alveolar edema. Pulmonary edema is much more common in cases with an acute onset of pulmonary congestion:

- *Stage 1 pulmonary congestion: pulmonary congestion without edema.* A baso–apical redistribution is noted in the upright chest radiograph. It is normal for hydrostatic pressure gradients to exist between the upper and lower portions of the lung. As a result, pulmonary veins are collapsed in the upper zones and engorged in the basal zones. However, the increased pulmonary venous pressure creates an elevated pressure throughout the lung, so that the pulmonary veins in the upper lobe show increasing dilatation (normal apical-to-basal ratio of vascular diameters = 1:3, changing to 1:1 when congestion is present). As the pressure rises, the pulmonary hila enlarge and are displaced laterally while the pulmonary vascular markings become generally more prominent (Fig. 20.**9**).
- *Stage 2 pulmonary congestion: interstitial pulmonary edema.* When the congestion exceeds the capacity of the pulmonary vessels, interstitial edema develops. Fluid accumulation around the bronchioles, arterioles, and venules may lead to a central loss of vascular boundaries. Edematous thickening of the interlobar septa appears as parallel horizontal linear opacities in the basal peripheral lung zones above the costodiaphragmatic recess: known as *Kerley B lines* (Fig. 20.**14**). Kerley lines are produced by widening of the lymphatic vessels and thickening of the interlobar spaces that enclose them. When Kerley lines are observed, this means that the pulmonary capillary wedge pressure is greater than 25 mmHg (normal range is 8–10 mmHg). They are distinguished from linear atelectasis by their sharp outlines. They are also narrower.
- *Stage 3 pulmonary congestion: alveolar pulmonary edema.* Rupture of the tight junctions between the alveolar cells leads to the development of alveolar edema, which creates areas of ground-glass opacity on radiographs. Acute pulmonary edema due to a cardiac cause initially affects the hilum and spreads from there to involve the rest of the lung ("butterfly edema"). Occasionally, however, the edema is distributed diffusely over the lung zones. Stage 3 is also characterized by increasing pleural effusions.

Echocardiography

Echocardiography (cardiac ultrasound) is the most important noninvasive imaging modality for examining the heart. With echocardiography, it is possible not only to evaluate the structures of the heart but also to describe their function. At the same time, *Doppler echocardiography* can be used to map the blood flow in the heart and measure the blood flow velocity through the cardiac valves, thus providing an indirect means of calculating

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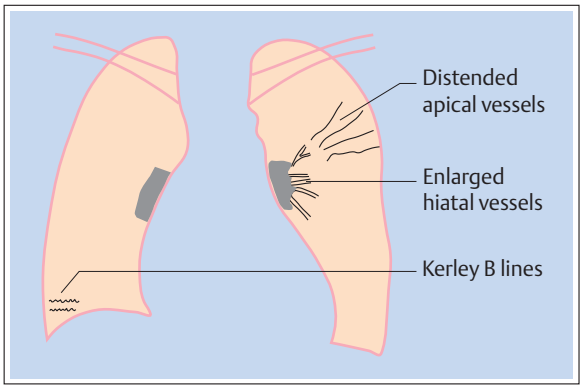

a

Fig. 20.**14** Severe pulmonary congestion with interstitial pulmonary edema. Radiographs show distended apical vessels, enlarged hilar vessels, and Kerley B lines.
a Schematic representation
b PA view
c Kerley B lines indicating pulmonary congestion.

b

c

the pressure gradients across the valves. In most cases the examination can be done noninvasively by scanning the heart through the chest wall (= transthoracic echocardiography). The principal techniques are *M-mode echocardiography* and *two-dimensional echocardiography*. M-mode echocardiography can record the precise dimensions of the walls, septa, and cardiac chambers. Two-dimensional echocardiography provides instantaneous two-dimensional sectional images through the heart (Fig. 20.**15**), making it possible not only to record the dimensions of the cardiac chambers but also detect anatomical variants and abnormalities. It is the simplest and fastest way to obtain information on the function of the heart. The examiner can quickly appreciate regional abnormalities of wall motion, such as those occurring in ischemia or myocardial infarction. This principle is applied in stress echocardiography, which can detect ischemic abnormalities of wall motion induced by physical exercise (treadmill or bicycle ergometry) or dobutamine infusion. *Stress echocardiography* has proven equivalent to radionuclide scanning in the detection of myocardial ischemia. At present, many cardiac diseases and cardiomyopathies are diagnosed entirely by echocardiography. It is also an excellent modality for detecting pericardial effusion and its functional consequences, looking for vegetations in endocarditis, and detecting thrombi or tumors involving the heart.

Doppler Echocardiography

Principle. Doppler echocardiography makes use of the physical principle that when sound waves encounter a moving object, they undergo a change of wavelength called a *frequency shift*. The moving objects in the bloodstream are erythrocytes, which are reflectors of ultrasound. The transmitted and reflected frequencies are compared, and the Doppler formula is used to calculate the velocity of the moving red cells. The frequency shift of the reflected ultrasound can be used to determine both the velocity and the direction of blood flow (erythrocytes!). The higher the flow velocity, the greater the

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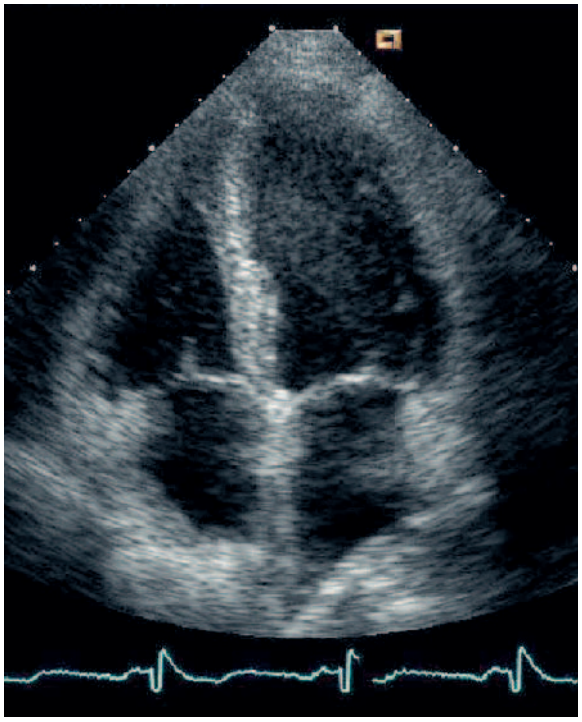

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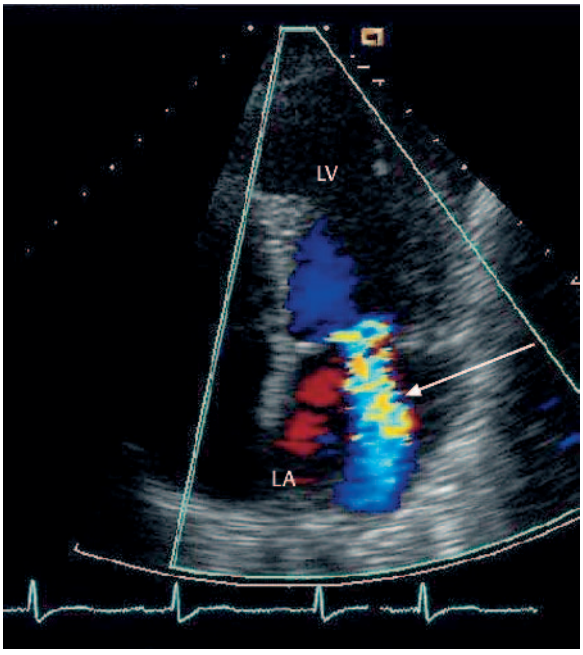

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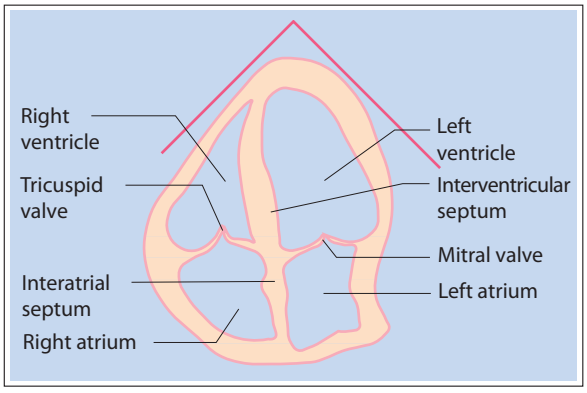

b

Fig. 20.**15** Echocardiography: apical four-chamber view of the heart.
a Two-dimensional echocardiogram immediately after closure of the mitral and tricuspid valves and before the start of systole.
b Correlative diagram showing the principal heart structures.
c Regurgitant jet from the left ventricle into the left atrium (arrow), demonstrated by color-coded Doppler echocardiography.

frequency shift. The frequency shift is also used to color-code the blood flow. By convention, blood flow toward the transducer (ultrasound probe) is encoded in red while blood flow away from the transducer is encoded in blue. This provides a visual means of detecting normal blood flow, regurgitation, and the shunting of blood (e. g., a ventricular septal defect).

Valvular Stenosis. The acceleration of blood flow velocity that occurs at sites of narrowing (e. g., stenotic heart valves) is used to calculate the *degree of severity* of the stenosis. The "modified Bernoulli equation" is used to derive a *pressure gradient* from the blood flow velocities. Modified Bernoulli equation:

$$\text{Pressure gradient (mmHg)} = 4 \times (\text{flow velocity in m/s})^2$$

Based on the pressure gradients calculated with Doppler echocardiography and the valve opening area determined by two-dimensional echocardiography, it is possible to measure aortic valve stenosis, mitral valve stenosis, and pulmonic stenosis noninvasively, and if necessary, refer the patient for operative treatment.

Valvular Insufficiency. Doppler echocardiography also makes it possible to measure the maximum blood flow velocity across an incompetent valve. The maximum velocity of the regurgitant jet is proportional to the pressure gradient between the two chambers. This principle is utilized for the noninvasive measurement of the pressure gradient between the right ventricle and right atrium in patients with tricuspid insufficiency. In most cases the pressure in the pulmonary circulation can be assessed noninvasively by this method (Fig. 20.**16**). Color-coded Doppler echocardiography can also be used to measure the width of the regurgitant jet at its origin, enabling a semiquantitative assessment of the severity of aortic insufficiency, mitral insufficiency, or tricuspid insufficiency.

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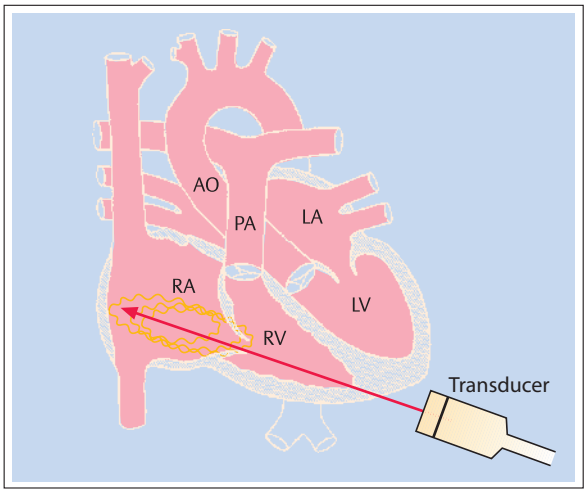

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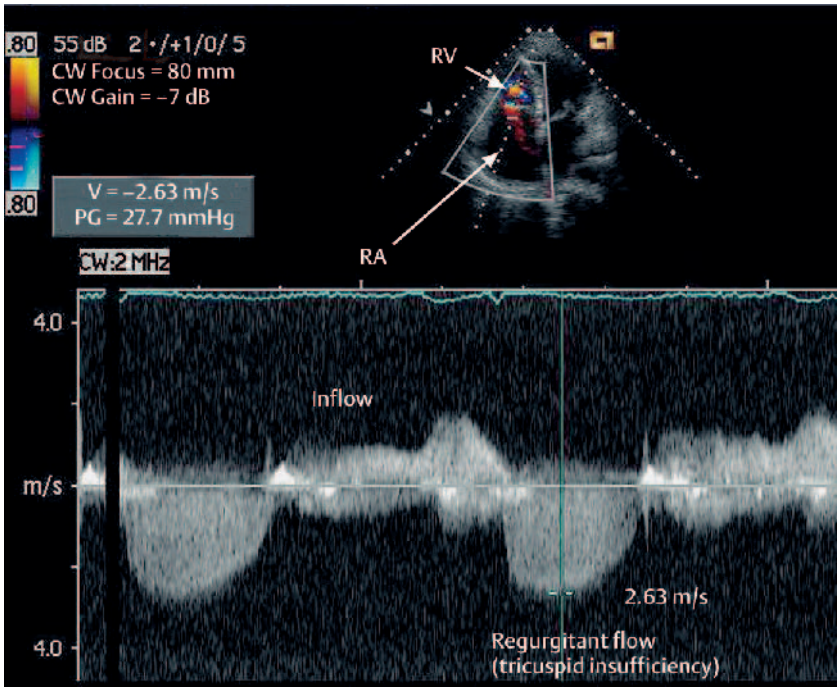

b

Fig. 20.**16** Doppler echocardiographic measurement of the pressure gradient (PG) between the right ventricle and right atrium.

a Schematic diagram; the continuous-wave (CW) Doppler beam is directed from the cardiac apex through the right ventricle and across the tricuspid valve into the right atrium.

b Doppler echocardiography measures the velocities of the inflowing blood and regurgitant jet in tricuspid insufficiency. The velocity of the regurgitant jet (2.63 m/s) is proportional to the pressure gradient between the RV and RA. Pressure difference between right ventricle (RV) and right atrium (RA) = four times the velocity squared = 4×2.63^2 = 27.7 mmHg. This corresponds to a normal systolic RV pressure.

AO = aorta
LA = left atrium
LV = left ventricle
PA = pulmonary artery

Hemodynamic Studies. Additionally, precise hemodynamic studies can be performed with Doppler echocardiography by recording the patterns of blood flow across the different AV valves, in the different cardiac chambers, and in the venous system and documenting their changes in response to respiration and position changes. This principle is applied in differentiating between constrictive and restrictive pathophysiology, diagnosing pericardial tamponade (see Fig. 6.**20**, Chapter 6), and evaluating the pathophysiological effects of congenital valvular defects.

Transesophageal Echocardiography

In transesophageal echocardiography, the ultrasound probe is passed down the esophagus and positioned just behind the left atrium in contact with the heart. This technique eliminates intervening bony structures, resulting in higher quality echocardiographic images. Transesophageal echocardiography is used in screening for endocarditis, evaluating prosthetic valve dysfunction, and looking for cardiac sources of emboli. Transesophageal echocardiography can also provide detailed morphological views of the AV valves. It has a special role in evaluating abnormalities of the aortic root, ascending aorta, aortic arch, and the thoracic part of the descending aorta. Transesophageal echocardiography is the diagnostic procedure of choice in suspected cases of

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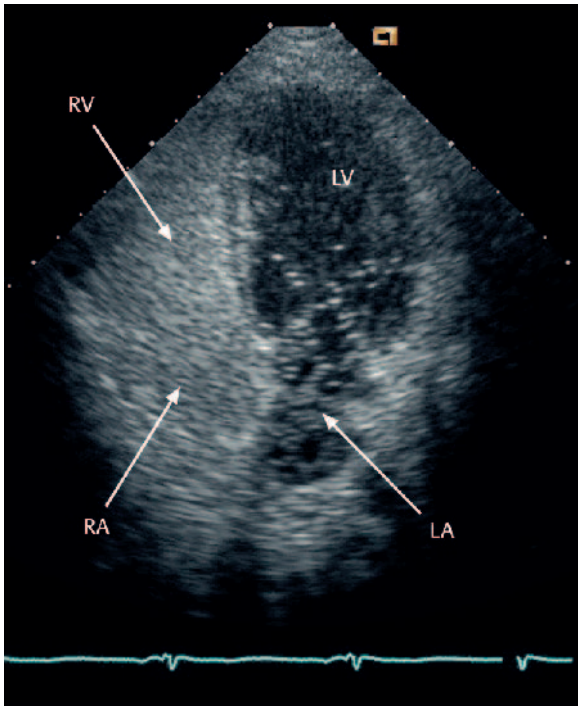

Fig. 20.**17** Right-to-left shunt demonstrated by contrast echocardiography. A saline solution is shaken with air and injected intravenously. The microbubbles are echogenic. The right atrium (RA) and right ventricle (RV) are completely filled with bubbles. After a Valsalva maneuver, bubble-enhanced blood has passed into the left atrium (LA) and left ventricle (LV), confirming the presence of a right-to-left shunt.

aortic dissection, and it is used in selected cases for the evaluation of congenital defects. An experienced examiner can resolve many questions by means of transesophageal echocardiography.

Contrast Echocardiography

The blood and erythrocytes are not visible in an ordinary echocardiogram. Occasionally it is important to make the blood visible, however, e. g., in order to improve delineation of the endocardium or to facilitate the detection of shunts. The normally invisible blood can be made visible in the echocardiogram by the injection of special ultrasound contrast agents. Blood that has been enhanced by the contrast agent produces a white "*snowstorm pattern*" on the ultrasound monitor. The least expensive echo contrast agent is *shaken saline solution*. Shaking the syringe (e. g., 16 mL of 0.9 % NaCl and 4 mL of air) causes tiny air bubbles (microbubbles) to enter the saline solution. The air above the solution is removed, and the shaken saline solution is injected into an arm vein. The progression of the microbubbles provides clear visualization of intracardiac shunts and also defines the boundaries of the cardiac chambers with greater clarity.

Besides its use in shunt defects, this technique is also used in screening for a *patent foramen ovale*. The patent foramen ovale may allow small emboli or gas bubbles to pass from the venous system into the arterial system, giving rise to paradoxical emboli. Thus, contrast echocardiography can be used after a cryptogenic stroke to look for a patent foramen ovale so that paradoxical emboli can be excluded or appropriate treatment can be initiated if a patent foramen is found. This is accomplished with the *bubble test*, in which shaken saline solution is injected into a vein. When the right atrium has filled, the patient performs a Valsalva maneuver and the examiner checks to see if bubbles pass into the left atrium (Fig. 20.**17**).

Special glucose and protein solutions are also available commercially for contrast echocardiography.

Intracardiac Echocardiography

A recent technique involves mounting the ultrasound probe on a cardiac catheter to permit intracardiac scanning. Intracardiac echocardiography supplies images that are comparable in quality to transesophageal echocardiograms. It is used mainly in interventional procedures for the repair of shunt anomalies (percutaneous closure of a type II atrial septal defect).

Computed Tomography (CT)

Computed tomography (CT) can be used to visualize the cardiac chambers. But its primary application is for investigating the *major arteries*, especially the aorta, in patients with a suspected aortic dissection. Increasingly, CT is able to define even very small structures. Currently, it can noninvasively detect stenotic lesions in the coronary arteries. Contrast-enhanced spiral CT is being used increasingly as an alternative to perfusion–ventilation scintigraphy in the diagnosis of acute pulmonary embolism.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) has found increasing applications in cardiology. It can provide highly detailed views of cardiac anatomy and of the arteries and veins supplying the heart. It can also be used to measure blood flow and detect perfusion discrepancies in the heart wall, enabling MRI to be used in the detection of myocardial ischemia (see Fig. 6.**12**, Chapter 6).

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Stress Testing

Because stress intolerance is an essential feature of heart failure and many cardiac diseases, the assessment of maximum stress tolerance is important for determining the severity of heart disease, making a prognosis, and evaluating response to therapy.

Three stress tests are currently used in routine clinical evaluations: bicycle or treadmill ergometry, spiroergometry, and the six-minute walking test. It is important to note, however, that none of these tests can adequately evaluate cardiac performance when used alone. Besides cardiac performance, exercise capacity depends on pulmonary function, oxygen transport capacity (hemoglobin content of the blood), and the individual level of physical conditioning. This must be considered in interpreting the test results.

Ergometry. The ergometric determination of *submaximal exercise capacity* is generally done on a calibrated bicycle or treadmill ergometer. The submaximal exercise capacity is the capacity that can be achieved at a "submaximal heart rate" of 170 bpm under relatively steady-state conditions with regard to pulse rate and respiration. The *submaximal pulse rate* decreases with advancing age. As a general rule of thumb, the submaximal pulse rate is 210 minus the patient's age (in years) bpm.

The ideal values for submaximal exercise capacity are statistical values based on examinations conducted in large normal populations (Fig. 20.**18**). They are dependent on age, gender, and height. It has proven useful to state the effective exercise capacity of a patient as a percentage of the ideal value. A value less than 80% of the ideal value is considered abnormal.

Spiroergometry. In spiroergometry, oxygen uptake is measured during application of the exercise stress. This makes it possible to determine the *anaerobic threshold*, or the point during exercise at which the respiratory quotient rises and lactic acid is produced. Exercise is continued to the point at which maximum oxygen uptake ceases to increase or until the patient must stop exercising due to dyspnea or exhaustion. The normal value for *maximum oxygen uptake* is 25 mL/kg/min. A reduction in maximum oxygen uptake is a good measure for the severity of heart failure and is used as an objective parameter in assessing the need for heart transplantation.

Six-Minute Walking Test. Because the level of exertion in daily activities is different from the exertion of maximum exercise capacity, the six-minute walking test has established itself as a useful supplementary test. It tests the *exercise capacity* of the patient at a constant level of effort *below the anaerobic threshold*. It measures how far the patient can walk on level ground in six minutes. The patient is allowed to stop and rest at any time during the six-minute test period. The distance covered is a measure of the patient's exercise capacity. This test is particularly useful in patients with severe heart disease and patients with pulmonary hypertension.

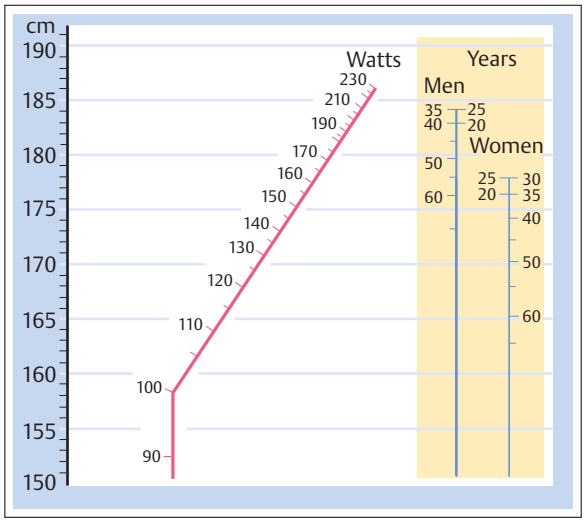

Fig. 20.**18** Nomogram for determining submaximal exercise capacity.

Cardiac Catheterization

A complete cardiac catheterization study includes catheterization of the left heart with pressure measurement and left ventricular angiography, catheterization of the right heart, and coronary angiography. It allows accurate measurements of *hemodynamics*, *contractility*, *volumes*, and the *left ventricular ejection fraction*. An important part of the study is to detect or exclude *coronary heart disease* by coronary angiography. Catheterization of the right heart with simultaneous oximetry makes it possible to measure the *cardiac output* and the *resistance* in the systemic and pulmonary circulations. Diagnostic cardiac catheterization is frequently done as an adjunct to echocardiography.

Cardiac catheterization is also being used increasingly for *therapeutic interventions*. Thus, mitral valvuloplasty has become the treatment of choice for mitral stenosis, even with partially calcified valves. Open heart surgery may be indicated after an unsuccessful percutaneous procedure or in patients with very heavily calcified valves. Pulmonic stenosis is treated almost exclusively by the percutaneous route. Similarly, shunt defects can be repaired percutaneously under favorable anatomical conditions. This applies to type II atrial septal defects, patent ductus arteriosus, and patent foramen ovale.

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20.5 Acute Heart Failure

It is helpful from a clinical standpoint to distinguish between acute and chronic heart failure. Acute heart failure is frequently a dramatic event that warrants immediate hospitalization and treatment. Patients present with acute exercise intolerance and often have dyspnea at rest due to acute pulmonary edema. Extreme cases may show rapid development of cardiogenic shock. Clinical manifestations include anxiety, restlessness, and possible confusion due to the rapidity of onset. In cases with a volume overload of rapid onset, the heart is unable to respond with compensatory mechanisms (dilatation, hypertrophy, neurohumoral adaptations). For example, the rupture of a mitral valve leaflet due to mucoid degeneration or infectious endocarditis leads to immediate, severe mitral insufficiency. The regurgitant blood volume is forced into the normal-sized left atrium, in which the filling pressures must rise dramatically, occasionally until the atrial and ventricular pressures become equal during systole. These high pressures are transmitted directly to the pulmonary venous system, causing immediate and massive pulmonary edema. By contrast, severe chronic mitral insufficiency that has led to dilatation of the left atrium may be associated with only a moderate rise of left atrial pressure without a significant v wave, and the patient maintains good functional capacity for years without significant symptoms.

Causes. Acute heart failure may be caused by an acute pressure or volume overload on the systemic or pulmonary circulation, impaired cardiac filling, an acute decrease in myocardial contractility, or cardiac arrhyth-

Table 20.**10** Causes of acute heart failure

Acute pressure overload (increased afterload, mechanical flow obstruction)
– systemic hypertension
– hypertensive crisis
– decompensation of long-standing hypertension
– pulmonary hypertension
– pulmonary embolism
– mechanical flow obstruction
– thrombosis of a mechanical prosthetic valve
– atrial myxoma
Acute volume overload
– acute mitral insufficiency
– partial or complete papillary muscle rupture in acute myocardial infarction, infectious endocarditis, myxomatous degeneration
– dysfunction of a mitral valve prosthesis
– acute aortic insufficiency
– aortic dissection
– infectious endocarditis
– ruptured sinus of Valsalva aneurysm
– prolapse of a valve leaflet
– paravalvular leak in an aortic valve prosthesis
– acute tricuspid insufficiency
– traumatic
– infectious endocarditis
– ventricular septal defect after myocardial infarction
– iatrogenic volume overload
– renal failure
– pregnancy
Acute filling impairment
– thrombus in a mitral or tricuspid valve prosthesis
– acute pericarditis
– pericardial tamponade
Acute contractility impairment
– acute pump failure due to myocardial ischemia
– myocarditis
– cardiac allograft rejection
– intoxication
– drug overdose (e. g., calcium antagonists)
Cardiac arrhythmias
– supraventricular and ventricular tachycardias
– bradycardic arrhythmias (e. g., complete AV block)

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mias. The most frequent causes are listed in Tab. 20.**10**. The leading cause, *myocardial ischemia*, should first be confirmed or excluded by ECG and enzyme assays. It should be noted that, in most cases, acute heart failure may lead to nonischemic, usually subendocardial myocardial damage and thus to a slight rise in troponin levels (see Tab. 6.**12**, Chapter 6). Consequently, a slightly elevated troponin level should not be interpreted as ischemia induced by coronary stenosis.

Differentiating Acute Heart Failure from Acutely Decompensated Chronic Heart Failure

Acute heart failure with rapid onset of dyspnea at rest is occasionally difficult to distinguish from noncardiac acute *dyspnea*. The differential diagnosis should include an acute asthma attack, an exacerbation of chronic obstructive lung disease, pneumothorax, pulmonary embolism, acute respiratory distress syndrome (ARDS), and laryngeal edema. Metabolic acidosis due to various causes (diabetic ketoacidosis, uremia, poisoning, drug overdose) may produce similar symptoms. Hysterical hyperventilation should also be considered.

Acute heart failure requires differentiation from the *acute decompensation of chronic heart failure*. The latter condition is present when chronic stable heart failure or a chronic stable heart disease decompensates acutely.

> Acutely decompensated heart failure usually has a reversible or treatable cause. It is important to identify this cause.

The most frequent causes of cardiac decompensation are a new myocardial ischemia or arrhythmia, a systemic infection, the discontinuation of chronic medication, or adding medications that may cause decompensation due to fluid retention (e. g., NSAIDs, steroids). The possible use of medications or other substances that have a negative inotropic effect (calcium channel blockers or alcohol) should also be considered. Occasionally, poorly controlled hypertension may lead to acute decompensation. Other medical conditions such as anemia or a metabolic disorder such as hyperthyroidism may also cause chronic heart failure to decompensate.

Acute heart failure, acutely decompensated heart failure, and chronic heart failure can often be differentiated from one another based on the history, symptoms, and findings (Tab. 20.**11**). Patients with acute heart failure often manifest pronounced symptoms of backward failure (pulmonary embolism, dyspnea, and orthopnea). Many patients with acutely decompensated heart failure additionally complain of fatigue and weakness as a sign of decreased perfusion. Before decompensating, they often experience weight gain due to a volume overload and increased peripheral edema. Evaluation of the perfusion status and volume status (see Tab. 20.**4**) is helpful for instituting appropriate treatment.

Table 20.**11** Differential diagnosis of acute, acutely decompensated, and chronic heart failure (modified from Givertz et al. In: Braunwald, Zipes, Libby [eds.] Heart Disease, 6th ed.)

Symptom or finding	Acute heart failure	Acutely decompensated heart failure	Chronic heart failure
Symptom severity	severe	severe	mild
Pulmonary edema	frequent	frequent	rare
Peripheral edema	rare	frequent	frequent
Weight gain	little or none	frequent	frequent
Fluid retention	little	marked to severe	little to marked
Cardiomegaly	unusual	typical (except with diastolic dysfunction)	typical (except with diastolic dysfunction)
Systolic ventricular function (ejection fraction)	impaired, normal or hypercontractile	impaired	impaired
Sympathetic nervous system activation	severe	severe	slight (to pronounced)
Reversible cause	in most cases	frequent	occasional

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Pulmonary Edema and Cardiogenic Shock

Pulmonary edema and cardiogenic shock are the two most dramatic clinical manifestations of acute heart failure. Both require immediate diagnosis and treatment.

Pulmonary Edema

Pathophysiology and Definition. Normally a constant fluid exchange takes place between the pulmonary vascular bed and the interstitium of the lung. Fluid that extravasates at the start of the capillary bed (transudate) is reabsorbed by the intravascular colloid osmotic (oncotic) pressure or is drained off by lymphatic vessels. Pulmonary edema develops when fluid extravasation outstrips reabsorption by the capillaries and exceeds the drainage capacity of the lymphatics. The rate of fluid reabsorption is determined by the intravascular and interstitial oncotic pressure. The normal pulmonary capillary pressure is 8–12 mmHg, and the normal oncotic pressure of the plasma is approximately 25 mmHg. This pressure differential ensures the complete reabsorption of the fluid. When the hydrostatic intravascular (pulmonary capillary) pressure rises and approaches 18–25 mmHg, interstitial edema occurs initially, and alveolar edema develops at higher pressures (Fig. 20.**19**).

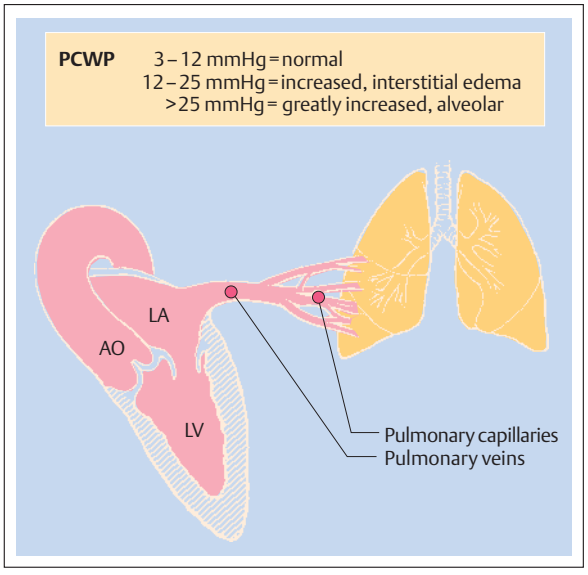

Fig. 20.**19** Pulmonary capillary wedge pressure (PCWP) and pulmonary congestion. The heart is shown in diastole with the mitral valve open to illustrate how the left ventricle (LV), left atrium (LA), and pulmonary veins form a common chamber connected to the capillary bed. As a result, the left ventricular diastolic pressure determines the PCWP and is responsible for the presence or absence of pulmonary congestion or pulmonary edema. AO = aorta.

Pulmonary edema may also result from damage to the alveolar capillary membrane or from a fall in the oncotic pressure. Insufficient lymphatic drainage is rarely a cause of pulmonary edema. Conversely, a compensatory increase of lymphatic drainage in patients with heart failure may be sufficient to prevent the development of clinically overt pulmonary edema at high pulmonary capillary pressures.

Three stages of pulmonary edema can be distinguished based on the degree of fluid accumulation:

- In stage 1, all excess fluid can still be cleared by lymphatic drainage.
- Stage 2 is characterized by the presence of *interstitial edema*.
- Stage 3 is characterized by *alveolar pulmonary edema* due to rupture of the alveolar membrane, which allows fluid and proteins to enter the alveolar space.

Clinical Features. Fully established pulmonary edema is a life-threatening event in patients with left ventricular heart failure. Typical symptoms are the development of very severe dyspnea within a very short time, anxiety, and a cough productive of frothy white, pink, or blood-tinged sputum. The patient either sits upright or stands (to reduce congestion at the lung apex), breathes very rapidly, and uses auxiliary muscle effort to assist respirations. He breathes loudly through flared nostrils. Areas of intercostal and supraclavicular retraction reflect the high negative intrapleural pressure that is necessary for inspiration.

Most patients present with *tachycardia* and *hypertension* (unless there is associated cardiogenic shock), which further exacerbate the left-sided heart failure and accentuate the symptoms of pulmonary edema. Other common features are cold sweats, pallor, and occasional cyanosis. A warm periphery would suggest that the pulmonary edema has a noncardiac cause.

Auscultation of the chest reveals coarse, moist bubbling rales and wheezing. The lung sounds make cardiac auscultation difficult, but it may be possible to hear a third heart sound and a prominent second heart sound (increased pulmonic component).

Diagnosis. The diagnosis of acute pulmonary edema is made from the clinical presentation, auscultation, and the chest radiograph. In most cases pulmonary edema is not a difficult diagnosis, but it may be difficult to determine its cause (Tab. 20.**12**). It is often necessary to postpone an accurate differential diagnosis and provide immediate symptomatic treatment. Once the patient has been stabilized, a detailed work-up may be performed.

Basically it is helpful to distinguish between cardiogenic and noncardiogenic pulmonary edema. A *detailed history* that includes questions about preexisting cardiac or pulmonary disease and cardiac medications may yield important information. In some cases the clinical

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situation and cause are obvious, as in patients who become symptomatic after smoke inhalation, near drowning, heroin or cocaine overdose, or excessive fluid infusion. Otherwise the patient should be questioned specifically about possible toxins (gases, medications, drugs), possible aspiration, radiation exposure, and infections.

Cardiac auscultation can supply important evidence of valvular disease or a congenital anomaly as a cardiac cause. Peripheral edema, hepatomegaly, and distended neck veins consistent with right-sided heart failure are important signs of preexisting cardiac failure.

Laboratory tests can provide evidence of an infection, electrolyte disorders, possible renal failure, and hypoproteinemia. A *blood gas analysis* is important in assessing the extent of hypoxemia. Approximately half of patients with pulmonary edema have hypocapnia and alkalosis as a result of hyperventilation. The remainder have eucapnia or even hypercapnia, which is frequently combined with acidosis.

In equivocal cases, *echocardiography* and *right heart catheterization* will usually make it possible to confirm or exclude a cardiac cause of pulmonary edema. Right heart catheterization, usually with a Swan–Ganz balloon-tipped catheter, can measure the pulmonary capillary *wedge pressure* in order to determine whether the edema stems from an elevated pulmonary venous pressure, which would most likely indicate a cardiac cause. It should be noted, however, that the pulmonary capillary pressure may return to normal after the initiation of treatment while clinical and radiograph signs of pulmonary edema still persist. This is because some time is needed for reabsorption of the excess fluid. *Oximetry* and *pressure measurements in all cardiac chambers* also makes it possible to detect a specific cardiac cause. If an abnormally high v wave (1.5 times the average wedge pressure) is found, it may signify a new onset of mitral insufficiency.

Noncardiac pulmonary edema should be suspected if the chest radiograph shows that the infiltrates have a more peripheral than perihilar distribution. Oximetry in noncardiac pulmonary edema often shows a large intrapulmonary shunt volume, and percutaneously aspirated lung fluid is found to have high protein content upon analysis. Cardiac pulmonary edema may also cause damage to the alveolar capillary membrane, however, and therefore the findings are often equivocal.

Table 20.**12** Causes of pulmonary edema, grouped according to causal mechanisms

Increased pulmonary capillary pressure
- cardiac causes (see Tab. 20.**10**, Causes of acute heart failure)
  - acute pressure overload (e. g., hypertension)
  - acute volume overload (e. g., mitral insufficiency, aortic insufficiency)
  - impaired filling (e. g., mitral stenosis)
  - acute pump failure (e. g., acute ischemia)
- noncardiac causes
  - fibrosis of pulmonary veins, stenosis of pulmonary veins (congenital or iatrogenic, pulmonary veno-occlusive disease)
- excessive iatrogenic fluid infusion

Alveolar–capillary membrane damage
- infectious (viral, bacterial, parasitic) pneumonia
- inhaled toxins (e. g., smoke, phosgene, ozone, chlorine, nitrogen dioxide)
- other toxins (snake venom, bacterial endotoxins)
- aspiration of gastric acid
- vasoactive compounds (histamine, kinins)
- disseminated intravascular coagulation
- immunogenic reaction (hypersensitivity pneumonia)
- uremia
- postirradiation pneumonia
- adult respiratory distress syndrome (ARDS)
- acute hemorrhagic pancreatitis

Decreased oncotic pressure
- hypoalbuminemia in renal failure, hepatopathy, enteropathy, malnutrition

Lymphatic insufficiency
- carcinomatous lymphangitis
- fibrosing lymphangitis (e. g., silicosis)
- after lung transplantation

Increased negative interstitial pressure
- after the rapid expansion of a pneumothorax

Complex or unknown mechanisms
- high-altitude pulmonary edema
- neurogenic pulmonary edema (e. g., after trauma, epilepsy, subarachnoid hemorrhage
- narcotic overdose (e. g., heroin, methadone)
- pulmonary embolism (very rare)
- eclampsia
- after cardioversion
- after general anesthesia
- after cardiopulmonary bypass
- bradycardic arrhythmias (e. g., complete AV block)

Causes. Virtually any heart disease that impairs the pumping ability of the heart or interferes with inflow to the heart may cause pulmonary edema acutely or by acute decompensation. By far the *most frequent causes* of acute cardiac pulmonary edema, however, are *hypertension*, *mitral insufficiency*, and *myocardial ischemia*. Pulmonary edema in hypertension is particularly common in older patients and shows a preponderance in women. Hypertension leads to concentric hypertrophy of the left ventricle, whose stiffness is further increased by age-associated fibrosis (formerly known as hypertensive hypertrophic cardiomyopathy in elderly women). This form of pulmonary edema is a classic example of how pure diastolic dysfunction can lead to pulmonary congestion (see Tab. 20.**1**). However, hypertension that has led to eccentric hypertrophy and impaired pump function may also be manifested by pulmonary edema. Often it is possible to diagnose ischemia based on the history and ECG. Acute mitral insufficiency is often more difficult to recognize. The otherwise typical holosystolic regurgitant murmur of mitral insufficiency may be shortened because the pressures between the atrium and ventricle have already equalized during systole. The murmur may even be absent if papillary

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muscle rupture has occurred, creating a condition known as "silent mitral insufficiency."

Special Forms of Pulmonary Edema. Some forms of pulmonary edema can not be definitely attributed to a known mechanism (see Tab. 20.**12**). But most of these forms can be identified by analyzing the circumstances and history.

High-altitude pulmonary edema occurs in otherwise healthy, usually young individuals who ascend rapidly to an altitude of more than 2500 m (> 8000 Ft) and then engage in strenuous physical activity. Although the hypoxia-induced rise in pulmonary arterial pressures is certainly an important pathogenic factor, it is still unclear why, at equal pressure levels, some patients develop high-altitude edema and others do not. Genetic predisposition and immunological factors must play a role.

Neurogenic pulmonary edema occurs in a number of cerebral disorders (epilepsy, trauma, subarachnoid hemorrhage). It is assumed that central stimulation of the sympathetic nervous system causes a redistribution of blood flow from the systemic to the pulmonary circulation, leading secondarily to a rise in the pulmonary capillary pressure.

Pulmonary edema in a setting of *preeclampsia* or *eclampsia* is found in approximately 3% of eclampsia patients. It is more common in older multiparous women with preexisting hypertension. It is associated with a high fetomaternal morbidity and mortality.

Pulmonary edema after a *heroin overdose* is probably a result of membrane injury. Other *narcotics* that may cause pulmonary edema are methadone, morphine, cocaine, and dextropropoxyphene.

Pulmonary edema *after general anesthesia* may be a side effect of the anesthetic agents, but is more likely due to other causes such as laryngospasm, hypoxia, or a hyperadrenergic state.

A number of *viral*, *bacterial*, and *parasitic infections* (e. g., *Hantavirus*) may cause noncardiac pulmonary edema. Infectious lung edema is usually preceded by fever, cough, malaise, and gastrointestinal symptoms.

Cardiogenic Shock

Pathophysiology and Definition. Circulatory shock may be caused by a cardiac disease or by a number of noncardiac diseases. Circulatory shock is a *state of inadequate tissue perfusion*, which, when untreated, leads to irreversible organ damage and death. The primary hemodynamic problem is not the hypotension that is often present but the inadequate tissue perfusion. In most patients with circulatory shock, the decreased organ perfusion develops over a period of several hours.

The development of cardiogenic shock can be divided into three stages:

- *Stage 1*: recruitment of compensatory mechanisms is evidenced by sympathetic nervous system activation with incipient peripheral vasoconstriction (cold extremities) and tachycardia. The patient is relatively free of complaints and is often still normotensive.
- *Stage 2* is marked by the initial signs and symptoms of inadequate organ perfusion. The blood pressure is usually reduced at this stage, tachycardia is present, and the patient is restless. Metabolic acidosis is present, and urine output falls to less than 20 mL/hour. This stage is also called preshock.
- *Stage 3* is characterized by a critical decline in organ perfusion. The extremities are cold and there is little or no urine output. The patient is hypotensive, tachycardic, and increasingly somnolent or comatose. Unless an adequate cardiac output can be restored in this fully established state of shock, a vicious cycle develops with a compensatory increase in vasoconstriction that further exacerbates the inadequate organ perfusion.

Causes of Circulatory Shock. Most cases have a cardiac etiology. Virtually all diseases that cause acute heart failure (see Tab. 20.**10**) or a chronic decompensated cardiac disorder may lead to cardiogenic shock.

The *most frequent cause* is an *extensive myocardial infarction* with left ventricular pump failure. Cardiogenic shock complicates approximately 5% of all myocardial infarctions. Additionally, an *extensive right ventricular myocardial infarction* and *mechanical complications* (ventricular septal defect, papillary muscle rupture, ventricular rupture; see Chapter 6) also lead to cardiogenic shock. A right ventricular infarction should be presumed in patients with distended neck veins, absence of pulmonary congestion in the chest radiograph, and hypotension due to an inferior myocardial infarction. Patients with a predominantly right ventricular infarction or ruptured ventricular septum present initially with signs of low cardiac output and right-sided heart failure. Patients with left ventricular pump failure or a papillary muscle rupture present initially with significant dyspnea and pulmonary edema. Mechanical complications and left ventricular pump failure generally occur in association with a large myocardial infarction. The exception is an ischemic papillary muscle rupture, which may result from even a small myocardial infarction located at the site of the papillary muscle. Mechanical complications are more likely to arise in elderly women who have suffered their first myocardial infarction. With the advent of reperfusion therapy (thrombolysis or primary angioplasty), mechanical complications have become less frequent (approximately 2% of infarctions) but occur earlier in the course of the infarction. While mechanical complications generally arise several days (up to a week) after an untreated myocardial infarction, the majority of reperfused patients experience mechanical complications during the first 12–48 hours after reperfusion therapy.

Among other cardiac causes, *valvular insufficiencies* are the most common diseases leading to cardiogenic shock. Severe mitral insufficiency may result from a partial or complete chordae tendineae rupture due to a myxomatous mitral valve or infectious endocarditis.

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Acute aortic insufficiency may develop as a consequence of endocarditis or an aortic dissection.

In patients with a prosthetic heart valve, valvular dysfunction is assumed to be the cause of cardiogenic shock until proven otherwise. The decompensation of a severe aortic stenosis or mitral stenosis or the mechanical obstruction of ventricular filling by an atrial myxoma are other potential causes of cardiogenic shock.

Diagnosis. In most cases the diagnosis is made from the history, ECG, and clinical examination. Questionable cases can generally be resolved by transthoracic or transesophageal echocardiography. Low or normal right and left ventricular filling pressures measured during right heart catheterization would suggest a noncardiac cause for the shock.

Differential Diagnosis. Cardiogenic shock requires differentiation from other forms of shock. *Hypovolemic shock* following trauma, burns, bone fractures, and copious diarrhea or vomiting is generally easy to recognize, based on the associated conditions. If hypovolemic shock is suspected but there are no external signs of bleeding, the patient should be examined for intestinal bleeding or other internal hemorrhage.

Septic shock is most commonly caused by infection with Gram-negative bacteria. Examination often reveals a warm periphery, hematologic signs of infection, and metabolic acidosis, suggesting the correct diagnosis.
Less frequent causes of circulatory shock are anaphylaxis, drug overdose, an Addison crisis, and myxedema. It is important to consider that the pumping ability of the heart may be impaired to some degree, even in noncardiogenic shock. This is probably due to the release of cytokines (such as TNF-α), NO, or endotoxins.

20.6 Chronic Heart Failure

Definition. Heart failure is a condition in which the heart is unable to supply enough blood to the peripheral organs at rest or during physical activity. Heart failure is diagnosed clinically in patients who show signs of pulmonary congestion or systemic venous congestion (distended neck veins, hepatomegaly, edema). Clinical examination and special tests will demonstrate structural changes (*remodeling*) and systolic or diastolic dysfunction of the left ventricle or other cardiac chambers and will usually show a decrease in cardiac output. Heart failure is generally a progressive syndrome.

Prevalence. The New York Heart Association classification is useful in describing the severity of heart failure (see Tab. 20.**3**). Chronic heart failure is the most prevalent heart disease in industrialized countries. It affects several million people worldwide and becomes more prevalent with the ageing of society. Its prevalence is 1% from 50–59 years of age and 5–10% from 80–89 years of age. Despite major therapeutic advances, heart failure is still associated with a high morbidity and mortality. Heart failure is the most frequent indication for hospital referral. NYHA class III or IV heart failure has a 20–40% mortality rate per year. Many patients die of ventricular arrhythmias or myocardial infarction.

Causes. A variety of heart diseases and mechanisms can lead to heart failure. The most important are listed in Tab. 20.**13**. The leading cause is *coronary heart disease* (> 50%), followed by *hypertensive heart disease* (> 20%), *cardiomyopathies* (5–10%), and *valvular heart disease* (5%). An accurate etiologic diagnosis is important in planning specific treatment. In some cases the disease can be permanently cured while in others it can only be controlled with pharmacologic agents. But even in these cases, an understanding of etiology and pathophysiology is important so that appropriate and specific therapy can be provided.

Table 20.**13** Causes of chronic heart failure

Causes	Examples
Pressure overload	hypertension – arterial hypertension – pulmonary hypertension obstruction of ventricular outflow – aortic stenosis – pulmonic stenosis
Volume overload	valvular insufficiencies – aortic insufficiency – mitral insufficiency – tricuspid insufficiency – pulmonary insufficiency increased blood flow – shunt defects (e. g., ASD, VSD, PDA) – increased peripheral demand (high output failure)
Impaired filling	stenosis of AV valves – mitral stenosis – tricuspid stenosis – tumors (e. g., atrial myxoma) pericardial changes – pericardial tamponade – constrictive pericarditis myocardial changes – hypertrophic cardiomyopathy – restrictive cardiomyopathy (e. g., myocardial fibrosis, amyloidosis, sarcoidosis, Fabry disease)
Impaired contractility	global myocardial disease – cardiomyopathies (e. g., dilatative, drug-induced) – myocarditis segmental myocardial disease – myocardial ischemia, coronary heart disease
Cardiac arrhythmias	tachycardic arrhythmias bradycardic arrhythmias (e. g., AV block, sick sinus syndrome)

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20.7 Causes of Heart Failure

Differential Diagnosis of Heart Failure Due to Pressure Overload

Basic Pathophysiologic Concepts

A pressure overload in the systemic or pulmonary circulation may be caused by a rise in the circulatory pressure or by a mechanical obstruction to outflow from the left or right ventricle. The pathophysiologic effects of this pressure overload depend very little on the cause of the pressure rise. The increased pressure places a strain on the myocytes, which must do more work and increase their oxygen consumption accordingly. The heart initially responds to this increased load with several compensatory mechanisms. If the pressure load persists or increases, these compensatory mechanisms may become overwhelmed, leading to decompensation and pump failure of the affected ventricle (Fig. 20.**20**).

Concentric Hypertrophy. The initial response to a pressure rise in the left ventricle is hypertrophy of the myocytes, i. e., the existing muscle cells enlarge in their transverse dimension. This leads to *concentric hypertrophy of the left ventricle*. This concentric hypertrophy tends to normalize the tension of the left ventricular wall. The Laplace law states that the wall tension of a spherical chamber is equal to the pressure (P) times the chamber radius (R) divided by twice the wall thickness (h): wall tension = P × R/2h. When the wall tension is normalized, the oxygen consumption also returns to normal. This beneficial response is reinforced by the structural transformation of the myocytes and of contractile proteins. Specifically, a "myosin isoenzyme shift" takes place (e. g., *beta myosin heavy chain*), which enables the myocytes to expend energy more efficiently. The development of concentric hypertrophy, then, is favorable in terms of energy consumption and systolic function. But it also decreases the *elastic compliance* of the left ventricle and leads to an impairment of diastolic function. The ventricle becomes progressively stiffer due to increasing interstitial fibrosis of the pressure-loaded chambers.

Clinically, this stage of concentric hypertrophy is characterized by signs and symptoms of *diastolic dysfunction*. Exercise, in particular, leads to pulmonary congestion and dyspnea while the left ventricle still maintains a normal size and a normal ejection fraction. The patient may also experience angina pectoris due to a decrease in the coronary flow reserve (see Chapter 6). For reasons still unknown, the hypertrophy is often most pronounced in the region of the ventricular septum, leading to *asymmetrical septal hypertrophy*. This can be demonstrated to some degree in almost all patients with severe aortic stenosis. It is particularly common in hypertensive women with concentric hypertrophy. Asymmetrical septal hypertrophy may lead to forward motion of the anterior leaflet of the mitral valve during systole ("*systolic anterior motion,*" *SAM*). This prevents complete closure of the mitral valve, resulting in mitral insufficiency.

Eccentric Hypertrophy. As the pressure overload persists, the ventricle undergoes a progressive eccentric hypertrophy. At this stage the myocytes not only thicken but

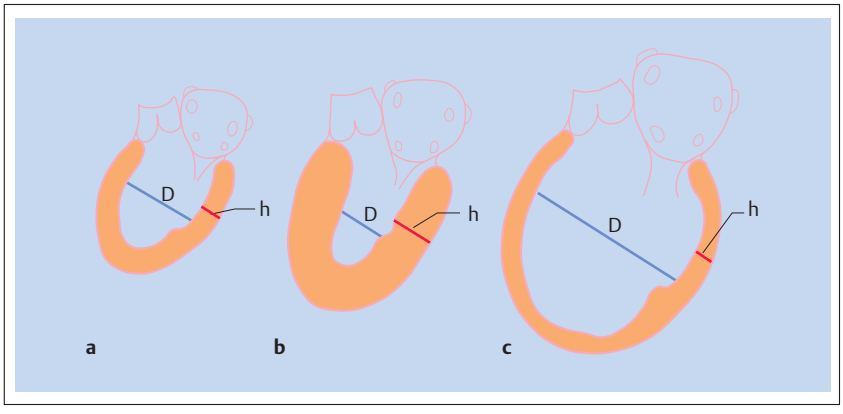

Fig. 20.**20** Adaptation and maladaptation of the left ventricle in response to an increased pressure load. A pressure load on the heart induces concentric hypertrophy of the left ventricle, causing a decrease in the intraventricular diameter (D) and an increase in wall thickness (h). The stage of concentric hypertrophy is characterized by a decrease in both the volume and compliance of the left ventricle. As the pressure-loaded heart decompensates, the hypertrophic ventricle becomes progressively dilated and its pumping ability is impaired.
a normal heart
b concentric hypertrophy
c eccentric hypertrophy (dilatation and decompensation).

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also elongate. The sustained pressure overload also leads to apoptosis and thus to the *destruction of myocardial cells*. The dead myocytes are replaced by fibrotic tissue. Morphologically, the ventricle increasingly enlarges while becoming less compliant, culminating in *decreased myocardial contractility*. This stage is characterized by signs of diastolic dysfunction (i. e., pulmonary congestion and dyspnea), during physical activity and occasionally even at rest, accompanied by signs of *systolic dysfunction* with marked exercise intolerance. In most cases, dilatation of the left ventricle also leads to dilatation of the mitral valve annulus and thus to *mitral insufficiency*. The increasing mitral valve incompetence leads to a progressively greater volume load, causing a further increase in wall tension and a further decrease in myocardial contractility.

Especially in cases where a mechanical outflow obstruction (aortic or pulmonic stenosis) is present, the ejection fraction is reduced not only due to decreased myocyte contractility but also in a large part due to the greatly *increased afterload*. Though still contractile, the myocytes are unable to shorten because of the high pressure load, and the ejection fraction is correspondingly reduced. This condition is called an "*afterload mismatch*." If the afterload can be reduced (e. g., performing an aortic valve replacement), the left ventricle may be able to recover its pumping ability. A significant improvement is often seen immediately after the operation, although it may take many months or several years to reestablish a completely normal ejection fraction or normal ventricular geometry. A decrease in myocytic hypertrophy is among the earliest changes, while the regression of heavy interstitial fibrosis takes much longer. The dominant clinical features at this stage are signs of diastolic dysfunction with pulmonary congestion and dyspnea on exertion.

Arterial Hypertension

The causes of arterial hypertension are described in Chapter 23. Hypertension is the leading cause of myocardial damage due to an increased pressure load. After coronary heart disease, it is the second leading cause of chronic heart failure.

Symptoms. The hypertensive patient remains asymptomatic for years. As diastolic dysfunction develops, dyspnea is increasingly experienced during physical activity. With the development of severe concentric hypertrophy, *acute pulmonary edema* may occur in extreme cases (see Pulmonary Edema, above). Besides acute pulmonary edema, a massive pressure increase may precipitate a *hypertensive crisis*. This is a condition in which signs of pulmonary edema are accompanied by signs of microvascular damage in other organs. Generally, the diastolic blood pressure must rise higher than 150 mmHg for this type of damage to occur. This stage is characterized by *microvascular lesions*, *hemorrhages*, and *exudates*, particularly in the eyes (retinal hemorrhage, papilledema), cerebrum (headache, confusion, somnolence, visual loss, epileptic seizures), and kidney (oliguria and azotemia). It is also marked by gastrointestinal symptoms such as nausea and vomiting. A hypertensive crisis requires immediate hypotensive therapy.

Hypertensive crisis requires *differentiation* from acute left-sided heart failure, uremia, stroke, subarachnoid hemorrhage, brain tumor, head trauma, epilepsy, collagen diseases, pharmacologic side effects, and hypercalcemia.

In cases where left ventricular decompensation occurs due to arterial hypertension, the patient presents with the typical symptoms of heart failure. The signs of left-sided heart failure are predominant, followed later by signs of right-sided heart failure with systemic venous congestion, hepatomegaly, and lower extremity edema.

Cardiac Findings. A *heaving widened apex* beat is noted on palpation. Auscultation reveals a loud second heart sound (accentuated aortic sound), and often there is an audible fourth heart sound indicating diastolic dysfunction. A third heart sound may also be heard in a later stage. A *systolic ejection murmur* is frequently present. In cases with concomitant mitral insufficiency, a typical systolic regurgitant murmur is audible over the cardiac apex. Signs of right-sided heart failure are also noted in patients with decompensated heart failure.

Diagnostic Studies

- *ECG:* this method demonstrates the typical features of left ventricular hypertrophy (see Tab. 20.**9**), although the ECG signs of hypertrophy are not very reliable.
- *Echocardiography:* currently, the left ventricular muscle mass can be accurately determined by echocardiography. This method can also be used to determine the ejection fraction and diastolic dysfunction based on Doppler gradients. Additionally, echocardiography can define the extent of a possible subaortic flow obstruction associated with asymmetrical septal hypertrophy, and it can document the presence of mitral insufficiency.
- *Chest radiograph:* the chest radiograph shows the typical signs of left ventricular hypertrophy or increasing ventricular dilatation (see Diagnostic Studies, p. 619 and Fig. 20.**10**, above).

Pulmonary Hypertension

Definition and Introduction. Pulmonary hypertension is defined as a persistent elevation of the mean pulmonary arterial pressure (> 25 mmHg at rest or > 30 mmHg during exercise) or of the systolic pressure (> 35 mmHg at rest or > 55 mmHg during exercise).

Severe pulmonary hypertension is a rare disease. It may be *idiopathic* or may be *associated* with numerous

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Table 20.**14** Clinical classification of pulmonary hypertension (Venice 2003)

1. Pulmonary arterial hypertension
- 1.1 Idiopathic pulmonary arterial hypertension
- 1.2 Familial pulmonary hypertension
- 1.3 Pulmonary hypertension associated with
  - 1.3.1 Connective-tissue disease
  - 1.3.2 Congenital left-to-right shunt
  - 1.3.3 Portal hypertension
  - 1.3.4 HIV infection
  - 1.3.5 Drugs and toxins
  - 1.3.6 Other conditions (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative syndromes, splenectomy)
- 1.4 Associated with significant pulmonary venous or capillary involvement
  - 1.4.1 Pulmonary veno-occlusive disease
  - 1.4.2 Pulmonary capillary hemangiomatosis
- 1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left-sided heart disease
- 2.1 Left-sided atrial or ventricular heart disease
- 2.2 Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung disease and/or hypoxemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep apnea syndrome
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Thromboembolic obstruction of distal pulmonary arteries
- 4.3 Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous causes
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (e. g., adenopathy, tumor, or fibrosing mediastinitis)

pulmonary, cardiac, or systemic diseases. It imposes an *increased pressure load on the right ventricle* and may induce eccentric hypertrophy and dilatation of the right ventricle. A heart with right ventricular hypertrophy and dilatation secondary to pulmonary hypertension is known also as cor pulmonale.

The incidence of idiopathic pulmonary hypertension is one to two cases/million/year. Women are predominantly affected. Many other diseases may cause or precipitate pulmonary hypertension (Tab. 20.**14**). Idiopathic and other forms of pulmonary hypertension are often undiagnosed or are diagnosed at a late stage. Patients with pulmonary hypertension show a significant decline in exercise tolerance and a significant reduction of life expectancy. Most patients live only a few years after their condition is diagnosed.

Table 20.**15** Symptoms and signs of pulmonary hypertension

Symptoms
– dyspnea (60 %)
– fatigue
– angina pectoris
– presyncope and syncope
– Raynaud phenomenon (10 %)
– palpitations (30 %
– rare: cough, hemoptysis, hoarseness
Signs
– louder second heart sound with accentuation of P2
– distended neck veins
– right precordial impulse (present in 38 %)
– hepatomegaly
– peripheral edema
– ascites
– systolic regurgitant murmur of tricuspid insufficiency (late sign)
– central or peripheral cyanosis (late sign)

Clinical Features. Patients with pulmonary hypertension often present with nonspecific signs and symptoms (Tab. 20.**15**).

> The clinical triad of dyspnea with a (nearly) normal chest radiograph, essentially normal pulmonary function, and a normal blood analysis should raise suspicion of pulmonary hypertension.

Dyspnea, *fatigue*, and *syncopal attacks* are the most common symptoms, reflecting an inability of the heart to increase its output during exercise. *Raynaud phenomenon* is a common finding in patients whose pulmonary hypertension is associated with an autoimmune disease. The pathogenic mechanism of *angina pectoris* in pulmonary hypertension is not fully understood (see Chapter 6). A rare symptom is hoarseness caused by compression of the left recurrent laryngeal nerve by the dilated pulmonary artery (Ortner syndrome). The symptoms of pulmonary hypertension are often difficult to distinguish from those of the associated pulmonary or cardiac diseases. In many patients, however, these diseases produce specific symptoms that point to the cause of the pulmonary hypertension.

Clinical abnormalities are basically limited to the cardiovascular system and include signs of *elevated pulmonary pressure*, followed by decompensation and *right-sided heart failure* (Tab. 20.**15**). A strong jugular pulse in the neck signifies tricuspid insufficiency, which develops late in the course of the disease. Similarly, central or peripheral cyanosis is a hallmark of very advanced disease. Clubbing of the fingers is not a typical feature of pulmonary hypertension and is a more likely indicator of cardiac disease. *Auscultation of the lungs* may provide important clues to the etiology of pulmonary hypertension. Wheezing suggests a chronic obstructive lung disease, basal rales indicate a cardiac dis-

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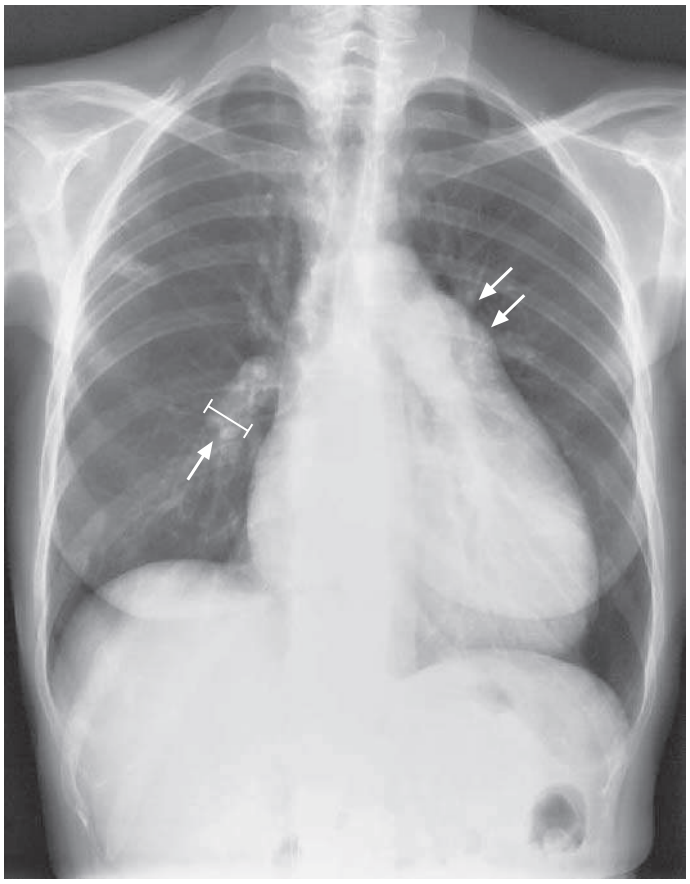

Fig. 20.**21** Chest radiograph in primary pulmonary hypertension shows global dilatation of the heart with a prominent pulmonary arterial segment (two arrows) and dilatation of the right lower lobar artery (one arrow). The lung fields appear normal.

ease or interstitial lung disease, and a high-pitched bruit may be audible over the lung in pulmonary hypertension due to a thromboembolic disease.

Diagnostic Studies

- *Chest radiograph:* in over 90% of cases, chest radiographs in pulmonary hypertension show enlargement of the pulmonary arteries and enlargement of the hilar vessels accompanied by attenuation of the peripheral lung vessels. The most sensitive sign of pulmonary hypertension in the chest film is an increased diameter (> 15 mm) of the right descending pulmonary artery (Fig. 20.**21**).
- *ECG:* the ECG shows signs of right ventricular hypertrophy in over 50% of patients (see Tab. 20.**9**, Fig. 20.**22**).
- *Pulmonary function test:* pulmonary function testing should be performed in patients with suspected pulmonary hypertension. The findings are almost always normal. Tests occasionally show a mild restrictive ventilatory defect, mild hypoxemia, and mild hypocapnea. A marked reduction of diffusion capacity is found only occasionally.
- *Echocardiography:* echocardiography is the diagnostic modality of choice when pulmonary hypertension is suspected. It permits the severity of pulmonary hypertension to be qualitatively and quantitatively assessed (see Fig. 20.**16**). Severe pulmonary hypertension causes a flattening of the interventricular septum with paradoxical motion of the septum during systole (Fig. 20.**23**). When pulmonary insufficiency is present, Doppler echocardiography can be used to assess the mean pulmonary arterial pressure. Echocardiography can also detect possible cardiac causes of pulmonary hypertension, most notably atrial and ventricular shunt defects, congenital heart diseases, valvular diseases, and impaired left ventricular function with elevated pulmonary venous pressures. Echocardiography is the cornerstone of the diagnostic work-up (Fig. 20.**24**).
- *Laboratory tests:* laboratory tests are an important aid to differential diagnosis. When pulmonary hypertension is present but its etiology is uncertain, it is always necessary to exclude an HIV infection. Other chronic viral infections, such as hepatitis B and C, may cause pulmonary hypertension that is secondary to the liver disease. The patient should be evaluated for autoimmune diseases such as systemic scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis by autoantibody testing (anticentromere, anti-Scl-70, anti-U1-snRNP, anti-Jo-1, anti-dsDNA, anti-SM) and rheumatoid factor testing if there is clinical

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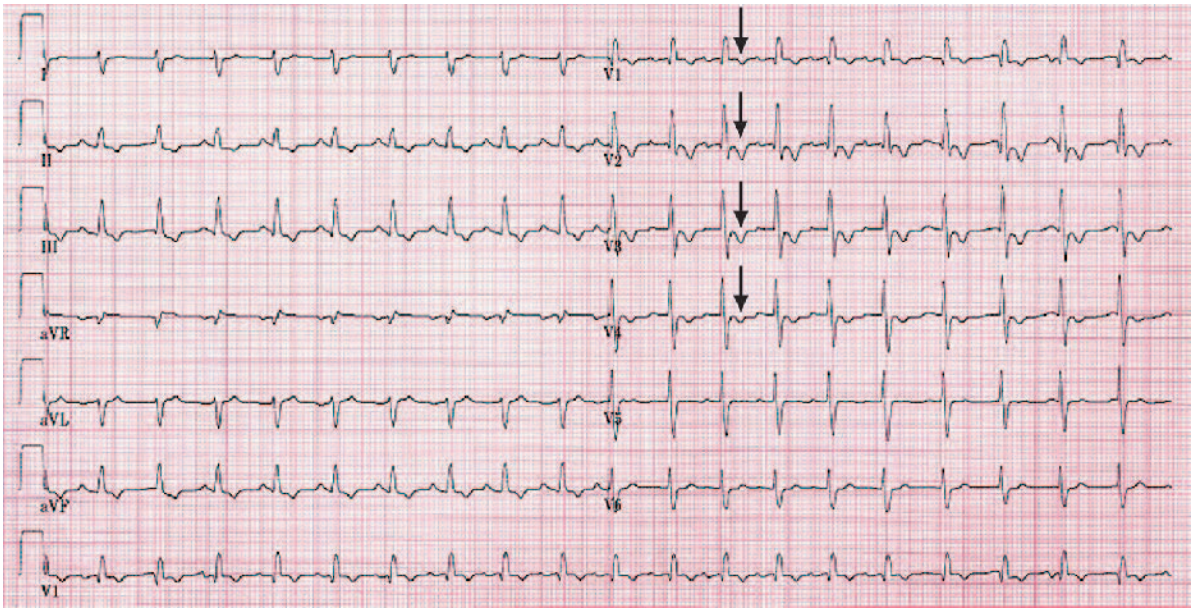

Fig. 20.**22** ECG in pulmonary hypertension. Typical findings are right axis deviation and the right ventricular delay (incomplete right bundle branch block with a persistent S wave through to V_6). The curved ("snow-shovel"-shaped) ST-segment depressions in V_1 through V_4 and ST-segment depression in II, III, and aVF are also typical.

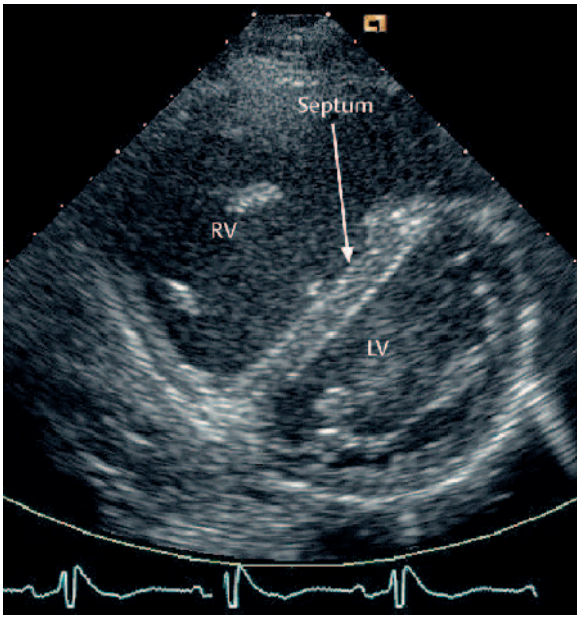

Fig. 20.**23** Two-dimensional echocardiogram (parasternal short-axis view) in pulmonary hypertension. Note the flattening of the interventricular septum and the "D"-shaped left ventricle (LV). The right ventricle (RV) is markedly dilated.

evidence that may suggest an autoimmune process. Thyroid disorders should be excluded by TSH testing.

Classification of Pulmonary Hypertension. Pulmonary hypertension was formerly classified into a primary and a secondary form. Any case for which a cause could not be identified was classified as primary pulmonary hypertension. It was later discovered, however, that this form may have a familial occurrence and may be precipitated by risk factors or other diseases. Both forms are characterized by similar morphological changes in the pulmonary arterioles. Consequently the terms primary and secondary pulmonary hypertension were abandoned, and currently this form of pulmonary arterial hypertension is distinguished from pulmonary arterial hypertension caused by other diseases (see Tab. 20.**14**).

The first category includes the following:

- idiopathic pulmonary hypertension (formerly called primary pulmonary hypertension)
- familial pulmonary hypertension
- pulmonary hypertension associated with other diseases and risk factors
- pulmonary hypertension combined with a concomitant disease of the pulmonary veins or capillaries
- persistent pulmonary hypertension in newborns (see Tab. 20.**14**).

Risk Factors. Certain risk factors promote the development of pulmonary hypertension. They include *medications* and *toxins* such as aminorex, fenfluramine, dexfenfluramine, and toxic rapeseed oil. It is likely that amphetamines, L-tryptophan, cocaine, and certain chemotherapeutic agents can also precipitate pulmonary hypertension. Female gender, pregnancy, and systemic hypertension are also considered to be risk factors. A Swiss study published in 1967 first established the link between an appetite suppressant (aminorex) and the development of pulmonary hypertension. When the appetite suppressant is discontinued, the pul-

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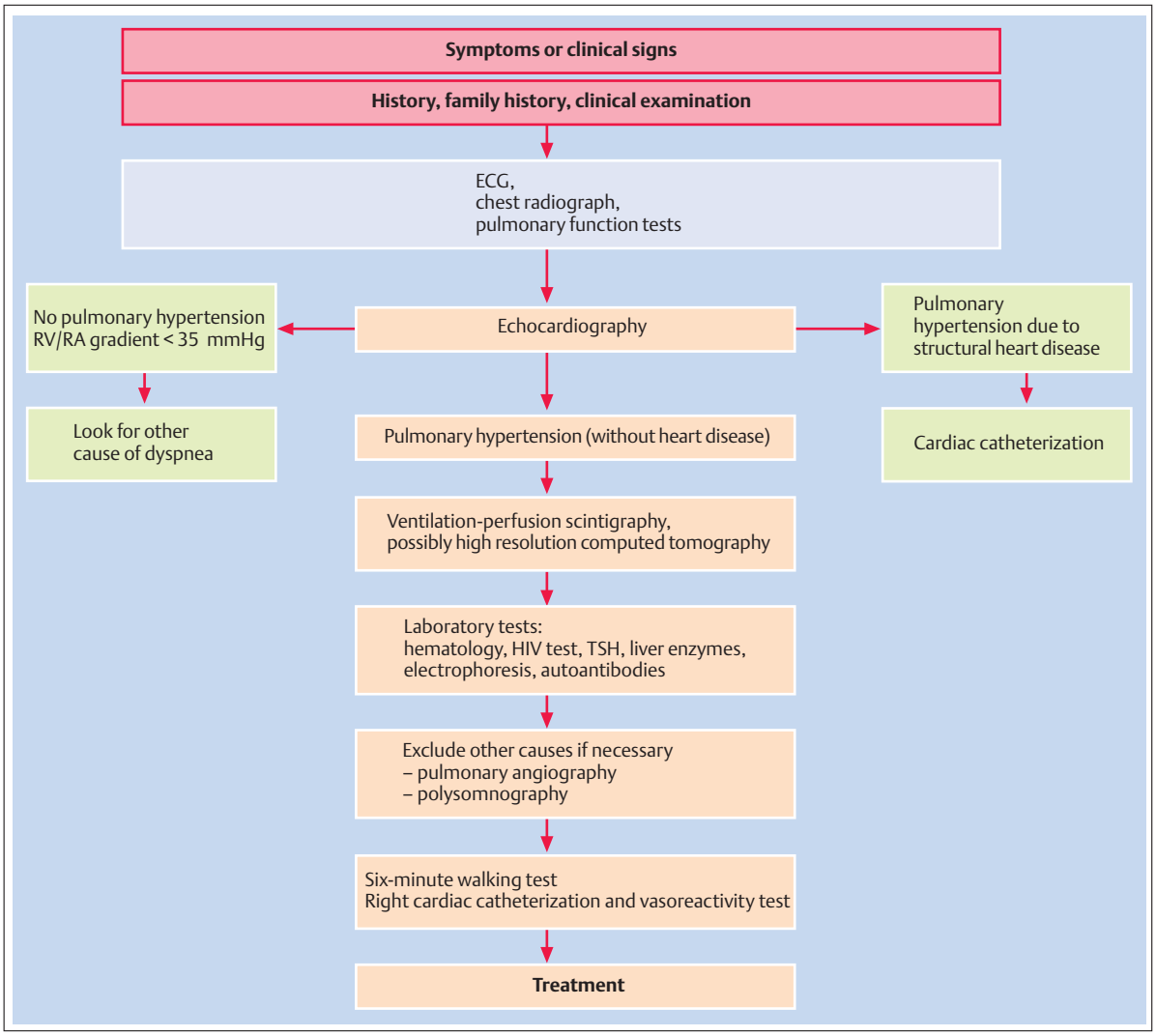

Fig. 20.**24** Algorithm for the investigation of pulmonary hypertension.

monary hypertension may resolve but does persist in some cases and may take a course similar to that of idiopathic pulmonary hypertension.

Associated Diseases. Diseases that may be associated with pulmonary hypertension are HIV infection, portal hypertension, collagen diseases, and congenital systemic left-to-right shunts. However, none of these diseases are precursors of pulmonary hypertension per se. Rather, they appear to trigger pulmonary hypertension in patients who already have a corresponding *genetic predisposition*. The prevalence of pulmonary hypertension in HIV infection, portal hypertension, and appetite suppressant use ranges from 1–2%.

An abnormal shunt at the ventricular level has been found to have a high association with pulmonary hypertension. On the other hand, pulmonary hypertension is relatively rare (< 5%) in patients with a left-to-right shunt at the atrial level (atrial septal defect, anomalous return of the pulmonary veins).

Other Underlying Diseases. The etiology of pulmonary arterial hypertension precipitated by other diseases is often easier to determine. In many cases a detailed history in itself will suggest the underlying causes or predisposing factors. In cases that present with orthopnea and a positive hepatojugular reflex, it is very likely that pulmonary arterial hypertension is secondary to *left-sided heart failure*. Both of these symptoms are absent in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension develops in 2% of patients with *hepatic cirrhosis* and *portal hypertension*. Portopulmonary hypertension is characterized by a more or less pronounced increase in pulmonary resistance and a marked rise of pulmonary pressure. More commonly, hepatic cirrhosis is associated with *hepatopulmonary syndrome*, in which the dilated pulmonary capillaries and shunt vessels lead to a substantial increase in cardiac output and increased pressures in the pulmonary circuit, but do not cause a significant increase in pulmonary resistance. Hepatopulmonary syndrome is

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associated with telangiectasias (spider nevi), digital clubbing, and dyspnea on exertion.

Chronic recurrent pulmonary embolism may lead to pulmonary hypertension. This condition is easily differentiated from idiopathic pulmonary hypertension by noting the segmental defects that are demonstrated by pulmonary scintigraphy, spiral CT, or pulmonary angiography. It is important to know that idiopathic pulmonary hypertension is also associated with local thrombus formation in the distal pulmonary arteries. As a result, pulmonary scintigraphy may also demonstrate subtle peripheral defects in idiopathic pulmonary arterial hypertension. Local thrombus formation probably contributes to the progression of pulmonary hypertension, and therefore all patients with pulmonary hypertension should be placed on anticoagulant therapy.

Aortic Stenosis

Etiology and Pathogenesis. Aortic stenosis creates a valvular obstruction of the left ventricular outflow tract. The most frequent cause in adults up to age 70 is a *calcified bicuspid aortic valve*. A congenital bicuspid aortic valve is present in approximately 1–2% of the population and is more common in men than in women. The bicuspid valves tend to calcify from their base due to incomplete opening. The most frequent cause after 70 years of age is *degenerative senile aortic valve calcification*. Three percent of patients over age 75 have severe aortic stenosis. Aortic valve stenosis due to a rheumatic valvular disease has become rare in industrialized countries. Very rare causes of aortic valve stenosis are Paget disease, alkaptonuria, and rheumatoid arthritis.

Aortic stenosis often develops slowly, causing a gradual increase in the pressure load on the left ventricle. The left ventricle adapts by undergoing a progressive *hypertrophy*. This enables it to maintain a normal cardiac output for some time. But left ventricular hypertrophy leads to an increase of coronary blood flow at rest, and thus to a diminished coronary reserve, which is responsible for the *angina pectoris symptoms* that arise during exertion. At the same time, the concentric hypertrophy and increasing interstitial fibrosis cause a decrease in left ventricular compliance, and the resulting diastolic dysfunction gives rise to *dyspneic complaints*. Eventually the ventricle can no longer surmount the increased pressure load. This leads to ventricular *dilatation* with a decrease in myocardial contractility. As the cardiac output falls, the decrease in cerebral blood flow may cause the patient to experience syncopal attacks during exercise. The decreased cardiac output is also responsible for a general decline of exercise tolerance in patients with aortic stenosis.

Table 20.**16** Symptoms and signs of aortic stenosis

Symptoms
Mild to moderate aortic stenosis: – often asymptomatic Severe aortic stenosis: – dyspnea on exertion – angina pectoris – syncope on exertion – sudden cardiac death – episodes of acute pulmonary edema – systemic embolism – gastrointestinal bleeding
Signs
– harsh, spindle-shaped systolic ejection murmur – pulsus parvus et tardus (not present with atherosclerotic calcification of the vessel wall!) – heaving, widened apex beat that may be displaced downward and to the left – signs of pulmonary congestion

Clinical Features. The most common symptoms of aortic stenosis are listed in Tab. 20.**16**. The presence of symptoms is usually an indicator of severe stenosis. Once symptoms have appeared, life expectancy falls dramatically and generally is less than five years. When heart failure supervenes, the average survival time without operative treatment is less than two years. *Dyspnea* is often precipitated by diseases or conditions that hamper diastolic filling. Typical examples are tachycardia and atrial fibrillation. Some 75% of patients with severe aortic stenosis complain of *angina pectoris*. Approximately 50% of these patients will have normal coronary arteries. *Syncope* is often caused by decreased cerebral blood flow but may also be triggered by an inadequate baroreceptor response or intermittent arrhythmias. Clouding of vision and dizziness are symptoms of *exercise-induced hypotension*. In rare cases aortic stenosis may be manifested by the systemic embolization of microthrombi or calcium fragments from the valve. Gastrointestinal bleeding may also be a sign of aortic stenosis. Angiodysplasia of the colon is common in patients with aortic stenosis.

The typical findings are summarized in Tab. 20.**16**. A *spindle-shaped systolic ejection murmur* is the most important clinical sign of aortic stenosis (Fig. 20.**25**). The ejection murmur is harsh and loud over the Erb point. Generally, the more severe the stenosis, the longer and more intense is the murmur. It radiates to the carotid arteries and is also transmitted toward the cardiac apex, where it assumes a distinctly musical quality. This transmitted murmur is difficult to distinguish from concomitant mitral insufficiency. The second heart sound in aortic stenosis may be very soft, and it may be virtually absent in severe aortic stenosis. The forceful atrial contraction associated with a stiffened left ventricle produces a fourth heart sound. If the valves are immobile due to valvular aortic stenosis, the systolic murmur begins with an ejection click. Frequently a thrill is palpable at the sternal border and in the jugular fossa.

The pulse rise is delayed in the presence of aortic stenosis. The pressure curve shows a *cockscomb pattern* (Fig. 20.**26**), which is responsible for the typical *pulsus parvus et tardus* ("small and late"). The *apex beat* is

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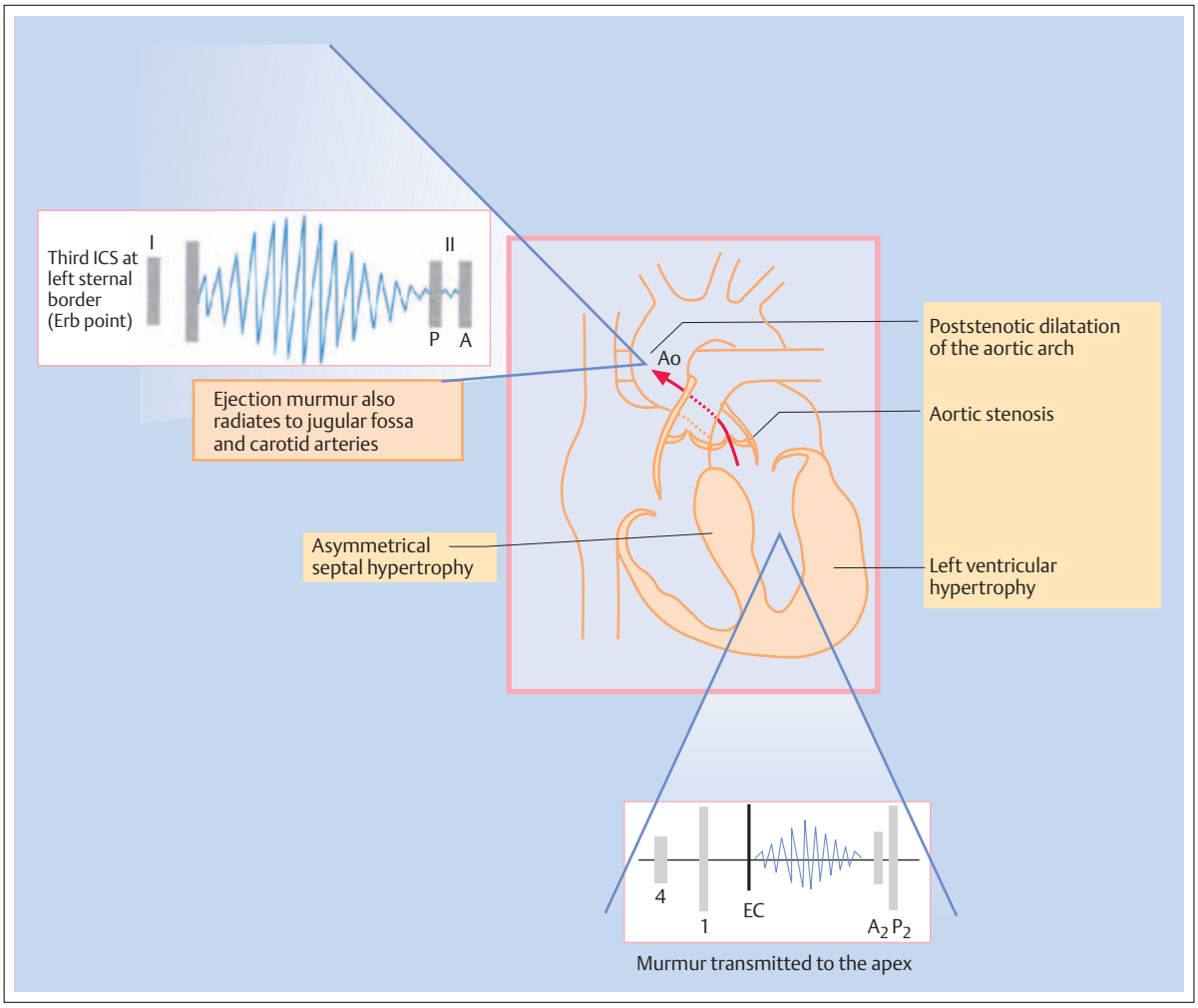

Fig. 20.**25** Schematic representation of aortic stenosis. Ao = aorta, EC = ejection click. The spindle-shaped ejection murmur is most clearly audible over the Erb point; it also radiates to the cardiac apex. Associated changes are left ventricular hypertrophy and frequent asymmetrical septal hypertrophy.

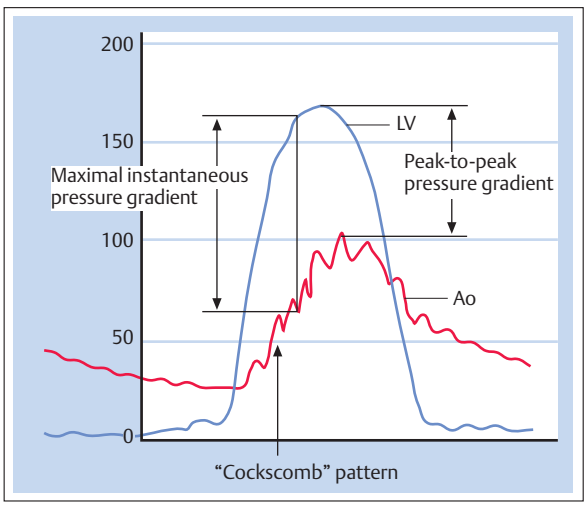

Fig. 20.**26** Pressure curves in aortic stenosis. Chart compares the left ventricular pressure (LV) with the simultaneously measured aortic pressure (Ao). The pressure rise in the aorta is delayed ("cockscomb" pattern), and a significant pressure gradient is present. The pressure gradient is measured invasively from peak to peak, and the mean pressure gradient is calculated. Doppler echocardiography measures the maximal instantaneous pressure gradient. Thus, when the peak pressure gradient is determined invasively and by echocardiography they are always different, but the mean pressure gradient is identical in both methods.

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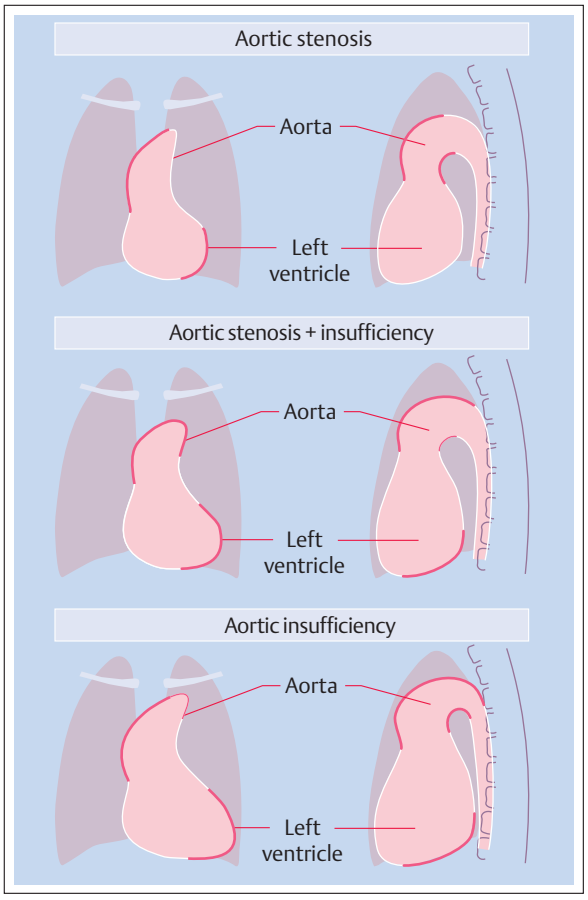

Fig. 20.**27** Aortic valve defects: configuration of the heart in the chest radiograph; PA view (left column) and lateral view (right column). With aortic stenosis the left ventricle is not enlarged but has a rounded apex. The ascending aorta shows poststenotic dilatation. With aortic insufficiency, the left ventricle and the aorta are markedly dilated and elongated. With a combined aortic defect, enlargement of the left ventricle is less pronounced than with aortic insufficiency alone. The ascending aorta is dilated and moderately elongated.

widened and heaving. In patients with left ventricular dilatation, the apex beat is displaced laterally downward (Fig. 20.**27**).

Diagnostic Studies

- *ECG:* (Fig. 20.**28**) the ECG generally shows signs of left ventricular hypertrophy. ST-segment depression, also called "left ventricular strain," is found in cases of severe hypertrophy.
- *Chest radiograph:* a chest radiograph taken in the lateral position will usually show calcifications in the middle third of the cardiac silhouette. The left ventricle appears rounded due to concentric hypertrophy (see Fig. 20.**27**). The heart generally displays a normal size. If cardiomegaly is present, the patient will manifest signs of left ventricular dysfunction or concomitant aortic insufficiency.
- *Echocardiography:* echocardiography will demonstrate a severely altered aortic valve with calcifications. The degree of left ventricular hypertrophy can be determined, as can the degree of asymmetrical septal hypertrophy, which is frequently present. It is common to find poststenotic dilatation of the aorta. *Doppler echocardiography* can measure the peak pressure gradient (instantaneous peak pressure gradient, Fig. 20.**29**). This gradient is higher than the peak pressure gradient between the aorta and left ventricle measured by cardiac catheterization (see Fig. 20.**26**). The mean pressure gradient can be calculated. *Planimetry* can also be used in echocardiography to estimate the opening area of the aortic valve. A mean pressure gradient higher than 50 mmHg and an aortic valve opening area less than 0.8 cm^2 indicate severe aortic stenosis. It should be noted that as left ventricular function declines, the pressure gradient also decreases and that even with severe aortic stenosis, the mean pressure gradient may measure less than 50 mmHg.
- *Cardiac catheterization:* aortic stenosis is usually correctly diagnosed based on good-quality echocardiograms. In equivocal cases, however, the left ventricle should be catheterized through the stenotic valve so that the pressure gradient can be measured see Fig. 20.**26**). Cardiac catheterization is also an important preoperative study for detecting concomitant coronary heart disease.

Indications for Operative Treatment. Operative treatment is indicated in all symptomatic patients with severe aortic stenosis. It is appropriate in asymptomatic patients who have left ventricular dysfunction or exercise-induced hypotension.

Pulmonic Stenosis

Etiology and Pathogenesis. Pulmonic stenosis is almost always *congenital*. Typically in these cases the pulmonary valve is formed without commissures and has a dome-shaped appearance when imaged by angiography or echocardiography. Over time, the abnormal valve undergoes fibrotic thickening or calcification. This is accompanied by the development of an increasing *secondary hypertrophic subpulmonic stenosis*. This infundibular stenosis due to muscular hypertrophy is also found in association with certain other anomalies such as ventricular septal defect, tetralogy of Fallot, and double-outlet right ventricle (see Chapter 21). Besides valvular and subvalvular infundibular pulmonic stenosis, less common forms are supravalvular stenosis (stricture in the pulmonary artery) and subinfundibular stenosis (anomalous muscle bands in the right ventricle). Rare causes of noncongenital pulmonic stenosis are rheumatic fever and carcinoid syndrome.

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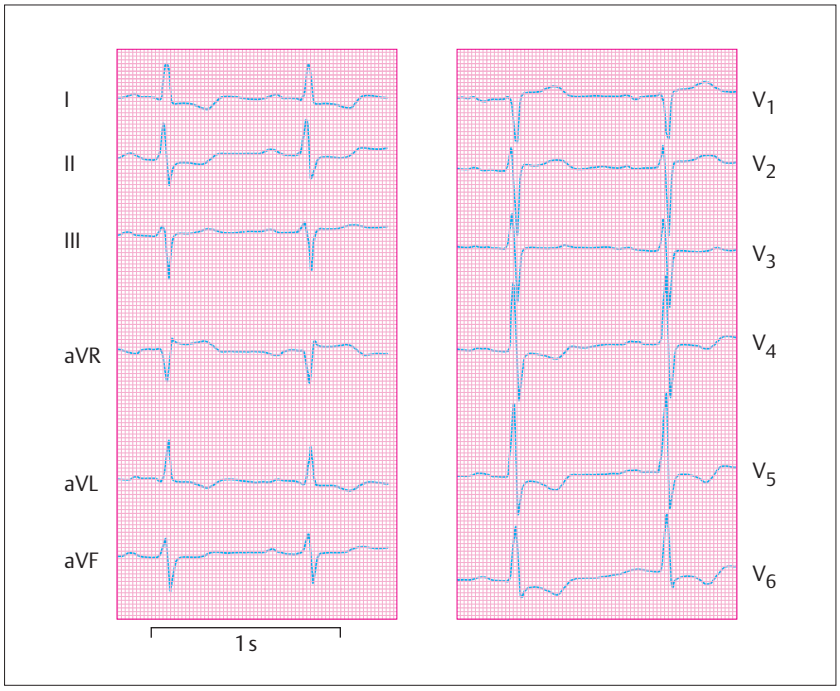

Fig. 20.**28** ECG in aortic stenosis shows left axis deviation with a pronounced repolarization abnormality in the left precordial lead and in I and aVL (strain).

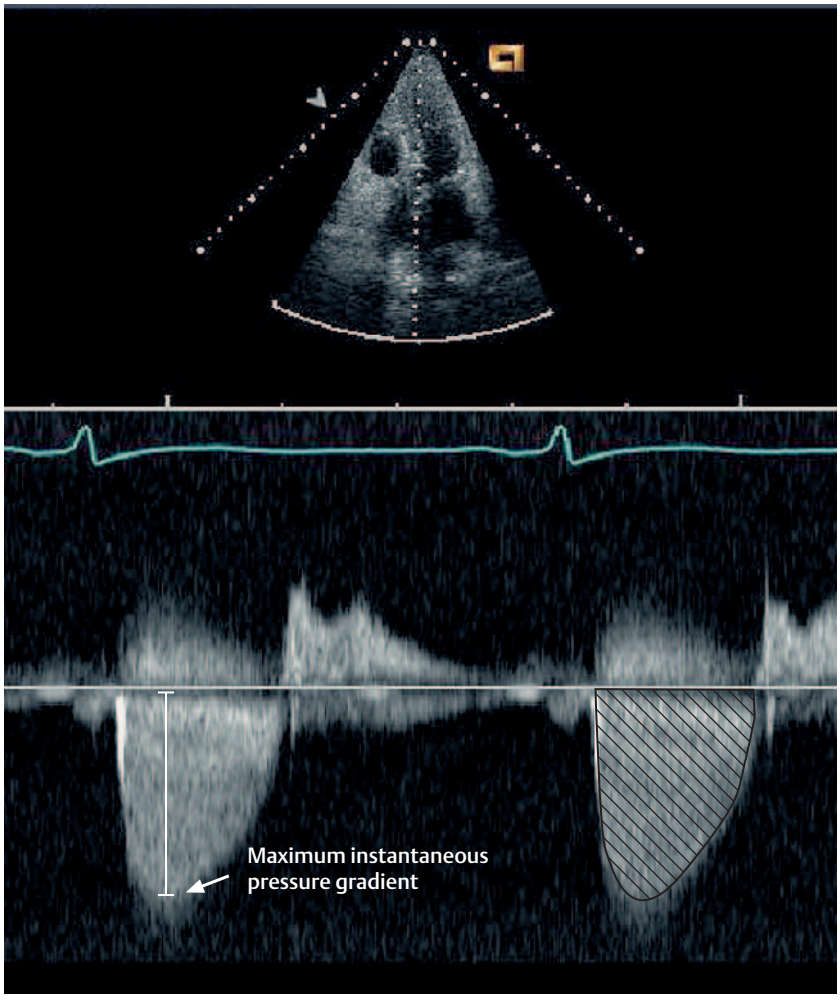

Fig. 20.**29** Aortic stenosis: measurement of the pressure gradient by Doppler echocardiography. The maximum velocity determined by Doppler echocardiography is 4 m/s. A maximum instantaneous pressure gradient of 64 mmHg is calculated from the Bernoulli equation ($4 \times 4^2 = 64$ mmHg). The mean pressure gradient is determined by calculating the mean pressure over the entire Doppler signal (shaded area).

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Table 20.**17** Symptoms and signs of pulmonic stenosis

Symptoms
– often asymptomatic – dyspnea on exertion – exercise intolerance – exercise-dependent fatigue – palpitations – presyncope and syncope (rare) – angina pectoris (rare)
Signs
– systolic ejection click – widely split second heart sound – harsh, spindle-shaped ejection murmur – left parasternal thrill (third ICS) – right ventricular impulse – distended neck veins – cyanosis, clubbing of the fingers (with ASD or PFO)

Clinical Features. Pulmonic stenosis often remains asymptomatic for years. The cardinal symptoms are *dyspnea on exertion* and *fatigue*, which reflect an inability of the heart to increase its output due to the obstruction in the right ventricular outflow tract (Tab. 20.**17**). Orthopnea does not occur in pulmonic stenosis because the pulmonary venous pressure is normal.

The ejection murmur in pulmonic stenosis is very similar to that in aortic stenosis (see Fig. 20.**6**). The detection of right ventricular enlargement may help to narrow the differential diagnosis. In cases with an atrial septal defect or patent foramen ovale, a right-to-left shunt develops that is manifested by cyanosis and possible clubbing of the fingers.

Diagnostic Studies

- *ECG:* the ECG shows signs of right atrial dilatation (P pulmonale) and right ventricular hypertrophy (see Tab. 20.**9**).
- *Chest radiograph:* the chest film shows signs of right atrial and right ventricular enlargement and prominent pulmonary arteries. There is no evidence of increased lung perfusion, and decreased perfusion of the peripheral lung vessels is occasionally noted.
  Doppler echocardiography can measure the pressure gradient across the pulmonary valve. In cases of severe pulmonic stenosis (valve opening area $< 0.5\ cm^2$) the pressure gradient exceeds 80 mmHg.
- *Cardiac catheterization:* at present most cases of pulmonary valve stenosis are treated by percutaneous valvuloplasty. Disruption of the valve shortens the length of the right ventricular outflow tract in adults. This leads to an increase in infundibular muscular stenosis, often necessitating a limited course of therapy with beta blockers.

Differential Diagnosis of Heart Failure Due to Volume Overload

Basic Pathophysiologic Concepts

Chronic Volume Overload. An increased volume load on the heart may be caused by an incompetent cardiac valve or by increased blood flow due to a cardiac or systemic disease. In many cases a chronic volume overload can be tolerated for years without symptoms. The volume overload gradually leads to *dilatation of the cardiac chamber(s)* and *myocardial hypertrophy*. Because of the increased filling pressure (= increased preload), myocardial contractility increases in accordance with the Frank–Starling mechanism. Despite continuous dilatation of the left ventricle, this increased contractility can maintain a normal stroke volume and forward volume for a considerable time. But eventually the increased preload and afterload will damage the myocardium and cause a *decrease in contractility*. The result is decompensation culminating in *left-sided heart failure, right-sided heart failure, or both*. The compensatory mechanisms described here are found most typically in chronic aortic insufficiency, which is well tolerated for a very long time and remains asymptomatic even during strenuous athletic activity. Aortic insufficiency is the anomaly in which the highest left ventricular volumes and greatest left ventricular mass may be found. Chronic mitral insufficiency is characterized by an alternating volume load between the left atrium and left ventricle and may also remain asymptomatic for some time.

Acute Volume Overload. By contrast, an acute volume overload generally leads to immediate *acute heart failure* (see Tab. 20.**10**). Acute aortic insufficiency leads to an immediate and substantial increase in the ventricular preload and afterload. This exceeds the force of myocardial contraction, resulting in forward and backward failure. Acute mitral insufficiency leads to backward failure with pulmonary congestion.

Acute Aortic Insufficiency

Pathophysiology. In acute aortic insufficiency, the "sudden" aortic regurgitant volume greatly increases the diastolic left ventricular filling pressure until it equals the diastolic aortic blood pressure. Blood flowing into the left ventricle during diastole causes the mitral valve to close prematurely. This impedes left ventricular inflow and leads to pulmonary congestion. Compensatory tachycardia further shortens the duration of diastole, causing additional impairment of ventricular filling.

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Clinical Features. The symptoms and findings of acute heart failure are listed in Tab. 20.**18**. Usually it is not difficult to distinguish this condition from chronic aortic insufficiency (Tab. 20.**19**). The symptoms of acute aortic insufficiency are often masked by the disease that caused the aortic incompetence. For example, severe exercise intolerance may also be the result of an endocarditis that causes acute aortic insufficiency.

During auscultation, it should be noted that the diastolic regurgitant murmur typical of aortic insufficiency is usually short and may be absent in patients with severe tachycardia. The vascular findings in chronic aortic insufficiency (such as a wide blood pressure amplitude) are entirely absent in acute aortic insufficiency.

Table 20.**18** Symptoms and signs of acute aortic insufficiency

Symptoms
– diaphoresis – severe exercise intolerance – dyspnea Severe acute aortic insufficiency is usually associated with pulmonary edema and/or cardiogenic shock
Signs
– tachycardia – hypotension – short, high-pitched diastolic murmur – tachypnea

Diagnostic Studies

- *ECG:* the ECG findings may be normal, except for tachycardia.
- *Chest radiograph:* the chest film often shows a normal-appearing cardiac silhouette accompanied by signs of pulmonary congestion or edema.
- *Echocardiography:* this test is important for the diagnosis of aortic insufficiency and its underlying cause (Fig. 20.**30**). Premature mitral valve closure can also be detected.

Causes. The leading cause of acute aortic insufficiency is *infectious endocarditis*. In the case of *aortic dissection*, acute aortic insufficiency may result from distortion of the aortic root and thus of the valvular apparatus. A rare cause is the prolapse of an abnormal aortic valve into the left ventricle. This may also occur with a perimem-

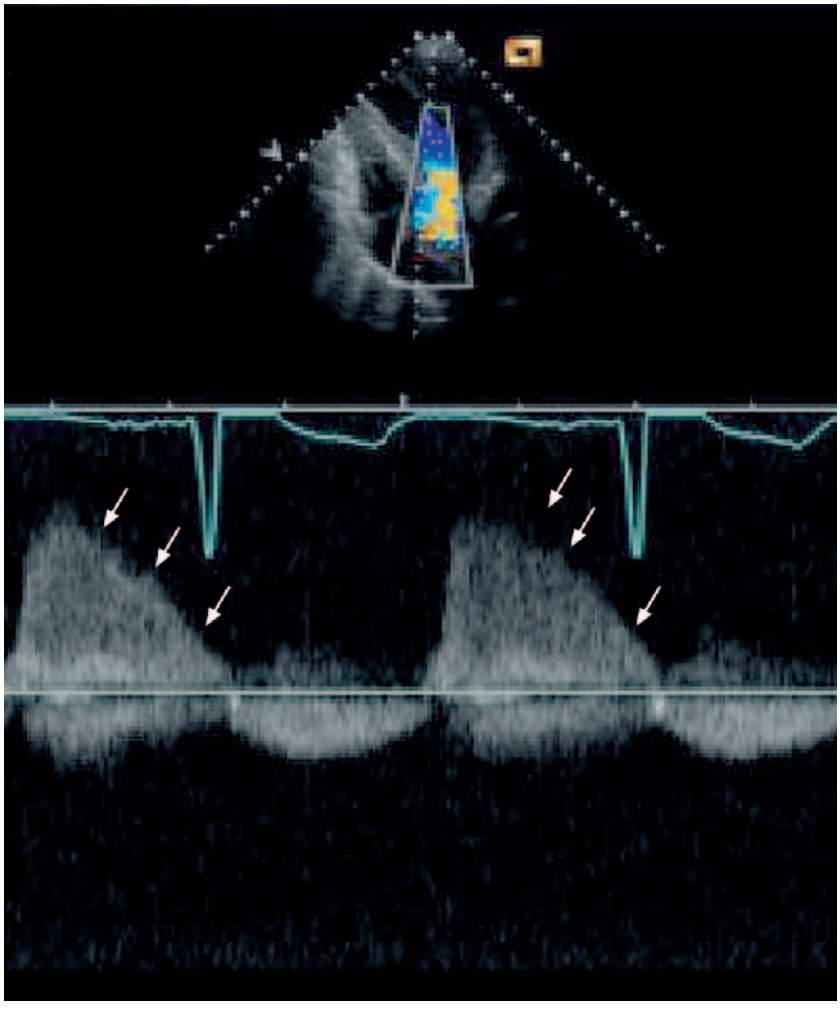

Fig. 20.**30** Acute aortic insufficiency; the velocity of the regurgitant jet (arrows) from the aorta into the left ventricle is measured by Doppler echocardiography. In contrast to chronic aortic insufficiency (see Fig. 20.**31**), the diastolic pressure in the left ventricle is greatly increased, and this lowers the velocity (arrows) and volume of regurgitation during diastole. This explains the disappearance of the diastolic regurgitant murmur.

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Table 20.**19** Differentiation of acute and chronic aortic insufficiency

	Acute aortic insufficiency	Chronic aortic insufficiency
Pulsus celer et altus	–	+++
Blood pressure amplitude	normal or slightly ↑	↑ ↑ ↑
Heart rate	↑ ↑	normal
Aortic diastolic murmur	until mid-diastole	persists throughout diastole
Austin–Flint murmur	short	continuous with presystolic accentuation
Moist rales (pulmonary congestion)	+++	+
ECG:		
– repolarization abnormalities	++	+++
– left ventricular hypertrophy	–	+++
Chest radiograph:		
– cardiomegaly	(+)	+++
– pulmonary congestion	+++	+
Echocardiogram:		
– LV dilatation	(+)	+++
– delayed mitral valve closure	common	rare

branous ventricular septal defect that deprives the aortic valve of its normal support mechanism. Traumatic ruptures or the rupture of a congenital fenestrated aortic valve are very rare causes.

A *ruptured sinus of Valsalva* may rarely produce symptoms similar to those of aortic insufficiency. Basically the sinus of Valsalva may rupture into any cardiac chamber, leading to an acute volume overload of the affected chamber. The most common site of occurrence is the right ventricle, followed by the right atrium. A ruptured sinus of Valsalva is usually associated with immediate cardiogenic shock.

Chronic Aortic Insufficiency

Occurrence. Chronic aortic insufficiency accounts for approximately 5 % of all valvular heart disease in adults. It is more common in men than women. Aortic insufficiency is frequently associated with other valvular defects and other congenital cardiac anomalies. For example, a bicuspid aortic valve with aortic regurgitation is almost invariably present in patients with coarctation of the aorta. Rheumatic mitral stenosis is commonly associated with aortic insufficiency.

Clinical Features. Chronic aortic insufficiency produces few if any symptoms for years (Tab. 20.**20**). The most common initial symptom is *dyspnea upon exertion*. In some cases, however, chronic aortic insufficiency occurs initially with paroxysmal nocturnal dyspnea. As in all defects that are associated with left ventricular hypertrophy, angina pectoris is probably the manifestation of a diminished coronary reserve. Nocturnal angina pectoris combined with diaphoresis (occurs in left lateral decubitus due to increased vagal tone) is virtually pathognomonic.

Signs. The principal finding on auscultation is a *blowing, diastolic regurgitant murmur* (Fig. 20.**31**). The murmur is most clearly audible along the left sternal border when aortic insufficiency is due to a valvular deformity. If aortic insufficiency is based on a dilatation of the ascending aorta, the diastolic regurgitant murmur is heard most clearly along the right sternal border. Sometimes the murmur is audible only when the patient is leaning forward.

A *low-pitched presystolic rumble* (called an *Austin–Flint murmur*) is audible over the cardiac apex. It is very similar in quality to the diastolic murmur of mitral stenosis. It is probably caused by a fluttering of the anterior mitral valve leaflet or by the relative mitral stenosis that occurs when the regurgitant jet impinges on the anterior mitral valve leaflet.

Besides a diastolic regurgitant murmur, a *systolic ejection murmur* is often audible. This does not reflect a concomitant aortic stenosis but is caused by the turbulence that the large stroke volume generates in the left ventricular outflow tract.

The large stroke volume leads to impressive pulse changes. The pulse is brisk and bounding. The width of the *blood pressure amplitude* correlates well with the severity of aortic insufficiency, and a normal blood pressure amplitude is sufficient to exclude severe chronic aortic insufficiency. *Palpitations* are caused by the large forward stroke volume in systole and the backflow in diastole. The pulsations may be vigorous enough to cause the entire body to vibrate. Over time, many typical findings have acquired their own names (see Tab. 20.**20**). All of these pulse signs are a manifestation of pure aortic insufficiency and are not found in patients with a combined aortic defect. A bounding pulse is also found in

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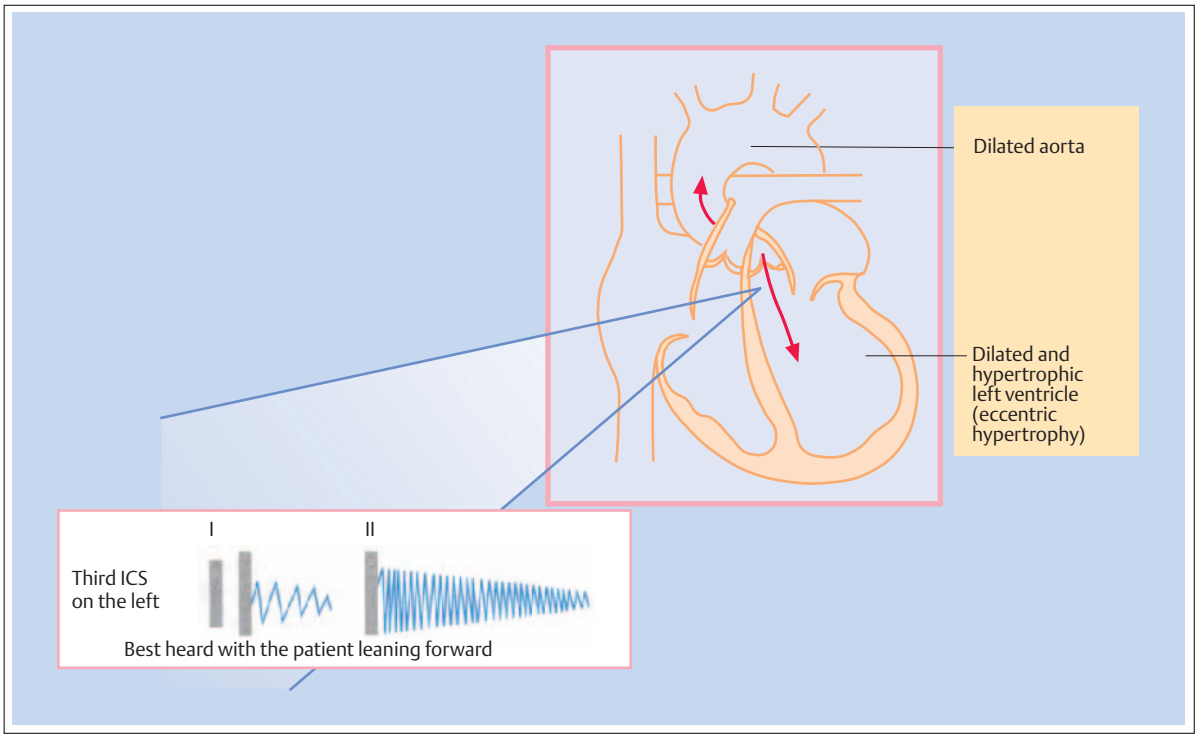

Fig. 20.**31** Schematic representation of aortic insufficiency. The diastolic regurgitant murmur is most clearly audible along the left sternal border. It is frequently accompanied by a systolic ejection click and systolic murmur. The left ventricle is enlarged and the ascending aorta may also be enlarged, depending on the underlying pathology. In echocardiography, color-coded Doppler can demonstrate the regurgitant jet.

other conditions that are associated with a hypercirculatory state, patent ductus arteriosus, large AV fistulas, Paget disease, hyperthyroidism, and septic fever.

Diagnostic Studies

- *ECG:* the ECG shows left axis deviation and signs of left ventricular hypertrophy. If concomitant atrial enlargement is also present, the ECG trace will show a broadened and notched P wave in lead II.
- *Chest radiograph:* the left ventricle may be enlarged and the cardiac apex displaced downward and laterally, depending on the severity of the aortic insufficiency (see Fig. 20.**27**). Occasionally, the cardiac apex may be displaced beneath the diaphragm (Fig. 20.**32**). Marked dilatation of the ascending aorta may be noted, depending on the underlying pathology.
- *Echocardiography:* the backflow into the left ventricle during diastole can be visualized by Doppler echocardiography (Fig. 20.**33**). Severe aortic insufficiency is associated with holodiastolic reflux even in the descending aorta (Fig. 20.**34**). Echocardiography can be used to measure the left ventricular dimensions and monitor them over time. If left ventricular dilatation increases by more than 15% in one year or the end-diastolic diameter exceeds 75 mm and the end-systolic diameter exceeds 55 mm, operative treatment is indicated even in an asymptomatic patient.

Table 20.**20** Symptoms and signs of chronic aortic insufficiency

Symptoms
Mild to moderate aortic insufficiency: – often asymptomatic – awareness of heartbeat – palpitations – chest pain in left lateral decubitus (heart beating toward chest wall) Severe aortic insufficiency: – dyspnea on exertion (most common symptom) – orthopnea – paroxysmal dyspnea – angina pectoris on exertion
Signs

– wide blood pressure amplitude
– strong pulse:
  – rapid pulse rise and rapid collapse (water-hammer pulse, Corrigan's pulse)
  – capillary pulsations in the nail bed or lip–Quincke sign
  – head and neck pulse–Musset sign
  – systolic pulsations of the uvula–Müller sign
  – loud systolic sound heard over femoral artery–pistol-shot pulse
  – systodiastolic murmur in the femoral artery–Duroziez sign
– blowing diastolic regurgitant murmur (principal finding)
– apical mid-diastolic murmur (Austin–Flint murmur)
– systolic ejection murmur
– third (fourth) heart sound
– heaving apex beat that is displaced laterally downward

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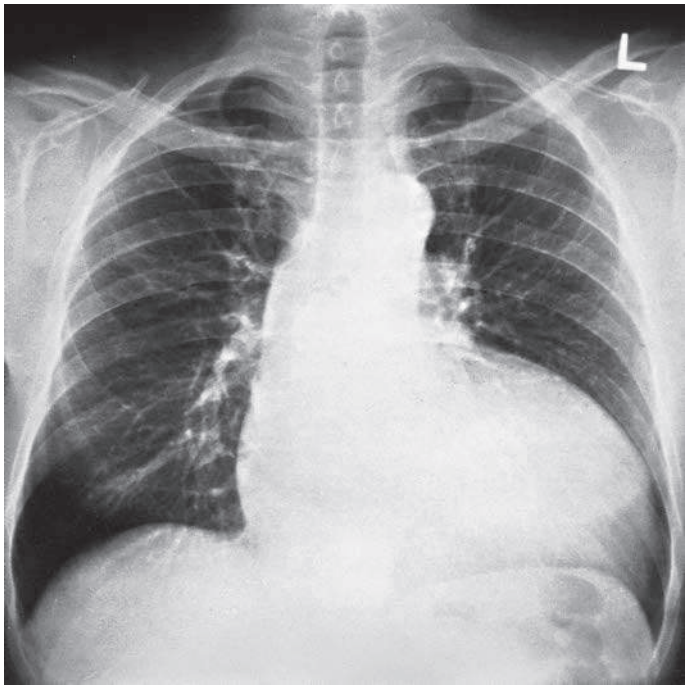

Fig. 20.**32** Severe aortic insufficiency (regurgitant fraction 52%) and advanced left ventricular dilatation with pulmonary congestion in a 51-year-old man, who had rheumatic fever at age 17. Heart/lung ratio = 0.64. The left ventricular ejection fraction (32%) is greatly decreased.

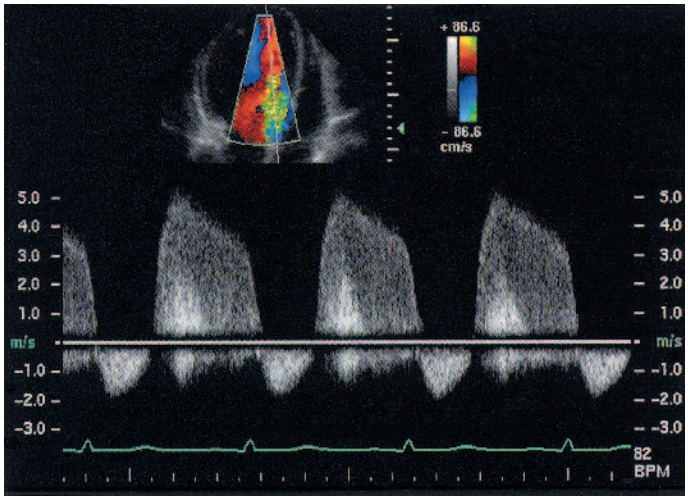

Fig. 20.**33** Doppler echocardiography in aortic insufficiency. Top: color-coded Doppler echocardiography during diastole in a 24-year-old man with moderately severe aortic valve insufficiency. The Doppler sample volume appears as a white spot on the radial beam in the left ventricular outflow tract (lower part of image). Bottom: blood flow velocity in the sample volume (m/s) is plotted against time (markers = 0.1 s). The regurgitant flow velocity is maximal in early diastole (5 m/s) while the maximum systolic velocity at that point is less than 2 m/s. BPM = beats per minute (heart rate = 82/min).

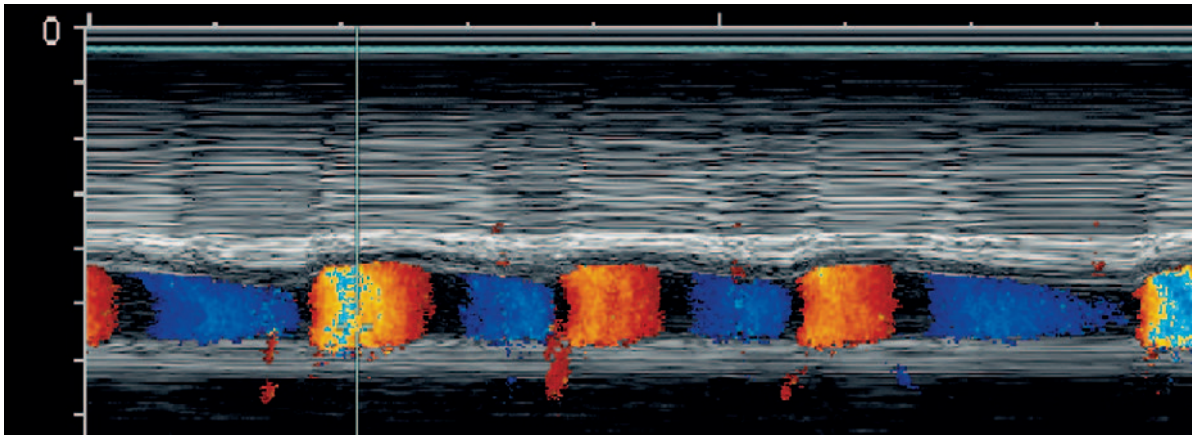

Fig. 20.**34** Flow in the abdominal aorta in severe aortic insufficiency. In cases of severe aortic insufficiency, forward blood flow occurs in systole (encoded red) and reverse flow in diastole (encoded in blue). This contributes to the rapid rise and fall of the palpable pulses in aortic insufficiency.

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Echocardiography can also demonstrate fluttering of the anterior mitral valve leaflet.

- *Cardiac catheterization and aortography:* these methods may be helpful in accurately defining the severity of the aortic insufficiency and accurately measuring the pressures and ejection fraction.

Causes and Differential Diagnosis. Chronic aortic insufficiency is caused either by pathology of the aortic root and ascending aorta or by disease of the aortic valve itself. The most frequent cause of chronic aortic insufficiency in adults is a *true aneurysm* of the ascending aorta. *Aortic ectasia* (sinus of Valsalva aneurysm) may also lead to aortic insufficiency. Connective tissue disorders such as Marfan syndrome, Ehler–Danlos syndrome, pseudoxanthoma elasticum, and osteogenesis imperfecta are commonly associated with aortic insufficiency. Currently, syphilitic aortitis is virtually unknown. Distortion of the aortic root due to ankylosing spondylitis is another potential cause of aortic insufficiency.

Among diseases of the aortic valve itself, a *bicuspid valve* is the most frequent cause of aortic insufficiency (Fig. 20.**35**). Destruction of the aortic valve by *infectious endocarditis* or as a late consequence of rheumatic fever may also occur. Less frequent causes are myxomatous degeneration, systemic lupus erythematosus, rheumatoid arthritis, Jaccoud arthropathy, Takayasu disease, Whipple disease, and Crohn disease.

The blowing diastolic regurgitant murmur of chronic aortic insufficiency requires *differentiation* from the murmur of pulmonary insufficiency. Pure pulmonary insufficiency is rare. In many cases it is associated with other congenital diseases that differentiate it from aortic insufficiency.

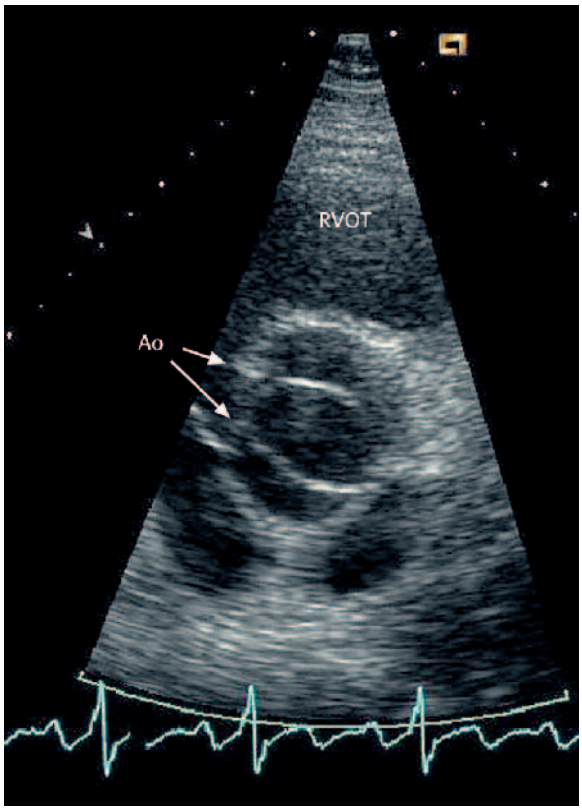

Fig. 20.**35** Bicuspid aortic valve. In a transverse scan through the aortic root, the three pocket-shaped cusps of the aortic valve normally produce a "Mercedes star" pattern. With a bicuspid aortic valve, only two cusps can be seen (arrows). Sometimes the third valve cusp is incompletely formed, producing a visible raphe. Ao = aorta, RVOT = right ventricular outflow tract.

Acute Mitral Insufficiency

Mitral insufficiency of acute onset causes a massive rise of pressure in the left atrium, leading to *pulmonary venous congestion* and *pulmonary edema* ranging to cardiogenic shock. The pathophysiology, signs, and symptoms of this condition are reviewed in Acute Heart Failure, above. It is important to note that because of the pressure rise in the left atrium, regurgitation across the mitral valve decreases during the second half of systole, resulting in a shorter systolic regurgitant murmur. Occasionally this murmur may be absent altogether (silent mitral insufficiency).

Diagnostic Studies

- *ECG:* the ECG may demonstrate signs of myocardial infarction as the cause of acute mitral insufficiency.
- *Chest radiograph:* signs of pulmonary edema dominate the radiographic findings.
- *Echocardiography:* this is the diagnostic procedure of choice, as it can demonstrate the regurgitation and provide important clues to its etiology.

Causes. The most frequent cause of acute mitral insufficiency is a partial or complete rupture of the chordae tendineae, which may be secondary to *infectious endocarditis* or to *mucoid degeneration in mitral valve prolapse*. Myocardial infarction may lead to avulsion of the papillary muscle or occasionally to a geometric displacement of the valvular apparatus that prevents coaptation of the valve leaflets.

In rare instances, myocardial ischemia may cause transitory malfunction of the papillary muscle. In these cases the acute mitral insufficiency may also be transitory, i. e., it may occur during exercise-induced ischemia and disappear after the ischemia has subsided.

Chronic Mitral Insufficiency

Pathophysiology. Chronic mitral insufficiency is a completely different entity from acute mitral insufficiency. Chronic mitral insufficiency leads to a *gradual dilatation* of the left atrium and left ventricle with no significant rise of pressure in the atrium. As a result of this, it remains asymptomatic for a long time (Fig. 20.**36**).

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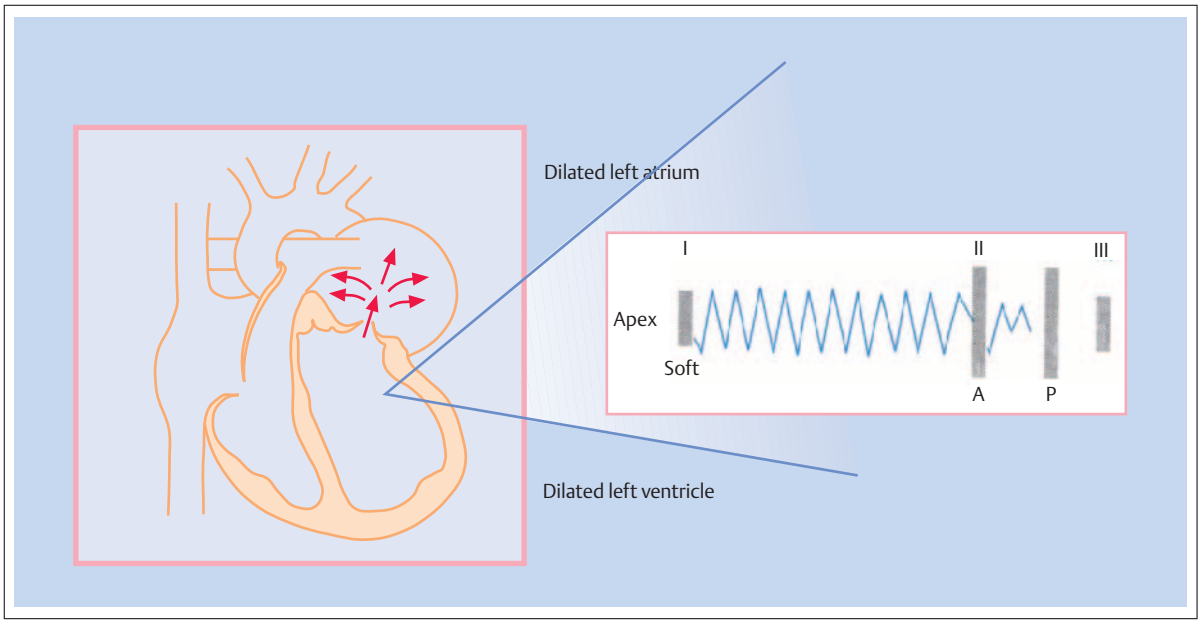

Fig. 20.**36** Schematic representation of chronic mitral insufficiency. The holosystolic murmur is most clearly audible over the apex. It radiates into the axilla. A third heart sound is almost always present in cases of severe mitral insufficiency. The left atrium and left ventricle are dilated.

Table 20.**21** Symptoms and signs of chronic mitral insufficiency

Symptoms
– fatigue, weakness, and exercise intolerance (most common symptom) – dyspnea, orthopnea, possible cough – palpitations – systemic embolism (rare) – hemoptysis (rare)
Signs
– arrhythmic pulse (atrial fibrillation or flutter) – apex beat heaving and laterally displaced – high-pitched apical holosystolic regurgitant murmur, radiating to the axilla (principal finding) – diminished first heart sound – third heart sound – apical systolic thrill – moist rales over the lung – distended neck veins, edema, hepatomegaly, ascites (late finding)

When symptoms arise, they often have an insidious onset. The chronic volume overload damages the myocardium and *decreases its contractility*. Because part of the blood is ejected from the left ventricle into the left atrium (= low-impedance system) in mitral insufficiency, this decreased contractility remains undetected for some time, and the ejection fraction appears normal. When the ejection fraction finally declines, there is already a severe impairment of myocardial contractility. This impairment can be appreciated after valve replacement surgery; the ejection fraction may decline after the operation. For this reason, patients with a greatly dilated left ventricle and a very low ejection fraction (< 30%) are considered to be inoperable. Asymptomatic patients with severe mitral insufficiency should undergo regular echocardiographic follow-ups. If these tests show evidence of left ventricular dilatation or decreased contractility, operative treatment should be considered.

Symptoms and Findings. The earliest and most common symptoms are *fatigue* and *exercise intolerance* (Tab. 20.**21**). Eventually the patient develops dyspnea and other classic manifestations of left-sided heart failure. The symptoms may be accentuated by *atrial fibrillation*, which supervenes in a large percentage of cases due to pronounced dilatation of the left atrium. *Systemic embolic events* are occasionally the earliest symptom of severe mitral insufficiency. Thrombi form in the large atrium, usually in the region of the atrial appendage, and may even form in the absence of atrial fibrillation.

A *high-pitched holosystolic regurgitant murmur* at the cardiac apex, which often continues over the second heart sound and is transmitted into the axilla, is the most important clinical finding in mitral insufficiency. With rupture of the chordae tendineae, the murmur may acquire a loud, shrill character that has been likened to a seagull cry. A prolapsing or "flailing" leaflet may produce a very musical murmur. The regurgitant murmur of mitral insufficiency requires differentiation from the transmitted ejection murmur of aortic stenosis. The latter is usually musical as well but it maintains its spindle shape. A high-pitched

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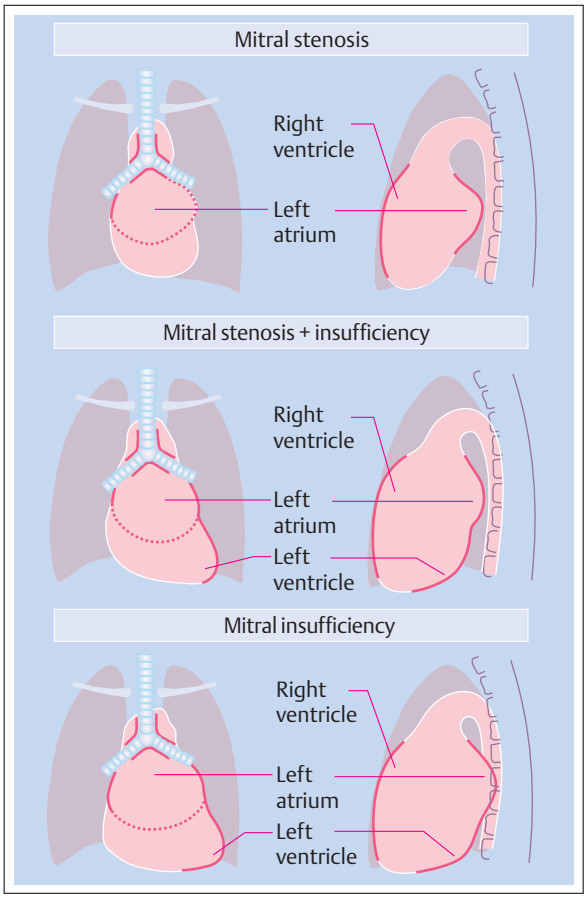

Fig. 20.**37** Mitral valve defects; configuration of the heart in the chest radiograph; PA view (left column) and lateral view (right column). With mitral stenosis, the left atrium is enlarged. The bifurcation (carina) of the trachea is splayed open, with a > 90° angle between the left and right main bronchi. With severe mitral stenosis, the right ventricle is enlarged (visible in the lateral radiograph!). With mitral insufficiency, the enlarged left atrium, splayed carina, and enlarged right ventricle are accompanied by marked enlargement of the left ventricle. With a combined mitral valve defect, the left ventricular enlargement is only moderately pronounced.

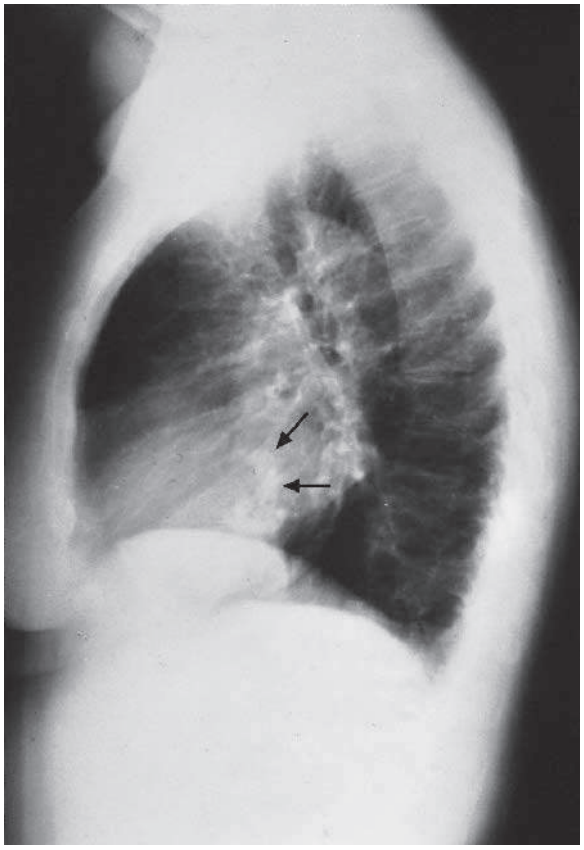

Fig. 20.**38** Chest radiograph of a 62-year-old woman with calcification of the mitral valve annulus; lateral view. The calcification appears as a reverse C-shaped density (arrows) located at the junction of the left atrium and left ventricle, just above the diaphragm. The left atrium is dilated.

holosystolic murmur at the cardiac apex may be caused by aberrant chordae tendineae. A third heart sound is often present and does not necessarily indicate poor left ventricular function; it may be produced by the large inflowing blood volume.

Diagnostic Studies

- *ECG:* the ECG shows signs of left atrial enlargement with a biphasic P wave in the V_1 lead. Signs of left ventricular hypertrophy are also found in one-third of the patients.
- *Chest radiograph:* the chest radiograph in mitral insufficiency often shows definite signs of left ventricular dilatation and left atrial enlargement (Fig. 20.**37**). Calcifications of the mitral valve annulus can occasionally be seen in the lateral projection (Fig. 20.**38**). Signs of pulmonary congestion are found in patients with decompensated left-sided heart failure.
- *Echocardiography:* echocardiography provides information on the anatomy of the mitral valve, chordae tendineae, and subvalvular apparatus. Transesophageal echocardiography is the best study for evaluating the mitral valve from the standpoint of surgical reconstruction. Echocardiography also yields important information on the etiology of mitral insufficiency, and it is important for determining the extent of mitral regurgitation (Fig. 20.**39**). Regurgitation extending into the pulmonary veins generally indicates severe mitral insufficiency. Moreover, echocardiography is an essential study for the periodic follow-up of left ventricular dimensions and ejection fraction.

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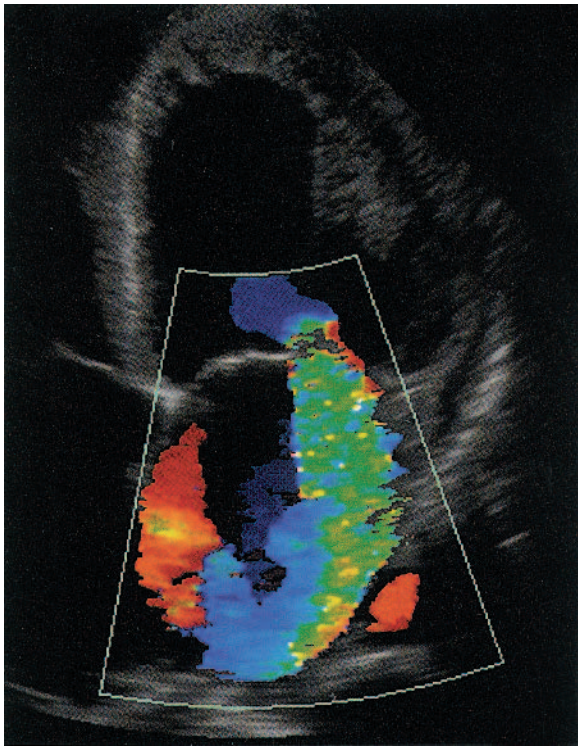

Fig. 20.**39** Doppler echocardiogram of eccentric mitral insufficiency during systole, scanned from the apex toward the base. The left ventricle is above, the left atrium below. Flow away from the transducer is always encoded in blue, flow toward the transducer in red. The speckled green indicates a very high flow velocity above the turbulence threshold. The jet in mitral insufficiency flows from the left ventricle along the lateral wall of the left atrium, displacing blood (blue) against the posterior wall, which in turn moves blood (red) along the atrial septum toward the mitral valve.

Table 20.**22** Frequent causes of chronic mitral insufficiency

Frequent causes of chronic mitral insufficiency
Incomplete mitral valve closure
– mitral valve prolapse
– hypertrophic obstructive cardiomyopathy
Structural change in the mitral valve leaflets
– rheumatic heart disease
– calcification of the mitral valve annulus
– late consequence to endocarditis
Dilatation of the mitral valve annulus
– ischemic heart disease
– LV dilatation due to cardiomyopathy

- *Cardiac catheterization:* the severity of mitral insufficiency can be determined by left ventricular angiography. Coronary angiography supplies information on associated coronary heart disease. Right heart catheterization is necessary for measuring concomitant pulmonary hypertension and resistance.

Indications for Operative Treatment. The need for operative treatment depends upon four key factors:

- symptoms
- left ventricular size and function
- pulmonary hypertension
- atrial fibrillation.

Operative treatment is advised as soon as *symptoms* have appeared. If the valves have undergone myxomatous change, it is possible in many cases to proceed with a valve reconstruction. These patients will benefit from an early operation. *Asymptomatic patients* should be referred for surgery if they show evidence of left ventricular dysfunction (ejection fraction $< 60\%$ and/or left ventricular end-diastolic diameter > 45 mm), if they have atrial fibrillation, or if pulmonary hypertension has developed.

Causes. The principal causes of mitral insufficiency are listed in Tab. 20.**22**. While *rheumatic heart disease* was once the most frequent cause of mitral valve disease, today the leading cause is *myxomatous degeneration* of the mitral valve (mitral valve prolapse).

Besides the causes listed in Tab. 20.**22**, a number of other diseases lead to mitral valve changes that culminate in mitral insufficiency. Paravalvular regurgitation after a cardiac valve replacement is a feared complication of mitral valve replacement surgery. Infiltrative processes such as amyloidosis, sarcoidosis, tumors, and granulomas may cause papillary muscle dysfunction leading to mitral insufficiency. Other rare causes are Marfan syndrome, Hurler syndrome, ankylosing spondylitis, and thoracic trauma. Mitral insufficiency in a setting of congenital heart disease is often based on a papillary muscle anomaly. The most important of these anomalies is the presence of only one papillary muscle, resulting in a parachute-shaped mitral valve. This anomaly may be found in association with endocardial cushion defects or transposition of the great vessels.

Mitral Valve Prolapse

Forms. Mitral valve prolapse is a condition in which one or both mitral valve leaflets prolapse into the left atrium during systole (Fig. 20.**40**). Mitral valve prolapse is classified etiologically as *primary* or *secondary* (e. g., in Marfan syndrome, Ehlers–Danlos syndrome). The primary form, caused by mucoid degeneration of the valve leaflets and chordae tendineae, is much more common than secondary forms. The overall prevalence of mitral valve prolapse in the adult population is approximately 4%. It is twice as common in women as in men.

Pathophysiology and Findings. Mitral valve prolapse may cause *mitral insufficiency*, depending on its severity. In the mildest form, the valve remains intact. Ballooning of the valve into the atrium during systole produces a *midsystolic click* (see Fig. 20.**5**). In the most severe form with regurgitation, the click is followed by a late systolic murmur that has a decrescendo shape. The murmur is

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softer in a squatting position than when standing (see Tab. 20.**7**). Occasionally the click is absent in patients with significant mitral insufficiency.

As the chordae tendineae progressively elongate, the regurgitation increases. If the chordae rupture, the regurgitant volume increases suddenly and dramatically, causing acute mitral insufficiency. This complication is rare before the fifth or sixth decade of life. Mitral valves that have undergone mucoid degeneration may prolapse even without significant elongation of the leaflets, causing mitral insufficiency. Mucoid valves are occasionally difficult to distinguish from endocarditic deposits by echocardiography.

Clinical Features. In cases where audible mitral insufficiency is present, the risk of developing *endocarditis* is as high as in any other form of mitral insufficiency, and prophylactic antibiotics should be prescribed. Besides mitral insufficiency, the prolapse is associated with a variety of signs and symptoms. Some patients present with grotesque, multiple, but benign *arrhythmias* and *atypical chest pain*. Mitral valve prolapse also poses a small risk of embolic stroke and transient ischemic attacks. The long-term prognosis is good, however.

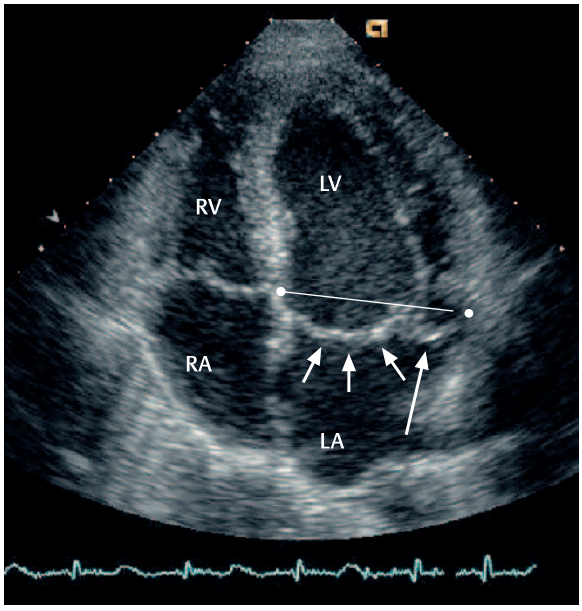

Fig. 20.**40** Echocardiography in mitral valve prolapse. Apical four-chamber view shows definite prolapse of the anterior leaflet (small arrows) and posterior leaflet (large arrow) of the mitral valve.

Tricuspid Insufficiency

A mild degree of tricuspid insufficiency is found in up to 80 % of patients. This fact is utilized to measure the pressure gradient between the right ventricle and right atrium by Doppler echocardiography and to estimate the pressure in the pulmonary artery. Severe tricuspid insufficiency is often found in association with other cardiac anomalies.

Clinical Features. Patients with tricuspid insufficiency presents with the signs and symptoms of *severe right-sided heart failure* (Tab. 20.**23**). The prominent venous pulses and the inspiratory rise in the venous pulse, instead of the normal fall, are the most impressive findings. The parasternal regurgitant murmur depends on the pressure in the right ventricle (Fig. 20.**41**). A low right ventricular pressure leads to a short, early diastolic murmur, while a high pressure leads to a holosystolic murmur that may simulate mitral insufficiency.

Table 20.**23** Symptoms and signs of tricuspid insufficiency

Symptoms
– fatigue – anorexia – painful abdominal swelling
Signs
– distended neck veins – prominent systolic pulsation of the jugular vein – high-pitched systolic regurgitant murmur, parasternal and in fourth ICS – right ventricular impulse – systolic pulsation of the enlarged liver – ascites, peripheral edema

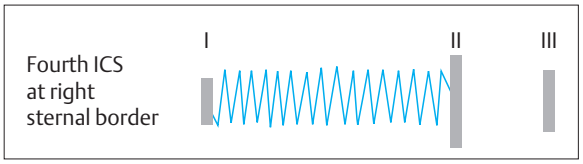

Fig. 20.**41** Phonocardiogram in tricuspid insufficiency.

Diagnostic Studies

- *ECG:* the ECG often shows signs of right ventricular hypertrophy and right atrial enlargement.
- *Chest radiograph:* radiographic abnormalities depend on the severity of the tricuspid insufficiency and the underlying pathology. In most cases, however, the chest film shows marked dilatation of the right atrium.
- *Echocardiography:* the characteristic findings are right ventricular dilatation and paradoxical septal motion.

Causes. Most cases of tricuspid insufficiency are secondary to *right ventricular dilatation.* Right ventricular dilatation may be caused by left-sided heart failure or by right-sided pathology such as pulmonic stenosis, primary pulmonary hypertension, Eisenmenger syndrome, or cor pulmonale. *Primary or organic tricuspid insufficiency* may be found in rheumatic heart disease, myxomatous degeneration of the tricuspid valve, carcinoid syndrome, or Epstein anomaly. Bacterial endocarditis of

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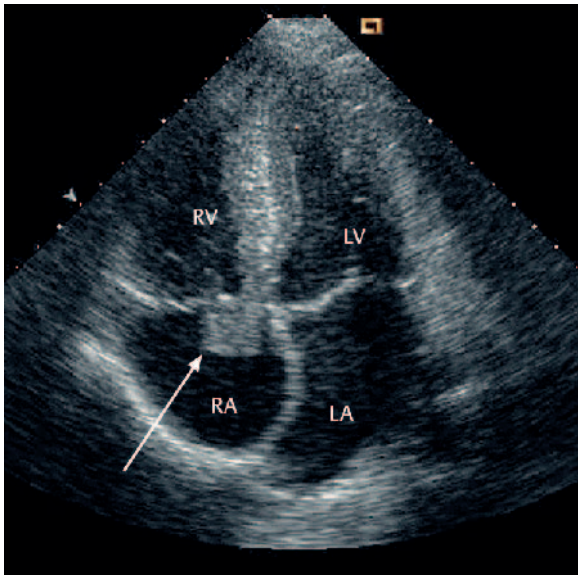

Fig. 20.**42** Endocarditis of the tricuspid valve. Apical four-chamber view shows a large vegetation on the tricuspid valve (arrow) measuring at least 2 cm in size. The endocarditis has destroyed the septal leaflet of the tricuspid valve, causing severe tricuspid insufficiency with pressure elevation in the right atrium (septum bulges to the left). RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium.

Table 20.**24** Differential diagnosis of chronic heart failure due to an increased cardiac output (high output failure)

- Systemic arteriovenous fistulas
  - congenital fistulas (hereditary hemorrhagic telangiectasia, hemangiomas)
  - acquired (posttraumatic, iatrogenic, hemodialysis fistula)
- Hyperthyroidism
- Anemia
- Beriberi (vitamin B_1 deficiency)
- Hepatic cirrhosis
- Paget disease
- Multiple myeloma
- Hyperkinetic heart syndrome
- Skin diseases (e. g., psoriasis)

Table 20.**25** Symptoms and signs of high output failure

Symptoms
– exercise intolerance
– dyspnea on exertion
– palpitations
– painful abdominal swelling
Signs
– tachycardia (90–100 bpm)
– wide blood pressure amplitude
– systolic bruit over the femoral artery (pistol shot sound)
– systolic bruits over the carotid arteries
– venous bruits (venous hum)
– systolic ejection murmur
– distended neck veins, lower extremity edema, hepatomegaly
– pulmonary congestion

the tricuspid valve occurs predominantly in intravenous drug users (Fig. 20.**42**). Blunt chest trauma may cause rupture of the chordae tendineae, leading to tricuspid insufficiency.

Pulmonary Insufficiency

Pulmonary insufficiency is rarely an isolated phenomenon. Usually it is caused by pulmonary arterial dilatation in a setting of *pulmonary hypertension*. Isolated pulmonary insufficiency is tolerated extremely well. Fatigue and symptoms of right-sided heart failure are occasionally reported. Auscultation in organic pulmonary insufficiency reveals a *low-pitched, harsh diastolic regurgitant murmur* at the upper left sternal border. Secondary pulmonary insufficiency produces a higher-pitched, blowing murmur known as a Graham Steell murmur.

A very mild degree of pulmonary insufficiency is often found in normal individuals undergoing Doppler echocardiography and has no clinical significance.

High Output Heart Failure

Pathophysiology. In rare cases, a disease that is associated with a high cardiac output may lead to heart failure. The chronic overload in these cases is the result of a *systemic or vascular disease* rather than a cardiac disease (Tab. 20.**24**). The cardiac output is usually more than twice the normal value (*normal cardiac index* > 2.5–4.0 L/min/m^2). A common feature of all of these conditions is an inadequate peripheral oxygen supply, making it necessary for the heart to increase its output. Despite the low peripheral resistance, the sympathetic nervous system and renin–angiotensin–aldosterone system are activated, and antidiuretic hormone levels are elevated as they are in heart failure. These neurohumoral adaptations plus the volume overload lead to *gradual dilatation* of the heart and eventual pump failure. The development of heart failure is accelerated by concomitant cardiac disease such as coronary stenosis. Thus, a patient with *high output heart failure* should be examined for an associated heart disease.

Clinical Features. The symptoms of high output heart failure (Tab. 20.**25**) are comparable to those of heart failure with a low cardiac output, and the findings closely resemble those of anomalies with a chronic volume overload (e. g., aortic insufficiency). Cardiac shunt defects or defects associated with a chronic volume overload should therefore be excluded before a disease with *high output heart failure* is diagnosed.

Causes. The most frequent causes of a persistently high cardiac output are *vascular diseases* associated with an arteriovenous shunt (see Tab. 20.**24**). Metabolic dis-

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orders and bone diseases may also lead to an increased cardiac output:

- *Systemic arteriovenous fistulas:* the magnitude of the AV fistulas, the size of the shunt, and the degree to which the peripheral resistance is lowered are proportional to the rise in the cardiac output. *Congenital* AV fistulas range from *cutaneous hemangiomas* to giant hemangiomas that may affect the growth of the entire limb (as in Kasabach–Merritt syndrome). *High output heart failure* may also develop in cases of hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease) where AV fistulas have formed in the lung and liver. *Acquired AV fistulas* may be posttraumatic (e. g., a stab wound of the femoral vessels) or *iatrogenic* (e. g., after cardiac catheterization or the surgical creation of a hemodialysis fistula). Heart failure often has a multifactorial etiology, however, in patients undergoing dialysis for renal failure. Contributing factors are the high-volume flow through the dialysis fistula, anemia, and overhydration that develop in hemodialysis patients, and the mitral insufficiency that may result from calcification of the mitral valve annulus.
- *Anemia:* anemia, even when severe, is rarely sufficient alone to cause heart failure. The cardiac output does not begin to rise until the hematocrit has fallen below 25 % or the Hb level has fallen below 7 g/dL. Heart failure may develop if the hematocrit remains below 15 % or the Hb level remains below 5 g/dL for an extended period of time.
- *Hyperthyroidism:* thyroid hormone raises the metabolic rate, lowers peripheral resistance, and increases myocardial contractility, thereby increasing oxygen consumption. All of these changes may precipitate heart failure in patients with a coexisting heart disease. The occurrence of (tachycardiac) atrial fibrillation also contributes to the pathogenesis of heart failure in hyperthyroidism.
- *Paget disease:* more than 33 % of the bones must be affected by Paget disease before the increased cardiac output can precipitate heart failure.
- *Hyperkinetic heart syndrome:* this poorly defined syndrome has been described in young patients. It is characterized by tachycardia and blood pressure elevation. Patients complain of palpitations, occasional chest pain, and exercise intolerance. Heart failure is not part of this syndrome, however.

Differential Diagnosis of Heart Failure Due to Impaired Ventricular Filling

Basic Pathophysiologic Concepts

The impaired filling of one or both ventricles leads to *congestion of the atria*, which undergo hypertrophy and dilatation. In most cases the ventricles are small and have normal systolic function. In some conditions (e. g., hypertrophic obstructive cardiomyopathy), diastolic dysfunction is the dominant pathophysiologic feature while in other conditions (e. g., mitral stenosis) the impaired filling is due to a mechanical obstruction. The resulting symptoms resemble those of diastolic dysfunction, regardless of the cause (see Tab. 20.**1**). Another common feature of all diseases associated with impaired ventricular filling is the strong dependence of ventricular filling on atrial contractions. When atrial contractions are profoundly impaired due to atrial fibrillation, ventricular filling is dramatically decreased (usually by more than 20 %). This typically leads to a massive increase in symptoms or may even precipitate heart failure.

Mitral Stenosis

Pathogenesis. The cause of mitral stenosis in 99 % of cases is *rheumatic heart disease*. This disease leads to *thickening and fusion of the mitral valve leaflets* accompanied by shortening and adhesion of the chordae tendineae. Eventually the valve and subvalvular apparatus calcify (Fig. 20.**43**). When the opening area of the mitral valve decreases from the normal value of 5 cm^2 to less than 2 cm^2, a pressure gradient develops between the left atrium and left ventricle (Fig. 20.**44**). This causes *pulmonary congestion* to develop in response to physical exertion and tachycardia. With severe mitral stenosis, even mild effort may precipitate symptoms. The increased pressure in the left atrium also leads to higher pulmonary venous pressures, promoting the development of *pulmonary hypertension*. This pulmonary hypertension may become established due to structural transformation of the pulmonary arteries. This creates a "second stenosis" that now overloads the right ventricle, eventually leading to *right-sided heart failure*.

Symptoms. The symptoms and findings depend strongly on the stage of the mitral stenosis. Most patients with mitral stenosis present clinically with *dyspnea on exertion* (Tab. 20.**26**). Fatigue and *exercise intolerance* reflect the inability of the heart to increase its output because of the stenotic valve. *Systemic embolic events* are occasionally the earliest sign of mitral stenosis. Undiscovered asymptomatic mitral stenosis may sometimes occur dramatically with pulmonary edema in cases where atrial fibrillation greatly shortens the diastolic flow time. In other cases, undetected mitral stenosis may occur initially with acute heart failure during pregnancy or delivery due to tachycardia and the increased volume load.

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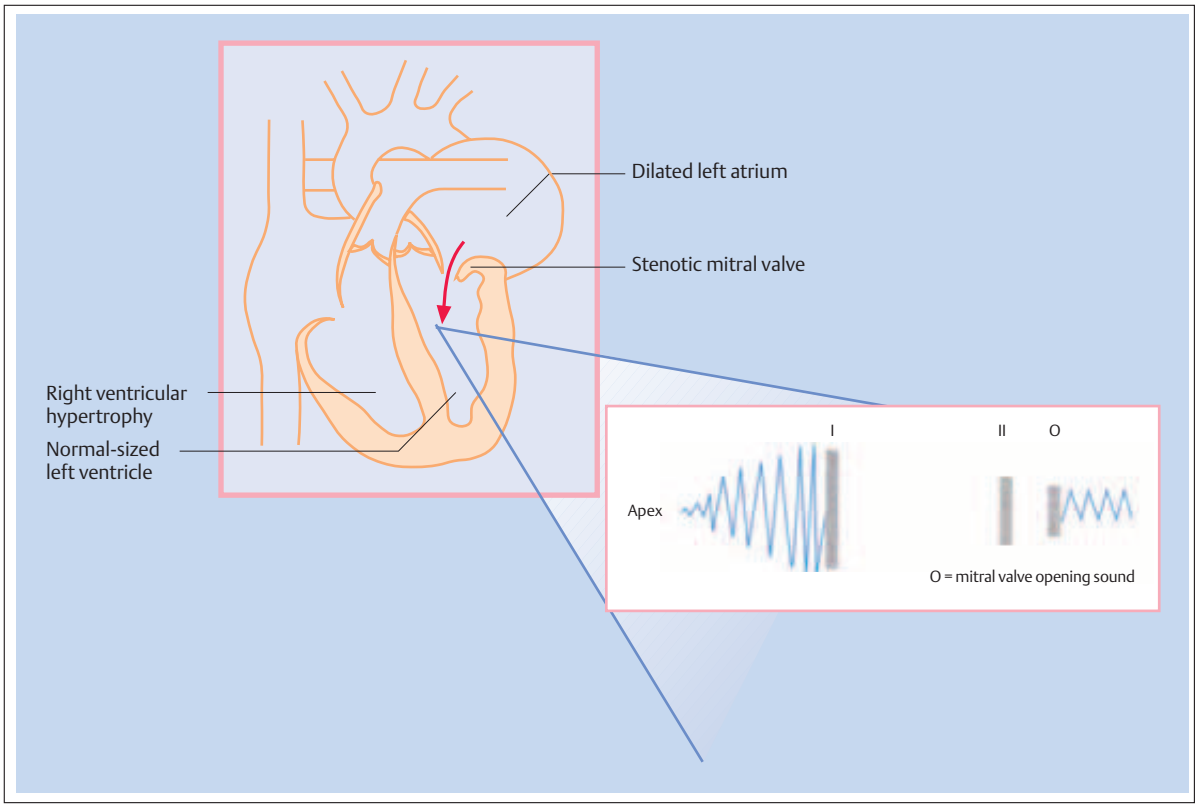

Fig. 20.**43** Schematic representation of mitral stenosis.

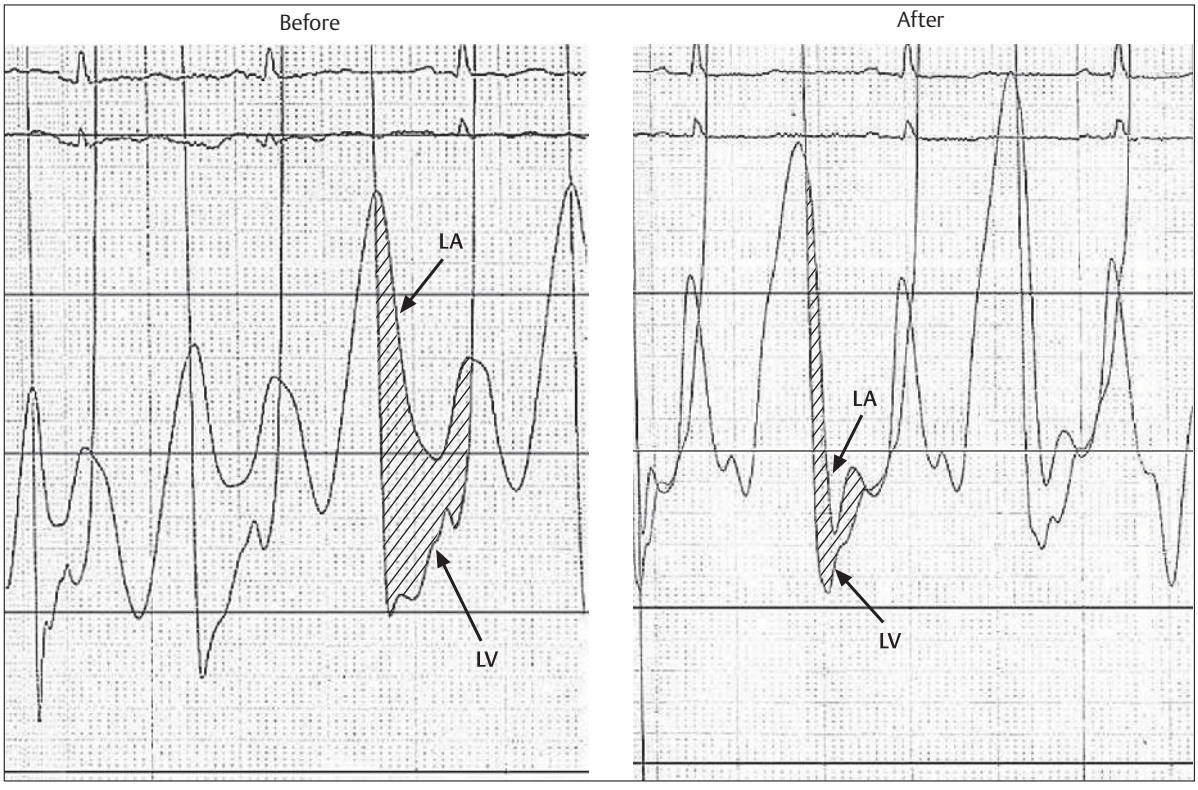

Fig. 20.**44** Pressure gradient across the mitral valve before and after valvuloplasty. Before valvuloplasty, the mean pressure gradient (shaded area) across the mitral valve is 11 mmHg. The calculated valve opening area is 0.9 cm^2. After valvuloplasty, only a minimal pressure gradient remains between the left ventricle and left atrium.

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Signs. The signs of mitral stenosis are initially subtle, but the pressures and forces that move the mitral valve leaflets become greater as the degree of stenosis increases. The first heart sound becomes abnormally loud and is described as an *accentuated first heart sound*. The *mitral valve opening sound* is always present when the valve is mobile. With increasing stenosis, this sound moves closer to the second heart sound. With a heavily calcified and immobile valve, the first heart sound and the mitral opening sound may no longer be audible in some cases.

> The mitral opening sound is virtually pathognomonic for mitral stenosis.

The turbulent flow of ventricular filling produces a characteristic low-pitched, late diastolic murmur (*diastolic rumble*). A diastolic thrill is also palpable in some cases. The diastolic rumble is most clearly audible in left lateral decubitus with the bell of the stethoscope. Presystolic accentuation of the murmur is heard during atrial systole. This presystolic murmur may be the only audible abnormality at the start of the disease. But as the stenosis becomes more severe, the diastolic sound becomes more prolonged.

When pulmonary hypertension supervenes, dilatation of the pulmonary artery may lead to the development of *pulmonary insufficiency*. This is audible at the sternal border as a *high-pitched early diastolic regurgitant murmur* (Graham Steell murmur).

Holosystolic regurgitant murmurs are audible in patients with concomitant mitral insufficiency or if tricuspid insufficiency develops in cases with severe right ventricular dilatation.

A typical *mitral facies*, characterized by flushing of the cheeks (telangiectasias) and cyanotic lips (decreased ejection), is frequently absent and thus has limited diagnostic value.

Diagnostic Studies

- *ECG:* mild mitral stenosis is not associated with ECG changes. With severe mitral stenosis, the ECG demonstrates typical P mitrale (Fig. 20.**45**). If pulmonary hypertension develops, the study also shows signs of right ventricular hypertrophy.
- *Chest radiograph:* the most important radiographic sign is left atrial enlargement (see Fig. 20.**37**). When greatly enlarged, the left atrium forms a double outline along the right atrium and may even form the right border of the cardiac silhouette. The lateral radiograph shows narrowing of the retrocardiac space and esophageal displacement due to the enlarged left atrium. This enlargement will be very pronounced, however, only if there is significant concomitant mitral insufficiency.
  The lung fields show signs of pulmonary venous congestion with vascular redistribution, interstitial

Table 20.**26** Symptoms and signs of mitral stenosis

Symptoms
– dyspnea (pulmonary congestion), possibly accompanied by coughing and wheezing – fatigue (decreased cardiac output) – edema, ascites (right-sided heart failure) – palpitations (atrial fibrillation) – hemoptysis (pulmonary congestion, pulmonary embolism) – hoarseness (rare) – symptoms of thromboembolic complications
Signs

– atrial fibrillation
– auscultation
  – loud first heart sound
  – mitral valve opening sound
  – loud second heart sound (with pulmonary hypertension)
  – diastolic murmur with presystolic accentuation (diastolic rumble)
– mitral facies
– signs of pulmonary congestion
– signs of pulmonary hypertension
– signs of right-sided heart failure in patients with severe mitral stenosis of long duration

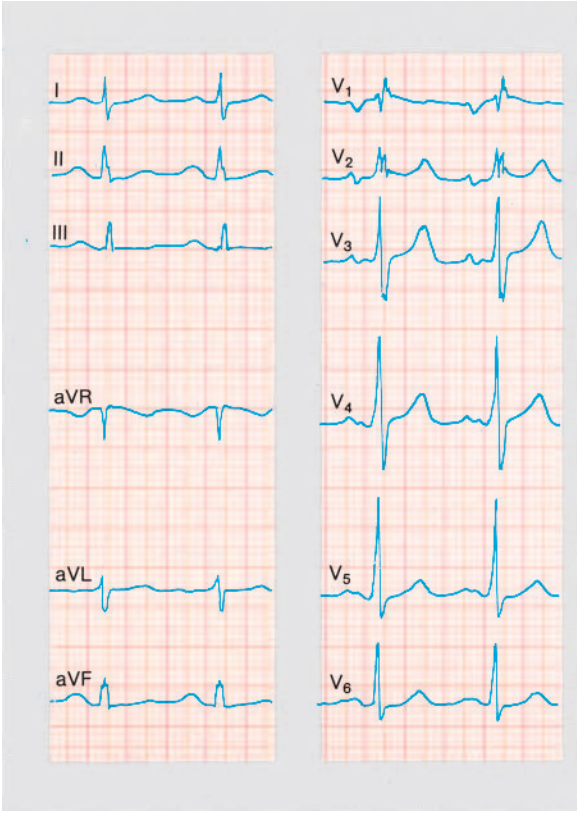

Fig. 20.**45** Severe mitral stenosis (valve opening area 0.4 cm^2). Typical P mitrale with widening of the P wave in II (> 0.12 s in II), notched P wave in V_5 and V_6, and biphasic P wave in V_1 through V_3; incomplete right bundle branch block.

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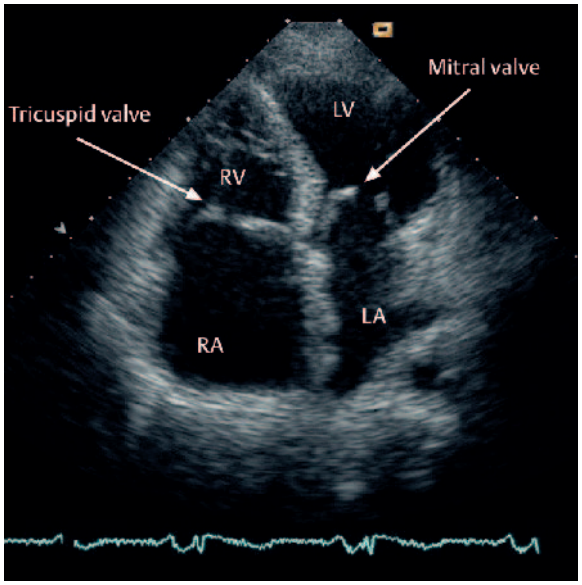

Fig. 20.**46** Echocardiography in mitral stenosis. The echocardiogram shows the doming of the non-calcified, but thickened, fused mitral leaflets from the left atrium (LA) into the left ventricle (LV). There is a concomitant tricuspid stenosis with thickening of the tricuspid valve and a less pronounced doming. The right atrium (RA) and the LA are dilated. (RV = right ventricle.)

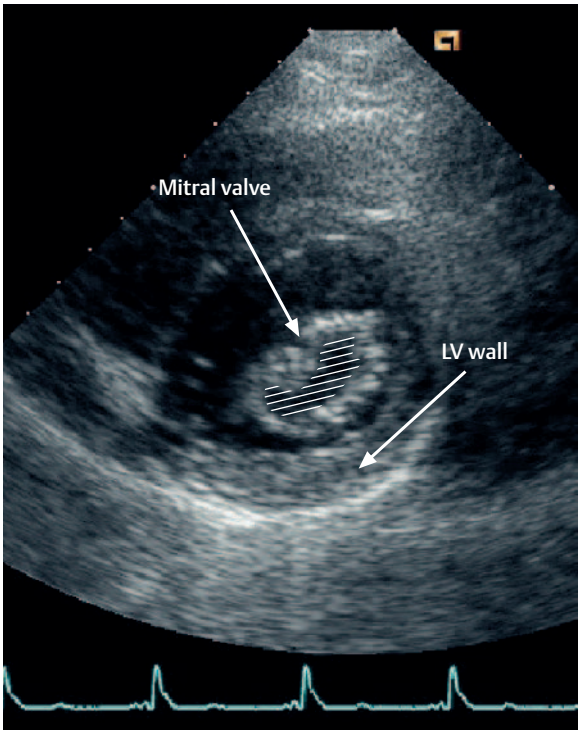

Fig. 20.**47** Mitral stenosis: measurement of the valve opening area; two-dimensional transverse scan through the left ventricle at the level of the mitral valve orifice. The thickened margins of the mitral valve leaflets are clearly visualized. The valve opening area (shaded) is determined planimetrically at the point of maximal opening (end diastole).

edema, and Kerley B lines. If pulmonary hypertension develops, the pulmonary artery becomes larger and dilated.

- *Echocardiography:* echocardiography can establish a definitive diagnosis of mitral stenosis (Fig. 20.**46**). It supplies information on the extent of valvular mobility and calcification, the size of the left atrium, and the morphology of the subvalvular apparatus. Three-dimensional echocardiography can be used for planimetric determination of the valve opening area (Fig. 20.**47**). Doppler echocardiography can additionally determine the pressure gradient across the mitral valve. The load on the right ventricle can also be assessed during echocardiography, and Doppler echocardiography can be used to determine the degree of possible pulmonary hypertension.
- *Cardiac catheterization:* cardiac catheterization is unnecessary for establishing a diagnosis in many cases, and currently it is mainly used therapeutically. Mitral valvuloplasty is the treatment of choice, even in patients with partially calcified valve leaflets or with a mitral stenosis, which has previously been treated, either operatively or with a percutaneous procedure (see Fig. 20.**44**). Mitral stenosis that is heavily calcified or is accompanied by significant mitral insufficiency will still require surgical treatment.

Differential Diagnosis. Differentiation is mainly required from impaired ventricular filling caused by a tumor in the left atrium. Cor triatriatum, a congenital web in the left atrium, can also mimic mitral stenosis.

Other diseases that are associated with impaired cardiac filling, such as constrictive pericarditis and hypertrophic obstructive cardiomyopathy, often pose no problems of differential diagnosis owing to their specific clinical features.

Atrial Myxoma

Impaired filling of the left ventricle may also be caused by a tumor in the left atrium. Atrial myxomas account for approximately 75% of these tumors in adults. Atrial myxomas are pedunculated tumors that can mimic mitral stenosis by prolapsing into the mitral valve (Fig. 20.**48**). Complaints (dyspnea, palpitations, cyanosis, syncope) that change with body position, appearing in certain positions and disappearing in others, are virtually pathognomonic for this tumor.

Clinical Features. Besides a diastolic murmur, auscultation reveals an *extra systolic sound* or *tumor plop* caused by prolapse of the myxoma during systole. Changing the patient's position alters the intensity of the audible findings. This does not occur in mitral stenosis. The diagnosis is established by echocardiography, which can positively distinguish atrial myxoma from mitral stenosis.

Atrial myxoma is associated with *noncardiac systemic symptoms* such as fever (50%), weight loss (25%),

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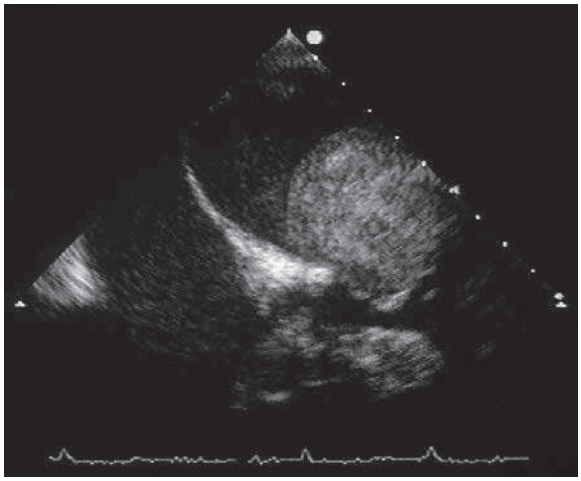

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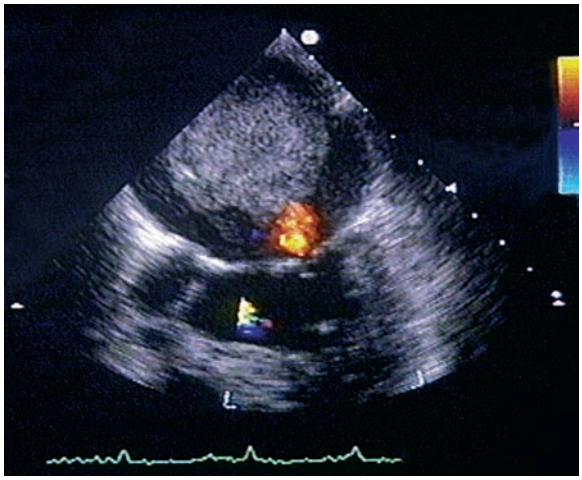

b

Fig. 20.**48** Atrial myxoma

a Transesophageal echocardiogram of a 68-year-old woman with a left-sided atrial myxoma; 2-D image in diastole. The left atrium is above, the left ventricle is below. The spherical myxoma enters the mitral valve during diastole, obstructing blood flow through the valve.

b Color-coded Doppler echocardiogram of the same patient in systole. The myxoma is back in the left atrium. There is minimal "flame-shaped" backflow through the otherwise closed mitral valve.

dizziness and presyncope (20%), anemia, signs of inflammation, and splenomegaly. Chronic signs of inflammation result from the production of inflammatory *cytokines* by the tumor itself. Atrial myxomas may lead to the systemic embolization of tumor fragments or thrombi. These emboli, which are usually multiple, may mimic vasculitis or infectious endocarditis.

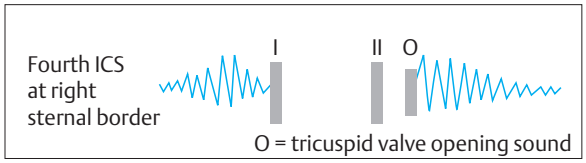

Fig. 20.**49** Phonocardiogram in tricuspid stenosis.

Tricuspid Stenosis

Causes. Tricuspid stenosis is a rare valvular disease. Patients almost always have a history of *rheumatic fever*, and the stenosis is associated with other rheumatic diseases (see Fig. 20.**46**). On the other hand, the tricuspid valve is affected in only 5% of patients with rheumatic heart disease. The second most frequent cause of tricuspid stenosis is *carcinoid syndrome*.

Clinical Features. Because the right atrium is a low-pressure system, even a small pressure gradient (> 2 mmHg) will cause inflow stasis leading to symptoms. It is common for symptoms (*fatigue, exercise intolerance*) to exist for years before the stenosis is diagnosed. With a pure tricuspid stenosis, the patient can lie flat despite edema and cyanosis because there is no pulmonary congestion. In most cases, however, the symptoms of other rheumatic heart diseases (mitral stenosis, aortic stenosis) are dominant.

Signs of *right-sided heart failure* (venous congestion, hepatomegaly, edema, ascites, cyanosis) are noted on clinical examination. The distended neck veins have a prominent diastolic pulse ("A" wave of atrial contraction). An opening sound is occasionally noted on auscultation (Fig. 20.**49**). The *diastolic murmur* is slightly higher-pitched than that of mitral stenosis and is most clearly audible along the right and left borders of the lower sternum. Presystolic pulsation of the enlarged liver may be noted.

Diagnostic Studies. The ECG and chest radiograph show signs of right atrial or biatrial enlargement. Echocardiography demonstrates the thickened, adherent tricuspid valve leaflets. The pressure gradient across the tricuspid valve can be measured by Doppler echocardiography.

Pericardial Tamponade

Pericarditis due to any cause (see Tab. 6.**13**, Chapter 6) may lead to the development of pericardial effusion (see Chapter 6). Pericardial tamponade is present when the effusion causes impairment of ventricular filling.

Clinical Features. The symptoms of pericardial tamponade are *exercise intolerance* and *dyspnea*. The principal findings are tachycardia, a narrow blood pressure

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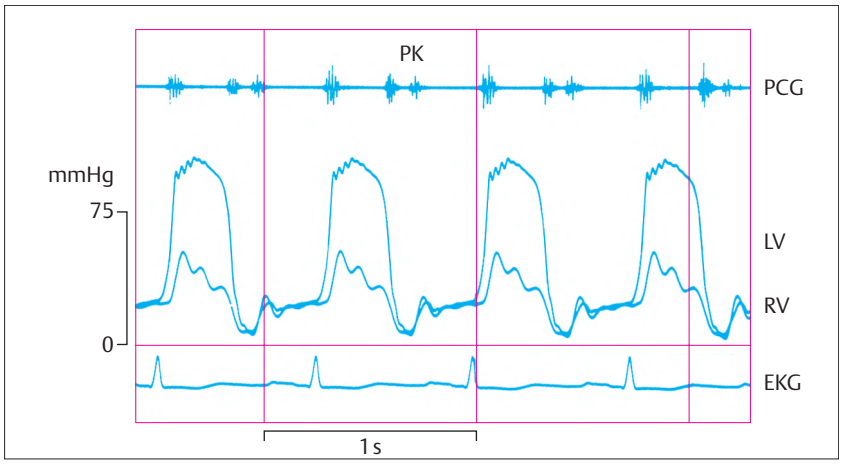

Fig. 20.**50** Left ventricular (LV) and right ventricular (RV) pressure in severe calcified constrictive pericarditis. The diastolic pressure curve is identical in both ventricles during diastole. There is an early diastolic dip followed by a diastolic plateau. The pericardial knock (PK) is clearly visible in the phonocardiogram (PCG). It coincides with the dip in the pressure curve. The time lines are spaced at one-second intervals.

amplitude, hypotension (in most patients), a paradoxical pulse, distended neck veins with an increase in venous distention during inspiration (Kussmaul sign), and hepatomegaly. "Paradoxical pulse" is a misnomer for an increase in the normal inspiratory fall of systolic blood pressure. The increased inflow of blood into the right ventricle during inspiration pushes the septum slightly to the left and leads to relative underfilling of the left ventricle during inspiration. This physiological pattern is accentuated by tamponade or any other cause of left ventricular compression, causing the inspiratory fall in pressure to exceed 10 mmHg. This "paradoxical pulse" is not pathognomonic for pericardial tamponade. It also occurs in constrictive pericarditis, restrictive cardiomyopathy, COPD, pregnancy, and morbid obesity.

Diagnostic Studies. The ECG typically shows low-voltage waveforms or electrical alternans (see Chapter 6). The chest radiograph demonstrates cardiomegaly (see Fig. 6.**19**, Chapter 6). Echocardiography can determine the size of the effusion and the degree of compression of the cardiac chambers (see Fig. 6.**20**, Chapter 6).

Constrictive Pericarditis

Causes. Constrictive pericarditis has become much less common since the eradication of *tuberculosis*. Thus, the calcifications typical of tuberculous constrictive pericarditis are now found in only about half of constrictive pericarditis cases. Today the most frequent causes of constrictive pericarditis are viral pericarditis and long-term consequences from the *irradiation* of malignant tumors. Other causes are previous cardiac surgery, hemopericardium, and uremia. It is important to know that some patients with viral pericarditis go through a phase of transient constrictive pericarditis, which then resolves spontaneously within a few months.

Constrictive pericarditis frequently is not included in the differential diagnosis. This entity should always be considered, however, in patients with right-sided heart failure and a small heart.

Pathophysiology. Constriction of the right and left ventricles raises the pressures in the atria. Consequently, blood flows rapidly into the ventricle when the semilunar valves open. The rapid inflow is abruptly halted by the constriction, producing an extra sound called a *pericardial knock* (Fig. 20.**50**). Further ventricular filling brings the filling pressures to an equal level in all the cardiac chambers. The end-diastolic equalization of pressures in the cardiac chambers is typical of constrictive pericarditis.

Clinical Features. The main symptoms and findings are listed in Tab. 20.**27**. The pericardial knock has approximately the same timing (0.08–0.12 seconds after A_2) as the mitral opening sound but has a lower pitch and shows respiratory variability.

Diagnostic Studies. The ECG usually shows peripheral low voltage. The absence of typical calcifications in the chest radiograph (Fig. 20.**51**) does not exclude constrictive pericarditis. Echocardiography demonstrates the thickened pericardium, and Doppler echocardiography shows the typical filling pattern of constrictive pericarditis. The atria are dilated in cases of postinfectious constriction, while in postactinic cases they usually show fibrotic changes without dilatation. Occasionally the thickened pericardium can also be demonstrated by MRI and CT.

Differentiation from Restrictive Cardiomyopathy. Occasionally it may be difficult to distinguish constrictive pericarditis from restrictive cardiomyopathy. The clinical symptoms are the same, and special investigations yield similar findings. Complex Doppler echocardio-

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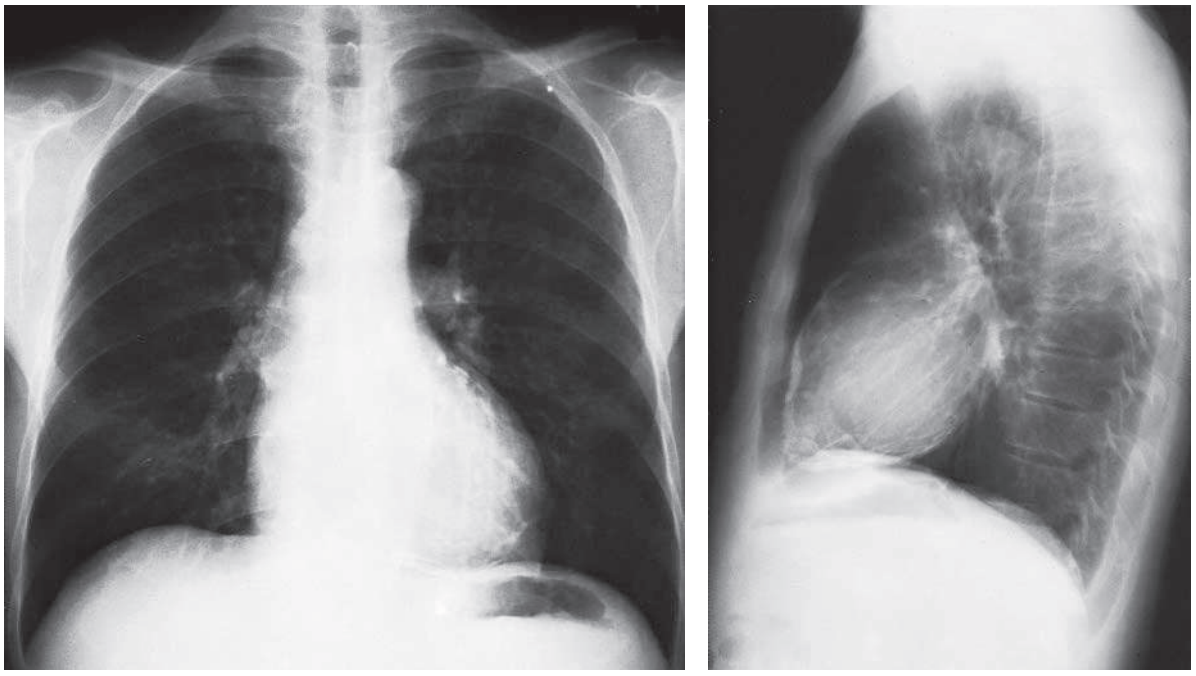

a b

Fig. 20.**51** Chest radiograph in constrictive pericarditis.
a PA view; calcified plaques are faintly visible along the lateral and inferior cardiac borders.
b Lateral view; the anterior, apical, and inferior calcified plaques are seen much more clearly than in the PA view.

graphic comparisons and hemodynamic measurements in the cardiac catheterization laboratory will usually narrow the differential diagnosis.

The best parameter is the *systolic pressure changes in the right and left ventricle upon respiration*. The two pressures show discordant patterns in constrictive pericarditis: the systolic pressure rises in the right ventricle and falls in the left ventricle during inspiration, and it rises in the left ventricle and falls in the right ventricle during expiration. This is different from the pattern seen in restrictive cardiomyopathy, in which both pressures show concordant changes during inspiration and expiration. Invasive pressure measurements in both conditions show rapid ventricular filling followed by a diastolic plateau (dip–plateau pattern, see Fig. 20.**50**). In constrictive pericarditis, the diastolic pressures are equal in all cardiac chambers and the systolic right ventricular pressure is < 40 mmHg. In restrictive cardiomyopathy, the diastolic pressures are higher on the left side than on the right (> 5 mmHg), and generally the systolic right ventricular pressure is well above 40 mmHg. Moreover, the ejection fraction may be decreased in restrictive cardiomyopathy while it is generally preserved in constrictive pericarditis.

Table 20.**27** Symptoms and signs of constrictive pericarditis

Symptoms
– fatigue
– exercise intolerance
– abdominal swelling
– dyspnea on exertion
Signs
– tachycardia
– distended neck veins (possible Kussmaul sign)
– hepatomegaly, ascites
– peripheral edema
– pericardial knock in early diastole

Definition and Classification of Cardiomyopathies

Cardiomyopathies are diseases of the myocardium that lead to impaired cardiac function. They are classified into five categories based on anatomical and physiological criteria (Tab. 20.**28** and Fig. 20.**52**).

Dilated cardiomyopathy accounts for approximately 60% of all cardiomyopathies, hypertrophic cardiomyopathy for approximately 30%, restrictive and arrhythmogenic cardiomyopathy of the right ventricle for 10–20%, and nonclassifiable cardiomyopathies for 1–2%.

Many diseases can precipitate a cardiomyopathy (Tab. 20.**29**). The cardiomyopathy caused by a specific

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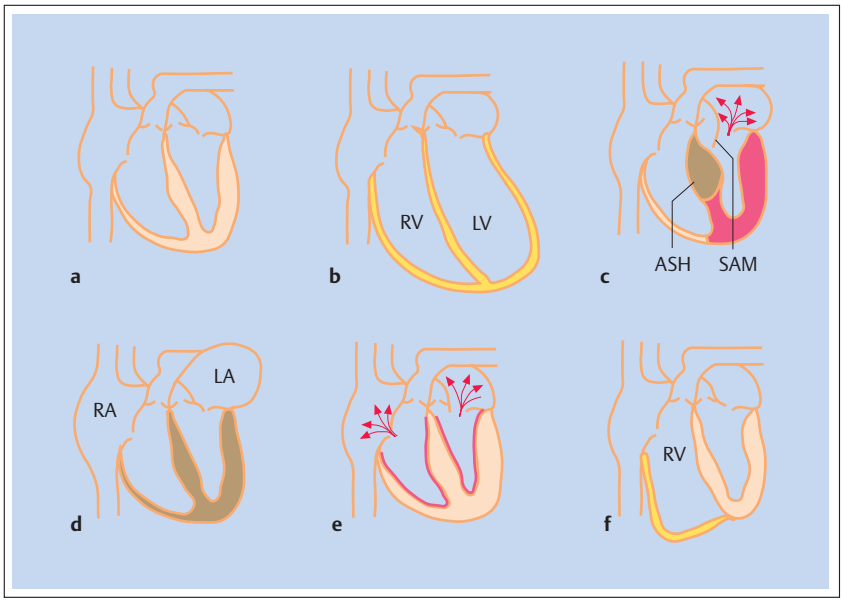

Fig. 20.**52** Schematic representation of cardiomyopathies.
a Normal heart
b Dilated cardiomyopathy
c Hypertrophic cardiomyopathy with left ventricular hypertrophy and asymmetrical septal hypertrophy (ASH). The systolic anterior motion (SAM) of the mitral valve leaflet leads to mitral insufficiency.
d Restrictive cardiomyopathy with dilatation of the both atria.
e Obliterative form of restrictive cardiomyopathy with involvement of the tricuspid and mitral valves.
f Arrhythmogenic right ventricular cardiomyopathy (explained further in the text).

Table 20.**28** Classification of cardiomyopathies

1. Dilated cardiomyopathy
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy
4. Arrhythmogenic right ventricular cardiomyopathy
5. Unclassifiable cardiomyopathies
   - fibroelastosis
   - noncompaction of the left ventricle
   - systolic dysfunction without dilatation
   - mitochondrial cardiomyopathies
   - hypertension

Table 20.**29** Classification of cardiomyopathies by specific etiology

1. Ischemic cardiomyopathy
2. Valvular cardiomyopathy
3. Hypertensive cardiomyopathy
4. Inflammatory cardiomyopathy
   a. infectious (Chagas, HIV, enterovirus, adenovirus, CMV, bacterial)
   b. autoimmune
   c. idiopathic myocardial inflammation
5. Metabolic cardiomyopathy
   a. endocrine (thyrotoxicosis, hypothyroidism, diabetes mellitus, acromegaly, Addison disease, pheochromocytoma)
   b. storage diseases (hemochromatosis, amyloidosis, glycogen storage diseases, Hurler syndrome, Fabry disease, sarcoidosis)
   c. deficiency diseases (potassium deficiency, magnesium deficiency, anemia, beriberi, kwashiorkor)
6. Systemic diseases (systemic lupus erythematosus, polyarteritis nodosa, scleroderma, dermatomyositis)
7. Muscular dystrophy (Duchenne disease, Becker disease, myotonic dystrophy)
8. Neuromuscular diseases (Friedreich ataxia, Noonan syndrome, lentiginosis)
9. Sensitivity reactions and toxic reactions (alcohol, cocaine, catecholamines, anthracycline, irradiation)
10. Peripartum cardiomyopathy

disease can usually be assigned to one or perhaps two categories in the anatomical and physiological classification. The cause should be identified whenever possible because specific therapy, when available, can significantly improve the prognosis.

Hypertrophic Cardiomyopathy

Etiology and Pathogenesis. Hypertrophic cardiomyopathy is a *genetic disease* that is characterized by hypertrophy of the left ventricle and sometimes of both ventricles (Fig. 20.**53**). The causative mutation involves sarcomeric troponin or myosin and is inherited as an autosomal dominant trait. More than 100 different mutations on five different chromosomes have been identified.

The morphological change is based on an abnormality of muscle fiber formation. Instead of normal parallel bundles, the muscle fibers are arranged in a disordered pattern. The resulting hypertrophy shows a variable distribution in the ventricle. Three main patterns are observed:

- general hypertrophy (hypertrophic nonobstructive cardiomyopathy)
- hypertension of the septum causing obstruction of the outflow tract (hypertrophic obstructive cardiomyopathy)
- hypertrophy mainly affecting the cardiac apex (apical hypertrophic cardiomyopathy, Fig. 20.**54**).

In all forms the hypertrophy leads to *diastolic dysfunction with impaired ventricular filling* and consequent congestion in the pulmonary venous system. In hypertrophic obstructive cardiomyopathy, the asymmetrical septal hypertrophy creates an outflow obstruction while the *systolic anterior motion* (*SAM*) of the mitral valve

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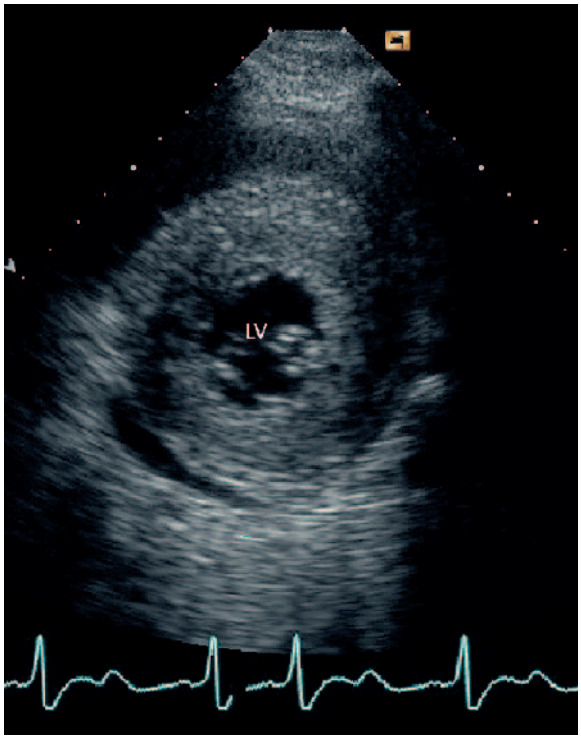

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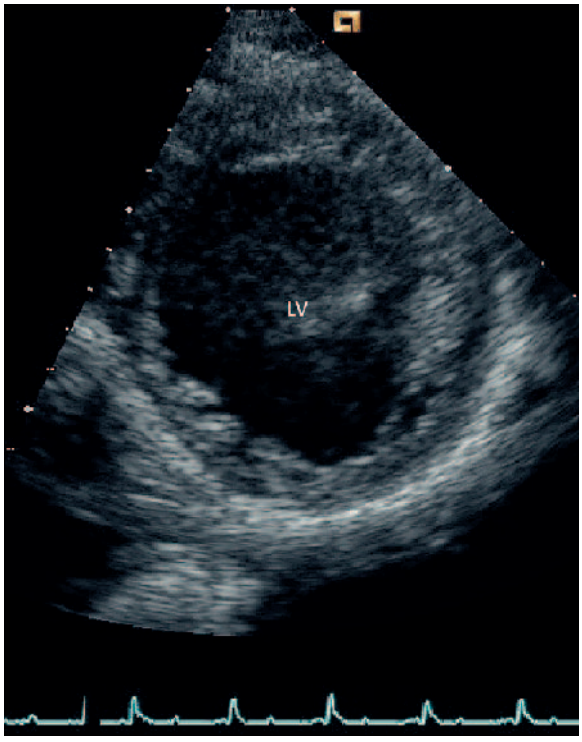
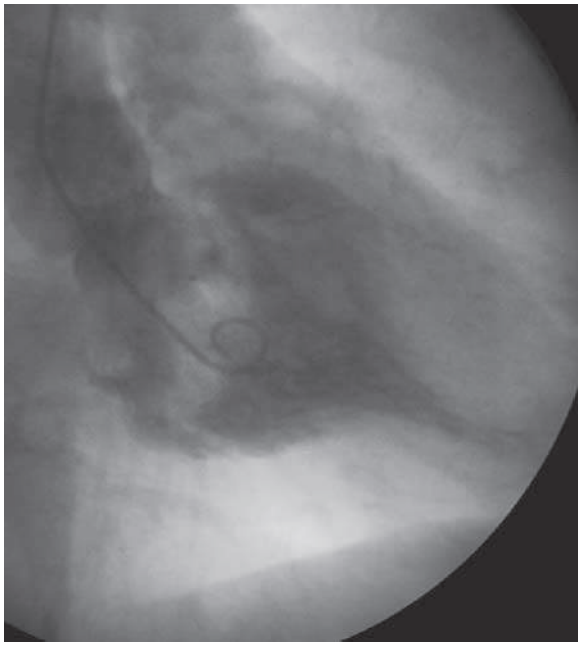


b

Fig. 20.**53** Hypertrophic and dilated cardiomyopathy.
a Transverse echocardiogram of the left ventricle (LV) at the start of systole in hypertrophic cardiomyopathy shows a greatly thickened wall with a small end-diastolic diameter of the left ventricle (concentric hypertrophy).
b In dilated cardiomyopathy, the ventricle is dilated and the ventricular wall is thinned.



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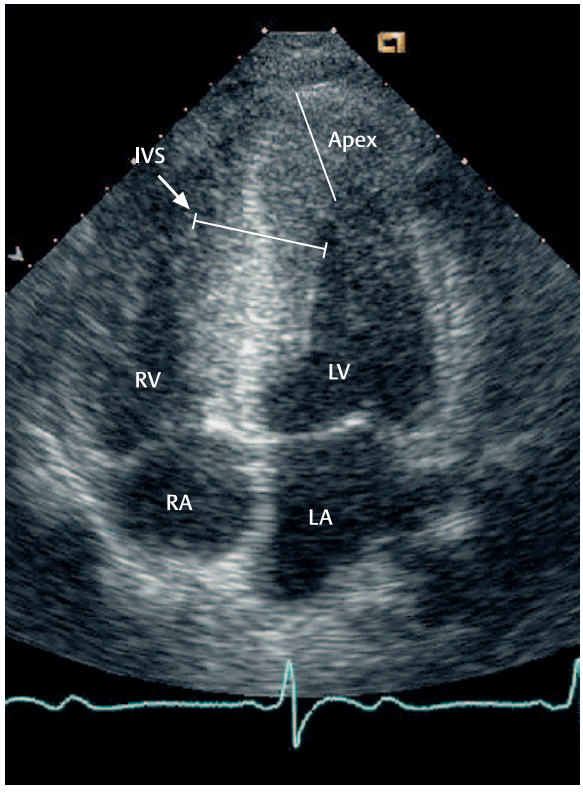

b

Fig. 20.**54** Apical hypertrophic cardiomyopathy
a LV angiography demonstrates apical hypertrophy, which has caused typical apical obliteration of the left ventricle, producing a "spade-shaped" ventricle.
b Echocardiography shows massive thickening of the interventricular septum (IVS) and massive apical hypertrophy. RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium.

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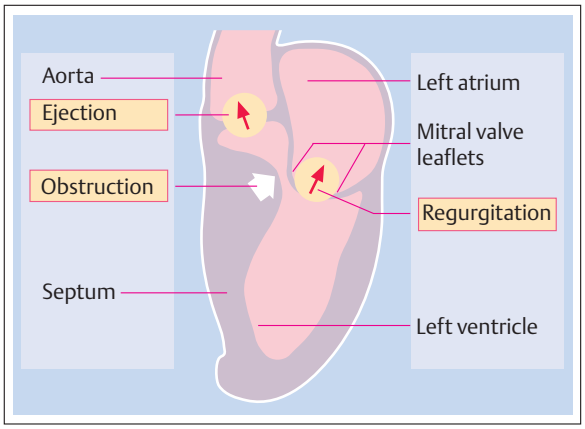

Fig. 20.**55** Schematic representation of hypertrophic obstructive cardiomyopathy. The hypertrophy in this condition predominantly affects the basal septum. This leads to obstruction of the left ventricular outflow tract accompanied by anterior motion of the anterior mitral valve leaflet. This opens up the valve leaflet, causing potentially severe mitral insufficiency.

Table 20.**30** Symptoms and signs of hypertrophic cardiomyopathy

Symptoms
– dyspnea on exertion – orthopnea, paroxysmal nocturnal dyspnea – angina pectoris – dizziness – presyncope or syncope on exertion – sudden cardiac death
Signs
– brisk, bisferiens pulse – forceful heaving apex beat – fourth heart sound – mesosystolic ejection murmur – holosystolic regurgitant murmur at the apex (in the presence of mitral insufficiency)

leaflet causes the mitral valve to open, leading to mitral insufficiency (Fig. 20.**55**). Both the outflow obstruction and the mitral insufficiency in these patients contribute to the symptoms and promote the development of heart failure. In a few cases, hypertrophic cardiomyopathy may dilate over time and come to resemble dilatative cardiomyopathy in its late form.

Clinical Features. The symptoms of hypertrophic cardiomyopathy are similar to those of aortic stenosis (Tab. 20.**30**). Even the *systolic ejection murmur* has a similar character. Hypertrophic cardiomyopathy is distinguished by the forceful pulse and the marked change in the ejection murmur that occurs at different degrees of ventricular filling (see Tab. 20.**7**). Auscultation in the standing and squatting positions makes it possible to differentiate the murmur from that of aortic stenosis and mitral insufficiency. It should be noted that the nonobstructive form of hypertrophic cardiomyopathy is also frequently associated with a systolic ejection murmur, which may also show dynamic changes. Thus, obstruction of the outflow tract can be detected only by Doppler echocardiography or invasive pressure measurements.

Sudden cardiac death from ventricular arrhythmia in hypertrophic obstructive cardiomyopathy typically occurs in adolescents during or after very strenuous athletic activity. The following are risk factors for the occurrence of sudden cardiac death:

- history of surviving cardiac arrest or of persistent ventricular tachycardia
- repeated syncopal attacks
- unfavorable genotype and a positive family history
- exercise-induced hypotension
- frequent and prolonged runs of ventricular tachycardia in the 24-hour ECG
- massive left ventricular hypertrophy.

Diagnostic Studies

- *ECG:* prominent Q waves in II, III, aVF and T-inversions in I, aVL, V_2 through V_6 are present, reflecting septal depolarization of the hypertrophic myocardium. Because these Q waves closely resemble the Q waves from a previous myocardial infarction, they are described as a pseudoinfarction pattern (Fig. 20.**56**). The apical form of hypertrophic cardiomyopathy is characterized by ST-segment depression and large deep negative T waves in the anterior leads (Fig. 20.**57**).
- *Echocardiography:* echocardiography is an essential study that can measure the distribution and extent of left ventricular hypertrophy as well as the subvalvular dynamic pressure gradient at rest and after provocative stress. The systolic anterior motion of the mitral valve leaflet can be visualized, and possible mitral insufficiency can be detected and quantified.

Differential Diagnosis. *Hypertensive heart disease* may lead to hypertrophy of the left ventricle with asymmetrical septal hypertrophy and obstruction of the left ventricular outflow tract that is morphologically indistinguishable from hypertrophic obstructive cardiomyopathy. Therefore, a diagnosis of hypertrophic cardiomyopathy should be made only in normotensive patients.

Although the clinical symptoms and findings are very similar, echocardiography in *aortic stenosis* can demonstrate the thickened and calcified aortic valve and define the structure of the pressure gradient across that valve, thereby distinguishing it from hypertrophic cardiomyopathy. However, a significant percentage of patients with aortic stenosis also have asymmetrical septal hypertrophy and show a certain subvalvular pressure gradient.

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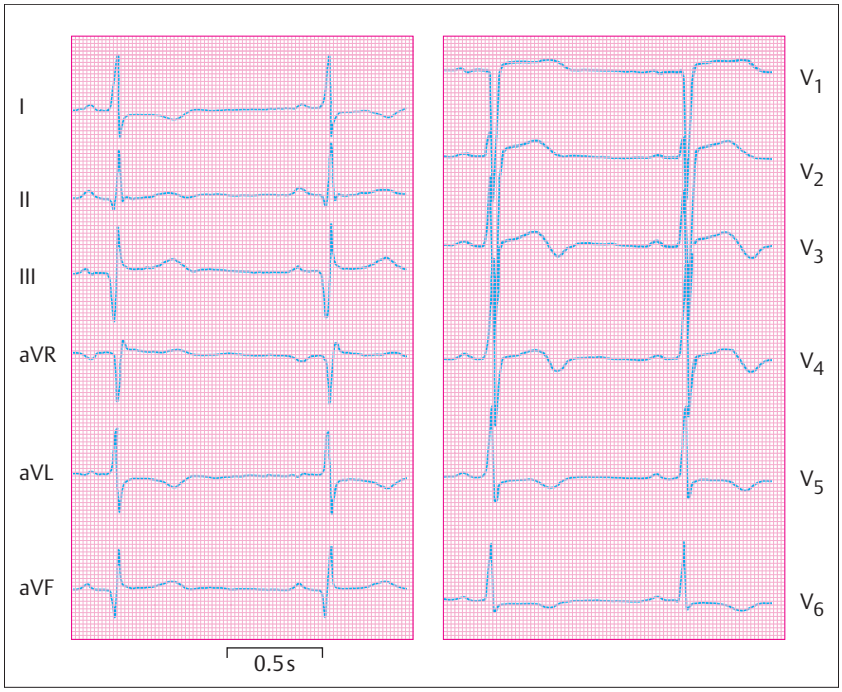

Fig. 20.**56** ECG of hypertrophic obstructive cardiomyopathy in a 29-year-old man. Note the negative T waves in V_3 through V_6, I, and aVL. The deep Q waves in III and aVF are typical (pseudoinfarction pattern; differential diagnosis: inferior wall infarction).

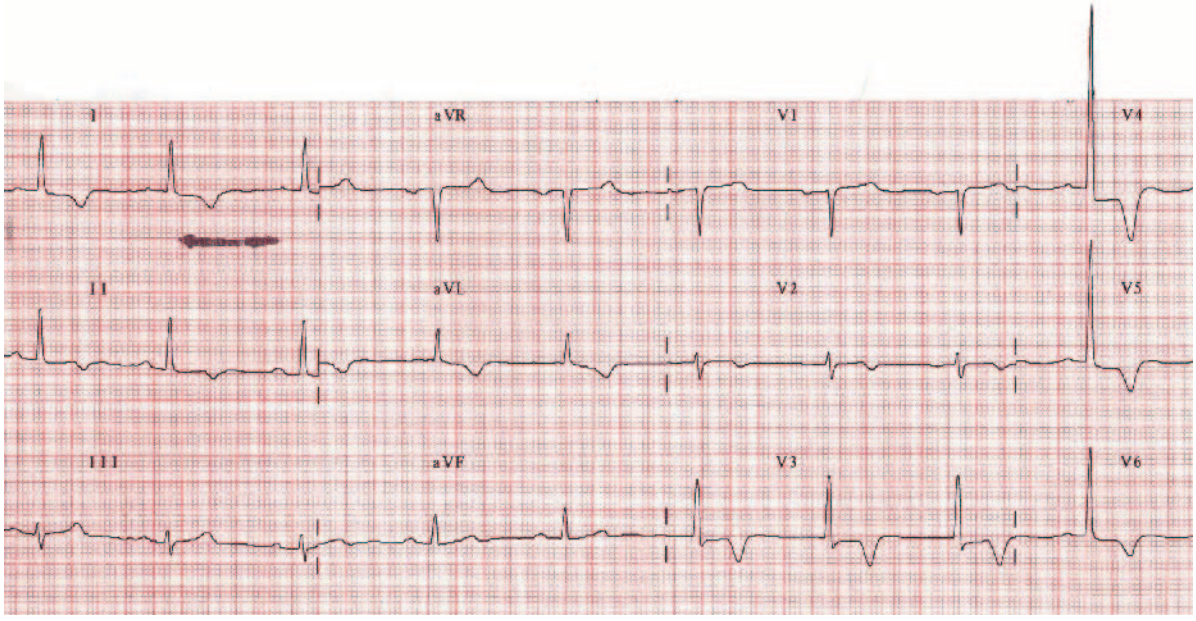

Fig. 20.**57** ECG of apical hypertrophic cardiomyopathy. Typical findings are the ST-segment depressions in V_3 through V_6 with deep negative T waves in these leads.

Restrictive Cardiomyopathy

Etiology and Pathogenesis. In restrictive cardiomyopathy, the disease of the myocardium or endocardium leads to the impaired filling of one or both ventricles (see Fig. 20.**52**). Most cases show no cardiac dilatation or hypertrophy. Systolic function is usually intact, at least at the start of the disease.

Restrictive cardiomyopathy is most frequently caused by infiltrative diseases and storage diseases (see Tab. 20.**29**). The most important causative diseases are amyloidosis, prior radiotherapy, sarcoidosis, hemochromatosis, and Fabry disease. Idiopathic restrictive cardiomyopathy is very rare. Restrictive cardiomyopathy may also result from scarring of the endomyocardium, which usually affects both ventricles. The mitral and tricuspid

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Table 20.**31** Symptoms and signs of restrictive cardiomyopathy

Symptoms
– fatigue – exercise intolerance – anorexia – angina pectoris (amyloidosis!) – symptoms of thromboembolic complications – dyspnea on exertion – orthopnea, paroxysmal nocturnal dyspnea
Signs
– sinus tachycardia – lower extremity edema – distended neck veins – hepatomegaly, ascites – pulmonary congestion (rales, pleural effusion)

valves are usually involved as well. The principal diseases that cause this obliterative form of restrictive cardiomyopathy are endomyocardial fibrosis and eosinophilic parietal endocarditis (Löffler endocarditis).

Clinical Features. Impairment of ventricular filling gives rise to a volume and pressure overload in the atria. As a result, the atria are moderately to severely dilated. This is why *symptoms of right-sided heart failure* are dominant in most restrictive cardiomyopathies (Tab. 20.**31**). *Dyspnea on exertion* and *orthopnea* may also occur, however. Chest pain or discomfort may be the initial symptom of amyloidosis.

Again, the principal findings are referable to right-sided heart failure. Auscultation often reveals a *third and/or fourth heart sound and regurgitant murmurs* indicating mitral and tricuspid insufficiency.

Diagnostic Studies

- *ECG:* supraventricular and ventricular arrhythmias are frequent ECG findings in restrictive cardiomyopathies. The most common arrhythmia is atrial fibrillation. Other common findings are peripheral low voltage, nonspecific ST-wave and T-wave changes, and conduction delays (left bundle branch block, AV block).
- *Chest radiograph:* the chest film may show pulmonary congestion with a slightly enlarged left ventricle and dilated atria.
- *Echocardiography:* this study may furnish an etiologic diagnosis (e. g., amyloidosis). Doppler echocardiography can demonstrate the restrictive filling pattern. Dilatation of the atria is also detected in most cases, and the left ventricle may show decreased pumping ability in the late stage.
- *Laboratory tests:* laboratory findings may provide important clues to the etiology of the cardiomyopathy (e. g., hypercalcemia in sarcoidosis, high iron levels in hemochromatosis).

Causes of Restrictive Cardiomyopathy

Amyloidosis. In amyloidosis, extracellular fibrils (subunits of serum proteins) are deposited in the heart. In *primary* amyloidosis, the fibrils consist of fragments of monoclonal light chain proteins that originate from the plasma cells of plasmacytoma or multiple myeloma. The deposits in *secondary* amyloidosis are fragments of serum amyloid A, which is found in chronic inflammations. Amyloid deposits are often present in the myocardium of patients over 80 years of age (senile amyloidosis). Cardiac involvement by primary amyloidosis leads to much more severe pump failure than in secondary amyloidosis. Senile amyloidosis is more likely to cause arrhythmias (atrial fibrillation).

The amyloid deposits make the ventricles stiffer, resulting in *diastolic dysfunction*. The replacement of myofibrils by amyloid leads to a gradual impairment of systolic function. Extreme cases progress to *stiff heart syndrome*, in which severe restrictive impairment of ventricular filling is combined with a decrease in the pumping ability of the heart.

The clinical presentation is dominated, at least initially, by *signs of right-sided heart failure*. Syncopal attacks are frequent. Angina pectoris results from amyloid deposition at the level of the small arterioles, and accordingly the coronary arteries appear normal by coronary angiography. When angina pectoris is the presenting complaint, it often occurs one to two years before amyloidosis is manifested in another organ.

ECG signs of amyloidosis are peripheral low voltage and AV blocks. *Echocardiography* often shows thickening of the ventricular myocardium and a thick interatrial septum. Amyloid deposits in the myocardium look like coarse clumps with bright inclusions ("*sparkling*" pattern, Fig. 20.**58**). Amyloidosis should be strongly suspected in patients who present with anemia, proteinuria, and bone pain. Paraproteins can be detected in the 24-hour urine and by serum immunoelectrophoresis. The diagnosis is supported by detecting amyloid deposits in the abdominal fat, rectum, or kidneys. Myocardial biopsy is definitive but is not always necessary in making the diagnosis.

Postirradiation Changes. Prior to 1990, the anterior myocardium was irradiated at over 40 Gy for the treatment of various malignancies. This caused damage to the pericardium, myocardium, and coronary vessels. Typically, these changes are still manifested more than 10 years later. The most common finding is constrictive pericarditis, but a restrictive cardiomyopathy is not unusual. In contrast to most other restrictive cardiomyopathies, the atria are also involved. The picture is often complicated by radiation-induced coronary heart disease.

Sarcoidosis. Although involvement of the pericardium or myocardium by sarcoidosis is found in approximately 25 % of cases, only a few patients develop cardiac symptoms. The most common clinical manifestations are

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pericarditis, arrhythmias, and conduction abnormalities. Restrictive or dilated cardiomyopathy may develop in rare cases. Sarcoidosis predominantly affects the basal portions of the left ventricle, and this often makes biopsy confirmation difficult. Sarcoidosis may also lead to pulmonary hypertension.

Hemochromatosis. Iron deposition in the sarcolemma of the cardiac myocytes can lead to cardiac dysfunction by various mechanisms. Restrictive cardiomyopathy is the most frequent disorder caused by hemochromatosis. The extent of the cardiomyopathy is directly dependent on the quantity of the iron deposition. The development of heart failure is marked by rapid deterioration with biventricular failure, peripheral edema, and hepatomegaly.

Fabry disease. Fabry disease is a glycolipid storage disease with an X-linked recessive mode of inheritance. It typically causes *neuropathy* and *skin lesions* (angiokeratomas). Cardiac involvement leads to ventricular hypertrophy, conduction abnormalities, and coronary heart disease. Patients frequently complain of palpitations, angina pectoris, and dyspnea. Cardiac involvement is diagnosed by measuring the serum level of α-galactosidase, which is low. Glycolipid deposits in myocardial biopsy samples can be detected only by electron microscopy.

Carcinoid. The disease has already reached a very advanced stage by the time the heart is involved by carcinoid syndrome. Hepatic metastases are generally present. The dominant feature is *right-sided heart failure* caused by impaired right ventricular filling due to endocardial thickening and also by tricuspid insufficiency. Occasionally the tricuspid valve also undergoes stenotic changes. The pulmonary valve and rarely the mitral valve may also be involved. Generally, the right cardiac chambers are only slightly enlarged because the endocardial thickening tends to inhibit chamber dilatation. The filling pressures on the right side are greatly increased, however. During a carcinoid flush, the patient may experience coronary arterial spasms with Prinzmetal-type angina. The ECG shows peripheral low voltage, right atrial overload, and right ventricular hypertrophy with a right bundle branch block.

Endomyocardial Fibrosis. Endomyocardial fibrosis is a restrictive obliterative disease that is endemic in tropical and subtropical Africa. The fibrosis affects the inflow tract and apex of one or both ventricles. Involvement of the right ventricle often leads to obliteration of the chamber by fibrous tissue or thrombi (Fig. 20.**59**). The tricuspid and mitral valves are usually affected as well, resulting in tricuspid and mitral insufficiency. The dominant feature may be right-sided or left-sided heart failure, depending on the affected chambers. Thromboembolic complications are common. The disease takes a relentlessly progressive course. The diagnosis is established by echocardiography or angiography.

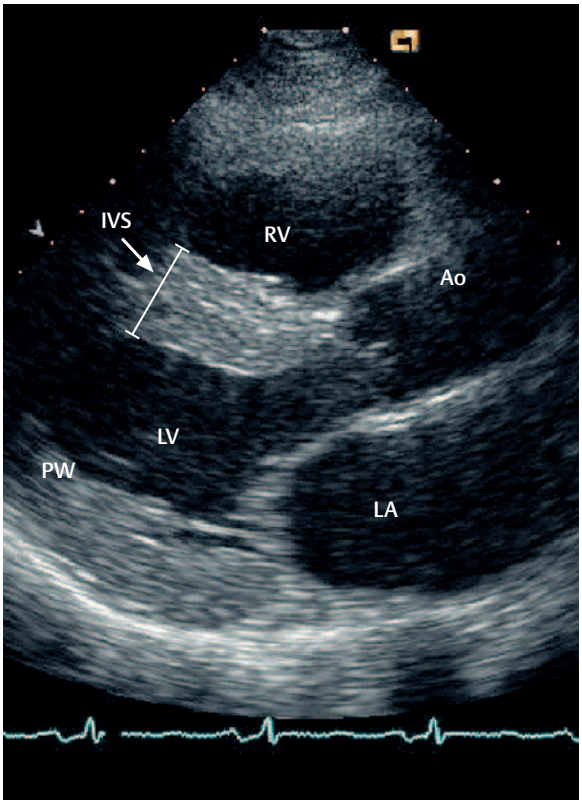

Fig. 20.**58** Parasternal longitudinal scan in a patient with amyloidosis. The posterior wall (PW) and interventricular septum (IVS) are thickened. The amyloid is sonodense, causing the myocardium to appear more echogenic. RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium, Ao = aorta.

Eosinophilic Fibroblastic Endocarditis (Löffler Endocarditis). Eosinophilia of long duration may lead to endomyocardial disease. Usually the disease is marked by endocardial thickening of both ventricles. Inflammatory eosinophilic myocarditis also develops in most cases, at least initially. The endocardium may reach a thickness of several millimeters and may be studded with thrombi. Patients often have fever, cough, and heart failure. Thromboembolic complications are frequent.

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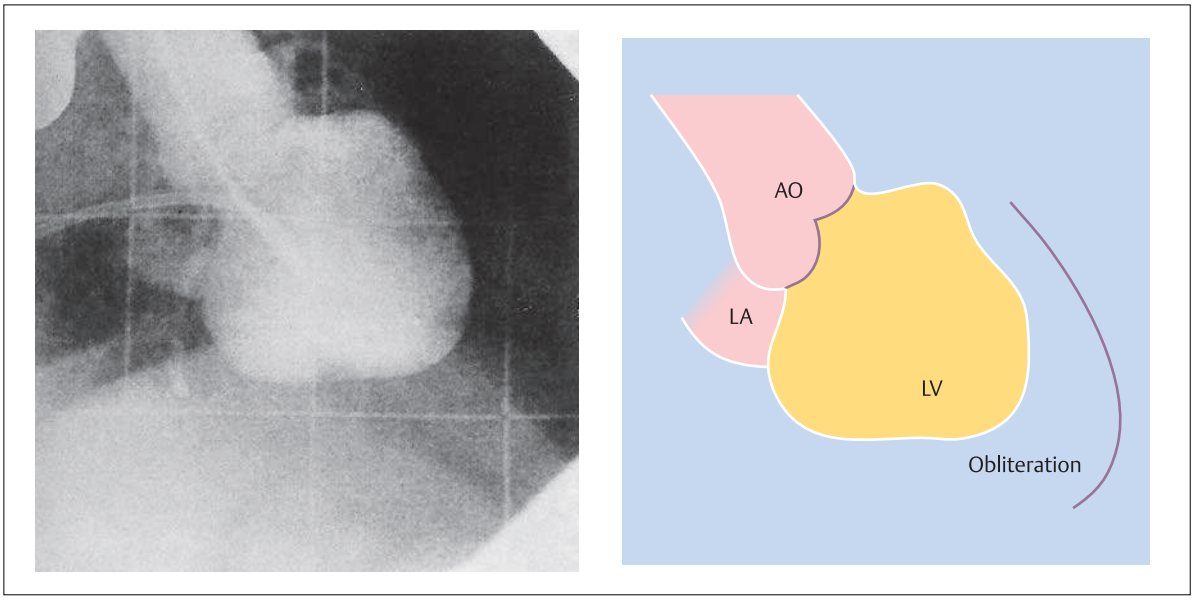

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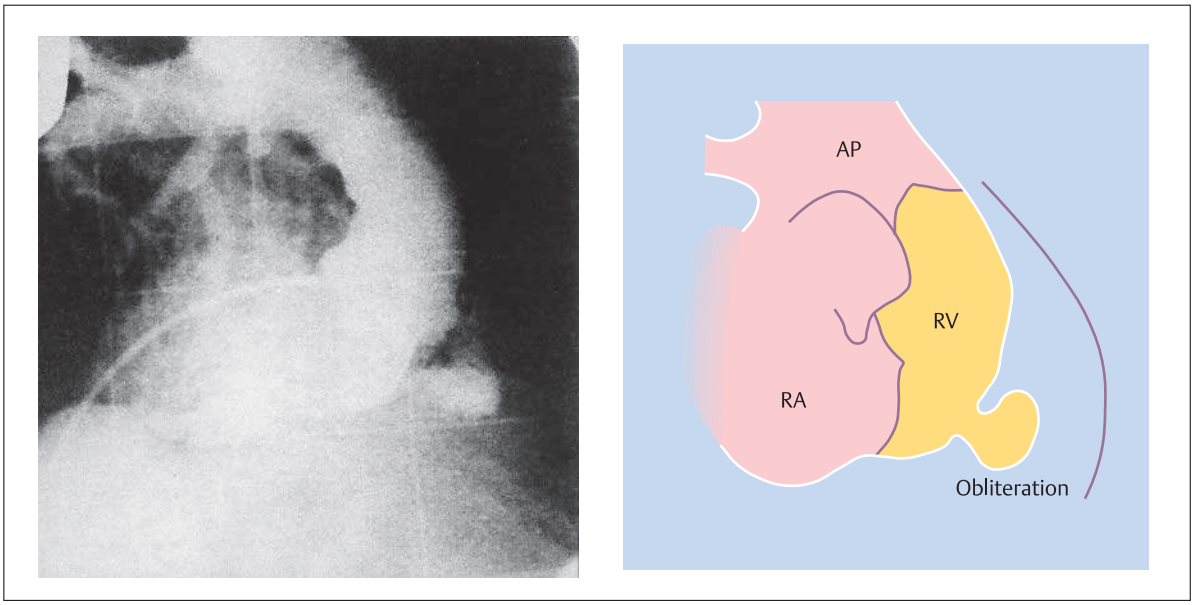

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Fig. 20.**59** Biventricular endomyocardial fibrosis in a 35-year-old woman.

a Left ventricular angiocardiogram: the apex of the left ventricle is obliterated. The inner surface of the left ventricle is abnormally smooth, having lost its trabecular structure. Mild mitral insufficiency is present. LV = left ventricle, LA = left atrium, AO = ascending aorta.

b Right ventricular angiocardiogram: the cavity of the right ventricle has been reduced to a tubular structure. A residual lacuna is present in the obliterated portion. Moderately severe tricuspid insufficiency is present. RV = right ventricle, RA = right atrium, AP = pulmonary artery.

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Differential Diagnosis of Heart Failure Due to Impaired Contractile Function

Dilated Cardiomyopathy

Dilated cardiomyopathy is characterized by the dilatation of one or both ventricles, whose walls may be normal or thinned and whose contractility is severely impaired (see Figs. 20.**52b**, 20.**53b**). The pathophysiology is based on the impaired systolic pumping function of the heart. Histologic examination shows a loss of myocytes, increased interstitial fibrosis, and often nonspecific inflammatory cells.

Clinical Features. Patients have typical symptoms of *right-sided and left-sided heart failure* (see Tab. 20.**2**). Symptoms of pulmonary congestion (dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea) and *exercise intolerance* reflecting the low cardiac output are the most prominent features. Many patients also manifest systemic venous congestion and anorexia as signs of right-sided heart failure. Angina pectoris is absent, however. Thromboembolic complications are not unusual and arrhythmias leading to dizziness, syncope, or even sudden death are a feared complication.

Signs of biventricular heart failure are noted on examination. Auscultation usually discloses a *third and fourth heart sound*, and it is common to find mitral insufficiency and tricuspid insufficiency. Mitral insufficiency is sometimes severe and results from dilatation of the mitral valve annulus. It may occasionally raise problems of differential diagnosis (see below). There may also be signs of *decreased peripheral blood flow* with cool skin and peripheral cyanosis, depending on the severity of the heart failure (see Tab. 20.**4**).

Diagnostic Studies

- *ECG:* the ECG frequently shows a left bundle branch block or other conduction abnormalities. The 24-hour ECG and stress ECG may show dangerous ventricular arrhythmias in some patients.
- *Chest radiograph:* the dominant radiographic signs are cardiomegaly and pulmonary congestion (see Figs. 20.**13**, 20.**14**). The differential diagnosis should include pericardial effusion, which must be excluded by echocardiography.
- *Echocardiography:* this test provides information on the extent of ventricular dilatation (see Fig. 20.**53b**), the severity of pump failure, and the extent of mitral and tricuspid insufficiency. Pulmonary hypertension can be assessed, and any thrombi in the atrium and ventricle can be visualized.
- *Cardiac catheterization:* cardiac catheterization can detect the low cardiac output, the increased peripheral resistance, and pulmonary hypertension.
- *Biopsy:* this test usually indicates nonspecific fibrosis. The value of biopsy in making an etiologic diagnosis is still uncertain.

Causes of Dilated Cardiomyopathy

Dilated cardiomyopathy may be caused by a number of diseases (see Tab. 20.**29**). In approximately 50% of cases the etiology remains unknown and the dilated cardiomyopathy is classified as idiopathic. A large percentage of other cardiomyopathies have a genetic cause or result from viral myocarditis. Hereditary forms of dilated cardiomyopathy are based on autosomal dominant gene mutations that affect the cytoskeleton and myocytes (e. g., dystrophin, lamin A and C, emerin, and metavinculin).

Viral Cardiomyopathy. Viral infection is the leading cause of myocarditis (Tab. 20.**32**). A previous viral myocarditis may well be responsible for many unexplained cases of dilated cardiomyopathy. The principal viruses that affect the myocardium are coxsackie viruses, influenza viruses, echoviruses, adenoviruses, cytomegaloviruses, and HIV.

- *HIV cardiomyopathy:* HIV may cause cardiomyopathy, pericarditis, and pulmonary hypertension. A large pericardial effusion may mimic a cardiomyopathy in these patients. Patients with HIV infection may develop accelerated coronary sclerosis, most likely caused by protease inhibitor-induced hypercholesterolemia. Coronary heart disease may also increase the severity of cardiomyopathy. Dilated cardiomyopathy in an HIV setting has a poor prognosis.
- *Chagas disease:* Chagas disease is caused by the parasite *Trypanosoma cruzi* and is the most frequent cause of dilated cardiomyopathy in Central and South America. After a period of acute myocarditis, the disease takes a chronic course and progresses to dilated cardiomyopathy in its end stage. Arrhythmias are extremely typical of Chagas disease. Apical left ventricular aneurysms detected by echocardiography or left ventricular angiography are pathognomonic for this disease.
- *Lyme disease:* approximately 10% of patients infected by *Borrelia burgdorferi* will develop myocarditis. The most frequent manifestations are AV blocks and bundle branch blocks. Cardiomyopathy due to Lyme carditis is uncommon.

Toxic Cardiomyopathy. Any drug or medication may cause a cardiomyopathy or influence its course. The most familiar causative agents are alcohol, cocaine, amphetamines, chemotherapeutic agents, and irradiation.

- *Alcohol:* alcohol has a cardiodepressant effect that may induce cardiomyopathy in some patients. Although a certain dose–response relationship exists, it is unclear why some patients develop cardiomyopathy and others do not. There appears to be a predisposition for the development of alcoholic

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cardiomyopathy. Abstinence from alcohol may lead to dramatic improvement of left ventricular function in patients with alcoholic cardiomyopathy. Because alcohol may also exacerbate a cardiomyopathy due to a different cause, it is important for all patients with cardiomyopathy to refrain from alcohol use.

- *Cocaine:* cocaine may cause coronary heart disease, pulmonary hypertension, and cardiomyopathy. Although cardiomyopathy is less common than coronary heart disease, cocaine use should be considered in the differential diagnosis of unexplained cardiomyopathies.
- *Medications:* medication-induced cardiomyopathy is most likely to occur after the use of chemotherapeutic agents such as anthracycline and doxorubicin. Trastuzumab is a new agent used in the treatment of breast cancer (monoclonal antibody against the erbB-2 receptor). It may induce cardiomyopathy or heighten sensitivity to anthracycline toxicity.

Peripartum Cardiomyopathy. Peripartum cardiomyopathy is a rare cause of dilated cardiomyopathy, and its pathogenesis is unclear. It is diagnosed in cases where cardiomyopathy occurs during the last month of pregnancy or within five months after delivery. A different cause should be carefully excluded. Peripartum cardiomyopathy should not be diagnosed in women with preexisting cardiac disease.

Differential Diagnosis of Dilated Cardiomyopathy

Mitral Insufficiency. Left ventricular dilatation leads to dilatation of the mitral valve annulus, and occasionally this may cause severe mitral insufficiency. In many cases, it is impossible to determine whether the patient has a dilated cardiomyopathy with secondary mitral insufficiency or a severe mitral insufficiency causing a secondary decline in ventricular function. Significant improvement of mitral insufficiency in response to afterload-reducing therapy would support a diagnosis of secondary mitral insufficiency.

Coronary Heart Disease. Severe triple-vessel coronary disease or main trunk disease may occasionally cause a diffuse global impairment of left ventricular function that is morphologically indistinguishable from dilated cardiomyopathy. Approximately 5% of patients with unexplained dilated cardiomyopathy and risk factors for coronary heart disease are found on invasive examination to actually have severe coronary disease. A revascularization procedure may improve the cardiomyopathy in cases of this kind. Occasionally the degree of pump dysfunction is not proportional to the severity of existing coronary disease (e.g., single-vessel disease). In this case it is more likely that dilated cardiomyopathy coexists with coronary heart disease.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy (ARVC, formerly called arrhythmogenic right ventricular dysplasia) is a rare and unique form of cardiomyopathy. It is characterized by a *regional* or *global replacement* of right ventricular muscle cells *by fat and fibrous tissue*. The most frequent sites of fibrofatty replacement are the apex, inflow tract, and outflow tract of the right ventricle. Occasionally the left ventricle is also affected. An extreme form of ARVC, or possibly a variant of it, is *Uhl disease*, in which the entire right ventricle is replaced by fibrotic material and the ventricular wall appears paperthin (Fig. 20.**60**). ARVC predominantly affects men, and several genetic defects have been identified. An increased prevalence of ARVC has been documented in Italy and on the Greek island of Naxos.

Clinical Features. ARVC remains asymptomatic for years and occasionally is detected incidentally on chest radiographs. *Ventricular arrhythmias* are a feared complication that often occur as the earliest symptom, and there are unfortunate cases in which the first sign of ARVC is *sudden cardiac death*. The arrhythmias have a right ventricular origin.

The ECG shows widening of the QRS complex, a complete or incomplete right bundle branch block, and precordial T-wave inversions. Approximately 30% of patients have an epsilon wave (a wave immediately following the QRS complex in V_1). Echocardiography may show localized dyskinesia or mild to severe right ventricular dilatation, depending on the stage of the disease (Fig. 20.**60b**). The fat deposits in the right ventricle can generally be identified on MR images.

Isolated Noncompaction of the Left Ventricle

Noncompaction of the left ventricle is a rare, unclassified congenital cardiomyopathy that results from a failure of normal myocardial compaction during embryonic development. Morphologically, left ventricular noncompaction is characterized by multiple trabeculations and deep intratrabecular recesses that communicate with the ventricular cavity. The trabeculations are most pronounced in the apical part of the left ventricle (Fig. 20.**61**). Angiography displays a double contour with contrast medium outlining the trabeculae and the contracting ventricle. This cardiomyopathy often occurs with heart failure or ventricular arrhythmias. A large percentage of patients suffer thromboembolic complications.

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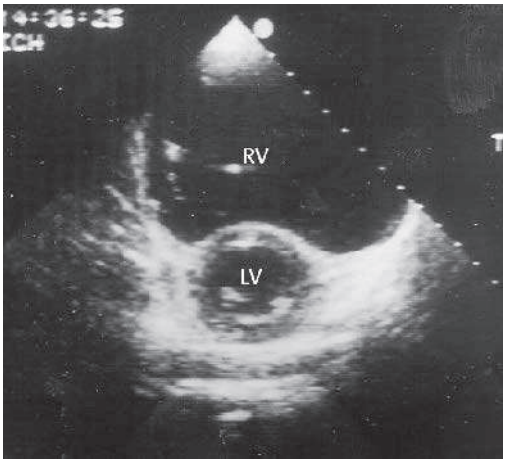

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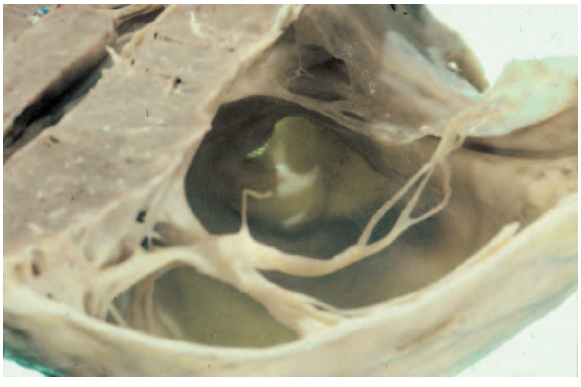

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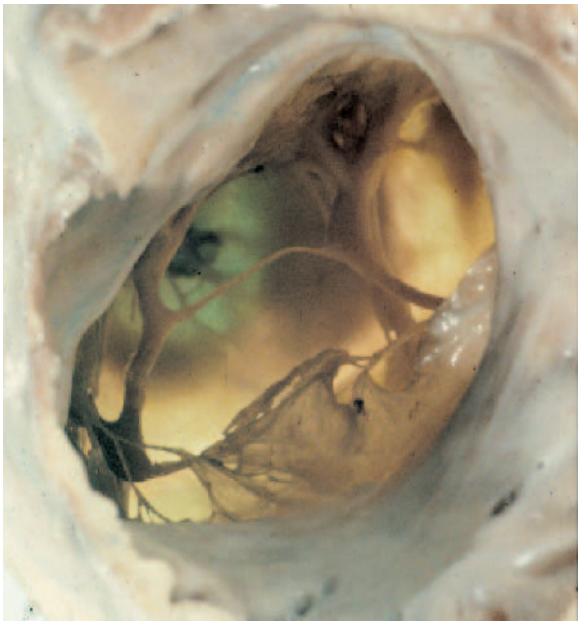

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Fig. 20.**60** Arrhythmogenic right ventricular cardiomyopathy.

a Chest radiograph shows grotesque dilatation of the right ventricle, which forms the left border of the cardiac silhouette.

b Echocardiography shows massive dilatation of the right ventricle (RV) with a normal-sized left ventricle (LV).

c The right ventricle is dilated and has a thin wall. The left ventricle appears normal.

d A view through the tricuspid valve shows how paper-thin the right ventricle is. This extreme form of right ventricular cardiomyopathy is also called Uhl disease.

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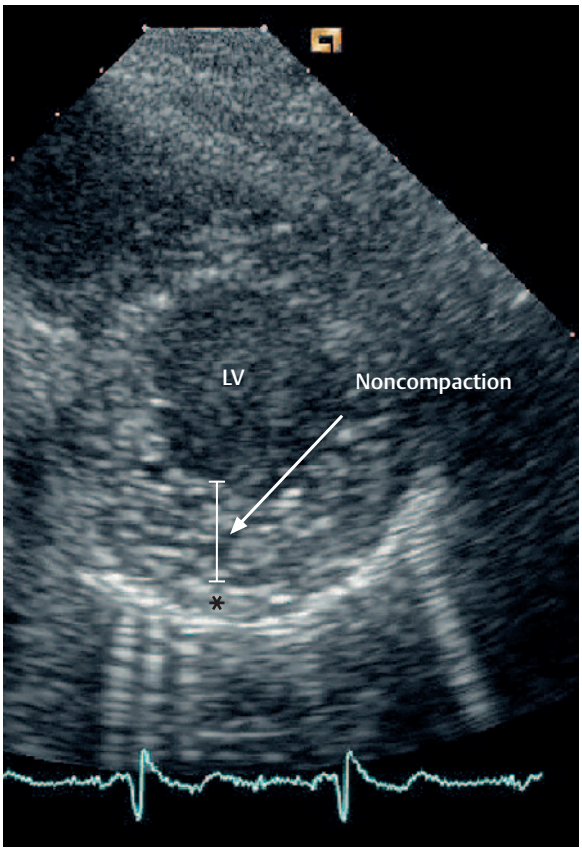

Fig. 20.**61** Noncompaction of the left ventricle. Transverse echocardiogram in this rare cardiomyopathy shows a two-layered myocardium consisting of a compact epicardial layer (*) and a greatly thickened, noncompact endocardial layer with numerous trabeculae and intertrabecular recesses, which are filled with blood from the left ventricular cavity. By definition, the thickness of the noncompact layer must be at least twice the thickness of the compact layer. The affected wall segments are hypokinetic. The ejection fraction may be normal or greatly decreased, depending on the stage of the disease.

Table 20.**32** Causes of acute infectious myocarditis

Viruses
Enteroviruses:
– coxsackie virus A
– coxsackie virus B
– echovirus
– poliovirus
Herpesviruses:
– *Cytomegalovirus*
– Epstein–Barr virus
– herpes simplex virus
– varicella-zoster virus
Human immunodeficiency virus
Other viruses:
– *Hepatitis B virus*
– *Hepatitis C virus*
– adenovirus
– *Influenzavirus A*
– *Influenzavirus B*
– *Rabies virus*
– *Parvovirus*
– *Measles virus*
– *Rubella virus*
Bacteria
Chlamydia pneumoniae
Chlamydia psittaci
Corynebacterium diphtheriae
Tropheryma whipplei (Whipple disease)
Neisseria meningitidis
Mycoplasma pneumoniae
Legionella pneumophila
Brucella melitensis
Salmonella typhi
Vibrio cholerae
Spirochetes
Borrelia burgdorferi (Lyme disease)
Treponema pallidum (syphilis)
Leptospira interrogans
Rickettsia
Rocky Mountain spotted fever
Q fever
Ehrlichiosis
Fungi
Aspergillus
Candida albicans
Histoplasma capsulatum
Cryptococcus neoformans
Mucormycosis
Parasites
Trypanosoma cruzi (Chagas disease)
Toxoplasma gondii
Trichinella spiralis

Myocarditis

Causes. Acute myocarditis is an acute, inflammatory, potentially reversible disease that may be caused by viral infections (see Tab. 20.**32**). The inflammation is mediated by the causative organisms themselves and by the toxins they release. Viral myocarditis is the most common form, and the coxsackie virus B and influenza A and B viruses are by far the most common viral pathogens. Myocarditis may occur up to several weeks after the acute viral infection.

Clinical Features. The clinical presentation of myocarditis is highly variable. Most cases resolve without consequences, but the worst cases develop an *acute fulminating myocarditis* leading to immediate acute heart failure and cardiogenic shock. Usually the dominant features of these cases are signs of right-sided heart failure and a dwindling cardiac output. A few patients with a previous history of myocarditis present with features of *dilated cardiomyopathy* and the typical clinical signs of left-sided heart failure.

The symptoms of acute florid myocarditis are *fatigue*, *shortness of breath*, *dyspnea on exertion*, *palpitations*, and *chest pain*. They are usually preceded by flulike symptoms, which most patients do not recall. If there is concomitant pericarditis, patients complain of chest

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pain similar to that of myocardial ischemia (see Chapter 6).

Auscultation reveals *tachycardia*, an occasional *third heart sound*, and a *systolic ejection murmur*. Patients with acute heart failure present the typical signs of biventricular failure.

Diagnostic Studies

- *ECG:* the ECG shows nonspecific ST-segment changes. Atrial and ventricular arrhythmias are common. Twenty percent of patients show a left bundle branch block. Transient AV blocks may cause sudden cardiac death. If pericarditis is present, typical pericarditic ECG changes will be found (see Fig. 6.**18**, Chapter 6).
- *Laboratory tests:* cardiac enzymes are elevated in most but not all patients. In the stage of dilated cardiomyopathy, however, the cardiac enzymes are generally normal.
- *Chest radiograph:* the chest radiograph shows many variations in acute myocarditis. In chronic myocarditis that has led to dilated cardiomyopathy, the radiograph demonstrates cardiomegaly and pulmonary congestion.
- *Echocardiography:* echocardiography also shows all the features of dilated cardiomyopathy and may supply specific diagnostic information in certain cases (e. g., Chagas disease with intraventricular aneurysms). Mural thrombi are found in approximately 15 % of cases.
- *Biopsy:* the diagnosis is established by endomyocardial biopsy. Histologic examination in the acute stage shows mononuclear cellular infiltrates and foci of myocardial necrosis. Biopsies in the subacute or chronic stage show interstitial fibrosis and nonspecific inflammatory cells. Specific viral pathogens can be identified by means of the polymerase chain reaction (PCR), although to date this capability has achieved little therapeutic significance.

Giant Cell Myocarditis

Giant cell myocarditis is a rare disease characterized by the presence of *multicellular giant cells in the myocardium* and may resemble viral myocarditis. The etiology is unknown, but the disease has a high association with systemic diseases such as sarcoidosis and systemic lupus erythematosus. Giant cell myocarditis is probably based on an *autoimmune response*, it takes a fulminating course, and heart transplantation is often indicated.

Ischemic Cardiomyopathy

Chronic coronary heart disease is the leading cause of heart failure in industrialized countries. Typically, an extensive scar leads to *aneurysm formation* in the infarcted area (Fig. 20.**62**), which is accompanied by *dilatation of the entire left ventricle* (see Fig. 20.**11**). The dilatation increases the wall tension (and afterload), further compromising the already impaired pumping ability of the heart. This results in a *low cardiac output* and *pulmonary venous congestion*. Patients have the typical signs of systolic and diastolic dysfunction and with symptoms of left-sided heart failure (see Tab. 20.**2**).

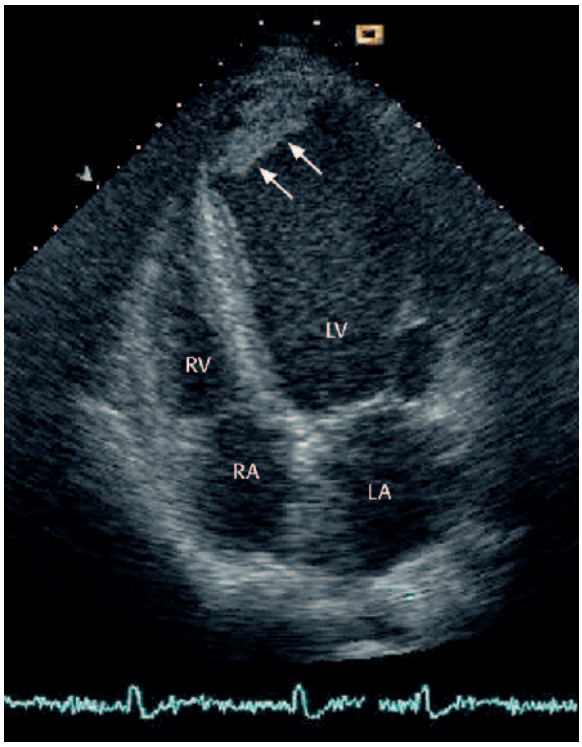

Fig. 20.**62** Ischemic cardiomyopathy; echocardiogram of a heart that sustained a large anterior-wall infarction. The left ventricle (LV) is dilated, and the infarction has led to aneurysm formation at the cardiac apex. A thrombus has formed within the aneurysm (arrows). The ejection fraction is substantially decreased.

The unfavorable remodeling process (left ventricular dilatation) is promoted by the presence of ischemia in the uninfarcted part of the ventricle, by diabetes mellitus, and by inadequate pharmacologic reduction of the afterload. An ischemic cause of the cardiomyopathy is easily established by *electrocardiography* and *coronary angiography* (see Chapter 6). It is difficult to distinguish between a postinfarction scar and a "*hibernating myocardium*." The latter term refers to the part of the myocardium that can no longer contract due to deficient blood flow, but whose myocytes are still viable. That portion of the myocardium should show a complete functional recovery following revascularization. Viability can be confirmed by radionuclide scanning (thallium scintigraphy) or positron emission tomography (PET).

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Differential Diagnosis of Heart Failure Due to Cardiac Arrhythmias

Tachycardia-Induced Cardiomyopathy

Almost any persistent *supraventricular tachyarrhythmia* may precipitate reversible left ventricular dysfunction or cardiomyopathy (see Fig. 20.**1**). This is less common with ventricular tachycardias. The pathogenesis of tachycardia-induced cardiomyopathy is not fully understood but probably relates to a fall in energy reserves, tachycardia-induced subendocardial ischemia, a disturbance of the beta receptors, and other factors.

Atrial fibrillation if the most common arrhythmia that is associated with cardiomyopathy. First, atrial fibrillation may increase the severity of a preexisting cardiomyopathy, usually due to impaired diastolic filling of the ventricle due to the ineffectual atrial contractions and concomitant tachycardia. Second, the rapid fibrillations themselves may lead to a dilated form of cardiomyopathy. In these patients with apparently idiopathic cardiomyopathy, cardioversion, or rate control can provide a dramatic improvement in pump function. Conversely, secondary atrial fibrillation in patients with dilated cardiomyopathy may cause a further deterioration of pump function.

Bradycardia-Induced Cardiomyopathy

An *acquired complete AV block* is the classic example of a bradycardic arrhythmia that impairs the pumping ability of the heart due to a decrease in heart rate. The severity of symptoms depends on the degree of bradycardia. Typical cases show *exertional dyspnea* during light to moderate exercise due to an insufficient rise in the heart rate. With extreme bradycardia, signs of heart failure may be present even at rest.

Various abnormalities of *supraventricular impulse formation* and *conduction* such as sinus arrest, sinoatrial block, sick sinus syndrome, and bradycardic atrial fibrillation may also impair the pumping ability of the heart.

Acknowledgements

The echocardiograms shown in Figures 20.**15a**, 20.**15c**, 20.**16b**, 20.**17**, 20.**23**, 20.**29**, 20.**30**, 20.**34**, 20.**35**, 20.**40**, 20.**42**, 20.**46**, 20.**47**, 20.**53**, 20.**54b**, 20.**58**, 20.**61**, and 20.**62** were kindly provided by R. Jenni and E. Oechslin, Zurich University Hospital, Switzerland.

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21 Cyanosis

E. Oechslin

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Abbreviations (Listed in Alphabetical Order):

AO	ascending aorta
ASD	atrial septal defect
AV	atrioventricular
AVSD	atrioventricular septal defect
ECG	electrocardiogram
ICS	intercostal space
LA	left atrium
LPA	left pulmonary artery
LV	left ventricle
MAPCAs	major aortopulmonary collateral arteries
PA	pulmonary artery
RA	right atrium
RV	right ventricle
TGA	transposition of the great arteries
VSD	ventricular septal defect
Blalock–Taussig shunt	Anastomosis between the subclavian artery and the ipsilateral pulmonary artery to increase pulmonary blood flow (palliative procedure).
Fontan circulation	A univentricular circulation with a morphologic right or left ventricle supporting the systemic circulation; the systemic venous return is diverted to the pulmonary artery, usually without the interposition of a subpulmonary ventricle; the central systemic venous pressure is the driving force for the blood flow through the lungs.
Potts shunt	Direct anastomosis between the descending aorta and the left pulmonary artery to increase pulmonary blood flow (palliative procedure).
Waterston shunt	Direct anastomosis between the ascending aorta and the right pulmonary artery to increase pulmonary blood flow (palliative procedure).

Medical History, Clinical Examination, and Definitions

Cyanosis is a sign, rather than a symptom, and may be observed either at rest or during exercise by both the patients and their family members. Cyanosis, which is more commonly detected by a family member than by the patient, affects many organ systems (multisystem disorder). Medical history, physical examination with characteristic features, ECG, chest radiograph, and color-coded Doppler echocardiography are the key tools in the diagnostic evaluation of patients with cyanotic congenital heart disease.

The medical history and the meticulous systemic clinical examination are critical in order to evaluate and to differentiate the wide spectrum of cyanosis (Fig. 21.**1**). Inspection of the fingers, toes, and mucous membranes provides clues for differentiation of central, as opposed to peripheral, cyanosis (Tab. 21.**1**). An accurate medical history (interview) is a clinical skill that is essential for the differential diagnosis!

Clinical detection and degree of cyanosis are affected by many factors, including the following: natural or pathologic (jaundice) skin pigmentation, state of the cutaneous capillaries, the thickness of the skin (epidermis), or room lighting. As a consequence, cyanosis can be missed in dark-skinned persons and may only be diagnosed if oxygen saturation is $< 80\,\%$. Cyanosis is most pronounced in the lips, nail beds of the fingers and toes, tongue, and mucous membranes of the mouth, although evidence of cyanosis can be better seen and evaluated in the mucous membranes and in the conjunctiva than in the skin.

Definitions. *True* cyanosis refers to a bluish discoloration of the skin or mucous membranes and results from hypoxemia due to an increased amount of deoxygenated hemoglobin. It is subdivided into *hemoglobin cyanosis* and *hemiglobin cyanosis* (Fig. 21.**1**).

Pseudocyanosis is different from true cyanosis and refers to a bluish discoloration of the skin and mucous membranes, caused neither by hypoxemia nor by peripheral vasoconstriction. It is due to skin pigmentation or deposits of exogenic substances, e. g., metals (silver nitrate, silver iodide, silver, lead) or drugs (amiodarone, chloroquine, phenothiazines).

Central cyanosis occurs with a bluish discoloration of both the skin (fingers, toes) and mucous membranes. It may be due to cardiac or pulmonary diseases.

Peripheral cyanosis is caused by peripheral vasoconstriction resulting in critically reduced cutaneous blood flow, increased peripheral oxygen extraction, and increased quantity of deoxygenated hemoglobin in the capillaries and venous vessels.

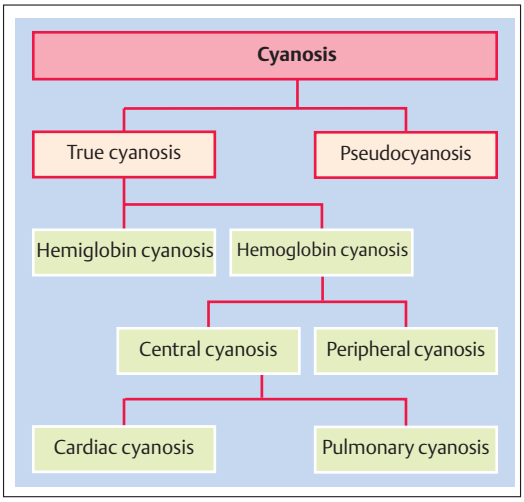

Fig. 21.**1** Flow diagram of cyanoses.

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Table 21.**1** Diagnostic approach in cyanosis

Medical history
- Family history: congenital heart and pulmonary diseases?
- When was cyanosis first observed?
- Cyanosis at rest or during exertion?
- Surgical procedures?
  - lung/thoracic wall surgery?
  - shunt procedures (Blalock–Taussig, Waterston, or Potts shunt)
  - Fontan circulation or Glenn shunt: pulmonary arteriovenous malformations
- Risk factors: smoking, occupational history/environmental exposure (toxic agents?)
- Liver cirrhosis (pulmonary arteriovenous malformations, portal hypertension, hepatopulmonary syndrome)

Inspection
- Cyanosis of the lips, toes, and mucous membranes?
- Differential cyanosis: absence of cyanosis in the head and upper limbs, presence of cyanosis in the lower limbs
- Scar tissue? (thoracic or cardiovascular surgery):
  - lateral thoracotomy: lung resection, Blalock–Taussig shunt
  - right anterolateral thoracotomy: Waterston shunt
  - left posterolateral thoracotomy: Potts shunt
  - median sternotomy: cardiovascular surgery
- Thoracic form
  - barrel chest (chronic obstructive pulmonary disease, emphysema)
  - precordial prominence of the chest wall
  - kyphoscoliosis

Palpation
- Thrill?
- Precordial lift?
- Cold or warm extremities

Auscultation
- Heart:
  - characteristics of the first and second heart sound?
  - systolic and/or diastolic murmur
  - continuous murmur
  - pulmonary ejection click
- Lung:
  - soft breath murmur
  - prolonged expiration
  - crackles/wheezes

21.1 Hemoglobin Cyanosis

Pathophysiology. Hemoglobin cyanosis is the most important form of cyanosis and is characterized by an increased quantity of reduced (unoxygenated) hemoglobin. Cyanosis is apparent if the mean capillary concentration of reduced hemoglobin exceeds 5 g per 100 mL blood (Fig. 21.**2**).

The absolute quantity of reduced hemoglobin is more important than the relative quantity for producing cyanosis. This fact has an important impact on clinical presentation: the relative quantity of reduced hemoglobin is very high when considered in relation to the total quantity of hemoglobin in the presence of severe anemia (e. g., 10 g Hb/dL blood), although the absolute amount of reduced hemoglobin is less than 5 g/dL blood. Thus, the patient does not display apparent cyanosis despite a markedly reduced oxygen saturation of 79 %. Conversely, a patient with a hemoglobin value of 20 g/dL blood may present with severe cyanosis due to the high absolute quantity of reduced hemoglobin, although the patient's oxygen saturation accounts for 85 %.

Associated Findings. Central cyanosis is a multisystem disorder (see Fig. 21.**2**). Thus, all clinical manifestations must be considered in the diagnostic evaluation:

➤ *Secondary erythrocytosis*, induced by increased erythropoietin levels, is a physiologic response to chronic hypoxemia and affects only the red blood cell lineage. This response results in an isolated increase in red blood cell count, hemoglobin, and hematocrit levels, and is an adaptive mechanism to the reduced oxygen delivery to the tissue. Thus, secondary erythrocytosis is completely different from polycythemia rubra vera (see Chapter 14).

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a

b

Fig. 21.**2** Central cyanosis in a 32-year-old man (complete TGA: atrioventricular concordance and ventriculoarterial discordance with D-TGA, nonrestrictive, subaortic VSD, and patent ductus arteriosus).
a Cyanotic lips and cheek, hyperemic conjuncitva.
b Cyanotic tongue.

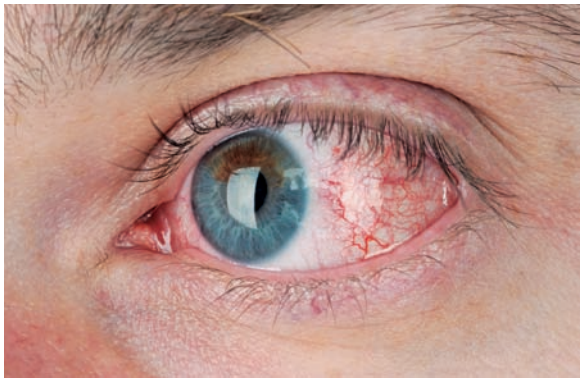

Fig. 21.**3** Dilated vessels of the hyperemic conjunctiva in a 34-year-old man with Eisenmenger syndrome due to a nonrestrictive VSD.

- *Dilatation of arterioles and capillaries* is apparent in the blood vessels of the conjunctiva (Fig. 21.**3**).
- *Clubbing of the fingers and of the toes:* this is a condition with selective bullous enlargement of the terminal phalanges of the fingers and toes resulting from proliferation of the connective tissue and of the periosteum (Fig. 21.**4**). This process is more evident in the dorsal surface than in the ventral part of the fingers and toes. The nails finally curve excessively and have a drumstick appearance. This pathology of the terminal phalanges is not specific for the presence of hemoglobin cyanosis, but it is also associated with other diseases. It may be idiopathic, hereditary, or acquired (infective endocarditis, metastatic malignancies of the lungs, bronchiectasia, lung abscess, cystic fibrosis, mesothelioma, liver cirrhosis, severe ulcerative colitis, etc.).
- *Other important findings:* heart failure, arrhythmias, hemoptysis, thromboembolic complications, infectious disease (brain abscess?), acute gouty arthritis, kyphoscoliosis (frequently associated with cyanotic congenital heart disease), cholecystolithiasis, or varicose veins (Fig. 21.**5**).

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a

b

c

d

Fig. 21.**4a–c** Central cyanosis with clubbing.

d Normal terminal finger for comparison.

Fig. 21.**5** Marked varicose veins and petechiae (more pronounced on the right than on the left lower leg), clubbing, and cyanosis (the same patient as in Fig. 21.**2**).

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Central Cyanosis

Central cyanosis is characterized by decreased oxygen saturation, resulting in cyanosis of both the skin and the mucous membranes. A useful tool and criterion is to compare both the color of the skin and that of the tongue: a bluish discoloration of both the skin and of the tongue is present in central cyanosis, whereas the tongue or the oral cavity beneath the tongue are spared and remain pink in peripheral cyanosis (see Fig. 21.**2**).

The *Lewis method* is useful in the clinical differentiation between central and peripheral cyanosis: central cyanosis is present when the ear lobe remains cyanotic after massage until the appearance of the capillary pulse. There may be combined clinical feature of both central and peripheral cyanosis. The presence of clubbing and/or warm hands is consistent with central cyanosis (see Fig. 21.**4**).

Table 21.**2** Etiologies of central hemoglobin cyanosis

Low oxygen content
- High altitude exposure

Cardiac etiologies

Congenital heart defects with normal or reduced pulmonary vascularity
- Defects with pulmonary outflow tract obstruction (subvalvular/valvular/supravalvular)
  - isolated, severe pulmonary stenosis
  - VSD with pulmonary stenosis (valvular/subvalvular)
  - tetralogy of Fallot
  - ventriculoarterial discordance with D-TGA, VSD, and pulmonary stenosis
  - atrioventricular and ventriculoarterial discordance (L-TGA) with VSD and pulmonary stenosis
  - pulmonary atresia with VSD and aortopulmonary collaterals/surgically created shunt
  - pulmonary atresia with intact ventricular septum and aortopulmonary collaterals/surgically created shunt
  - tricuspid atresia with ASD and VSD
- Defects without pulmonary outflow tract obstruction
  - Ebstein anomaly with secundum ASD

Congenital heart defects with increased pulmonary vascularity (Eisenmenger syndrome)
- Isolated defects without pulmonary outflow tract obstruction
  - nonrestrictive VSD
  - ASD (usually not the primary cause for cyanosis, but coincides with genetic predisposition to pulmonary vascular disease)
- Complex defects without pulmonary outflow tract obstruction
  - tricuspid atresia with ASD and VSD
  - AVSD
  - ventriculoarterial discordance (D-TGA) with nonrestrictive VSD
  - atrioventricular and ventriculoarterial discordance (L-TGA) with VSD
  - common arterial trunk
  - anomalous pulmonary venous connection
  - common atrium
- Aortopulmonary connections (nonrestrictive)
  - patent ductus arteriosus
  - aortopulmonary window
  - major aortopulmonary collateral arteries (MAPCAs) in pulmonary atresia
  - surgically created aortopulmonary connections (Waterston or Potts shunt)

Pulmonary etiologies
- Abnormal ventilation pattern: obstructive/restrictive
- Reduced diffusion capacity
- Vascular etiologies

ASD: atrial septal defect; AVSD: atrioventricular septal defect; VSD: ventricular septal defect.

Causes. Central cyanosis is most frequently caused by *cardiac and pulmonary diseases*, either congenital or acquired (Tab. 21.**2**). Low oxygen content in the ambient air may occasionally cause central cyanosis. The medical history and clinical examination are crucial in order to differentiate between cardiac and pulmonary disease. Combined forms (cardiac and pulmonary disease) may also occur (see Tab. 21.**1**).

Clinical Examination

Medical History. The differentiation between pulmonary and cardiac cyanosis based on medical history is not difficult. The medical history must start with the foetal period and the mother's pregnancy and the perinatal period: congenital heart disease may be suspected and diagnosed due to the presence of a heart murmur or cyanosis in the postpartal period. Cyanosis may appear during childhood, during adolescence, or may be occasionally observed during adulthood, e. g., in patients with progressive pulmonary vascular disease (Eisenmenger syndrome) or in patients with increasing right-to-left shunting in the presence of a perimembranous VSD associated with progressive severe obstruction of the right ventricular outflow tract. Most patients with congenital heart disease have been limited in their exercise tolerance since childhood and/or have signs of cyanosis during exercise.

A comprehensive medical history is crucial to differentiate between pulmonary and cardiac cyanosis (e. g., patients with cystic fibrosis have both pulmonary and gastrointestinal complaints). The occupational history (e. g., exposure to dust, or toxic agents) is useful in the differentiation between pulmonary and cardiac cyanosis. Family history is important to evaluate the occurrence of congenital heart disease or cystic fibrosis (see Tab. 21.**1**).

Inspection. Precordial prominence of the chest wall may be a frequent and important finding, in addition to clubbing (see Fig. 21.**4**) and hyperemic conjunctiva (see Fig. 21.**3**). It reflects the presence of cardiac enlargement with sternal bowing. Precordial prominence, most striking when cardiac enlargement develops before puberty, is caused by a hypertrophic, volume and/or pressure overloaded ventricle located retrosternally or left para-

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sternally, respectively (there is either a morphologic right or left ventricle depending on the congenital cardiac defect).

Thoracic deformities (e. g., barrel chest, low diaphragm, kyphoscoliosis) are consistent with pulmonary or combined (pulmonary and cardiac) cyanosis. Kyphoscoliosis is frequently associated with cyanotic congenital heart disease. The medical history and the location of incisions (scar tissue) refer to prior surgical procedures (e. g., shunt operations; see Tab. 21.**1**).

Palpation. A *systolic thrill* caused by turbulent flow due to a high blood flow velocity from a high pressure to a low pressure system is present in patients with a restrictive VSD or severe obstruction of the right or left ventricular outflow tract. A *diastolic thrill* can be found in patients with pulmonary regurgitation in the setting of severe pulmonary arterial hypertension.

Auscultation. Auscultation is crucial for differentiating between pulmonary and cardiac cyanosis. The auscultation of patients with congenital heart disease is difficult and requires expertise because of the frequent coexistence of complex cardiac anomalies and murmurs. The presence of isolated congenital heart defects is rare.

Systolic murmurs, starting with or after the final component of the first heart sound, are caused by subvalvular, valvular, or supravalvular obstruction in the right and/or left ventricular outflow tract, most frequently in the presence of stenotic semilunar valves (aortic and pulmonary valve). The loudness of the ejection murmur across the right ventricular outflow tract may increase during inspiration, resulting in an increased return of systemic venous blood to the right atrium and right ventricle (or systemic venous ventricle). Systolic murmurs starting with the first heart sound (with the exception of prolapse syndrome) are soft and usually holosystolic. These are caused by regurgitant AV valves (tricuspid or mitral valve) or a shunt at the ventricular level. The larger the VSD, the softer the murmur. A murmur is absent in the presence of a large VSD with equal pressures in both ventricles.

Regurgitant semilunar valves cause *diastolic murmurs* (e. g., high-pitched diastolic murmur in the presence of pulmonary regurgitation in patients with severe pulmonary arterial hypertension).

Continuous murmurs are caused by a rapid blood flow through a vessel (shunt, collateral arteries, obstructed vessel) or blood flow from a high pressure to a low pressure system (e. g., rupture of a congenital aneurysm of the sinus of Valsalva into the right or left atrium or right ventricle). Continuous murmurs either never stop, and are truly continuous throughout systole and diastole, or the murmur goes beyond the second heart sound but stops before the next first heart sound. A patent ductus arteriosus, a patent Waterston shunt, and a patent Blalock–Taussig shunt are typical examples of continuous murmurs.

Special attention should be paid to the *second heart sound*. The first questions to be answered are whether there is presence of both an aortic and pulmonary component or presence of a single closure sound (e. g., pulmonary atresia, common arterial trunk, or severe pulmonary valvular stenosis). The meticulous evaluation of the aortic and pulmonary components of the second heart sound can give important hints to the pathophysiology of the congenital heart defect. A widely split second heart sound is present in the following:

- Delayed onset of right ventricular activation (e. g., right bundle branch block).
- Prolonged systole of the right ventricle (e. g., ASD).
- Dynamic obstruction of the right ventricular outflow tract (infundibular pulmonary stenosis).
- Shortened left ventricular systole (e. g., VSD, mitral regurgitation).

Severe pulmonary arterial hypertension, in the absence of a shunt lesion, is associated with a widely split second heart sound including a loud pulmonary component. In the presence of secondary pulmonary hypertension, the characteristics of the second heart sound are determined by the pathophysiology of the underlying shunt lesion. The second heart sound is widely split or fixed in the presence of a large ASD; it is narrowly split or it may become single in the presence of a large VSD (both ventricles function as a single chamber); or it is normal or narrowly split in patients with a patent ductus arteriosus.

A *pulmonary ejection click* is frequently heard in the presence of pulmonary hypertension or dilatation of the main pulmonary artery. In contrast to pulmonary valvular stenosis, the pulmonary ejection click does not move with respiration in the presence of pulmonary hypertension or dilatation of the main pulmonary artery, and it is better heard lower down on the chest (in the fourth or fifth left ICS).

A simple "oxygen test" can differentiate between pulmonary and cardiac cyanosis. Oxygen saturation improves in the presence of pulmonary cyanosis during nasal oxygen application. In contrast, no improvement of oxygen saturation is observed if cyanosis is of cardiac origin.

Diagnostic Studies

ECG. The ECG is not useful for differentiation between pulmonary and cardiac cyanosis, because ECG changes are not specific in both types. Electrocardiographic evidence of right atrial and ventricular overload may be present in both pulmonary and cardiac cyanosis due to pulmonary arterial hypertension (P pulmonale, right axis deviation). Left axis deviation is a characteristic feature of AVSD. Ebstein anomaly is frequently associated with Wolff–Parkinson–White (WPW) syndrome (several accessory pathways are frequently present). Q-wave inversion (e. g., Q wave in V_1, no Q wave in V_6) is a typical feature in patients with congenitally corrected TGA.

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Chest Radiograph. Interpretation of the chest radiograph must refer not only to the cardiac silhouette and to the lungs, including vascular and nonvascular structures, but also to extracardiac structures including thoracic form, deformities of the vertebral column, the stomach bubble to identify gastric and hepatic situs (abdominal situs solitus or situs inversus?), and the position of the aortic arch (right aortic arch?). In the presence of abdominal situs solitus (left-sided stomach bubble), a right aortic arch (the descending thoracic aorta crosses the right main bronchus) is frequently associated with conotruncal anomalies (e. g., tetralogy of Fallot in 25 % of patients, pulmonary atresia, or common arterial trunk in 50 % of patients).

The evaluation of the pulmonary vasculature must address the following points:

- *Normal pulmonary vascularity.*
- *Prominent pulmonary vascularity* (acyanotic and cyanotic shunt lesions): the diameter of the right descending pulmonary artery exceeds 17 mm. The diameter of a pulmonary artery branch is larger than that of its accompanying bronchus.

> Anemia, pregnancy, hyperthyroidism, and pulmonary arteriovenous malformations can simulate prominent pulmonary vascularity (a shunt lesion).

- *Diffuse or asymmetrically decreased pulmonary vascularity* (e. g., tetralogy of Fallot, severe infundibular pulmonary stenosis associated with ventricular septal defect, or lung emphysema). In patients with cyanotic congenital heart disease, differentiation between those with and those without VSD is important (Ebstein anomaly, severe pulmonary stenosis).
- *Evidence of pulmonary arterial hypertension* (e. g., Eisenmenger syndrome): calcification of the pulmonary trunk and hilar vessels, or so-called pruned tree or rat tail appearance of the pulmonary artery branches.

Color-Coded Doppler Echocardiography. This imaging modality is the method of choice to describe cardiac anatomy definitively: large systemic and pulmonary veins, great arteries, AV and semilunar valves, myocardium and myocardial function, atrial and ventricular septal defects, anomalous connections, etc. A skilled echocardiographer with expertise in congenital heart disease can evaluate most of the hemodynamic problems by the use of color-coded Doppler echocardiography. As a consequence, diagnostic heart catheterization is less frequently performed currently than in the past. This technique is, however, the method of choice for calculating pulmonary vascular systems or to measure a shunt quantitatively. The standard indicator dilution curves (by injection of indocyanine green into an arm vein) are not now performed.

CT and MRI. These imaging modalities give unrestricted access to both the intra- and extracardiac structures and make important contributions to diagnosis. They are complementary to Doppler echocardiography, which is still the gold standard, and are mainly used to evaluate the right heart and to visualize and describe extracardiac pulmonary pathologies.

Cardiac Cyanosis

Cardiac cyanosis is caused by a right-to-left shunt at the atrial, ventricular, or arterial level (see Tab. 21.**2**):

- *Congenital heart defect with normal or restricted pulmonary blood flow:* these congenital heart defects are often associated with obstruction across the pulmonary outflow tract. Subvalvular and/or valvular obstruction is frequent. Supravalvular obstruction may occasionally occur (e. g., tetralogy of Fallot, surgical banding of the pulmonary artery).
- *Congenital heart defect with increased pulmonary blood flow:* in the absence of pulmonary outflow tract obstruction, isolated or complex cardiac defects with a shunt at the atrial, ventricular, or arterial level causes hyperemia of the pulmonary vascular bed resulting in pulmonary vascular disease (Eisenmenger syndrome).

Conotruncal Anomalies

The migration of cells originating from the neural crest during embryogenesis is crucial for the septation of the conotruncus and normal development of the pulmonary and aortic outflow tract. If the migration process of the neural crest cells is interrupted, conotruncal anomalies develop: common arterial trunk, pulmonary atresia, tetralogy of Fallot, interrupted aortic arch, tricuspid atresia, single ventricle or double outlet right ventricle with D-TGA, or isolated ventricular septal defect. CATCH 22 is a syndrome due to a microdeletion at chromosome 22q11 resulting in a wide clinical spectrum of symptoms (DiGeorge syndrome, Shprintzen syndrome, velocardiofacial syndrome); cardiac defects include conotruncal defects (CATCH stands for: **c**ardiac defect, **a**bnormal facies, **t**hymic hypoplasia, **c**left palate, and **h**ypocalcemia). There is autosomal dominant inheritance of this syndrome.

The *presence or absence of a stenosis across the pulmonary outflow tract* is crucial in most congenital cardiac defects for determining the long-term prognosis and impacts therapeutic (surgical) options (see Tab. 21.**2**).

Tetralogy of Fallot

Anatomy. In 1888, Etienne-Louis Arthur Fallot published his classic paper entitled "L'Anatomie Pathologique de la Maladie Bleue." However, the pathologic–anatomic characteristics of the cardiac defect reported by Fallot were originally described by the equally distinguished

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anatomist, geologist, and theologian Niels Stensen more than 200 years earlier in 1671 (Fig. 21.**6**):

- VSD
- pulmonary stenosis (which may be subvalvular, valvular, and supravalvular)
- overriding aorta
- concentric hypertrophy of the right ventricle.

These four characteristic features result from misalignment of the infundibular septum with the muscular, trabecular septum. The misalignment is the result of anterior deviation of the infundibular septum. This septum does not align with the trabecular septum and creates a VSD at the site of misalignment. The anterior deviation of the infundibular septum causes an infundibular pulmonary stenosis and a biventricular overriding aorta. A small ASD is a frequent occurrence (Fig. 21.**6**).

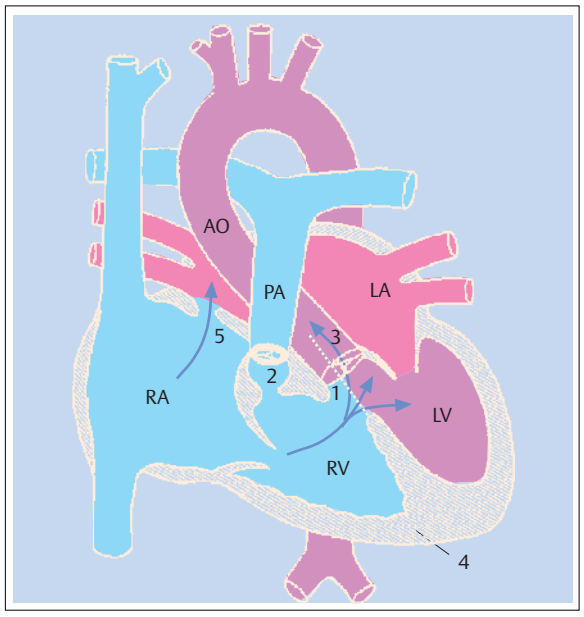

Fig. 21.**6** Tetralogy of Fallot: 1. subaortic VSD, 2. infundibular and valvular pulmonary stenosis, 3. overriding aorta, 4. right ventricular hypertrophy, 5. secundum ASD.

Clinical Features. The clinical spectrum is wide: ranging from a misaligned VSD with an overriding aorta and mild right ventricular outflow tract obstruction to a severe right ventricular outflow tract obstruction or pulmonary atresia. Central cyanosis is caused by a right-to-left shunt across the nonrestrictive VSD. The pathophysiologic consequences, appearance, and degree of central cyanosis depend on the *severity of the obstruction across the right ventricular outflow tract*. Progressive cyanosis due to increase in right ventricular outflow tract obstruction, which may be exaggerated by muscular hypertrophy in the infundibulum, is the classic clinical presentation. Squatting for increasing systemic vascular resistance, diverting blood from the right ventricle into the pulmonary artery, and thus improving pulmonary blood flow is the typical position during blue spells.

Although right ventricular outflow tract obstruction varies widely, the pulmonary vasculature is protected against the development of pulmonary vascular disease (pulmonary arterial hypertension). Patients with pulmonary atresia and large aortopulmonary collaterals (MAPCAs: **m**ajor **a**orto**p**ulmonary **c**ollateral **a**rteries) are the exception: MAPCAs may not be restrictive enough to protect against the development of pulmonary vascular disease and subsequent pulmonary arterial hypertension.

Tetralogy of Fallot has been diagnosed during childhood for many years and successfully repaired, although the pathologic and anatomic spectrum of right ventricular outflow tract obstruction and the clinical spectrum are very wide. This is the reason why adults with unoperated upon tetralogy of Fallot are rarely seen in the Western countries. Patients with only mild cyanosis may present during adulthood with mild right ventricular outflow tract obstruction and balanced physiology between the systemic and pulmonary blood flow. Tetralogy of Fallot may occasionally be diagnosed in adult immigrants from non-Western countries who are cyanotic.

Auscultation. In addition to the characteristic findings of central cyanosis, there is an inverse relationship between the severity of right ventricular outflow tract obstruction and the *loudness and the length of the systolic murmur*, respectively: the more severe the obstruction, the larger the right-to-left shunt across the nonrestrictive VSD and the softer and shorter the systolic murmur. An aortic ejection click reflects aortic dilatation, which is a frequent finding in patients with tetralogy of Fallot; a diastolic murmur reflects aortic regurgitation as a result of aortic root dilatation.

Progressive cyanosis may be caused not only by an increase in right ventricular outflow tract obstruction, but also by progressive obstruction, or even spontaneous closure, of aortopulmonary shunts. Systemic-to-pulmonary shunts, including Blalock–Taussig, Waterston, or Potts shunts, are performed for palliation during childhood or adulthood for the purpose of increasing pulmonary blood flow, hence systemic oxygenation, and improving central cyanosis. Physicians must look for a *continuous murmur* in the presence of a *systemic-to-pulmonary shunt*. However, restriction of pulmonary blood flow is difficult in Waterston and Potts shunts. They are frequently too large and not restrictive enough to avoid high pulmonary blood flow. Thus, they may be complicated by pulmonary vascular disease and unilateral pulmonary arterial hypertension resulting in increased cyanosis. As a consequence, patients with established pulmonary arterial hypertension are not suitable for reparative surgery. Acquired stenosis of the right or left pulmonary artery, due to distortion at the site of a Blalock–Taussig shunt, occurs. Waterston and Potts shunts are not performed currently, because of the serious long-term problems.

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ECG. Right-axis deviation of the QRS complex and evidence of right ventricular hypertrophy are present in patients with unrepaired tetralogy of Fallot. The classical features of right atrial overload are lacking because the right atrium is not enlarged and the force of the right atrial contraction is not increased. The P wave may be peaked, but its amplitude is seldom increased. Electrocardiographic signs of left ventricular hypertrophy, due to left ventricular overload, may be recorded in the presence of a palliative systemic-to-pulmonary shunt.

Chest Radiograph. The configuration of the heart in patients with tetralogy of Fallot is distinctive because of its boot-shaped or "coeur-en-sabot" appearance. This characteristic feature is rarely seen because most patients have had reparative surgery during childhood. This distinct configuration results from the concentrically hypertrophied right ventricle and the underfilled small left ventricle, which is located above the horizontal interventricular septum. The cardiac silhouette in cyanotic patients is normal in size. The central pulmonary arteries are concave. Pulmonary vascularity is decreased in unoperated tetralogy of Fallot patients. This reduced vascularity is most obvious in the middle and outer third of the lung fields. Characteristic radiologic findings based on the type of palliative procedure may be present: unilaterally increased pulmonary vascularity according to the type of shunt, rib notching in the presence of a Blalock–Taussig shunt, or unilateral pulmonary arterial hypertension (e. g., Waterston or Potts shunt). Previous thoracotomies are frequently associated with deformities of the fourth or fifth rib. A right-sided aortic arch occurs in 25 % of tetralogy of Fallot patients. Dilatation of the ascending aorta is frequently observed due to increased aortic blood flow and abnormalities of the aortic wall (media).

Echocardiography. This is the method of choice to describe the pathologic and anatomic characteristics including all variations. Hemodynamics are assessed by color-coded Doppler echocardiography.

Common Arterial Trunk

Anatomy. A common arterial trunk is a rare anomaly: a single artery (trunk) overrides a subtruncal, nonrestrictive VSD, arises from the base of the heart, and receives blood from both ventricles because of failure of proximal division into the pulmonary artery and aorta. Both pulmonary and systemic arteries, as well as coronary arteries, arise from the trunk. The number of cusps of the single semilunar valve (truncal valve) varies between two and six cusps; the truncal valve is frequently quadricuspid and may be stenotic and/or regurgitant. The common arterial trunk is the prototype of conotruncal anomalies and is frequently associated with CATCH 22.

Common arterial trunks are classified into four types based on the origins of the pulmonary arteries:

- *Type I:* a short main pulmonary artery arises from the trunk and gives rise to the left and right pulmonary artery (Fig. 21.**7a**).
- *Type II:* there is no main pulmonary artery. The right and left pulmonary arteries originate from separate ostia, which are very close together (Fig. 21.**7b**).
- *Type III:* there is no main pulmonary artery. The right and left pulmonary arteries originate from separate ostia at either side of the trunk (Fig. 21.**7b**). Types II and III are now considered as one category.
- *Type IV:* there are no pulmonary arteries. The lungs are fed by large aortopulmonary collaterals (MAPCAs: major aortopulmonary collateral arteries). This type is considered a variation of pulmonary atresia with VSD (Fig. 21.**7c**).

Right aortic arch is frequently observed in truncus arteriosus.

Both pathophysiology and long-term prognosis are determined by the size of the pulmonary arteries and pulmonary vascular resistance. Long-term prognosis is frequently complicated by severe pulmonary arterial hypertension (Eisenmenger syndrome) and increasing cyanosis.

Clinical Presentation and Auscultation. During long-term follow-up, the clinical presentation is characterized by the Eisenmenger physiology including all clinical findings of central cyanosis. A *loud truncal ejection click* caused by the severely enlarged common arterial trunk is heard after the normal first heart sound. The characteristics of grades 2/6 to 4/6 systolic murmurs are modified by the presence of a truncal valvular stenosis. The second heart sound is single and loud. A diastolic murmur reflects truncal regurgitation. Congestive heart failure may develop during long-term follow-up.

ECG. Right atrial overload and right ventricular hypertrophy are obvious findings due to pulmonary arterial hypertension.

Chest Radiograph. The chest radiograph in adults with established Eisenmenger physiology shows a reduced pulmonary vascularity, a prominent main pulmonary artery, and enlarged right and left pulmonary arteries (Fig. 21.**8a**). A right-sided aortic arch is frequently found (in up to 50 % of patients).

Echocardiography. Echocardiography visualizes the large common arterial trunk overriding the subtruncal ventricular septal defect (Fig. 21.**8b**). It depicts the absence of both a pulmonary outflow tract and a second semilunar valve.

Pulmonary Atresia

Anatomy. Pulmonary atresia, with or without VSD, is characterized by the absence of an anatomical connection between the right ventricle and the pulmonary ar-

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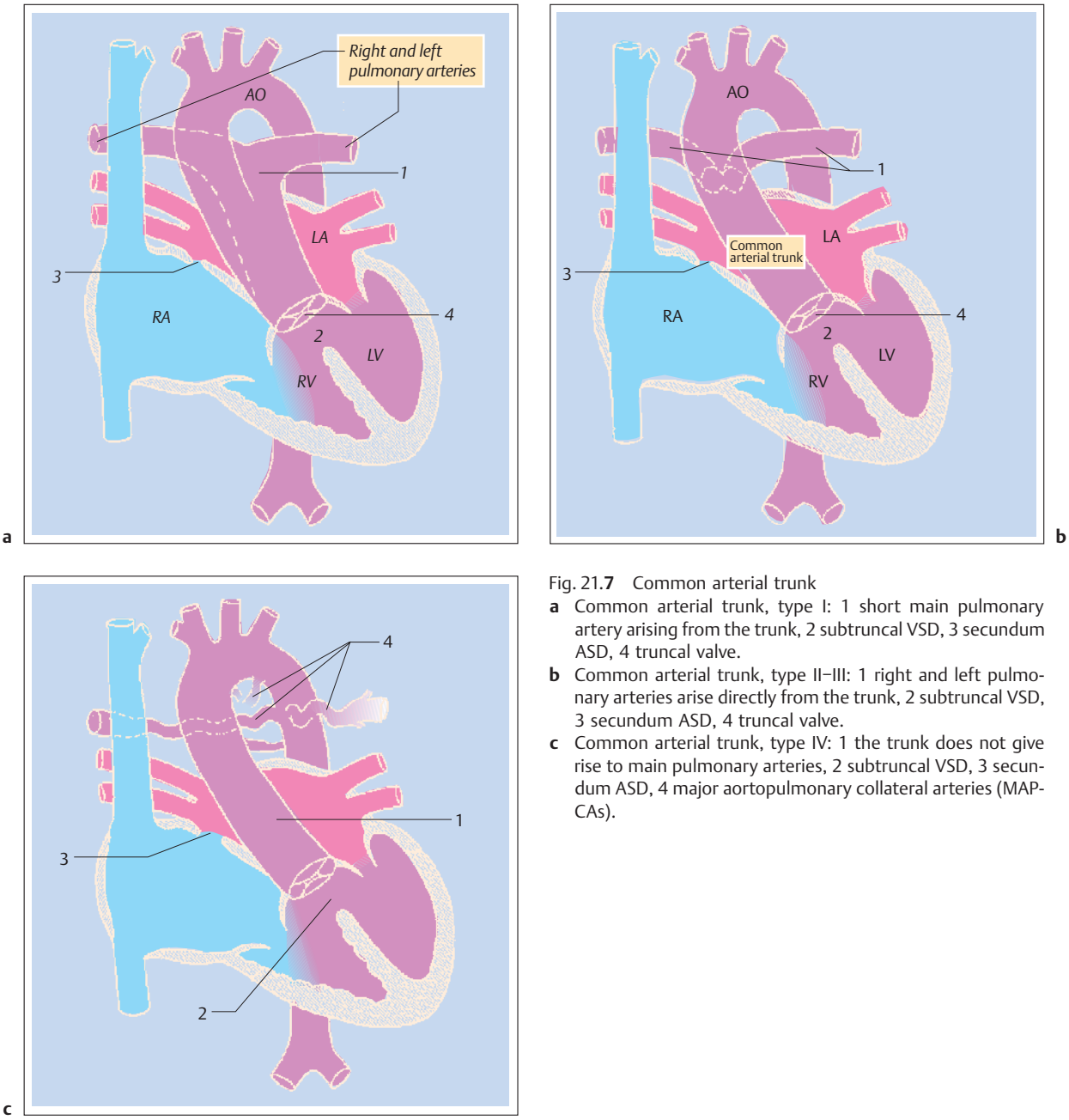

Fig. 21.**7** Common arterial trunk

a Common arterial trunk, type I: 1 short main pulmonary artery arising from the trunk, 2 subtruncal VSD, 3 secundum ASD, 4 truncal valve.

b Common arterial trunk, type II–III: 1 right and left pulmonary arteries arise directly from the trunk, 2 subtruncal VSD, 3 secundum ASD, 4 truncal valve.

c Common arterial trunk, type IV: 1 the trunk does not give rise to main pulmonary arteries, 2 subtruncal VSD, 3 secundum ASD, 4 major aortopulmonary collateral arteries (MAPCAs).

teries (pulmonary atresia, with or without atresia of the main pulmonary artery). The perfusion of the lungs is completely dependent on a patent ductus arteriosus and from other aortopulmonary collateral vessels.

Clinical Presentation and Auscultation. A *single second heart sound and continuous murmurs* are heard in cyanotic patients (with the classical findings of central cyanosis). The continuous murmurs caused by the aortopulmonary collateral vessels or by a patent ductus arteriosus are best heard from the patient's back. A systolic ejection murmur follows the truncal ejection click. Severely enlarged central pulmonary arteries, increased pulmonary vascularity, including the so-called pruned tree or rat tail appearance of the pulmonary artery branches, are seen in patients with severe pulmonary arterial hypertension due to a nonrestrictive patent ductus arteriosus (Fig. 21.**9**).

Tricuspid Atresia

Anatomy. Tricuspid atresia includes the following characteristic features:

- no anatomic connection between the morphologic right atrium and morphologic right ventricle

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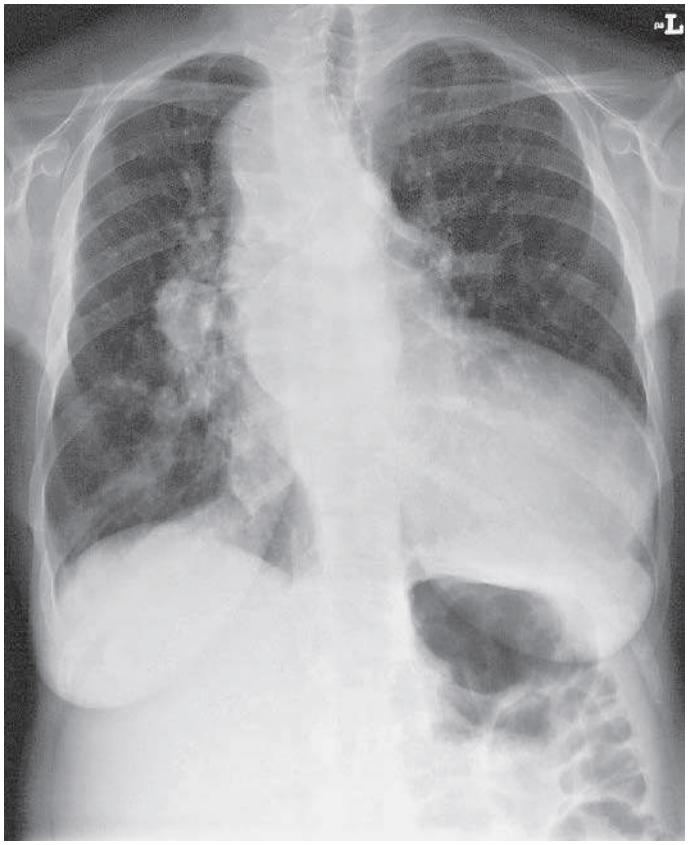

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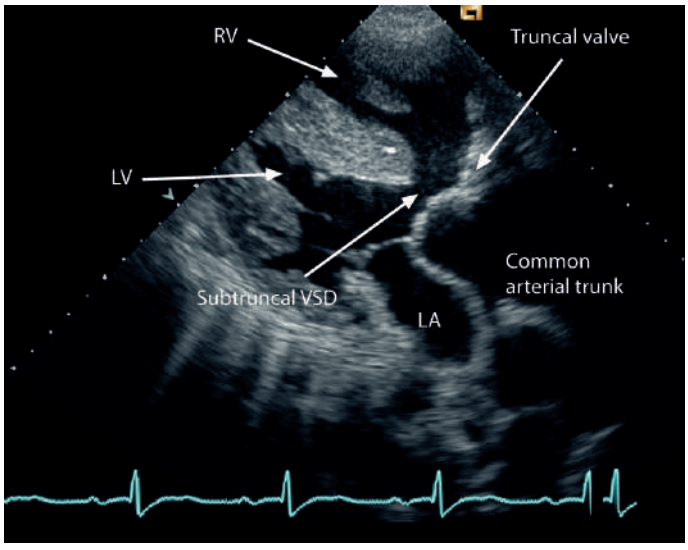

b

Fig. 21.**8** Common arterial trunk, type II in a 46-year-old woman.

a Marked cardiomegaly, aneurysmal central pulmonary arteries, pruned tree and rat tail appearance of the pulmonary artery branches in the periphery, right aortic arch (!), widening of the subcarinal angle beyond 90°, left-sided stomach bubble.

b Parasternal long axis view of the same patient: subtruncal, nonrestrictive VSD, markedly dilated arterial trunk with thickened cusps of the truncal valve, concentric left ventricular hypertrophy.

- hypoplastic right ventricle
- interatrial communication (patent foramen ovale, or less frequently, secundum ASD)
- VSD
- connection of the morphologic mitral valve with the morphologic left ventricle.

The connection at the atrial and ventricular level establishes the communication between the systemic and pulmonary circulation (Fig. 21.**10**). The presence or absence of subvalvular or valvular pulmonary stenosis determines the pathophysiology, the clinical features, and thus, the patient's long-term prognosis.

The great arteries are not transposed in 90% of patients. A restrictive VSD or bulboventricular foramen, respectively, communicates with the hypoplastic right ventricle in patients with nontransposed great arteries (Fig. 21.**10a**). This restrictive VSD gives the advantage of

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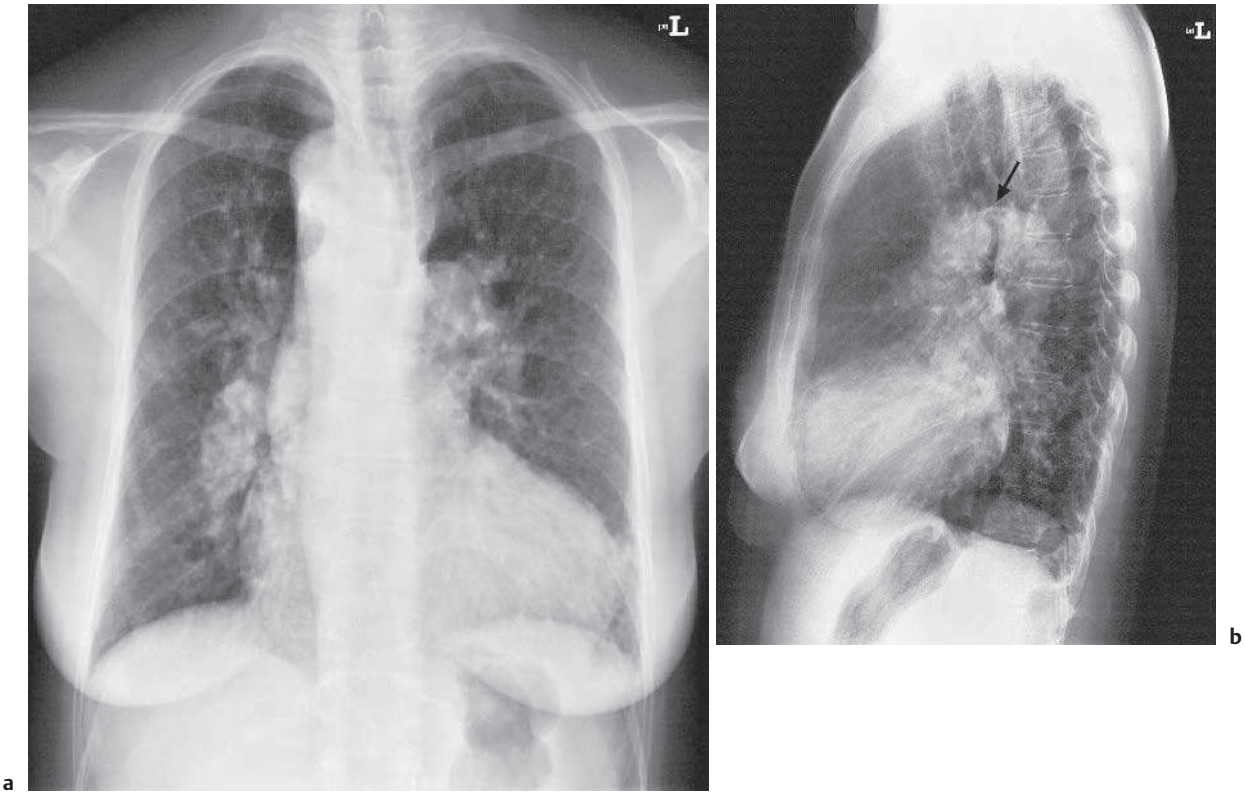

a b

Fig. 21.**9** Pulmonary atresia with VSD, major aortopulmonary collateral arteries, and a nonrestrictive patent ductus arteriosus in a 47-year-old woman.
a Severely enlarged cardiac silhouette, right aortic arch, severe dilatation of the central pulmonary arteries, pruned tree and rat tail appearance of the pulmonary artery branches in the periphery, and left-sided stomach bubble.
b Calcification at the site of the patent ductus arteriosus (arrow).

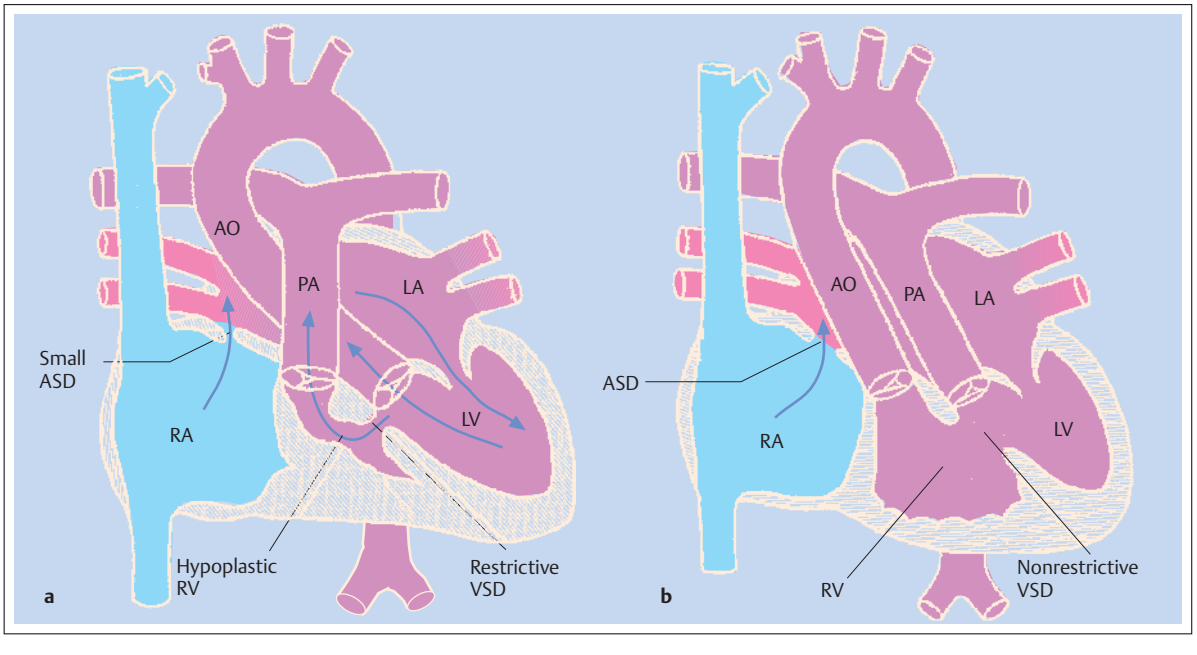

Fig. 21.**10** Tricuspid atresia with ASD and VSD.
a Nontransposed great arteries, restrictive VSD, and pulmonary outflow tract obstruction.
b Transposed great arteries, nonrestrictive VSD, and absent pulmonary outflow tract obstruction.

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a subpulmonary stenosis, resulting in restriction of pulmonary blood flow and protection against pulmonary vascular disease. The long-term prognosis is good in the presence of a balanced physiology (i. e., pulmonary blood flow is adequate, but not too excessive).

Tricuspid atresia with complete TGA (10% of patients) is usually associated with a nonrestrictive VSD without subpulmonary obstruction. Subsequently, pulmonary blood flow is excessive and pulmonary vascular disease develops early in life (Fig. 21.**10b**).

Clinical Features. The clinical presentation depends on the presence or absence of an obstruction across the pulmonary outflow tract (valvular/subvalvular pulmonary stenosis or restrictive VSD?). Cyanosis results from the mixture (right-to-left shunt) of systemic and pulmonary venous blood in the morphologic left atrium. The degree of cyanosis depends on the severity of pulmonary outflow tract obstruction. Cyanosis is more prominent in patients with, than in those without, a pulmonary outflow tract obstruction.

Auscultation. Characteristics are determined by the anatomic substrates and their variations beyond the mitral valve. A *holosystolic murmur* is heard after the *single first heart sound* (mitral valve) in the presence of both a restrictive and a nonrestrictive VSD. Pulmonary blood flow decreases after the development of pulmonary vascular disease and pulmonary arterial hypertension in patients with TGA: the systolic VSD murmur softens, shortens, and, finally, disappears.

A midsystolic murmur is generated by the presence of a pulmonary or subpulmonary obstruction. Its length and loudness vary inversely with the severity of obstruction across the pulmonary outflow tract: the more severe the stenosis, the more blood is diverted into the aorta, and the shorter and softer the murmur appears. The second heart sound is heard loudly in patients with TGA (anterior location of the transposed aorta).

ECG. Right atrial overload (peaked right atrial P waves), left axis deviation, and evidence of left ventricular hypertrophy are typical and diagnostic in the presence of central cyanosis.

Chest Radiograph. The chest radiograph helps to distinguish between increased and normal or decreased pulmonary vascularity.

Tricuspid atresia with transposed arteries and a nonrestrictive VSD depicts not only *enlarged right and left atria*, but also *increased pulmonary vascularity* (Fig. 21.**11a**). The vascular pedicle is narrow because of the TGA. Pulmonary vascularity decreases when pulmonary vascular disease develops and establishes.

The chest radiograph shows an enlarged right cardiac silhouette (*dilated right atrium*) and *decreased pulmonary vascularity* as a result of pulmonary outflow tract obstruction in tricuspid atresia without TGA; the ascending aorta is prominent.

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to visualize and to describe all pathologic and anatomic structures and to evaluate hemodynamics (Fig. 21.**11b**).

Transposition of the Great Arteries (TGA) with VSD

Terminology of Transposition of the Great Arteries (TGA)

General. Dextro- (D-) and levo- (L-)transposition of the great arteries are distinguished in the context of transposed great arteries (TGA). Atrioventricular connection describes the connection between the atria and the ventricles, ventriculoarterial connection describes the connection between the ventricles and the great arteries. The atrioventricular and ventriculoarterial connections can be concordant or discordant.

Atrioventricular Concordance and Ventriculoarterial Discordance (Complete TGA). There is appropriate connection of the morphologic right atrium to the morphologic right ventricle, and of the morphologic left atrium to the morphologic left ventricle. However, there is inappropriate connection of the morphologic right ventricle to the aorta, and of the morphologic left ventricle to the pulmonary artery, respectively.

Atrioventricular and Ventriculoarterial Discordance (Double Discordance or Congenitally Corrected TGA). This is an anomaly wherein the aorta arises from the morphologic right ventricle and the pulmonary artery from the morphologic left ventricle, and, in addition, the atrioventricular connection is discordant such that the morphologic right atrium connects to the morphologic left ventricle and the morphologic left atrium connects to the morphologic right ventricle.

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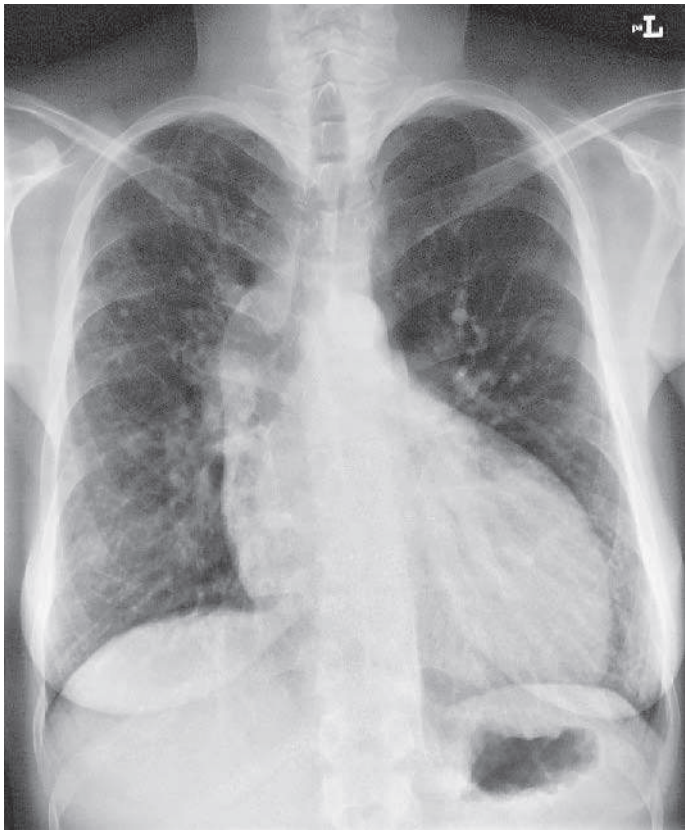

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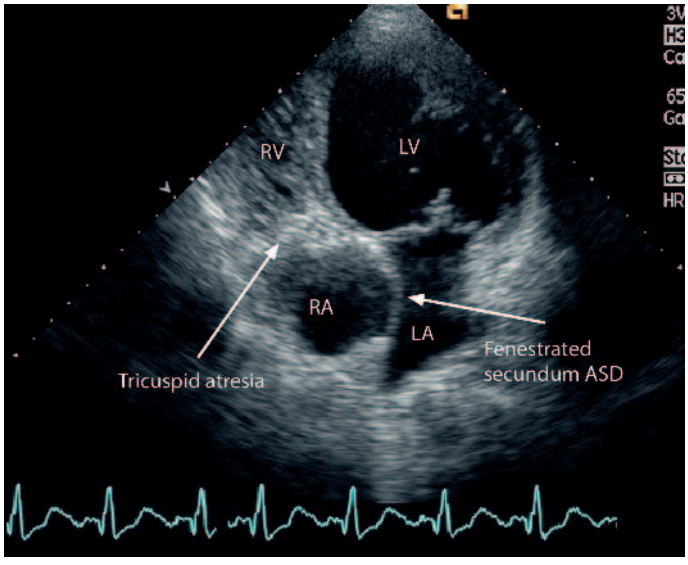

b

Fig. 21.**11** Tricuspid atresia with ASD, VSD, and TGA in a 31-year-old woman.
a Marked enlargement of the cardiac silhouette, increased pulmonary vascularity, pruned tree and rat tail appearance of the pulmonary artery branches in the periphery, small aortic knuckle, left-sided descending aorta, and left-sided stomach bubble.
b Apical four-chamber view at early systole: fenestrated secundum ASD with the interatrial septum bulging to the left.

Complete Transposition of the Great Arteries (D-TGA)

Anatomy. The anatomic substrate includes *atrioventricular concordance* and *ventriculoarterial discordance* (the morphologic right ventricle gives rise to the aorta and the morphologic left ventricle gives rise to the pulmonary artery, Fig. 21.**12**). D-TGA refers to the normal rightward bend of the embryogenic heart tube (D-ventricular loop): the inflow portion of the morphologic right ventricle lies to the right of the morphologic left ventricle; the aorta is anterior, and usually, to the right of the pulmonary artery; the great arteries are in a parallel position and do not cross, as they do in normal hearts. This

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isolated discordant connection between the ventricles and the great arteries implies a complete, physiologic transposition: the systemic and pulmonary circulations are in parallel (Fig. 21.**13**). This physiology does not permit survival in the absence of a communication between these two circulations. Thus, children with complete TGA cannot survive without intervention unless the pulmonary and systemic circulation is joined by communications at the atrial, ventricular, or arterial level (ASD, VSD, or patent ductus arteriosus).

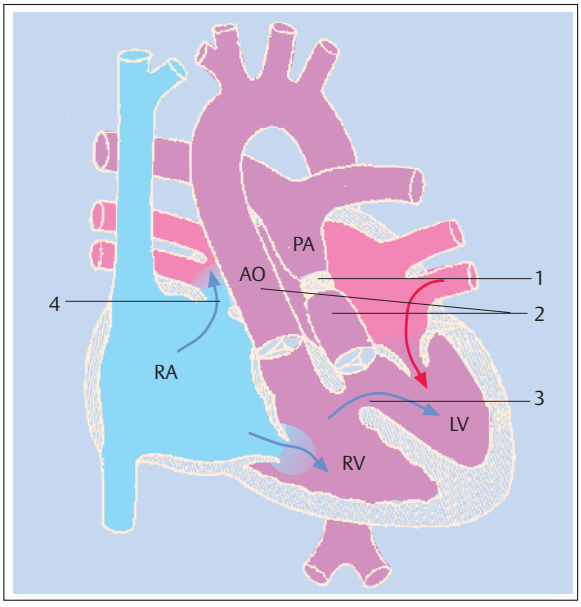

Fig. 21.**12** Atrioventricular concordance and ventriculoarterial discordance with D-TGA (complete TGA): 1. pulmonary artery banding to restrict pulmonary blood flow, 2. TGA, 3. VSD, 4. secundum ASD.

Children with atrioventricular concordance, ventriculoarterial discordance, and D-TGA can survive until adulthood only if complete TGA is associated with a shunt at the atrial, ventricular, or arterial level.

Clinical Features and Auscultation. Patients with complete TGA associated with a shunt lesion are cyanotic. However, most patients with this anatomy have been operated on during childhood (Senning or Mustard atrial switch procedure, arterial switch procedure) and are not cyanotic.

The pathophysiology, clinical presentation, and clinical findings are determined by the associated defects in unoperated adults; VSD, obstruction across the pulmonary, left ventricular outflow tract (15%), patent ductus arteriosus. In addition to the typical findings of central cyanosis, one can hear a *pulmonary ejection click* originating in the dilated pulmonary trunk (pulmonary hypertension) and a *loud, narrowly split second heart sound* caused by the anterior position of the aorta. Systolic and diastolic murmurs are determined by the size of the VSD, obstruction in the pulmonary outflow tract, or a patent ductus arteriosus, respectively.

Chest Radiograph. Retrosternal filling (anterior location of the aorta to the pulmonary artery) in the lateral view and a narrow vascular pedicle in the posteroanterior projection are visible. The size of the cardiac silhouette depends on associated anomalies: it may be normal or markedly enlarged. Normal or decreased pulmonary vascularity is obvious in the presence of pulmonary outflow tract obstruction. An aneurysm of the pulmonary trunk or central pulmonary arteries and increased pulmonary vascularity, associated with a so-called pruned tree or rat tail appearance of the pulmonary artery

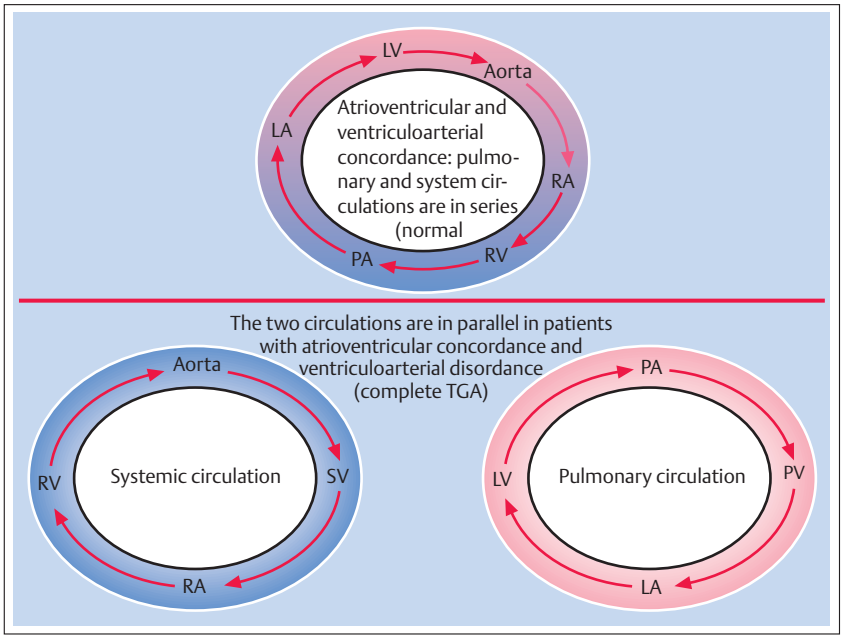

Fig. 21.**13** Pathophysiology in atrioventricular concordance and ventriculoarterial discordance with D-TGA (complete TGA). LA: left atrium, LV: left ventricle, PA: pulmonary artery, PV: pulmonary veins, RA: right atrium, RV: right ventricle, SV: systemic veins.

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Fig. 21.**14** Atrioventricular concordance and ventriculoarterial discordance with D-TGA (complete TGA), VSD, and a nonrestrictive patent ductus arteriosus in a 32-year-old man (the same patient as in Fig. 21.**2**).

a Severe dilatation of the central pulmonary arteries and their branches (arrow), pruned tree and rat tail appearance of the pulmonary artery branches in the periphery due to pulmonary arterial hypertension, acinar consolidation in the right middle/lower lobes (intrapulmonary hemorrhage).

b Retrosternal filling due to TGA.

branches, can be seen in patients with increased pulmonary blood flow due to a large shunt, and in those with pulmonary arterial hypertension (Fig. 21.**14**).

ECG. Electrocardiographic findings are determined by the underlying pathophysiology: right or left atrial overload and right or left ventricular hypertrophy, respectively, may be present.

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy, including associated anomalies, and to evaluate hemodynamics.

Congenitally Corrected Transposition of the Great Arteries (L-TGA)

Anatomy. The atrioventricular connection of both atria to the ventricles and ventriculoarterial connection of both ventricles to the great arteries are discordant. This double discordance results in a single circulation. The systemic and pulmonary circulations are connected in series ("physiologic correction" of TGA) and permit survival until adulthood, even in the absence of associated anomalies, i. e., these patients are not cyanotic. The great arteries are in L- (levo-)transposition: there is a leftward bend of the embryogenic heart tube. The inflow portion of the morphologic right ventricle lies to the left of the morphologic left ventricle and the position of the aorta is left and usually anterior to the pulmonary artery. The great arteries do not cross, as they do in normal hearts.

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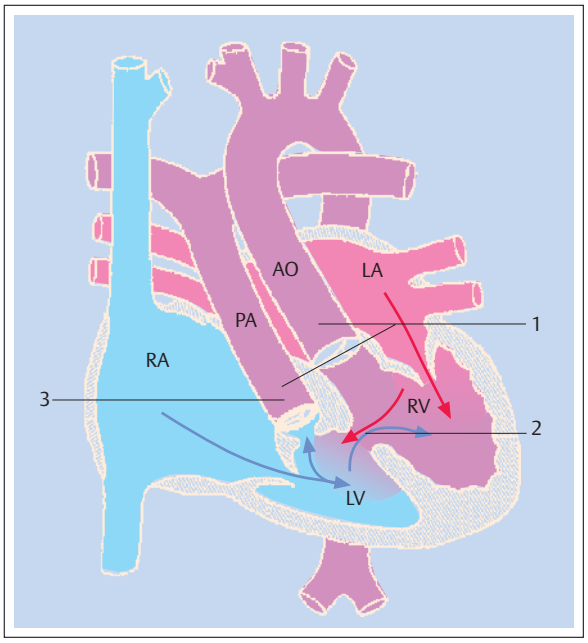

Fig. 21.**15** Congenitally corrected TGA (1) with VSD (2), subvalvular and valvular pulmonary stenosis (3).

Clinical Features and Auscultation. Congenital corrected TGA is frequently (90%) associated with additional abnormalities (Fig. 21.**15**) that determine the clinical presentation and the severity of central cyanosis: VSD (50–75% of patients), obstruction across the pulmonary outflow tract (75% of patients), Ebstein-like deformation of the tricuspid valve (50% of patients). The characteristics in auscultation are determined by these associated anomalies (see complete TGA, above).

ECG. The ECG presents three characteristic features:
- disturbance in AV conduction
- characteristic features in QRS and T waves (Q-wave inversion reflecting ventricular inversion)
- modifications of the P, QRS, and T waves caused by associated anomalies.

Disturbances in AV conduction (first degree, second degree, or complete AV block) are caused by the abnormal location and course of the conduction system (anterior position of the AV node, long penetrating AV bundle, descending onto the anterior aspect of the interventricular septum). The conduction fibers are replaced by fibrous tissue with aging. Complete heart block increases with age at a rate of 2% per year during adulthood. Thus, congenitally corrected TGA is one differential diagnosis in young adults (< 60 years of age), presenting with a new onset of complete heart block.

Q-wave inversion is caused by inversion of the right and left Tawara branches with reversed septal activation proceeding from right to left (in contrast to the normal heart with left-to-right activation of the interventricular septum): a Q wave is present in lead V_1 and it is absent in lead V_6! Tall R waves are recorded in lead V_1, as in all transposition complexes. Accelerated conduction through Wolff–Parkinson–White accessory pathways is frequently associated in patients with Ebstein-like deformation of the tricuspid valve (delta wave may be recorded in lead V_1).

Chest Radiograph. The pulmonary segment on the chest radiograph is absent: the vascular pedicle is narrow (in the PA view) and the retrosternal space is filled by the aorta, which is located anteriorly (in the lateral view). The presence of associated congenital heart defects modifies additional radiologic features (normal, reduced, or increased pulmonary vascularity; signs of pulmonary arterial hypertension).

Atrioventricular Septal Defect (AVSD)

Anatomy. The atrioventricular septal defect (AVSD), previously called AV canal defect or endocardial cushion defect, includes a wide anatomic spectrum caused by the abnormal development of the endocardial cushion during embryogenesis.

The anatomic hallmark is the complete absence of the AV septum with a common AV junction guarded by a common AV valve (Fig. 21.**16**). In the normally developed heart, both AV valves have two separate fibrous rings (mitral and tricuspid annular rings), which are located in different planes within the ventricles: the tricuspid annular ring lies slightly apical to the mitral annular ring. The five leaflets of the AV valve have a single fibrous ring and are positioned at the same horizontal plane in patients with AVSD. In the setting of AVSD, there is neither a true mitral nor a true tricuspid valve. Morphologic variations of the five AV valve leaflets result in different types of AVSD:
- *Partial AVSD includes:* ostium primum ASD, separate right-sided and left-sided AV valves, cleft in anterior left AV valve leaflet, intact inlet septum.
- *Intermediate AVSD includes:* ostium primum ASD, separate right-sided and left-sided AV valves, restrictive VSD in the inlet septum.
- *Complete AVSD includes:* ostium primum ASD, nonrestrictive VSD in the inlet septum, common AV valves (with morphologic variations; Fig. 21.**16**).

The long-term course in patients with a *partial AVSD* and an *intermediate AVSD* is comparable with that of patients with a large secundum ASD with the exception of earlier presentation of symptoms due to regurgitation of the left-sided AV valve ("mitral regurgitation").

Patients with a *complete AVSD* develop severe pulmonary arterial hypertension (Eisenmenger syndrome) during follow-up. Pulmonary arterial banding during infancy is performed to restrict pulmonary blood flow and to protect the pulmonary vascular bed against the development of pulmonary vascular disease. Patients with Down syndrome have an increased incidence of congenital heart disease and are frequently born with a VSD or an AVSD (up to 70% of patients with an AVSD

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have Down syndrome). A genetic predisposition facilitates the development of pulmonary vascular disease in Down syndrome patients. In addition, the development of pulmonary arterial hypertension is facilitated by the presence of an obstructive ventilation pattern in the upper airways and subsequent hypoventilation in patients with Down syndrome.

Clinical Features. The clinical hallmark in patients with complete AVSD is the development of severe pulmonary arterial hypertension (Eisenmenger syndrome) including all characteristic features of central cyanosis.

Auscultation. A *single first heart sound* (in the presence of a common AV valve), signs of pulmonary arterial hypertension (*pulmonary ejection click; loud, widely split or fixed second heart sound*), and a middiastolic murmur caused by the augmented inflow across the left, right, or common AV valves are characteristic. The aortic component of the second heart sound is difficult to hear because of the *long systolic murmur* (secondary to AV valve regurgitation or VSD). Thus, only the pulmonary component may be identified. The systolic regurgitant murmur across the AV valves radiates more frequently to the sternum than to the axilla.

ECG. A *first degree AV block* is frequently present as a result of a delayed intra-atrial and AV nodal conduction (inferoposterior position of the AV node to the coronary sinus). A complete AV block may develop during follow-up. A typical feature is QRS left axis deviation associated with dominant S waves in leads II, III, and aVF (abnormal activation of the ventricles resulting in abnormal position of the right and left Tawara branches). Electrocardiographic signs of right atrial overload and ventricular hypertrophy can be present.

Chest Radiograph. The radiologic features in adults are characterized by the underlying pathophysiology: large, central pulmonary arteries and so-called pruned tree or rat tail appearance of the pulmonary artery branches in the periphery reflect *pulmonary vascular disease* (Eisenmenger syndrome). The appearance of the pulmonary vascularity (increased, normal, or decreased vascularity) is based on the pulmonary vascular resistance and the amount of pulmonary blood flow. The cardiac silhouette is frequently enlarged. Pulmonary venous congestion can be identified in the coexistence of severe left-sided AV valve regurgitation ("mitral" regurgitation). The 12th rib may be absent (Fig. 21.**17a**), or the lateral chest radiograph may disclose a double manubrial ossification center in patients with Down syndrome.

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy and to evaluate hemodynamics (Fig. 21.**17b**).

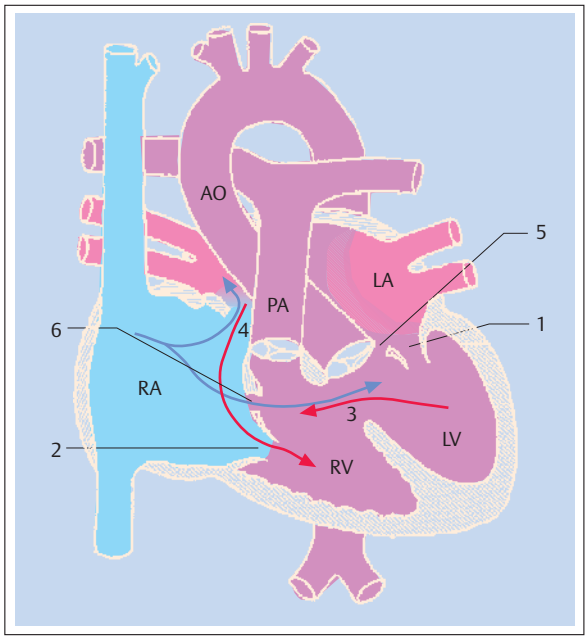

Fig. 21.**16** Atrioventricular septal defect (AVSD). 1. left-sided AV valve, 2. right-sided AV valve, 3. inlet septal defect, 4. primum ASD, 5. cleft of the left-sided AV valve, 6. cleft in the right-sided AV valve.

Double Inlet Ventricle

Anatomy. The connection of both atria to a dominant ventricle is defined as double inlet ventricle (definition: more than 50% of both AV valves must connect to the dominant ventricle). This (univentricular) AV connection guarding the inlet of the univentricular heart can consist of two separate valves or a common AV valve. The ventricle is referred to as a left, right, or indeterminate ventricle depending on the morphologic characteristics. The AV valves connect most frequently to a morphologic left ventricle (double inlet left ventricle in 80–90% of cases; Fig. 21.**18a**). They occasionally connect to a morphologic right ventricle. The physiologic consequence is the mixture of systemic and pulmonary venous blood at the ventricular level. The ventriculoarterial connection can be either concordant or discordant. This ventriculoarterial connection occurs through a nonrestrictive or restrictive VSD and rudimentary RV or outlet chamber (= no AV connection; Fig. 21.**18b**). The pathophysiology in the lungs is determined by the presence or absence of a valvular or subvalvular pulmonary stenosis: pulmonary outflow tract obstruction is frequent and protects the pulmonary vascular bed against pulmonary vascular disease.

Clinical Presentation. The clinical presentation, including *central cyanosis*, is determined by the pathophysiology (severity of pulmonary outflow tract obstruction and the amount of pulmonary blood flow) and associated congenital heart defects. Cyanosis can be mild in the pres-

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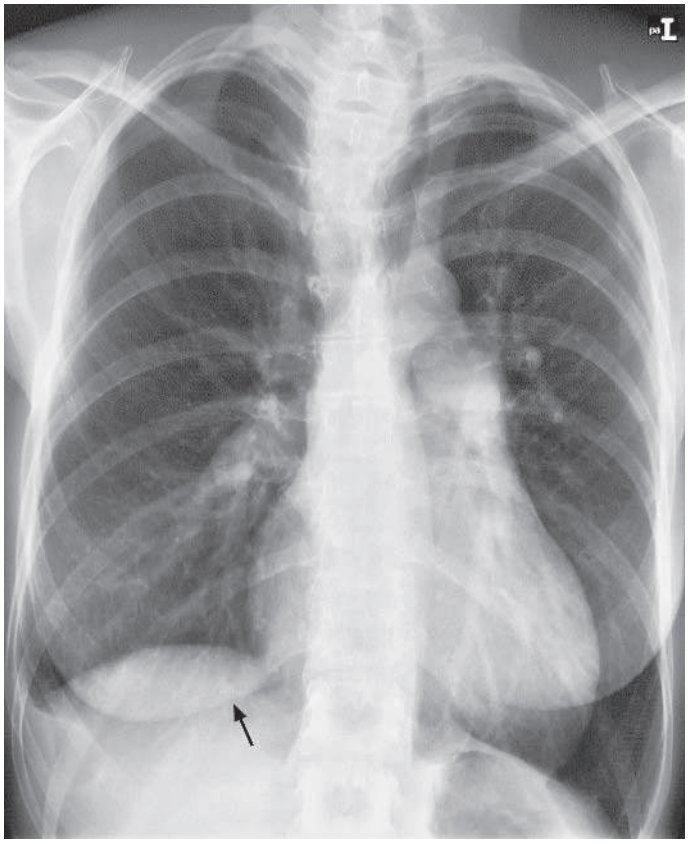

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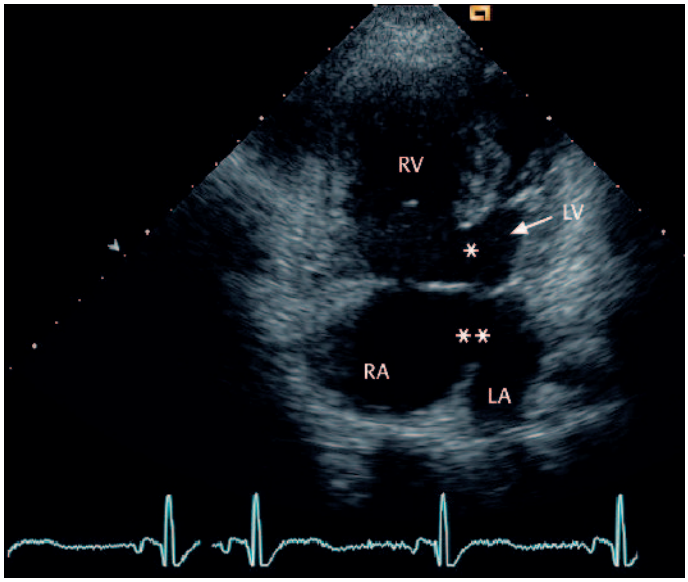

b

Fig. 21.**17** AVSD in a 36-year-old woman with Down syndrome.
a Dilated central pulmonary arteries, mildly increased pulmonary vascularity, enlarged cardiac silhouette. 11th rib (arrow), absence of the 12th rib (a characteristic finding in patients with Down syndrome).
b Apical four-chamber view (midsystolic still frame): right atrial and ventricular enlargement with eccentric hypertrophy of the right ventricle. * inlet VSD, ** primum ASD.

ence of a balanced physiology (moderate to severe valvular or subvalvular pulmonary stenosis and absence of aortic outflow tract obstruction). These children may reach adulthood without major complications and problems. If pulmonary outflow tract obstruction is absent, progressive severe cyanosis, based on pulmonary vascular disease, develops during adulthood, following disappearence of childhood congestive heart failure symptoms caused by the large left-to-right shunt.

Auscultation. The *first heart sound is single*. The characteristics of the *systolic murmur* are determined by the presence or absence of an obstruction across the pulmonary and/or aortic outflow tract. The high blood flow across the outlet chamber causes a protosystolic decrescendo murmur in the presence of a large left-to-right shunt, without obstruction in the pulmonary outflow tract. The pulmonary ejection click, originating from a stenotic, mobile pulmonary valve, is soft because of the

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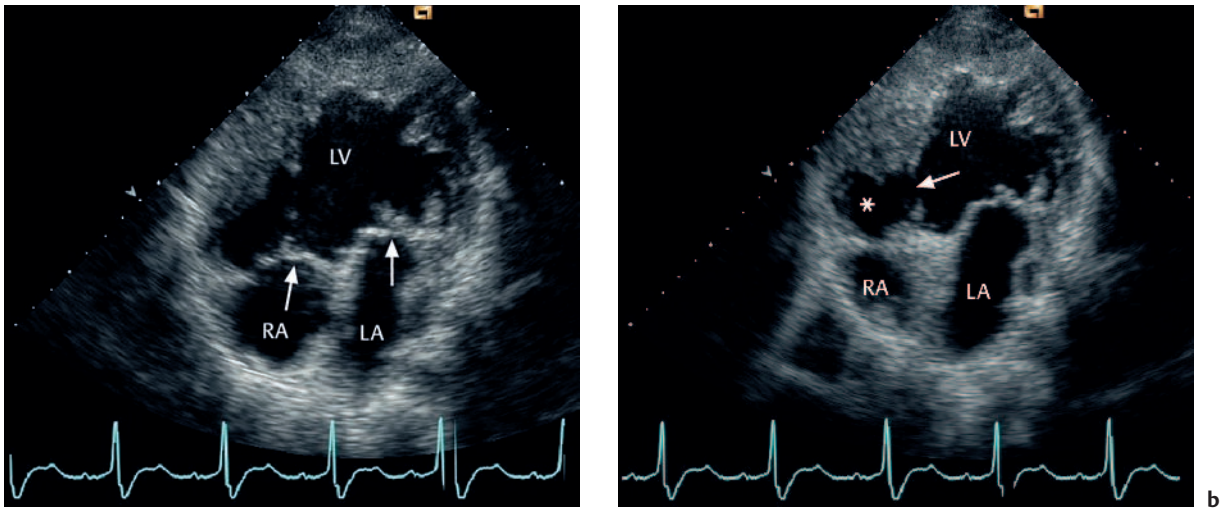

a b

c

Fig. 21.**18** Double inlet left ventricle with D-TGA without pulmonary and aortic outflow tract obstruction in a 42-year-old man.

a Apical four-chamber view: both atria connect via two AV valves to a morphologic left ventricle. Arrows: right-sided and left-sided AV valves.

b Modified apical four-chamber view: the nonrestrictive VSD (arrow) connects to the subaortic rudimentary RV (= outlet chamber *).

c Severely dilated pulmonary arteries, obvious findings of pulmonary arterial hypertension (pruned tree and rat tail appearance of the pulmonary artery branches in the periphery), displacement of the trachea to the right, left aortic arch, and left-sided stomach bubble.

posterior position of the pulmonary trunk, but it is absent in the presence of subvalvular pulmonary outflow tract obstruction.

The systolic murmurs, caused by subvalvular obstruction in the pulmonary outflow tract, are best heard at the middle or lower left sternal border. Their length and loudness vary as to the degree of stenosis: the more severe the subpulmonary stenosis, the larger the right-to-left shunt (blood diverted into the aorta), and the softer and shorter the systolic murmur caused by blood entering the pulmonary trunk. A subvalvular aortic stenosis in the setting of a restrictive VSD causes a midsystolic murmur.

The *second heart sound* is normally split in the absence of pulmonary arterial hypertension. Splitting of the second heart sound disappears when pulmonary arterial hypertension develops (as it does in patients with a nonrestrictive VSD) and subvalvular aortic stenosis is

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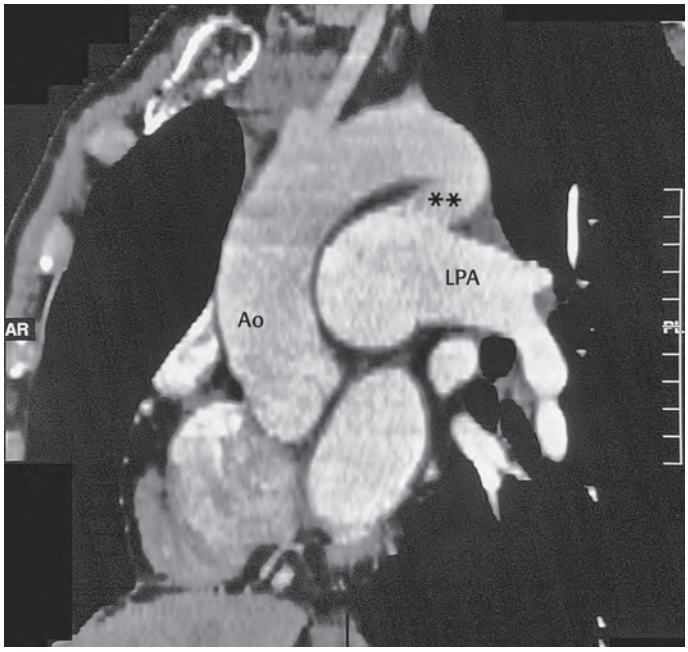

Fig. 21.**19** Nonrestrictive patent ductus arteriosus (**) with Eisenmenger syndrome in a 29-year-old man. Ao: ascending aorta; LPA: left pulmonary artery.

present. The aortic component of the second heart sound is loud in TGA (anterior location of the aorta).

Two types of *diastolic murmurs* can be identified: a middiastolic murmur is heard if pulmonary and subsequent blood flow through the AV valves is high. This middiastolic murmur disappears when pulmonary arterial hypertension develops: a high-pitched, early diastolic murmur appears, which is consistent with pulmonary regurgitation (Graham Steell murmur).

Chest Radiograph. The pathophysiology defines the radiologic characteristics: there is normal or reduced pulmonary vascularity in the presence of balanced physiology or pulmonary outflow tract obstruction, respectively. However, the absence of pulmonary outflow tract obstruction results in increased pulmonary vascularity and grossly enlarged pulmonary arteries (see Fig. 21.**18c**).

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy and to evaluate hemodynamics (see Fig. 21.**18a, b**).

Aortopulmonary Connections

Anatomy. Large nonrestrictive aortopulmonary connections with subsequent development of pulmonary vascular disease can be congenital or acquired.

Congenital connections include aortopulmonary window (connection between the ascending aorta and main pulmonary artery), patent ductus arteriosus (Fig. 21.**19**), and major aortopulmonary collateral arteries (e. g., in patients with pulmonary atresia).

Acquired aortopulmonary connections include surgically created shunts e. g., Waterston and Potts shunt. Both procedures are palliative and direct aortopulmonary anastomoses for the purpose of increasing pulmonary blood flow and, hence, systemic oxygen saturation in congenital heart disease, associated with a restricted pulmonary blood flow, due to a hemodynamically relevant obstruction across the pulmonary outflow tract. The *Waterston shunt* is a direct anastomosis between the ascending aorta and the right pulmonary artery. The *Potts shunt* is a direct anastomosis between the descending aorta and the left pulmonary artery. Both shunts are not performed currently because of their long-term complications (however, there are still adults with these shunts). Restriction of pulmonary blood flow through these direct aortopulmonary anastomoses is difficult, and thus, these shunts are often complicated by pulmonary vascular obstructive disease and pulmonary arterial hypertension, if too large (unilateral pulmonary arterial hypertension, according to the type of shunt). In addition, distortion of the pulmonary artery at the site of anastomosis may occur.

Clinical Features. The clinical presentation is characterized by *central cyanosis*. In addition, enlargement of the systemic ventricle and congestive heart failure can develop due to volume overload. Eisenmenger syndrome, secondary to patent ductus arteriosus, shows the typical findings of *differential cyanosis* (Fig. 21.**20**). The reversed shunt across the patent ductus arteriosus is caused by the severely increased pulmonary vascular resistance, and thus, deoxygenated blood enters the descending aorta distal to the left subclavian artery. As a result, cyanosis and clubbing are absent in the upper

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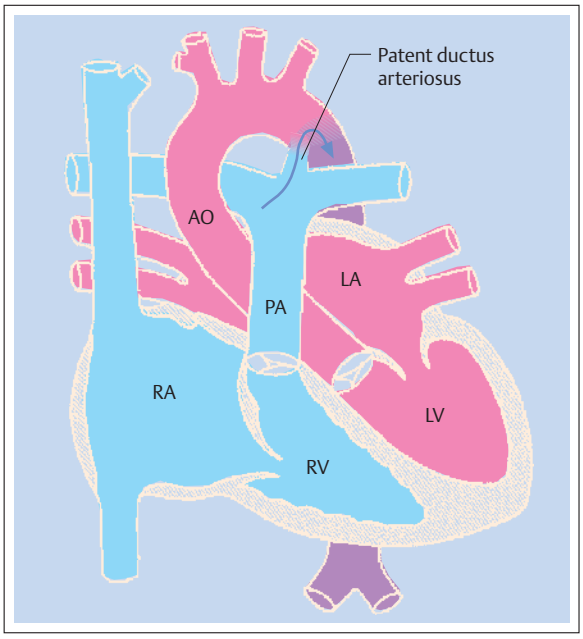

a

b

Fig. 21.**20** Differential cyanosis in the presence of a nonrestrictive patent ductus arteriosus with Eisenmenger syndrome.
a Right-to-left shunting across a large patent ductus arteriosus located distally to the left subclavian artery: the upper limbs are pink, the lower limbs are cyanotic.
b Differential cyanosis in a 32-year-old woman with Eisenmenger syndrome due to a large patent ductus arteriosus. In contrast to the left hand, the left foot is cyanotic!

limbs, but they are present in the lower limbs. Deoxygenated blood may also enter the left subclavian artery depending on the site of the patent ductus arteriosus and result in cyanosis and clubbing in the left hand, whereas the right hand and the mucous membranes in the mouth are pink.

ECG. *Left ventricular overload* is present in the presence of an isolated aortopulmonary shunt with subsequent left-to-right shunt. If pulmonary arterial hypertension and reversed shunt are established during the long-term follow-up, *right atrial overload* with right ventricular hypertrophy will be obvious.

Chest Radiograph. The chest radiograph shows increased pulmonary vascularity including a prominent pulmonary segment and central pulmonary arteries in patients with an aortopulmonary window or patent ductus arteriosus, respectively. Pulmonary vascularity decreases as pulmonary vascular resistance increases. The typical radiologic findings of pulmonary vascular disease are present (Fig. 21.**21**). Calcification at the site of the ductus arteriosus may be frequently observed in the lateral view (see Fig. 21.**9b**). In addition to malformations of the fourth and/or fifth rib as a result of previous thoracotomies, unilateral signs of pulmonary arterial hypertension may be present in patients with surgically created shunts.

Ventricular Septal Defect (VSD)

Anatomy and Pathophysiology. Classification of VSDs is based on their localization:

- Perimembranous VSD (located in the membranous portion of the interventricular septum with variable extension into the contiguous portion of the inlet, trabecular, or outlet septum).
- Muscular VSD (entirely surrounded by muscular interventricular septum).
- Doubly committed VSD (located in the outlet portion of the interventricular septum, such that there is a fibrous continuity between the aortic and pulmonary valves, with the VSD situated directly beneath both semilunar valves).

One has to distinguish between restrictive and nonrestrictive VSD in all forms:

- *Restrictive VSD:* there is a high pressure gradient between the right and left ventricle, the shunt is small (Qp:Qs < 1.5:1.0), and there is no evidence of ventricular volume overload.
- *Partially restrictive VSD:* the shunt is hemodynamically relevant (Qp:Qs = 1.5–2.5:1.0) with progressive left ventricular volume overload.
- *Nonrestrictive VSD:* the pressures are equal in both ventricles and Eisenmenger syndrome develops (Fig. 21.**22**).

The fibrous support apparatus of the aortic and pulmonary valves is frequently underdeveloped in patients with a perimembranous and doubly committed VSD. As a consequence, prolapse and regurgitation of the semilunar valves may occur. The perimembranous VSD can

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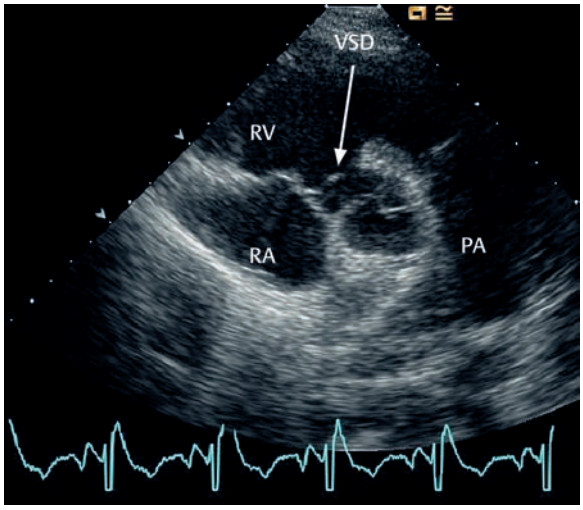
Fig. 21.**21** Chest radiograph of the same patient as in Fig. 21.**19**. Markedly enlarged central pulmonary arteries, pruned tree and rat tail appearance of the pulmonary artery branches in the periphery.



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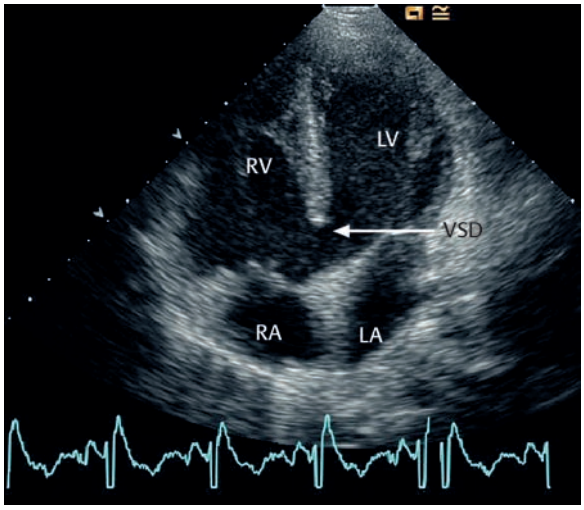

b

Fig. 21.**22** Perimembranous, nonrestrictive VSD extending into the inlet septum in a 26-year-old woman.
a Parasternal short-axis view with perimembranous VSD (arrow).
b Apical four-chamber view with the VSD extending into the inlet septum (arrow).

be associated with right ventricular outflow tract obstruction with important pathophysiologic implications: the pulmonary vascular bed is protected against the development of Eisenmenger syndrome (Fig. 21.**23**).

Clinical Features. Pathophysiology determines the clinical presentation.

A restrictive VSD does not cause any symptoms. A partially restrictive VSD can result in volume overload and progressive enlargement of the left ventricle with dyspnea on exertion, but without cyanosis. A nonrestrictive VSD results in the classic features of Eisenmenger syndrome.

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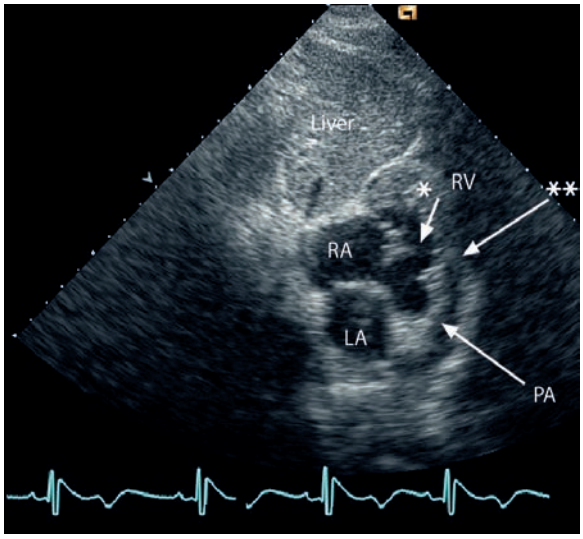

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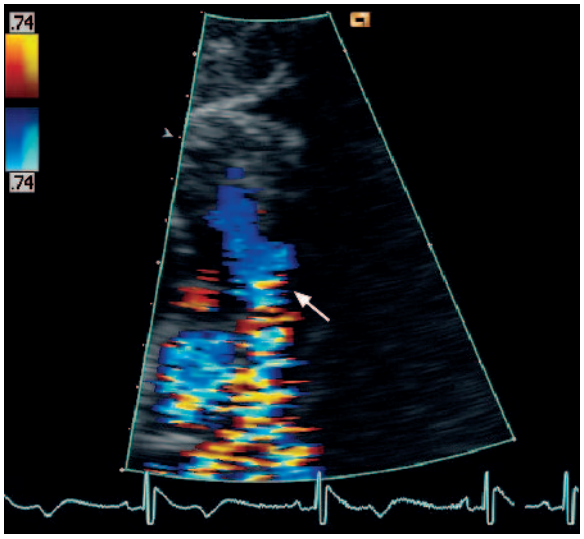

b

Fig. 21.**23** Perimembranous VSD with severe infundibular pulmonary stenosis in a 19-year-old woman.
a Subcostal, midsystolic still frame showing the perimembranous VSD (arrow with one asterisk) and the severe infundibular stenosis (arrow with two asterisks).
b Color-coded Doppler echocardiography demonstrating turbulent blood flow starting at the level of the infundibulum (arrow), passing the main pulmonary artery, and going to both the right and the left pulmonary artery branches (this is the same view as in Fig. 21.**23a**).

A partially restrictive VSD or a nonrestrictive VSD can be associated with moderate or severe *infundibular pulmonary stenosis* protecting the pulmonary vascular bed against increased blood flow, high pulmonary pressure, and the development of pulmonary vascular disease (plexiform arteriopathy; see Fig. 21.**23**). The infundibular stenosis can even worsen during follow-up resulting from progressive hypertrophy of the infundibular myocardium, whereas cyanosis increases due to right-to-left shunting at the ventricular level. In contrast to patients with an Eisenmenger syndrome, cyanotic patients with a VSD associated with severe infundibular stenosis can be operated upon: plexiform arteriopoathy in the pulmonary vascular bed is absent.

Auscultation. Pathophysiology determines the feature of auscultation. A restrictive VSD causes a *loud, high-pitched, crescendo systolic murmur*, best heard in the third and fourth left ICS. The murmur of a VSD, with volume overload of the left ventricle, is similar to that in patients with a restrictive VSD. In addition, there may be a diastolic, low-pitched inflow murmur through the mitral valve and/or a third heart sound over the apex caused by the increased blood flow across the mitral valve. A high-pitched, decrescendo diastolic murmur is heard in the presence of regurgitation of a semilunar valve. The clinical findings in patients with a nonrestrictive VSD are discussed in Eisenmenger Syndrome, below.

ECG. Electrocardiographic findings are normal in patients with a restrictive VSD. *Left atrial and left ventricular overload*, including *left ventricular hypertrophy*, are recorded in patients with a VSD resulting in volume overload of the left ventricle (Sokolow index as an electrocardiographic criterion for left ventricular hypertrophy is evaluated for patients older than 35 years of age).

QRS right-axis deviation and right ventricular hypertrophy are present in *Eisenmenger syndrome* with *right ventricular hypertrophy*. The same electrocardiographic feature is recorded in patients with a VSD associated with severe infundibular stenosis.

The *differential diagnosis* between a VSD with infundibular pulmonary stenosis and a nonrestrictive VSD complicated by Eisenmenger syndrome is simple: the characteristic features for patients with a VSD associated with infundibular stenosis are a loud and long, crescendo systolic murmur, best heard in the second and third right ICS and reaching the second heart sound, and normal or reduced pulmonary vascularity on the chest radiograph.

Chest Radiograph. Pathophysiology determines the radiologic features. Pulmonary vascularity reflects pulmonary blood flow, pulmonary vascular disease, and pulmonary hypertension, respectively: normal or reduced pulmonary blood flow in patients with a VSD associated with severe infundibular pulmonary stenosis; increased pulmonary vascularity in patients with a partially restrictive VSD or a nonrestrictive VSD *without* pulmonary stenosis. In Eisenmenger syndrome, the central pulmonary arteries are enlarged, the peripheral vascular bed shows a so-called pruned tree or rat tail appearance of the pulmonary artery branches, and the pulmonary vascularity decreases as the left-to-right shunt decreases and reverses, respectively. In contrast to severe pulmonary arterial hypertension associated with

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a secundum ASD, the size of the cardiac silhouette is not enlarged in Eisenmenger VSD. Volume overload of the left ventricle causes progressive increase in cardiac silhouette.

Color-Coded Doppler Echocardiography. Color-coded Doppler echocardiography is the method of choice to describe the anatomy and physiology (see Fig. 21.**22** and Fig. 21.**23**).

Eisenmenger Syndrome

Eisenmenger Complex and Eisenmenger Syndrome

In 1897, Victor Eisenmenger first described both the clinical and pathologic features and characteristics of irreversible pulmonary vascular disease in a 32-year-old cyanotic man with a nonrestrictive perimembranous VSD. Sixty years later, Paul Wood elucidated the distinctive clinical and physiologic characteristics in 127 individuals with Eisenmenger physiology in his classic work on the Eisenmenger syndrome.

Wood reserved the term *Eisenmenger complex* for describing the presence of severe pulmonary hypertension due to high pulmonary vascular resistance (>800 dyne $\cdot$ sec $\cdot$ cm^{-5}) with reversed or bidirectional shunt through a large ventricular septal defect. Because of the fact that any large communication between the systemic and pulmonary circulations may result in similar physiologic changes when a markedly increased pulmonary vascular resistance occurs, and that localization of the defect is difficult at the bedside, Wood suggested using the term Eisenmenger syndrome.

Wood defined Eisenmenger syndrome as pulmonary hypertension with reversed or bidirectional shunting at the atrial, ventricular, or arterial level to embrace all conditions that behave physiologically like Eisenmenger complex. "It matters very little where the shunt happens to be." Thus, the term Eisenmenger syndrome describes pulmonary vascular conditions with markedly increased pulmonary vascular resistance due to a nonrestrictive communication between the systemic and pulmonary circulations at any level (see Tab. 21.**2**).

Development. Eisenmenger syndrome is commonly established during the first two years of life, if the shunt is interventricular or aortopulmonary. As pulmonary vascular resistance decreases early after birth, predominant left-to-right shunting increases through a large communication at any level. Congestive heart failure due to volume overload is usually the first symptom and cyanosis may be observed on exertion. As pulmonary vascular disease progresses and pulmonary vascular resistance rises, left-to-right shunting decreases and symptoms of heart failure disappear. Frank cyanosis at rest, due to a reversed shunt, may become apparent as the structural changes in the pulmonary vascular bed progress.

Clinical Features. *Central cyanosis*, a precordial lift, and possibly a palpable second heart sound are characteristic clinical features when Eisenmenger syndrome is established.

Auscultation. A *pulmonary ejection murmur* follows the pulmonary ejection click. A high-pitched diastolic murmur (pulmonary regurgitation) can follow the second heart sound. This pulmonary regurgitation murmur, secondary to pulmonary hypertension, is also called a Graham Steell murmur. Additional findings are determined by the underlying anatomy and pathophysiology (see paragraphs on the different congenital heart defects).

ECG and Chest Radiograph. Electrocardiographic and radiologic findings are determined by the underlying anatomy and pathophysiology of the congenital heart defect (see paragraphs on the different congenital heart defects). ECG often reveals *right atrial overload* and *right ventricular hypertrophy*. The chest radiograph shows markedly enlarged central pulmonary arteries, which may be calcified, and a so-called pruned tree or rat tail appearance of the pulmonary artery branches (Fig. 21.**24**). The pulmonary vascular bed appears plethoric in the presence of a large left-to-right shunt. However, pulmonary vascularity decreases as left-to-right shunt decreases and the shunt reverses.

In contrast to patients with idiopathic pulmonary arterial hypertension, extrapulmonary and intrapulmonary radiologic features of patients with Eisenmenger syndrome include thrombus formation in the aneurysmally enlarged proximal pulmonary arteries and intrapulmonary embolic infarction. There is a therapeutic dilemma in the context of an increased risk of bleeding tendency with fatal outcome. Mural calcification of the pulmonary arteries are frequent.

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy and to evaluate pathophysiology.

Atrial Septal Defect (ASD)

Types of ASD: ASD are most frequently diagnosed during adulthood and are more frequent in women than in men. Types of ASD are as follows:

- *Secundum ASD:* located at the level of the oval fossa; it is called secundum ASD despite the fact that the oval fossa is the septum primum (Fig. 21.**25**). Secundum ASD is the most common type of ASD and can exceed the true borders of the oval fossa.
- *Primum ASD:* primum ASD is part of the spectrum of AVSD. It is caused by a deficiency in the development of the AV septum during embryogenesis of the endocardial cushion. It is located anterior and inferior to

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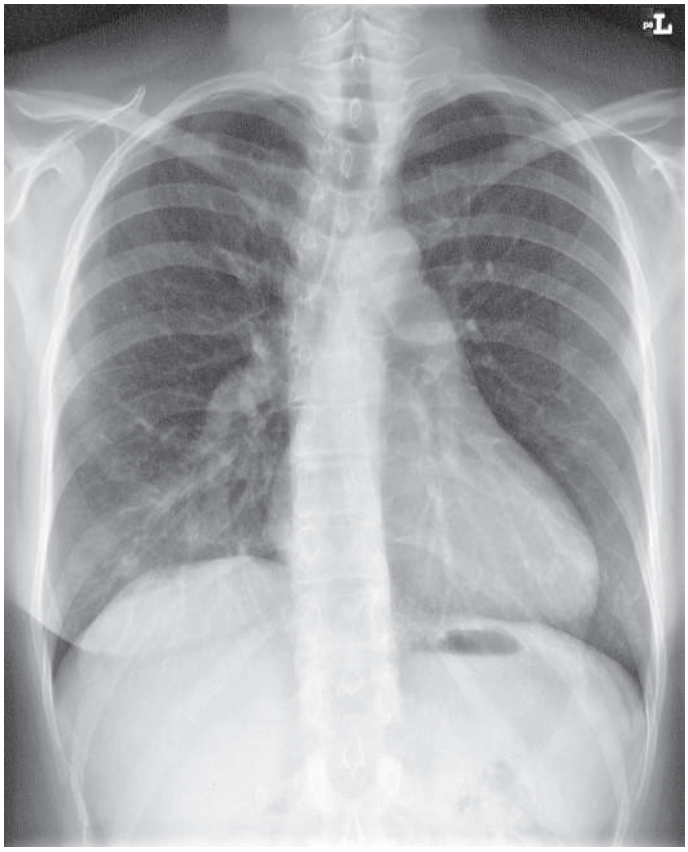

Fig. 21.**24** Eisenmenger syndrome in a 54-year-old woman with a perimembranous VSD.

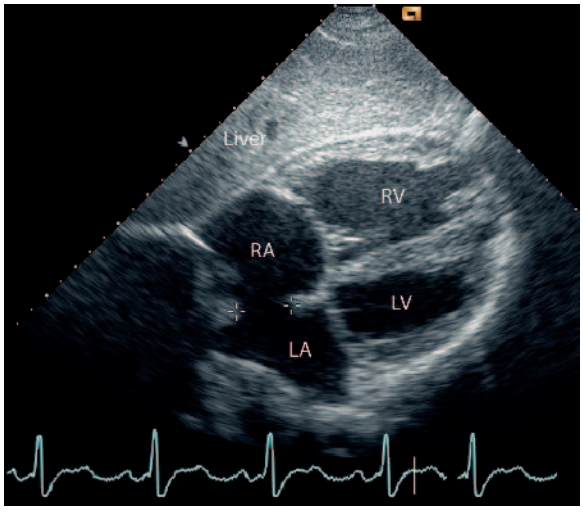

Fig. 21.**25** Severe pulmonary arterial hypertension in a 31-year-old man with a secundum ASD (subcostal view). + + margins of the secundum ASD (27 mm in diameter). RV: eccentric hypertrophy of the right ventricle.

the oval fossa, such that there is no atrial septal tissue between the lower edge of the defect and the AV valves, which are located on the same plane. It is bounded superiorly by the inferior border of the oval fossa and inferiorly by the superior and inferior bridging leaflet. Additional malformations are described in Atrioventricular Septal Defect (AVSD), above.

- *Sinus venosus defect:* this defect is caused by a deficiency of infolding of the atrial wall in the region of the embryogenic sinus venosus. There are two types of sinus venosus defects:
  - The *superior sinus venosus defect* includes an interatrial communication located posterosuperior to the oval fossa and within the mouth of the superior vena cava, with the defect protruding over the rim of the oval fossa. Partial anomalous pulmonary venous connection to the superior vena cava is common (most often anomalous return of the right upper pulmonary vein). Total anomalous pulmonary venous connection of the right-sided pulmonary veins is rare.
  - The *inferior sinus venosus defect* is located postero-inferiorly at the mouth of the inferior vena cava (it is very rare).
- *Coronary sinus defect:* there is an interatrial communication between the coronary sinus and the left atrium through the mouth of the coronary sinus (very rare). In its most extreme form, a left superior vena cava connects directly to the left atrium due to deficiency in the entire wall of the coronary sinus.

An ASD may be associated with a valvular pulmonary stenosis, mitral valvular prolapse, or Ebstein anomaly.

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Pathophysiology. Volume overload of the right atrium and right ventricle due to a large left-to-right shunt is determined by the size of the interatrial communication. Pulmonary arterial hypertension and diastolic dysfunction with increased right ventricular filling pressures may develop in the presence of a hemodynamically relevant shunt during adulthood (usually in the fifth or sixth decade of life). The degree of left-to-right shunt decreases with age and may be bidirectional.

Severe pulmonary vascular disease with markedly increased pulmonary vascular resistance cannot be caused nor explained by an interatrial communication alone. A genetic predisposition to develop pulmonary vascular disease is present in patients with severely increased pulmonary vascular resistance; the pulmonary vascular bed is hyperreactive (see Fig. 21.**25**). The high pulmonary blood flow in the presence of a shunt acts as a trigger to initiate pathologic changes in the pulmonary vascular bed ending in the development of plexiform lesions. An interatrial shunt is never the only cause for pulmonary vascular disease. Patients with Down syndrome or TGA have a genetic predisposition to develop pulmonary vascular disease.

Clinical Features. Patients with a small left-to-right shunt, without volume overload, and without dilatation of the right ventricle do not complain of any symptoms. The diagnosis of an ASD is established, by chance, during the evaluation of a heart murmur or other disease.

Patients with a large left-to-right shunt and subsequent dilatation of both the right atrium and the right ventricle can *complain of fatigue* and *dyspnea on exertion*.

When severe pulmonary arterial hypertension has developed (which is rare, but facilitated in genetic predisposition), the shunt becomes bidirectional or reversed; the patients are symptomatic and cyanotic.

Early cyanosis is present in patients with a coronary sinus defect because systemic venous blood enters directly into the left atrium.

Precordial lift reflects right ventricular volume and pressure overload.

Auscultation. An *early or midsystolic murmur*, best heard in the second and third left ICS, can be recorded and is determined by the amount of the left-to-right shunt. It is caused by the increased blood flow through the pulmonary valve (relative pulmonary stenosis). The *second heart sound* is widely split with a prominent pulmonary component. In the presence of a large left-to-right shunt, variation with respiration is attenuated, the second heart sound can be fixed split, and a low-pitched diastolic inflow murmur through the tricuspid valve can be heard (increased blood flow through the tricuspid valve).

ECG. A partial *right bundle branch block* is frequently present (a complete right bundle branch block is rare). An ectopic atrial rhythm is frequently associated with the presence of a superior sinus venosus defect. If severe pulmonary arterial hypertension is established, a right atrial P wave (*P pulmonale*) and *right ventricular overload* are recorded. *QRS left-axis deviation* reflects the presence of a primum ASD or AVSD.

> Atrial fibrillation can be the first symptom of a hemodynamically relevant ASD in patients older than 50 years of age.

Chest Radiograph. Right atrial enlargement, prominent pulmonary segments, and increased pulmonary vascularity are obvious in the presence of a hemodynamically relevant shunt. Radiologic signs of pulmonary arterial hypertension may or may not be present in the periphery of the lungs (Fig. 21.**26**). The aortic knuckle can be small or appear small due to the large pulmonary segment.

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy and to evaluate hemodynamics.

Congenital Heart Defect with Normal Pulmonary Vascularity and No Obstruction in the Pulmonary Outflow Tract: Ebstein Anomaly

Wilhelm Ebstein in 1864 described a malformation of the tricuspid valve in a 19-year-old laborer, who had complained of cyanosis and palpitation since childhood and who died from heart failure. The malformation bearing Ebstein's name is characterized by the following:

- The basal attachments of both the septal and posterior leaflets of the tricuspid valve are apically displaced from the AV ring (Fig. 21.**27**). Apical displacement of the septal tricuspid valve leaflet of more than 8 mm/m^2 is diagnostic. As a consequence, the tricuspid valve orifice is displaced into the right ventricular cavity and the right-sided heart chambers consist of three components:
  - *True right atrium:* area of the anatomic right atrium including the anatomic tricuspid annulus (Fig. 21.**27**).
  - *Atrialized right ventricle:* this belongs to the right ventricle from an anatomic and electrocardiographic point of view, but it is functionally integrated with the right atrium (Fig. 21.**27**). It encompasses the area between the tricuspid annulus and the orifice of the tricuspid valve.
  - *Functional right ventricle:* the more pronounced the apical displacement, the larger the atrialized portion of the right ventricle and the smaller the functional right ventricle (Fig. 21.**27**).
- Malformations of the anterior tricuspid valve leaflet (very large and abnormally attached to the right ventricular wall).
- Obstruction in the right ventricular outflow tract (frequent).

The severity of tricuspid regurgitation (mild to severe) depends on the degree of tricuspid valvular malforma-

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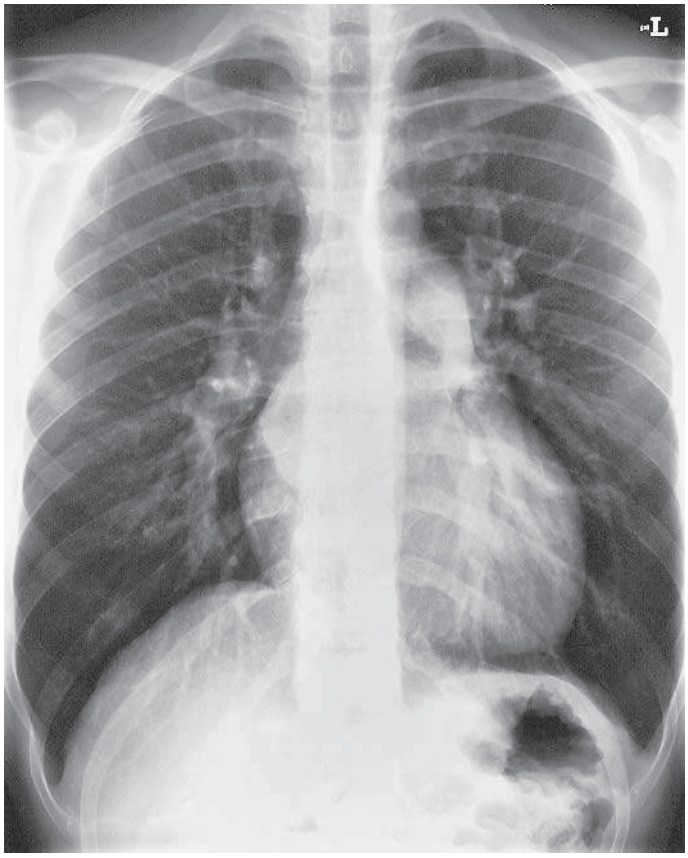

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b

Fig. 21.**26** Chest radiographs of a 31-year-old man shown in Fig. 21.**25**.
a Right atrial enlargement; severe dilatation of the central pulmonary arteries. Radiologic feature of pulmonary arterial hypertension is obvious.
b Retrosternal filling caused by right ventricular enlargement.

tion. A patent foramen ovale or a secundum ASD are frequently (up to 50%) associated anomalies in patients with Ebstein anomaly (interatrial communication). Multiple accessory pathways (WPW syndrome) can be present in up to 25% of patients.

Other congenital heart defects can be associated with Ebstein-like deformation of the tricuspid valve: congenitally corrected TGA, VSD, or tetralogy of Fallot.

Clinical Features. Both the morphologic and clinical spectra are very wide, thus, the clinical presentation differs. Patients with severe forms of Ebstein anomaly cannot survive: intrauterine death or death soon after birth may occur. On the other end of the spectrum, Ebstein anomaly can be diagnosed, by chance, in asymptomatic adults undergoing diagnostic echocardiography.

Patients may have a broad spectrum of symptoms based on the severity of tricuspid valvular malformation; *fatigue*, *dyspnea on exertion*, *palpitations* (atrial flutter, atrial fibrillation). Cyanosis may also be a symptom if an interatrial communication is present. It may be more pronounced in the presence of a coexisting right ventricular outflow tract obstruction.

Although tricuspid valve regurgitation is severe, the jugular venous pulse can be normal and a v wave rarely

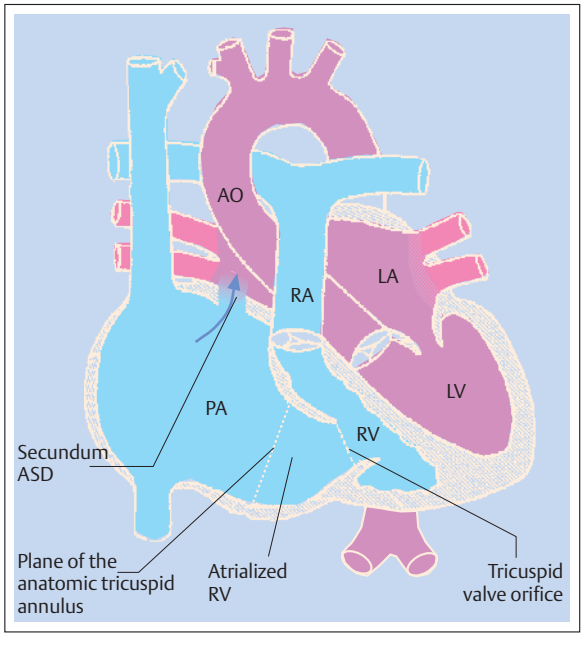

Fig. 21.**27** Ebstein anomaly: apical displacement of the basal attachment of both the septal and posterior tricuspid valve leaflets.

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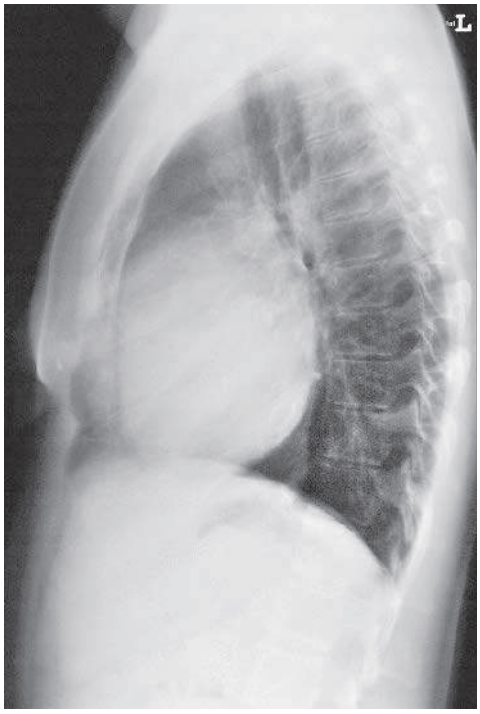
a



b

Fig. 21.**28** Ebstein anomaly associated with a secundum ASD in a 23-year-old woman.
a Severe enlargement of both the right and left borders of the cardiac silhouette ("spheroid configuration of the heart"). Normal pulmonary vascularity and small aortic knuckle.
b Retrosternal filling caused by the severely enlarged right heart.

appears. The severely enlarged right atrium and the thin-walled atrialized right ventricle dampen the v wave; regurgitation in the low pressure system is another reason. An a wave is also rarely visible.

Auscultation. The sail sound is typical: the first component of the widely split first heart sound coincides with closure of the mitral valve; the abnormally large anterior tricuspid valvular leaflet snapping like a sail catching the wind causes the delayed closure (second component). The sail sound is not an ejection click, although it may simulate one. A grade 2/6 or 3/6 tricuspid *regurgitant murmur* can be heard. The loudness and intensity of this systolic murmur do not increase during inspiration because the functional right ventricle is small and can not increase the stroke volume. The second heart sound can be single (the pulmonary component is not audible because of the low pulmonary arterial pressure). Complete right bundle branch block can rarely cause a widely-split second heart sound. The following sounds can be heard as well: third and fourth heart sounds, tricuspid opening sound (early diastolic sound).

ECG. ECG can be characteristic (broad and tall P waves), but it can reveal many other features: right atrial overload, prolonged PQ interval, intraventricular conduction delay (right bundle branch block), or deep Q waves in leads V_1 through V_4 and in the inferior leads. A WPW syndrome can be frequently identified (more than one accessory pathway can coexist in Ebstein anomaly).

Chest Radiograph. There is a wide spectrum of radiologic features ranging from a nearly *normal to a grossly enlarged cardiac silhouette* (Fig. 21.**28**). The right atrial silhouette is almost always enlarged. Pulmonary vascularity is reduced in patients with a severe form of Ebstein anomaly due to the reduced pulmonary blood flow. The vascular pedicle is narrow (small pulmonary trunk and ascending aorta).

Color-Coded Doppler Echocardiography. Echocardiography is the method of choice to describe the anatomy and pathophysiology (Fig. 21.**29**).

Pulmonary Cyanosis

Pulmonary cyanosis can be caused by many factors (see also Chapter 17).

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Abnormal Ventilation. All forms of acute or chronic hypoventilation cause central cyanosis. Hypoventilation can be partial or global. Arterial hypoxemia is caused by hypoventilation of some lung segments, hypercapnia (increased arterial Pco_2) is absent (partial hypoventilation). Both arterial hypoxemia and hypercapnia are present in patients with global hypoventilation.

Reduced Diffusion Capacity. All forms of pulmonary disease result in diffuse parenchymal lung disease with subsequent reduction in gas exchange area and/or reduced diffusion capacity. Diseases affecting the lung interstitium (intrinsic or interstitial lung diseases) and diseases with reduction in both the ventilated and perfused lung segments cause reduced diffusion capacity.

Vascular Etiologies. The cause of pulmonary cyanosis is found in the arterial, capillary, and/or venous vascular beds (frequently combined etiologies). This group of pathologies also includes arteriovenous shunts (congenital or acquired).

Mixed Patterns. Usually not only a single etiology, but multiple mixed pathologies are responsible in the development of pulmonary cyanosis. A ventilation mismatch is always associated with a perfusion mismatch, and vice versa (ventilation to perfusion mismatch or perfusion to ventilation mismatch: poorly ventilated lung segments are poorly perfused, and poorly perfused lung segments are poorly ventilated).

Chronic Pulmonary Cyanosis

A restrictive or obstructive ventilation pattern can cause central cyanosis. A primarily abnormal ventilation pattern always results in a reduced diffusion capacity and in pathologic changes of the pulmonary vascular bed with subsequent development of pulmonary arterial hypertension. Conversely, a primarily reduced diffusion capacity can cause a pathologic ventilation pattern.

Primary Parenchymal Etiologies. The key (primary) pathology is parenchymal (alveoli, interstitium, etc.). Subsequent vascular changes aggravate pulmonary cyanosis:

- *Intrapulmonary etiologies:* all forms of lung fibrosis, atelectasis, inflammatory lung disease (infectious and noninfectious diseases), pneumoconiosis, tumors, lung emphysema, asthma bronchiale, chronic bronchitis, etc.
- *Extrapulmonary etiologies:* chronic pleural effusion, tumors, thoracic abnormalities, kyphoscoliosis, myopathies with subsequent hypoventilation due to weakness of the respiratory muscles (congenital or inflammatory muscle diseases), paretic diaphragm, obesity (Pickwick syndrome), or various forms of sleep apnea syndrome.

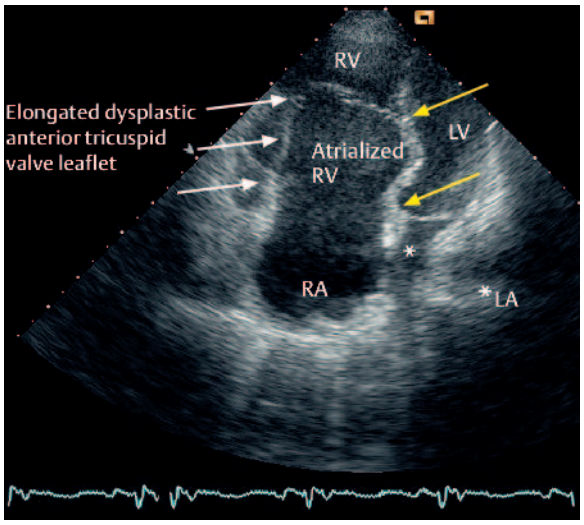

Fig. 21.**29** Ebstein anomaly associated with a secundum ASD in a 60-year-old woman. Apical four-chamber view showing the typical echocardiographic features and morphology. Yellow arrows: marked apical displacement of the basal attachment of the septal tricuspid valve leaflet, * left atrium.

Primary Vascular Etiologies

- *Arterial etiologies:* chronic recurrent thromboembolic events, pulmonary arterial hypertension (idiopathic, pulmonary arterial hypertension associated with connective tissue disorders, congenital heart disease, and other forms of pulmonary arterial hypertension).
- *Venous etiologies:* chronic heart failure syndrome, severe mitral valve stenosis; severe heart failure is always associated with peripheral cyanosis secondary to severely reduced cardiac output; central cyanosis is frequently not obvious (see Chapter 20).
- *Arteriovenous shunts:* congenital arteriovenous malformations (Osler disease), acquired arteriovenous malformations secondary to liver cirrhosis, in the presence of Fontan physiology (univentricular circulation without subpulmonary ventricle), Glenn anastomosis (connection between the superior vena cava and the right pulmonary artery in congenital heart disease to improve pulmonary blood flow); the severity of cyanosis depends on the size and the quantity of intrapulmonary shunts.

Acute Pulmonary Cyanosis

- *Acute airway obstruction:* aspiration, laryngospasm, asthma attack.
- *Primarily parenchymal etiologies:* pneumothorax, tension pneumothorax (including impaired blood flow through the superior vena cava), hematothorax (traumatic injury).
- *Vascular etiologies:* acute pulmonary emboli, fat emboli, acute pulmonary edema (heart failure, acute mitral regurgitation secondary to ruptured papillary muscle, toxic lung edema, etc.).

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Peripheral Cyanosis

Peripheral cyanosis is caused by peripheral vasoconstriction with subsequently reduced blood flow, increased oxygen extraction, and increased content of deoxygenated hemoglobin in the capillary and venous bed. Arterial oxygen saturation is normal. Exposure to cold air or to water is the most frequent cause of peripheral cyanosis.

Peripheral Cardiac Cyanosis

Acral cyanosis due to increased oxygen extraction in the capillaries can be caused by low cardiac output due to any cause, especially in the setting of exposure to cold temperatures. Myocardial dysfunction is the most frequent cause of cyanosis in the presence of *myocardial or valvular heart disease* (see Chapter 20). Shock, due to any cause, with subsequent impairment of myocardial function, can cause peripheral cyanosis.

Peripheral Cyanosis in Blood Diseases

Precipitation of cryoglobulins or cold agglutinins in the presence of *cryoglobulinemia* and *elevated titers of cold agglutinins*, respectively, or aggregation of red blood cells in capillaries of patients with erythrocytosis can occasionally cause blood stasis with peripheral cyanosis due to oxygen extraction.

Peripheral Local Cyanosis

Peripheral local cyanosis is caused by local pathologies of the arterial or venous vessels. The extremity is marbled (and not cyanotic) in the presence of total occlusion of a peripheral artery. Peripheral cyanosis caused by pathologies in the *arterial system* is mild. Peripheral cyanosis caused by pathologies in the *venous system* can be very pronounced due to blood stasis in the veins, e. g., deep vein thrombosis, impaired blood flow in the superior vena cava caused by a tumor with subsequent vein distension in the upper half of the body, etc.

Acrocyanosis, Erythrocyanosis Crurum, and Livedo Reticularis. Atonic–hypertonic dysregulation of the venous–capillary system is the cause for this peripheral local cyanosis. The mechanism is poorly understood:

- *Acrocyanosis:* acral discoloration of the skin resulting from vegetative dystonia, especially when exposed to water and to cold temperature.
- *Erythrocytosis crurum:* cyanotic discoloration and pasty swelling of the lower limbs, which may or may not be painful, is found in young women or in patients with neurologic disorders (postpoliomyelitis, paraplegia, etc.).
- *Livedo reticularis:* peripheral (arms, legs) cyanosis of the skin occurring with a laminar or reticular pattern; it may result from venous stasis of any cause.

Neurovascular Shoulder Girdle Syndromes and Brachialgias. Although pain and neurological findings, due to compression of the neurovascular bundle or a single nerve serving the arm, are the key symptoms, any compression syndrome can cause peripheral, local cyanosis: scalenus anterior syndrome, supernumerary cervical ribs, thoracic outlet syndrome, Klippel–Feil syndrome, etc.

21.2 Hemiglobin Cyanosis

Methemoglobinemia

Pathogenesis. Hemiglobin (methemoglobin) is an altered state of hemoglobin in which the ferrous (Fe^{2+}) irons of heme are oxidized to the ferric (Fe^{3+}) state. Hemiglobin (ferric hemes) has lost its capacity to transport oxygen.

Continuous oxidation of a small amount of hemoglobin ($HbFe^{2+}$) and formation of hemiglobin ($HbFe^{3+}$) occurs spontaneously in the red blood cells of healthy people. Reduction of hemiglobin ($HbFe^{3+}$) to hemoglobin ($HbFe^{2+}$) is mediated either enzymatically, by NADPH methemoglobin reductase (which is the most important pathway), or nonenzymatically, via a number of alternative pathways. The physiologic concentration of hemiglobin or methemoglobin ($HbFe^{3+}$) varies between 0.1–0.6% in adults (it may reach or even exceed 10% of the total hemoglobin in smokers). Methemoglobin concentration is elevated in the presence of increased oxidation or impaired reduction (Fig. 21.**30**).

A methemoglobin concentration exceeding 1.5 g/dL is defined as *methemoglobinemia*. Cyanosis becomes

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clinically visible when methemoglobin concentration exceeds 1.5 g/dL. A highly elevated concentration of methemoglobin causes a slate-blue or green appearance of the skin, which is in contrast with the generally asymptomatic state of the patients. Clinical symptoms, including light-headedness, easy exhaustion, or tachycardia, are complaints of patients with a methemoglobin level exceeding 40% of the total hemoglobin. The lethal level of methemoglobin is at 70–80% of total hemoglobin.

Hereditary Methemoglobinemia

Pronounced cyanosis is typically already present at birth or shortly after birth in these rare disorders. Absence of cardiovascular symptoms masks to the presence of cyanotic congenital heart disease. Toxic methemoglobinemia occurring with cyanosis must be excluded in neonates, because fetal hemoglobin is very vulnerable to developing methemoglobinemia following exposure to substances causing methemoglobin (Heinz body formation). General health, exercise tolerance, and life expectancy are hardly affected; clubbing is not observed.

Hemoglobinopathy M

In hemoglobinopathy M, a fraction of the hemoglobin consists of the pathologic hemoglobin M. It is inherited as an autosomal dominant disease. There is a change in the amino acid sequence of the betaglobin molecule due to genetic mutations. As a consequence, the imbalance between oxidation and reduction favors the oxidation process resulting in an increased methemoglobin ($HbFe^{3+}$) formation. Hemoglobinopathy M is confirmed by spectrophotometry or by hemoglobin electrophoresis.

NADPH Methemoglobin Reductase Deficiency

This is an autosomal recessive hereditary disorder. Deficiency in NADPH methemoglobin reductase increases the amount of methemoglobin in the blood to up to 15–30% of the total hemoglobin.

Low Oxygen Affinity Hemoglobins

These very rare disorders, with an autosomal dominant inheritance, include hemoglobins with reduced oxygen affinity. Representatives of Hb Kansas and Hb Beth Israel hemoglobinopathy typically occur with cyanosis. Although the Po_2 is normal, arterial oxygen saturation may be only 50%.

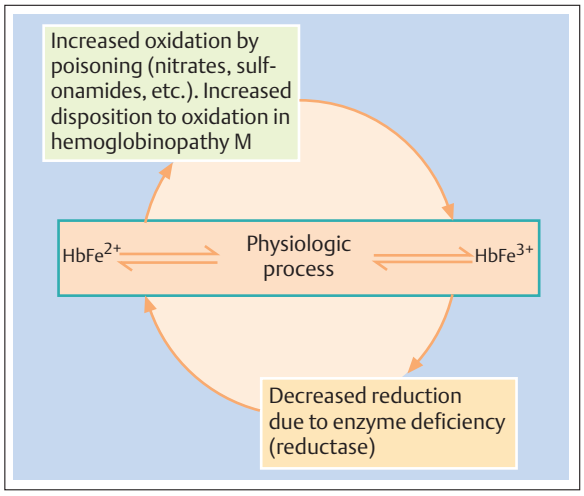

Fig. 21.**30** Formation of hemoglobin and hemiglobin.

Toxic Methemoglobinemia

Causes. Various exogenic chemical agents and drugs directly or indirectly induce the oxidation process:

- nitrites (used as supplements to food, amyl nitrite, nitroglycerin)
- nitrates (silver nitrate, bismutum subnitricum, salts)
- nitrobenzene (perfume and explosives industry)
- nitrogases (autogenous welding)
- chlorates (potassium chlorate)
- analgetics (phenacetin, acetanilide, etc.)
- sulfonamides
- aniline derivates (dyes)
- local anesthetic agents in the amide class.

Clinical Features. Criteria suggesting methemoglobinemia in the presence of cyanosis of unknown origin are as follows:

- Relationship between the onset of cyanosis and exposure to substances causing methemoglobinemia.
- Transient cyanosis if intake of the toxic agent is not chronic.
- The blood appears dark brown, brownish, or chocolate in color immediately after withdrawal. In contrast to normal venous blood, the color does not change with addition of oxygen or agitation in the air.
- Heinz bodies, which are normally not present in red blood, occur in red blood cells. They are present in most acquired forms of methemoglobinemia and become visible by the use of a special staining (supravital dye, e. g., crystal violet).
- Hemolytic anemia may occur in special cases, especially in neonates.

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Diagnosis and Differential Diagnosis of Methemoglobinemia

Methylene Blue. Methylene blue is both a diagnostic and a therapeutic agent for toxic and hereditary methemoglobinemia such as NADPH cytochrome b5 reductase deficiency. It acts as an artificial electron acceptor for the reduction of methemoglobin and provides partial or complete regression of hemiglobin cyanosis depending on the severity of methemoglobinemia. It is not effective in hemoglobinopathy M. Methylene blue is administered slowly (over five minutes) in a dose of 1–2 mg/kg (by means of a 0.1–1 % methylene blue solution). A second dose of 2 mg/kg can be given if cyanosis does not disappear within one hour.
A cumulative dose exceeding 7 mg/kg can cause vomiting, dizziness, tremor, mental confusion, hemolysis, and cardiovascular symptoms including dyspnea and chest pain. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency since it can cause severe hemolysis due to its potential for oxidation. Ascorbic acid involved in oxidation–reduction reactions does have the same effect, but it is less effective than methylene blue.
Differential diagnosis between peripheral cyanosis and methemoglobinemia can be very difficult in patients with cardiovascular disease: in those treated with nitroglycerin, in those given sodium nitroprusside in the intensive care unit, or in those treated with silver nitrate for cauterization of wounds or removal of granulation tissue. Toxic methemoglobinemia is a rare disorder despite the frequent administration of toxic exogenic agents. Predisposition to methemoglobin formation may be based on a coexisting deficiency of enzymes.

Sulfhemoglobinemia

Rarely, sulfhemoglobinemia may occur after the intake of phenacetin, sulfonamides, or poisoning with hydrosulphides resulting in gastrointestinal problems (obstipation). Sulfhemoglobin can be demonstrated by spectrometry (irreversible oxidation of heme). The brown-violet discoloration of the skin is obvious already at low concentrations of sulfhemoglobin; the blood appears greenish.

21.3 Pseudocyanosis

Pseudocyanosis refers to a bluish discoloration of the skin and mucous membranes caused by skin pigmentation or by deposit of exogenic substances. The most important exogenic substances incorporated into the skin and mucous membranes are silver (*argyrosis*), gold (*chyriasis*), and arsenic exposure and poisoning (*arsenic melanosis*).

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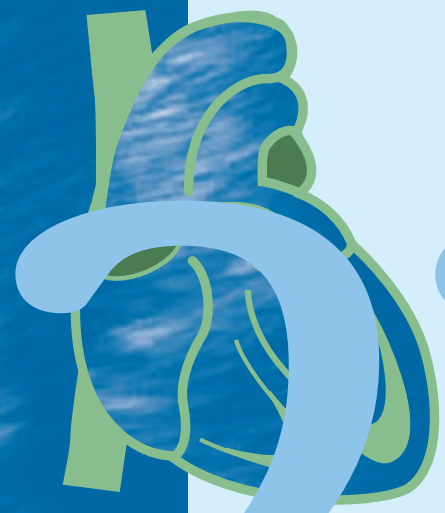
22 Arrhythmias

C. Scharf and F. Duru



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Origin of Cardiac Arrythmia

The normal heartbeat is initiated in the sinus node (impulse formation) and travels over the conduction system (atrium, atrio-ventricular [AV] node, His–Purkinje system) to the ventricles (impulse conduction). *Sinus rhythm* is defined by presence in the electrocardiogram (ECG) of a sinus P wave, which is positive in lead II, and is followed by a QRS complex (except in case of an AV block). *Ectopic rhythms* are those having an origin outside of the sinus node. Normal sinus rhythm is not completely regular. Physiologic variations in heart rate can be associated with irregular respiration or with vagotonic/sympathicotonic stimulation.

Bradyarrhythmias arise from an absence of the normal impulse formation (e. g., sinus node arrest) or from a blocking of the normal impulse propagation (e. g., AV block). *Tachyarrhythmias* occur when an abnormal impulse is formed (focal arrhythmias) or an abnormal conduction is present (reentrant tachycardias), or from a combination of both (i. e., atrial fibrillation). Arrhythmias of all types and frequencies can result (i. e., from slow to fast and from regular to completely irregular). Many arrhythmias occur without an identifiable cause (primary arrhythmias). In secondary arrhythmias an underlying cardiac disease or systemic disease is arrhythmogenic.

22.1 Differential Diagnosis of Arrhythmias

Medical History

A detailed medical history is vital to any diagnosis, including that of arrhythmias.

Family History. The family history can reveal inherited causes of sudden cardiac death (long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, hypertrophic obstructive cardiomyopathy, etc.). If the cause of a sudden death of any family member is unclear, review of the ECG or medical records can be extremely helpful to identify the nature of an inherited disorder.

Personal History. In patients with structural heart disease (e. g., myocardial infarction, cardiomyopathy), cardiac arrhythmias and syncope have a serious impact on prognosis. On the other hand, in structurally normal hearts most arrhythmias are not associated with a worse prognosis.

> The prognosis of arrhythmias depends on the presence or absence of structural heart disease. In normal hearts arrhythmias are not dangerous, but in the presence of structural heart disease they can be life-threatening.

The *age* at first presentation of the arrhythmia can also provide clues to the etiology. Reentrant tachycardia over an accessory pathway is often symptomatic in infancy and adolescence, whereas atrial tachycardias often arise in the elderly and AV nodal reentrant tachycardia can become manifest at any age.

Paroxysmal supraventricular tachycardias have a *sudden onset* and a *sudden end*, like a light switch, and are often accompanied by diuresis provoked by release of atrial natriuretic peptide (ANP). In focal tachycardias (i. e., in atrial tachycardia) a gradual acceleration (warming up) and deceleration (cooling down) of the arrhythmia can be observed.

If the patient experiences *syncope*, especially in the presence of structural heart disease, a potentially dangerous condition must be assumed and hospitalization is required for evaluation (see Chapter 31). Caution: *epilepsy* can also be a secondary phenomenon caused by cardiac arrhythmia (asystole or ventricular fibrillation).

Clinical Examination

Central and Peripheral Pulse. In the arrhythmic patient counting the pulse (centrally with a stethoscope and peripherally) can provide useful information of hemodynamic relevance (e. g., pulse deficit) and about the synchronicity of atrial and ventricular contraction. If the atrium and ventricle are not synchronized, as during ventricular tachycardia, the first heart sound varies in intensity and character. The clinical examination can also uncover signs of underlying valvular cardiac disease, which can be directly relevant to the arrhythmia. A regular resting pulse with single pauses is a sign of extrasystoles leading to a compensatory pause, which are generally insignificant.

If an absolute pulse arrhythmia is present, together with a pulse deficit (i. e., a higher pulse at heart auscultation than at palpation of the radial artery), then the diagnosis of atrial fibrillation can be made even without the ECG.

The heart rate itself does not provide any information about the type of the arrhythmia and its criticality.

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Although ventricular tachycardias are often fast and can lead to syncope, particularly in patients with structural heart disease, they can also be slower and hemodynamically well tolerated over hours and days. In every case, however, they require urgent treatment and monitoring. Conversely, supraventricular tachycardias, especially in patients with a normal heart, are usually better tolerated and may be terminated by the patient with coughing, pressure, or carotid sinus massage.

Carotid Sinus Massage. Carotid sinus massage is an integral component of the physical examination and should always be performed with ECG monitoring. Gentle pressure on the carotid sinus, in the middle of the neck, provokes vagotonic stimulation, which slows impulse frequency from the sinus and AV node. This has diagnostic significance and is also a therapeutic maneuver, which can stop an arrythmia (e. g., during supraventricular tachycardia where the AV node is part of the reentrant circuit). Focal arrhythmias can be slowed (atrial tachycardia) or flutter waves unmasked by slowing conduction over the AV node.

Carotid sinus massage (Tab. 22.**1**) should also be performed in syncopal patients to detect bradycardia-induced AV block, a dangerous condition with a poor prognosis (warranting immediate pacemaker implantation; see Chapter 31).

Table 22.**1** Procedure for carotid sinus massage

- Auscultation on both carotids (a murmur or sign of stenosis is a contraindication for CSM)
- Gentle pressure on one side, the ipsilateral pulse of the temoral artery should be palpable
- Continuous ECG monitoring
- Duration of massage approximately 5 s
- Emergency treatment for hypotension, bradycardia, and cardiac arrest available

Electrocardiogram (ECG)

The systematic analysis of the ECG begins with the analysis of the frequency of atrial (P waves) and ventricular (QRS complex) excitations and their relation. Then the size, width, and axis of P waves and QRS complexes should be analyzed. The repolarization phase (ST and T segments) and the presence of U waves can provide important information on the origin of arrhythmias. The duration of the longest QT interval should also be measured and corrected for the heart rate, since this can also play a major role in arrhythmias. In addition to the diagnosis of arrhythmias, the ECG can give important information about previous myocardial infarction, ischemia, pulmonary or systemic hypertension, pericarditis, cardiomyopathy, and congenital anomalies.

Additional Tools for the Diagnosis of Arrhythmias

Stress ECG. A continuous ECG recording during physical exercise (treadmill, bicycle) can provoke stress-induced arrhythmias or provide important information about increased sinus node rates (chronotropic competence) and the conduction properties of accessory pathways (delta waves in Wolff-Parkinson-White [WPW] syndrome).

Holter ECG. Continuous ECG monitoring over 24 or 48 hours can diagnose intermittent (paroxysmal) arrhythmias, provided that the symptomatic arrhythmia actually appears again during this time. Checking the correlation between the ECG and the symptoms logged is also important. In addition, the Holter ECG can give information about the function of the sinus node, the heart rate variability, and detect pauses which can be important for the patient's prognosis.

Event Recorder. If the arrhythmia occurs rarely and is unlikely to be captured by a Holter ECG, then a longer recording using an event recorder is preferable. These recorders can either function as a continuous loop recorder or can be held over the heart in case of symptoms. If potentially dangerous arrhythmias must be detected (i. e., in case of syncope), a loop recorder can be implanted subcutaneously for several months. This can then record the ECG automatically above and below programmable pulse limits (i. e., below 40 beats/min and above 180 beats/min). In addition, patient-initiated recordings are also possible (e. g., a normal ECG during suspicious symptoms points to an extracardiac origin).

Electrophysiologic Investigation. The electrophysiologic study is an invasive procedure for diagnosis of unclear arrhythmias and patients with syncope. It is also employed therapeutically for radiofrequency ablation treatment of supraventricular and ventricular arrhythmias (i. e., thermal ablation of the responsible focus or reentrant circuit). However, documentation of the arrhythmia by the noninvasive methods described above should always be carried out beforehand to match induced arrhythmias with clinical ECG tracings.

Further Diagnostic Tools. A tilt table, which suddenly shifts the patient from a recumbent to an upright position, can provoke a neurocardiogenic syncope, which if correlated with the clinical symptoms, has diagnostic significance. However, unspecific findings are frequent. Further analysis of ECG intervals can noninvasively identify patient groups at increased risk for arrhythmias or sudden death (e. g., heart rate variability as a measure of autonomic innervation, signal-averaged ECG, T-wave alternans, etc.). Unfortunately, none of these tests has proved to be of sufficient sensitivity and specificity in unselected patients to justify routine clinical use.

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22.2 Bradyarrhythmias

Bradycardias are frequent and can be as low as 30 beats/min in healthy individuals during the night or in athletes, even during the day at rest. Treatment of bradycardia is indicated only in case of correlating symptoms.

Sinus Node Dysfunction

Particularly in elderly patients, the function of the sinus node can be impaired (sick sinus syndrome). This is usually expressed by the absence of heart rate increase as a response to physical exercise (chronotropic incompetence), sinus node pauses of over 3 seconds, or a marked increase in beat to beat variation (over 15% of cycle length). If an inappropriate sinus or atrial tachycardia is found in the same patient, then the diagnosis of a *brady–tachycardia syndrome* can be made.

The differentiation of the exact nature of the *sinus node dysfunction* (i. e., conduction block [*sinoatrial block*] versus absent impulse formation [*sinus arrest*]) is of little prognostic or therapeutic interest. More important is the correlation of symptoms with the ECG findings, because only the symptoms (e. g., syncope, exertional dyspnea, fainting) justify invasive therapies (e. g., pacemaker implantation).

A *secondary sinus node dysfunction* can result from hypothyroidism, drugs, electrolyte imbalances, sleep apnea syndrome, etc. (Tab. 22.**2**).

In about 20% of patients with sinus node dysfunction, concomitant AV node dysfunction can be observed, since the causes are similar (Tab. 22.**2**). A transient suppression of sinus node function can be observed after conversion of rapid atrial arrhythmias (e. g., atrial fibrillation or flutter [prolonged sinus node recovery time]).

Treatment of sinus node dysfunction is indicated only when corresponding symptoms are present.

Table 22.**2** Causes of bradyarrhythmias

- Drugs (beta-blockers, digoxin, calcium antagonists, antiarrhythmics, neuroleptics, sedatives, narcotics, etc.)
- Vagal tone (e. g., valsalva, carotid massage, athletes)
- Electrolyte imbalances (e. g., hyperkalemia)
- Coronary artery diseases (with involvement of AV conduction system)
- Myocarditis (e. g., rheumatic fever)
- Infectious endocarditis
- Other cardiac infections (borreliosis, tuberculosis, Chagas disease, toxoplasmosis)
- Systemic disorders (amyloidosis, sarcoidosis, hemochromatosis)
- Mechanical (cardiac surgery, trauma)
- Metastatic cancer
- Degenerative changes
- Congenital heart block
- Neuromuscular disease

Atrioventricular Block

Atrioventricular conduction block is classified according to three degrees. In first degree AV block conduction is slowed, but present for every heartbeat. In second degree AV block some P waves are conducted, whereas others are blocked. In third degree AV block all P waves are blocked.

First Degree AV Block

In first degree AV block the PQ interval is prolonged over 200 ms. Intermittent first degree AV block can be observed with increased vagal tone, in advanced age, and with drugs. If first degree AV block persists during sympathetic activation (exercise), then pathologic AV node function or a congenital anomaly must be suspected. First degree AV block, especially with coincident bundle branch block, can be a sign of severe conduction system disease below the AV node. If the PQ interval becomes very long (up to 300 ms) the atrial systole can occur during ventricular systole, against closed AV valves, leading to palpitations, fainting, and limited exercise tolerance.

Second Degree AV Block

In second degree AV block fewer QRS complexes than P waves are seen, but an association between the two is maintained. Depending upon the origin, and particularly for prognostic reasons, second degree AV block is classified into two types:

Type 1. In second degree AV block type 1 (*Wenckebach type*) there is a progressive prolongation of PQ intervals, until a single P wave block (Fig. 22.**1**). The diagnostic criterion is the shortened PQ interval after the blocked P wave. The progressive reduction of the RR intervals, which is known as Wenckebach periodicity, results from the slowed progression of the PQ prolongation. The place of origin is generally the AV node, which has a conduction delay due to increased vagal tone. Progression to a higher degree AV block is rare.

Second degree AV block type 1 (Wenckebach) is defined by a shorter PQ interval after the pause than before the pause. In half of the patients progressive PQ prolongation can also be observed, leading to Wenckebach periodicity of RR intervals. The prognosis is usually good.

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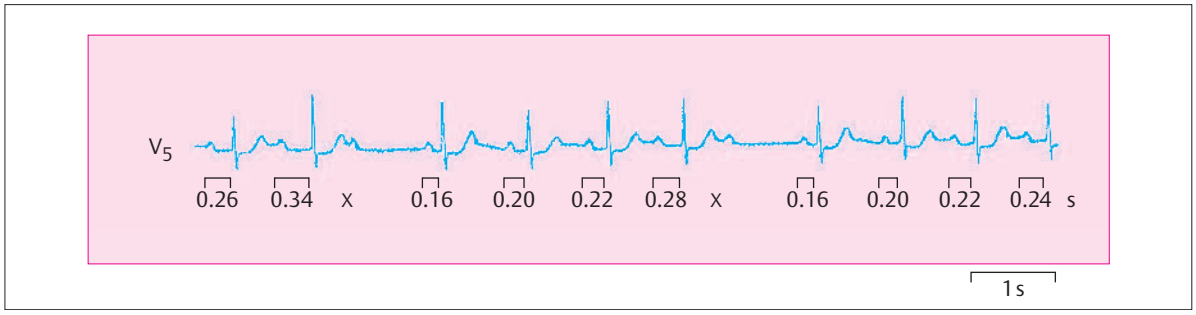

Fig. 22.**1** Second degree AV block type 1 (Wenkebach). Progressive PQ prolongation until AV block with subsequent shortening of PQ interval.

Type 2. In second degree AV block type 2 (Mobitz) P waves are blocked in a more or less fixed ratio (2:1, 3:1, or 4:1) *without prolongation* of the PQ interval and *without shortening* of the PQ interval after the pause. As the origin of type 2 Mobitz block is below the AV node, usually within the His–Purkinje system, progression to complete AV block is frequent. The PQ intervals are usually short because of increased sympathetic tone and show no variation at all.

Differentiation. In the case of second degree AV block with 2:1 conduction, a differential diagnosis of the two types can be difficult and usually becomes possible only when the beginning and end of the block, as well as further signs are taken into consideration. In Wenckebach type 1 nodal block there are frequently signs of increased vagal activity (sinus bradycardia), while in Mobitz type 2 infranodal block there is, on the contrary, increased sympathetic tone (sinus tachycardia).

Third Degree AV Block

Third degree AV block is defined by a lack of conduction between the atria and the ventricles. Fortunately, in most cases an escape rhythm below the AV node takes over. Otherwise, the patient develops syncope due to asystole (Adams–Stokes). Escape rhythms are usually regular and are narrow if they arise high in the His bundle, wider if they arise more distally in the Purkinje system. If they have typical left bundle branch block morphology, they arise from the right bundle and vice versa.

Caution: AV blocks are also associated with atrial flutter and atrial fibrillation. In the case of atrial flutter, a healthy AV node conducts the flutter waves in the ratio of 2:1, which results in a typical ventricular rate of around 130–150 beats/min. Slower rates at 3:1 or 4:1 conduction are usually the result of slowed AV node conduction, caused by drugs or propagation system disorders. If regular ventricular rhythm suddenly occurs, instead of absolute arrhythmia with atrial fibrillation, then a total AV block must be assumed.

> Regular ventricular rhythm in atrial fibrillation is a sign of total AV block with escape rhythm!

High grade AV block (intermittent third and second degree block) is most often idiopathic or caused by degeneration of the normal conduction system. Secondary causes should be investigated in line with the clinical findings (see Tab. 22.**2**).

Differential Diagnosis of Vagotonic (Functional) Versus Organic AV Block

Vagotonic AV Block. Typically in patients with a healthy heart, increased vagal tone can produce a bradycardia and even pauses of several seconds in the sinus node, as well as in the AV node. Since the vagal influence is intensified by the sympathetic nervous system, such bouts of syncope primarily occur during emotional excitement, pain, or intense heat. In the ECG the vagal influence can be detected (i. e., *simultaneous slowing of the sinus nodes and* AV blocking [first degree or second degree Wenckebach type 1]). This is the key to the diagnosis in the ECG (Fig. 22.**2**). After the pause, reflex tachycardias can appear. Classical symptoms are a protracted hypotension after the event, which leads to feeling unwell, pallor, sweating, and sickness. These episodes are distressing but not dangerous.

Organic AV Block. In contrast to organic AV block, the pauses induced by a pathologic state (i. e., a disease of the propagation system) are followed by a strongly increased sympathetic tone. For instance, organic AV block due to hypotension leads to *stimulation of the sympathetic system* and a *simultaneous sinus tachycardia* (reduction of the PP interval during the AV block; Fig. 22.**3**). After termination of the AV block, the patients have high to normal blood pressure and feel well (Tab. 22.**3**).

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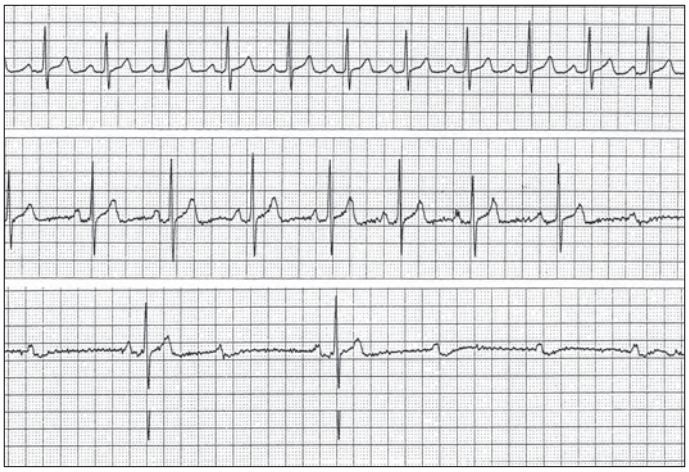

Fig. 22.**2** Vagotonic AV block during venous puncture, with syncope. Initially, there is sinus tachycardia (emotional stress), which slows down (vagotonic due to pain from puncture) and is followed by third degree AV block. The sinus rate during AV block is slower than before the block.

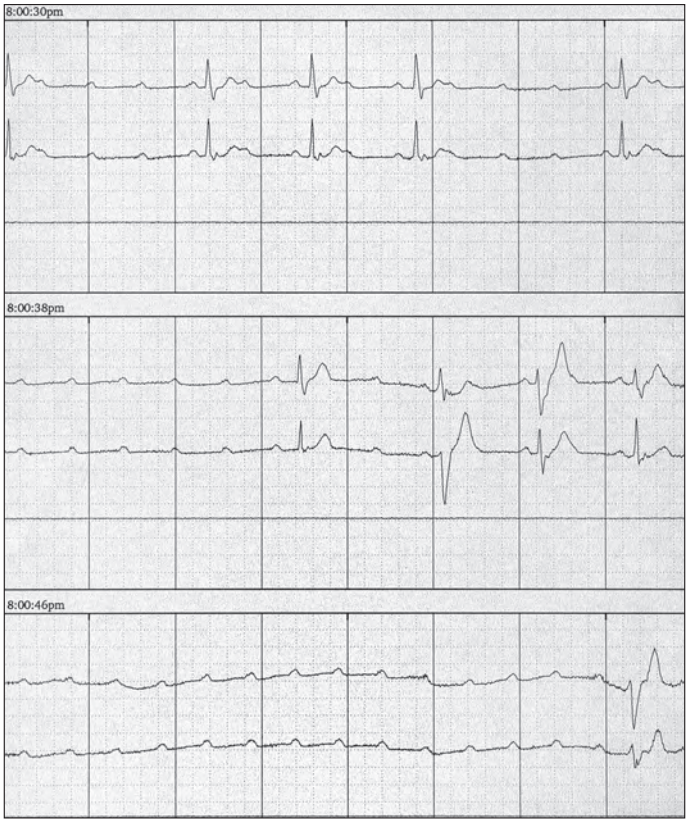

Fig. 22.**3** Organic AV block. Initially, 2:1 and 4:1 followed by third degree AV block. A vagotonic block can be excluded because of the high sinus rate (150 beats/min) during the block.

Table 22.**3** Differential diagnosis of functional (vagotonic) versus organic AV Block

	Vagotonic AV block	Organic AV block
Location of block	AV node	His–Purkinje system
Most frequent etiology	Vagotonic	Organic (ischemia, degenerative)
Prognosis	Good	Worse (progression frequent)
Sinus rate during block	Lower	Higher than before/after
Conduction at increased heart rate	Better	Worse
Conduction during carotid massage	Worse	Better
Retrograde conduction (VA)	Never	May be present
Variation of PQ intervals	If > 100 ms	If < 50 ms

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Bradyarrhythmias with Acute Myocardial Infarction

Bradyarrhythmias (sinus bradycardia up to third degree AV block) can be provoked by vagotonia after morphine administration or pain, and are common during reperfusion, especially in inferior infarctions. Rarely, acute ischemia is responsible for sinus node dysfunction. In this event a very proximal occlusion of the right or circumflex coronary artery is present. The first branches of the left anterior descending (LAD) coronary artery supply the His bundle and the right and left Tawara bundle. Therefore, a *newly acquired bundle branch block* (suggested by a septal Q wave) indicates a very proximal LAD occlusion with high risk of progression to complete AV block.

22.3 Junctional Rhythms

The AV junction can serve as a secondary pacemaker in case of sinus arrest or can generate accelerated junctional rhythms faster than the sinus rate. The latter is mostly due to abnormal impulse formation (Digoxin, excessive catecholamines, fibrinolysis and reperfusion, cardiac surgery). Retrograde P waves are grounds to assume a junctional rhythm. A gradual deceleration is observed after carotid sinus massage and an acceleration is possible (Fig. 22.**4**). Accelerated junctional rhythms may also be observed, particularly in adolescents. However, the diagnosis can be confirmed only by electrophysiologic studies. Retrograde P waves are typically narrow and negative in inferior leads (II, III, aVF).

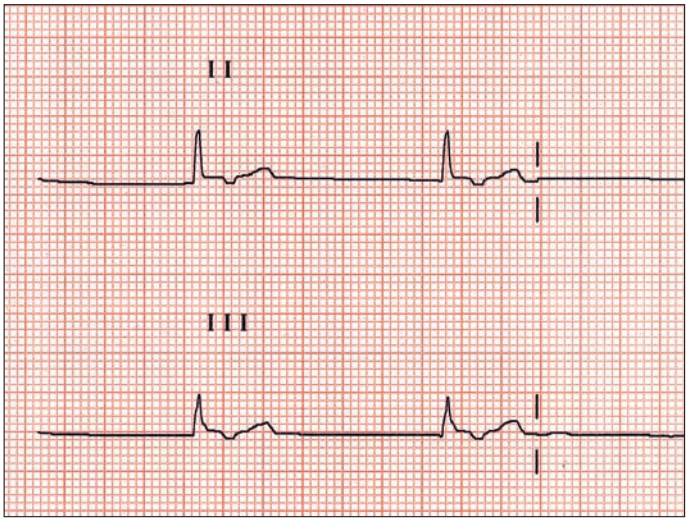

Fig. 22.**4** Junctional rhythm with retrograde P waves (negative, narrow P waves indicate atrial activation from the lower septum).

22.4 Extrasystoles

Extrasystoles are single beats caused by abnormal impulse generation anywhere in the heart (atria, ventricles, conduction system). Extrasystoles are frequently observed in healthy hearts. They can occur as single beats, alternating with one normal sinus beat (bigeminus) or two sinus beats (trigeminus) or can occur in series of two (couplet) or three (triplet) beats. More than three ventricular extrasystoles in a row define nonsustained ventricular tachycardia. In most patients extrasystoles are asymptomatic. However rarely, they can evoke disturbing symptoms such as palpitations, panic attacks, dyspnea, or hyperventilation.

Supraventricular Extrasystoles

Supraventricular extrasystoles originate in the atrium, in the atrial myocardium, or in the AV node. They manifest as an early P wave, which has a morphology corresponding to the origin of the focus (negative if lower atrial focus, biphasic if left atrial, etc.). The QRS complex can be normal or widened because of aberrancy. Frequently, the conduction of the supraventricular extrasystoles is blocked, so that a pause occurs, which is further extended by the subsequent sinus

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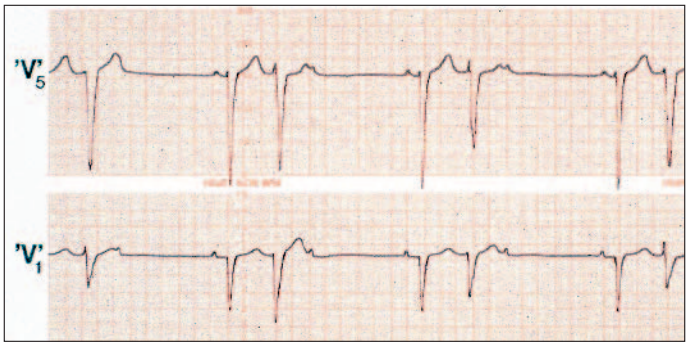

Fig. 22.**5** Supraventricular extrasystoles with physiologic block.

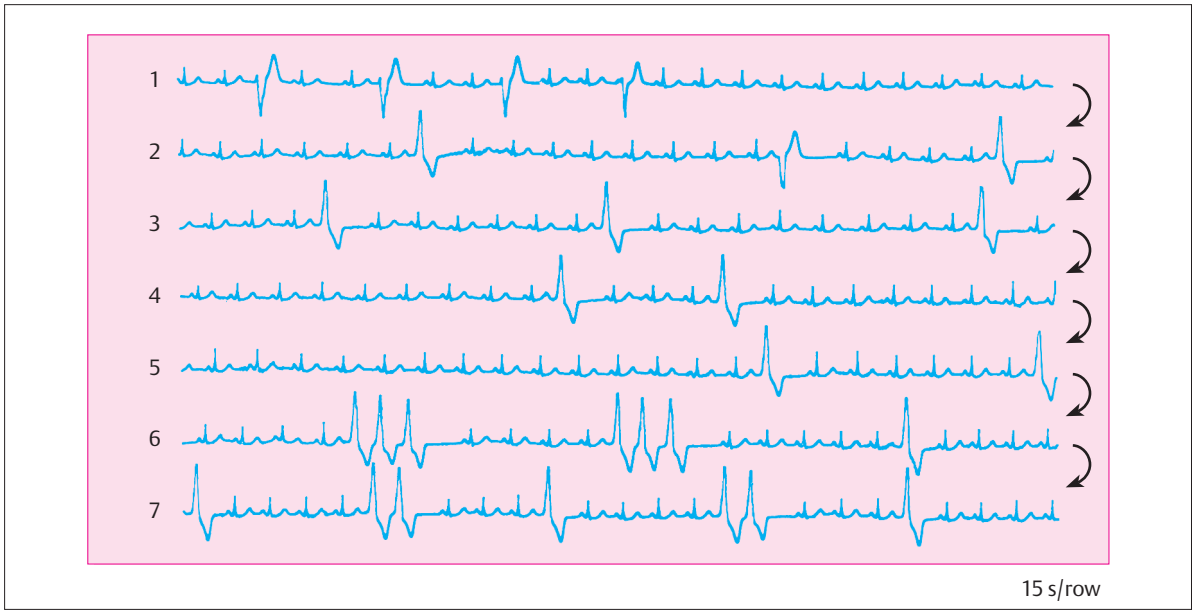

Fig. 22.**6** Ventricular extrasystoles in a Holter ECG (lead V_5). Isolated monomorphic ventricular extrasystoles in rows 1–7; couplets in row 7 and triplets in row 6.

pause (Fig. 22.**5**). Supraventricular extrasystoles have no prognostic significance but can induce sustained arrhythmias.

The most frequent cause of pauses is supraventricular extrasystoles with physiologic block. The symptoms are caused by the pause rather than the extrasystole.

Ventricular Extrasystoles

Ventricular extrasystoles can be differentiated from supraventricular extrasystoles by the following (Fig. 22.**6**):

- no preceding P wave (no constant PQ interval)
- different QRS morphology, width, and axis
- altered repolarization (T wave opposite to QRS vector)
- compensatory pause.

Single ventricular extrasystoles have no proven prognostic value, especially in the absence of structural heart disease. More than three consecutive ventricular extrasystoles are considered to be ventricular tachycardia, which represents a risk factor in patients with coronary heart disease or hypertrophic cardiomyopathy.

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22.5 Tachyarrhythmias

Tachyarrhythmias are classified as *supraventricular* or *ventricular*, depending on the origin of the arrhythmia (Tab. 22.**4**). The symptoms in all tachyarrhythmias are similar (e. g., light-headedness, palpitation, presyncope, and syncope). If a tachyarrhythmia is hemodynamically stable, it is usually supraventricular, but ventricular tachyarrhythmias may also present without hemodynamic compromise. Termination of a tachyarrhythmia with vagal maneuvers (such as drinking cold water, carotid sinus massage, Valsalva maneuver) suggests involvement of the AV node in the tachycardia (AV nodal reentrant tachycardia, AV reentrant tachycardia).

The medical history is particularly useful for the differentiation of supraventricular and ventricular tachyarrhythmias. History of myocardial infarction increases the likelihood of a ventricular tachycardia. The Q waves may also be visible during the tachycardia. On the other hand, if a patient has a very long history of palpitations, the tachycardia is most likely of supraventricular origin.

In daily practice, an initial differentiation is based on the duration of the QRS complex during the tachycardia.

Table 22.**4** Clinical differentiation of tachycardias

	Paroxysmal supraventricular tachycardia	**Ventricular tachycardia (VT)**
Symptoms	Palpitations Diaphoresis Nausea Sweating Dyspnea Diuresis Rarely syncope	Palpitations Diaphoresis Nausea Sweating Dyspnea – Syncope common
Structural heart disease	Rare	Common
Hereditary causes	Very rare	Occasional
Adenosine and vagal stimulation	Termination common	Termination seldom
QRS vector	Similar to that seen in sinus rhythm	Different from sinus rhythm
Q waves during tachycardia	Narrow	often > 140 ms
QRS width	Sometimes aberrant	Very rarely narrow (septal VT)
Fusion beats	never	If present, diagnostic
AV synchrony	almost always	facultative

Narrow-Complex Tachycardia

In narrow-complex tachycardia the QRS width is, by definition, less than 120 ms and these arrhythmias are, with rare exceptions, almost always of supraventricular origin (Fig. 22.**7**).

Sinus Tachycardia

In sinus tachycardia the morphology and axis of the P wave are similar to that observed during sinus rhythm. The rhythm typically speeds up and slows down gradually. Sinus tachycardia is a common finding and is typically *secondary* to other causes, such as heart failure, pain, pulmonary emboli, as well as central nervous system and other disturbances, which are associated with increased adrenergic stimulation. In addition, some *drugs* (e. g., antihypertensives) or withdrawal of some drugs (e. g., beta-blockers) may cause sinus tachycardia. Rarely, the sinus node may show a hypersensitive response to endogenous catecholamines, causing inappropriate sinus tachycardia. This is a diagnosis of exclusion when other possible causes for sinus tachycardia are eliminated and when the sinus node reacts very rapidly after minimal exercise (e. g., pulse > 150 beats/min after 10 knee bends).

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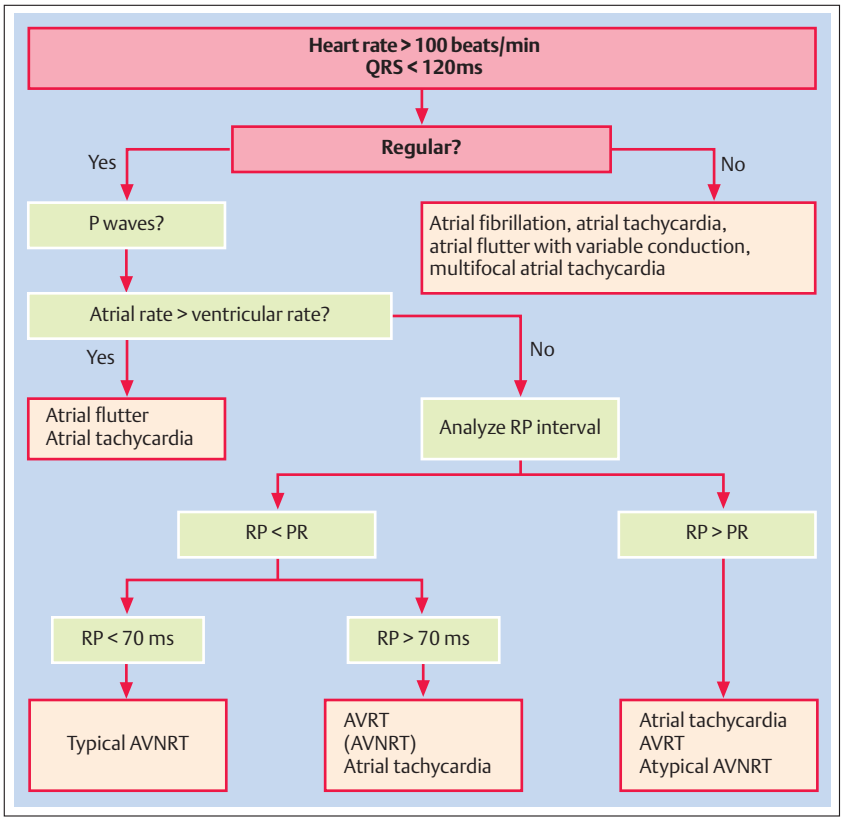

Fig. 22.**7** Differential diagnosis of narrow complex tachycardia. HR: heart rate, RP: Interval between R peak to P waves during the tachycardia, AVNRT: AV nodal reentrant tachycardia, AVRT: AV reentrant tachycardia.

Atrial Tachycardia

In atrial tachycardia the atrial rate is usually 150–250 beats/min and the P wave morphology is different from that observed during sinus rhythm (Fig. 22.**8**). The ECG derivation with a negative initial P wave suggests the origin of the tachycardia (V_1 right atrium; aVL left atrium). Atrial tachycardia may show some irregularity and patients with this arrhythmia usually have atrial ectopic beats originating from the same focus with similar P-wave morphology.

Atrial tachycardia may be a sustained arrhythmia and may have a single or multiple origins. In the latter case, the so-called *multifocal atrial tachycardia*, there are often secondary causes, and the atria are often dilated due to pressure or volume overload of the atria, hypertension, or hyperthyroidism. Atrial tachycardia can also arise from the pulmonary veins and may trigger atrial fibrillation. In this case, short bursts of fast, irregular beats arising from the pulmonary veins are commonly observed.

Atrial Flutter

The atrial rate during atrial flutter is usually 220–350 beats/min, and the atrial rhythm is more or less regular. The mechanism of atrial flutter is always an *abnormal pulse propagation* (macroreentry), which in 80 % of cases involves the entire right atrium. The flutter waves typically have a saw-tooth appearance and since some parts of the atria are constantly electrically active, there is no isoelectric line in between these waves, as opposed to the flat isoelectric line observed in atrial tachycardia. In the most common form of atrial flutter, the flutter waves are negative in inferior derivations (II, III, aVF) suggesting a caudo–cranial (counterclockwise) activation pattern along the atrial septum (Fig. 22.**9**). In patients who have surgical scars in the atria, the reentry may occur around these scars and different flutter wave patterns may arise.

AV Conduction. The conduction over the AV node to the ventricles is usually 2:1. Therefore, the typical pulse during atrial flutter is usually 130–150 beats/min. Under catecholaminergic influence or in patients receiving class I antiarrhythmic therapy (e. g., flecainide), the tachycardia may show 1:1 conduction, usually with wide complexes due to rate-dependent aberration, and become life-threatening due to its rapid rate. Conversely, the AV conduction may slow down (e. g., 3:1 or 4:1) with carotid massage or by application of various

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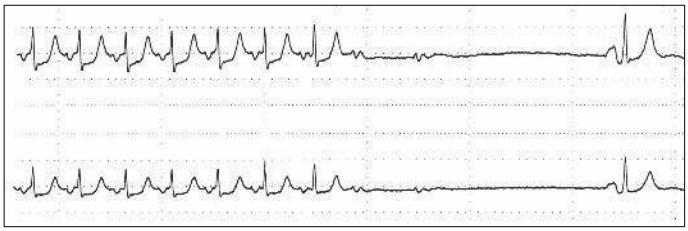

Fig. 22.**8** Atrial tachycardia. The ectopic atrial tachycardia has a different P wave morphology from that of the sinus beat. Adenosine can terminate focally-induced atrial tachycardias. In this example, adenosine terminates the tachycardia shortly after causing AV block. Note the two P waves without conduction to the ventricles prior to termination of this tachycardia.

Fig. 22.**9** Typical atrial flutter. The negative flutter waves in inferior derivations (II, II, aVF) suggest a counterclockwise activation within the right atrium.

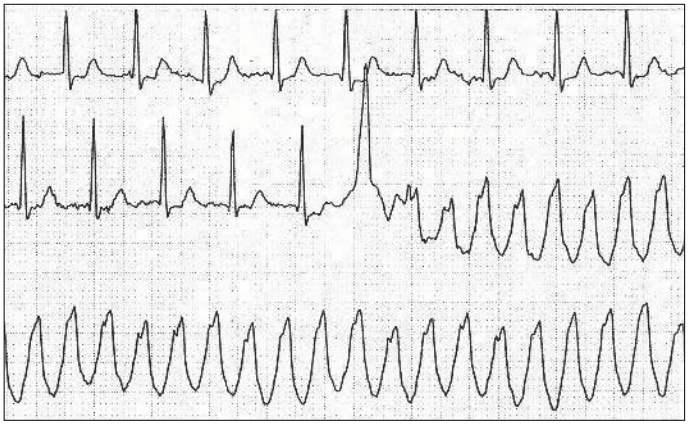

Fig. 22.**10** Atrial flutter with 2:1 conduction converting into 1:1 conduction with aberration. The initial tachycardia is regular at a rate of 150 beats/min and has a narrow complex. The second tachycardia is exactly twice as fast as the initial tachycardia, which is unlikely to occur by chance. If the initial tachycardia were not documented, it would be difficult to differentiate atrial flutter from ventricular tachycardia in this patient.

drugs resulting in the unmasking of the flutter waves (Fig. 22.**10**). The ventricular rate during atrial flutter has a certain regularity, differentiating it from atrial fibrillation, which has a totally irregular rhythm. Atrial flutter is responsive to curative therapy with radiofrequency catheter ablation in which the macroreentry is interrupted at a narrow electrical isthmus.

Atrial Fibrillation

Atrial fibrillation is one of the *most common arrhythmias*, affecting 7 % of the population at age 60 or older (Fig. 22.**11**). In contrast to atrial flutter, the ventricular rate during atrial fibrillation is absolutely irregular due to the chaotic fibrillatory activity in the atria at very high rates (> 300 beats/min). However, the arrhythmia may become somewhat regular at rapid ventricular rates. Every absolutely irregular rhythm is considered atrial fibrillation until proven otherwise, even in the absence of identifiable P waves and even with wide QRS

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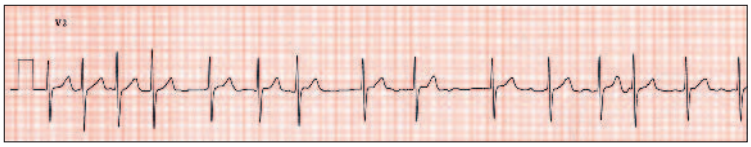

Fig. 22.**11** Atrial fibrillation. Note the absolutely irregular rhythm and the lack of P waves.

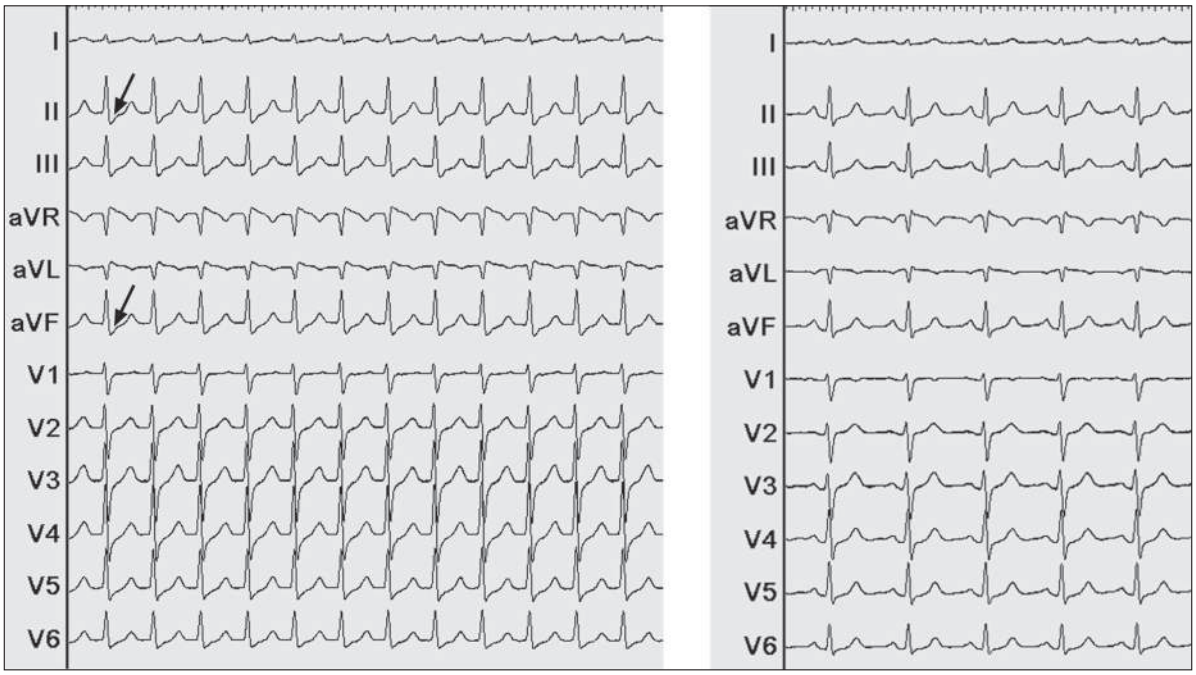

Fig. 22.**12 a** AV nodal reentrant tachycardia. Note the narrow P waves that are negative in inferior (II, III, aVF) derivations (arrows). **b** In comparison, sinus rhythm ECG of the same patient.

Table 22.**5** Causes of atrial fibrillation

- Pulmonary vein tachycardia
- Hypertensive heart disease
- Heart failure
- Ischemic heart disease
- Sick sinus syndrome
- Cardiomyopathies
- Rheumatic valve disease
- Hyperthyroidism
- Myocarditis, pericarditis
- Preexcitation syndrome (WPW syndrome)
- Alcohol, caffeine
- Postcardiac surgery
- Pulmonary diseases

complexes. Conversely, a very regular tachycardia rules out the diagnosis of atrial fibrillation (DD: atrial flutter, junctional rhythm).

Atrial fibrillation is classified as being *paroxysmal* (self-terminating), *persistent* (sustained atrial fibrillation that can only be returned to sinus rhythm by cardioversion), or *permanent* (sustained atrial fibrillation that is either resistant to, or not appropriate for cardioversion). The causes of paroxysmal atrial fibrillation are listed in Tab. 22.**5**. Commonly, atrial fibrillation, atrial flutter, and atrial tachycardias occur in the same patient and can induce one another.

AV Nodal Reentrant Tachycardia

AV nodal reentrant tachycardia is the most common regular, paroxysmal, supraventricular tachycardia, which represents approximately 60% of cases. The mechanism is reentry that occurs in the region of the AV node using the so-called slow pathway, a second structure that is considered to be physiologic in many individuals and conducts at a lower rate as compared to the fast pathway. Typically, the tachycardia causes simultaneous contraction of the atria and the ventricles. Since the atrial contraction occurs as the atrioventricular valves are closed, patients commonly feel pulsation in the neck veins during the tachycardia and commonly report increased diuresis following the arrhythmia.

In the ECG, *retrograde P waves* may be identified within or shortly after the QRS complex. In the V_1 lead this pattern may mimic the presence of an incomplete right bundle branch block. Therefore, it is important to compare the QRS complexes during the tachycardia with those obtained during sinus rhythm (Fig. 22.**12**).

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The P waves during the tachycardia are usually small and negative in inferior derivations due to the simultaneous activation of both atria from the region of the AV node.

In the less commonly observed atypical form of AV nodal reentrant tachycardia, the reentry occurs in the opposite direction and the P waves can be readily identified with RP intervals longer than the PR interval. Some patients with AV nodal reentrant tachycardia may have PQ intervals less than 120 ms in sinus rhythm.

AV nodal reentrant tachycardia is catecholamine-dependent and can typically be terminated with vagal maneuvers (Valsalva, carotid massage) or adenosine injection.

AV Reentrant Tachycardia with Antegrade Conduction over the AV Node

Patients with AV reentrant tachycardia have, in addition to the AV node, an *accessory electrical conduction* between the atria and the ventricles. These accessory pathways may be found in the left or right atrioventricular groove or may even be multiple in the same patient. Approximately 60% of these connections only have the ability for retrograde conduction (from the ventricles to the atria). The conduction is bi-directional in 30% and only antegrade in 10%. In WPW syndrome, there is antegrade conduction over the accessory pathway during sinus rhythm, which results in preexcited QRS complexes (delta waves).

Physiologically, an AV reentrant tachycardia using the AV node as the antegrade pathway and the accessory bundle as the retrograde pathway is far more common (Fig. 22.**13**). These tachycardias have a normal QRS morphology and the P wave is found at least 60 ms after the QRS complex. Occasionally, electrical alternans occurs with varying amplitude, but constant width of the QRS complexes.

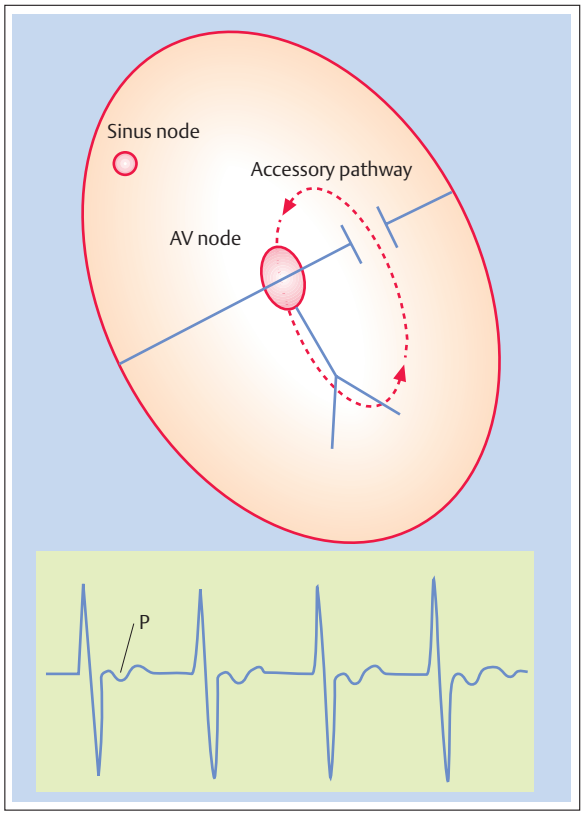

Fig. 22.**13** AV reentrant tachycardia with antegrade conduction over the AV node.

Wide-Complex Tachycardia

Differential Diagnosis of Wide-Complex Tachycardias

In 80% of wide-complex tachycardias the diagnosis is ventricular tachycardia. The remaining 20% are due to supraventricular tachycardia with aberration, pre-existing bundle branch block, or preexcitation (WPW syndrome). The differential diagnosis of a wide-complex tachycardia is extremely important. Depending on the diagnosis, the therapy and prognosis are very different. A structured approach is advisable for the differentiation of wide-complex tachycardias:

Medical History. In *postmyocardial infarction* patients, ventricular tachycardia is more likely to occur than other arrhythmias. Pathologic Q waves can be recognized even during the tachycardia on derivations corresponding to the scar left by a transmural myocardial infarction. A previous ECG can be very useful for identifying delta waves and possibly preexisting intraventricular conduction disturbances, bundle branch block, etc.

Ratio of Atrial and Ventricular Beats. It is important to carefully study the ratio of P waves to QRS complexes on tachycardia ECGs. Approximately one-third of ventricular tachycardias exhibit retrograde conduction over the AV node, producing regular associated P waves with a 1:1 AV relationship. Conversely, demonstration of AV dissociation (independent rhythm in the ventricles and the atria) is considered to be diagnostic for ventricular tachycardia. *Carotid sinus massage* may provide diagnostic information by slowing or interrupting the retrograde conduction over the AV node, thus demonstrating dissociation of the atrial and ventricular excitation. Intermittent occurrence of fusion or capture beats due to antegrade conduction over the AV node is also diagnostic of ventricular tachycardia.

Ventricular Activation Axis. The *axis of ventricular activation* helps to identify the origin of the arrhythmia. For

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example, an axis between 180° and 270° suggests that the arrhythmia originates from the apical portion of the ventricles and it is practically impossible for this so-called indeterminate axis to occur in supraventricular rhythms with aberration.

QRS Duration. In the interpretation of the *QRS width*, a number of basic considerations are important in the context of the medical history. The more diseased a ventricle and its pulse propagation system, the broader and more fractioned will be the QRS complex in sinus rhythm, particularly at increased frequencies. This means that a rise in the heart rate (sinus tachycardia or atrial tachycardia) in a diseased heart causes widening of the QRS complex (aberration) and conversely, that a ventricular tachycardia in an otherwise healthy heart (idiopathic ventricular tachycardia) can have a relatively narrow QRS complex (up to 110 ms). In addition, QRS widening can appear physiologically with irregular beat sequences (long–short) or after extrasystoles, and can then be propagated through retrograde invasion of the conduction system, thus mimicking a wide-complex tachycardia.

As a rule of thumb, very wide QRS complexes (> 140 ms with a right bundle branch block pattern; > 160 ms with a left bundle branch block pattern) are markers of ventricular tachycardia. On the other hand, ventricular tachycardia with a narrow QRS complex (even narrower than that during sinus rhythm) may occur due to the arrhythmia originating from the ventricular septum.

Additional Diagnostic Tips. An absolutely arrhythmic wide-complex tachycardia is suggestive of atrial fibrillation with aberration or with accessory pathway conduction (WPW syndrome). The morphologic criteria for the differential diagnosis of ventricular versus supraventricular tachycardias are listed in Tab. 22.**4**.

If an arrhythmia cannot be readily classified as being supraventricular or ventricular, it is advisable to consider it a ventricular tachycardia and manage accordingly, including acute measures such as electrical cardioversion.

AV Reentrant Tachycardia with Antegrade Conduction over the Accessory Pathway

This tachycardia with antegrade conduction over the accessory pathway occurs in patients with *WPW syndrome*. The conduction sequence is exactly the opposite of the sequence shown in Fig. 22.**13**. In other words, conduction is antegrade over the accessory pathway and retrograde over the AV node. For this reason, maximal preexcitation is observed since the activation of the whole ventricle occurs solely over the accessory pathway. QRS complexes are very wide since the origin of the accessory activation is epicardial and morphologically this arrhythmia may electrically mimic a ventricular tachycardia originating from the area of initial activation.

These arrhythmias may demonstrate cycle length variability if there are multiple accessory pathways. Termination is sometimes possible by carotid sinus massage or vagal maneuvers, which block the retrograde conduction over the AV node.

In the *differential diagnosis*, atrial flutter or other supraventricular tachycardias with accessory pathway conduction but without macroreentry must be considered. If adenosine is considered for diagnostic or therapeutic purposes, it is important to have an external defibrillator available since this drug may cause atrial fibrillation and if the accessory pathway has very short refractory periods, then the rapid fibrillatory activity may conduct to the ventricles and cause ventricular fibrillation. As mentioned previously, electrical cardioversion is considered the safest and most efficacious way of terminating a wide-complex tachycardia.

Table 22.**6** Criteria for diagnosis of ventricular tachycardia

- Ventriculoatrial dissociation
- Fusion beats
- QRS width > 140 ms (> 160 ms in left bundle branch block pattern)
- QRS axis: northwest axis (180°–270°)
- Absence of an RS complex in V_1 and V_6
- RS interval < 100 ms in precordial derivations
- Morphology criteria:
  - right bundle pattern: monophasic or biphasic QRS complex in V_1
    - if V_1 triphasic, R >R'
    - R/S ratio < 1 in V_6
  - left bundle pattern: wide R in V_1 with notching of the S wave
    - small Q wave with a large R or QS complex in V_6

Monomorphic Ventricular Tachycardia

Monomorphic ventricular tachycardias have a constant rate and morphology and occur due to abnormal impulse conduction (reentrant) in the area of an anatomic substrate (e.g., infarction scar; Fig. 22.**14**). These are *potentially life-threatening arrhythmias*, particularly in patients with a structural heart disease.

Ventricular tachycardia in coronary heart disease patients usually shows Q waves in the region of the scar. The vector of the tachycardia should therefore correspond to the region of the infarct. A negative concordance (negative QRS complexes in leads V_1–V_6) is diagnostic for ventricular tachycardia originating from an apical infarct scar. The activation of the left ventricle, which does not proceed over the normal pulse propagation system, characteristically shows a conduction delay during the tachycardia (R wave to maximum S over

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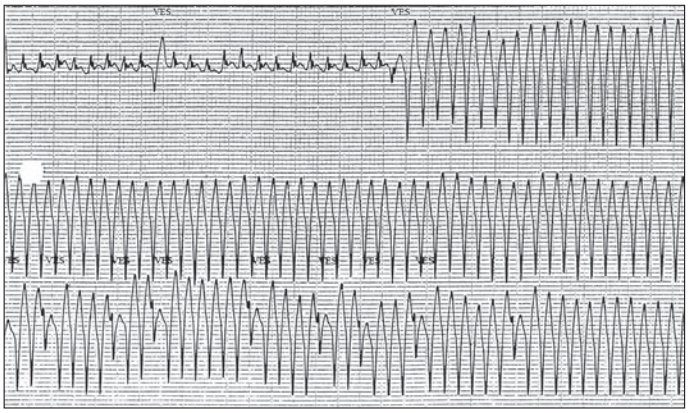

Fig. 22.**14** Ventricular tachycardia with fusion beats. Initial rhythm is sinus rhythm with bundle branch block morphology, which later degenerates during physical exercise into monomorphic ventricular tachycardia. During early recovery, occasional beats have a different morphology due to fusion with antegrade conduction over the AV node. These fusion beats are diagnostic of ventricular tacyhcardia.

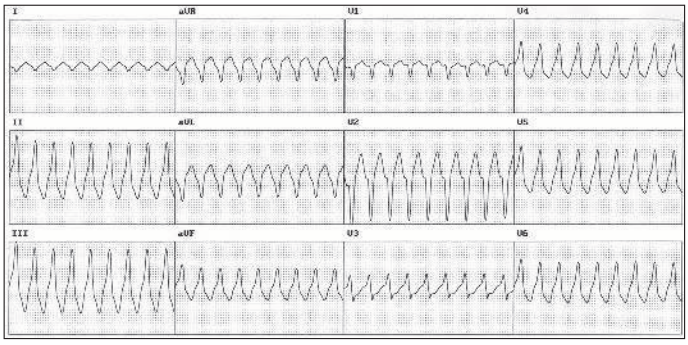

Fig. 22.**15** Idiopathic ventricular tachycardia; the patient has a structurally normal heart and the arrhythmia is not life-threatening. The positive axis in II, III, and aVF and the negative axis in V_1 suggest that the tachycardia originates from the outflow tract of the right ventricle.

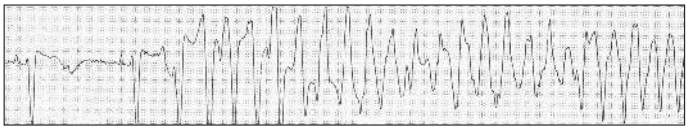

Fig. 22.**16** Polymorphic ventricular tachycardia (torsade de pointes) in a patient with long QT intervals. The long R–R interval (1500 ms) due to second degree AV block shows a long QT interval (800 ms, QTc: 530 ms). A ventricular ectopic beat in the vulnerable phase of the T wave initiates the torsade de pointes.

100 ms). The criteria for the diagnosis of ventricular tachycardia are summarized in Tab. 22.**6**.

In patients with ventricular tachycardia and hemodynamic compromise, electrical cardioversion can be acutely necessary, even without a definitive differential diagnosis. Since ventricular tachycardia commonly occurs due to reentry around anatomic substrates (e. g., old infarction scars), the possibility of residual tachyarrhythmias must be discussed with the patient after termination of the acute arrhythmic event.

Idiopathic ventricular tachycardias occur in patients with normal hearts. These arrhythmias are usually monomorphic and arise from anatomically defined foci (e. g., from the right ventricular outflow tract [left bundle branch block pattern with inferior axis; Fig. 22.**15**] or from the posterior fascicle of the left ventricle [right bundle branch block pattern and superior axis]). The rate of these tachycardias is partially associated with physical exertion and vagal tone and may vary depending on autonomic influences.

Polymorphic Ventricular Tachycardia and Torsade de Pointes

Polymorphic ventricular tachycardias have constantly varying morphology and intervals and occur usually as a result of ischemia (Fig. 22.**16**). If the QRS vector turns (torsade) about a point (pointes) and if a long QT interval is present, the arrhythmia is, by definition, a *torsade de pointes*. This arrhythmia usually begins with a short interval following a long pause (*long–short pattern*) due to dispersion of refraction times in the ventricles.

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Fig. 22.**17** Artifact mimicking a tachycardia. Correct diagnosis can be made by identification of QRS complexes at regular intervals.

Ventricular Fibrillation and Sudden Cardiac Death

Ventricular fibrillation can be diagnosed if no distinct QRS complexes can be identified. Immediate defibrillation is essential since the heart is not able to pump due to fibrillatory electrical activity. Ventricular fibrillation can be preceded by ventricular tachycardia, but it can also manifest spontaneously in the context of the diseases listed in Tab. 22.**7**.

Table 22.**7** Arrhythmias responsible for sudden cardiac death

Ventricular tachyarrhythmias (80 %):
– coronary artery disease
– cardiomyopathy (hypertrophic cardiomyopathy, obstructive or nonobstructive cardiomyopathy, dilative cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, congenital heart diseases)
– ion channel anomalies in structurally normal hearts (long QT syndrome, Brugada syndrome)
– acquired QT prolongation (drugs, bradycardia)
– idiopathic ventricular fibrillation
Bradyarrhythmias—AV block without intrinsic rhythm (20 %)

Pacemaker-Mediated Tachycardia

In patients with implanted dual-chamber (atrioventricular synchronous) pacemaker systems, a *pacemaker-mediated tachycardia* may occur, which typically shows paced QRS complexes at or near the maximal tracking rate of the device. This occurs in patients with ventricular ectopic beats with retrograde conduction to the atria, which are then sensed by the atrial lead and then conducted to the ventricular lead for pacing. Diagnostically, termination by application of a magnet (which temporarily sets the pacemaker to the lower magnet frequency) is possible, without a relapse when the magnet is removed. In the *differential diagnosis*, an atrial fibrillation with maximum conduction through the pacemaker must be considered. In this case, the tachycardia returns after the magnet is removed.

ECG Artifact Mimicking Tachyarrhythmias

Occasionally, ECG artifacts may mimic tachyarrhythmias. Small identifiable notches on the ECG occurring at regular intervals and coinciding with pulse activity are used for differentiation from real tachyarrhythmias (Fig. 22.**17**).

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23 Systemic Arterial Hypertension

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23

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Systemic arterial hypertension accounts for one of the most common diagnoses in primary care facilities and represents an important risk factor for the development of cardiovascular disease. Therefore, blood pressure measurement should be performed regularly in all patients, regardless of the current patient problem. In case of an elevated blood pressure level, the following interventions are recommended:

- confirmation of the diagnosis hypertension by repetitive blood pressure measurements
- exclusion of secondary forms of hypertension
- decision to initiate antihypertensive therapy based on evaluation of the overall cardiovascular risk and assessment of other risk factors
- introduction, monitoring, and modification of antihypertensive therapy.

Definition and Classification of Hypertension

The definition and classification of hypertension, according to the World Health Organization and the International Society of Hypertension, are described in Tab. 23.**1**. Both normotension (optimal, normal, high–normal) and hypertension (mild, moderate, severe) were classified separately because of a direct correlation of cardiovascular risk with the entire range of blood pressure values. The upper limits of normotension are a systolic pressure of 139 mmHg and a diastolic pressure of 89 mmHg. Isolated systolic hypertension is common among the elderly.

If systolic and diastolic blood pressure values are increased to various degrees, the value with the highest degree of hypertension should be considered. Many years ago it was thought that diastolic blood pressure value was more important. Recent surveys, however, have shown that both the systolic and diastolic values are of prognostic importance. Therefore, both values must be considered in the classification of hypertension. In the elderly, the difference between systolic and diastolic blood pressure values is associated with cardiovascular events. However, it remains unclear whether this parameter is an independent predictor of clinical events.

The classification of hypertension is based on blood pressure measurements obtained from upper arm cuff devices rather than wrist cuff devices. The upper blood pressure limits are lower during ambulatory (24-hour) blood pressure monitoring. However, normal ranges for ambulatory blood pressure monitoring have not yet been validated. Nevertheless, both methods are well accepted among primary health care providers. The latter method is especially useful to exclude "white coat" hypertension, i. e., the presence of elevated blood pressure levels at medical institutions, but normal blood pressure levels during self-measurements.

Table 23.**1** Definition and classification of hypertension according to the World Health Organization (values in mmHg)

Category	Systolic	Diastolic
Normotension		
– optimal	< 120	< 80
– normal	120–129	80–84
– high–normal	130–139	85–89
Hypertension		
– grade 1 (mild)	140–159	90–99
– grade 2 (moderate)	160–179	100–109
– grade 3 (severe)	≥ 180	≥ 110
– isolated systolic hypertension	≥ 140	< 90

23.1 Diagnostic Management of Hypertension

For patients with confirmed elevated blood pressure levels, either by repetitive measurements at primary care facilities or during ambulatory blood pressure monitoring, a primary analysis that includes recognition of secondary forms of hypertension and risk assessment is recommended. Risk assessment is essential for evaluation of indication for treatment and treatment goals. Findings from the medical history, clinical examination, and laboratory tests serve for both evaluation of secondary forms of hypertension and for risk assessment (Fig. 23.**1**).

Evaluation of Secondary Hypertension

The rate of secondary forms of hypertension ranges between 4 and 8% in different patient populations (primary care, secondary care clinics, or specialized cardiovascular centers) (Tab. 23.**2**). It would be considerably higher if patients with sleep apnea syndrome were included. The majority of secondary hypertension cases are due to chronic renal disease, and therapy often includes antihypertensive medications. Only 1–2% of secondary hypertension cases can be cured by treatment of the underlying disease. Therefore, the effort of extensive, diagnostic evaluation should be weighed against the treatment options of the various forms of secondary hypertension.

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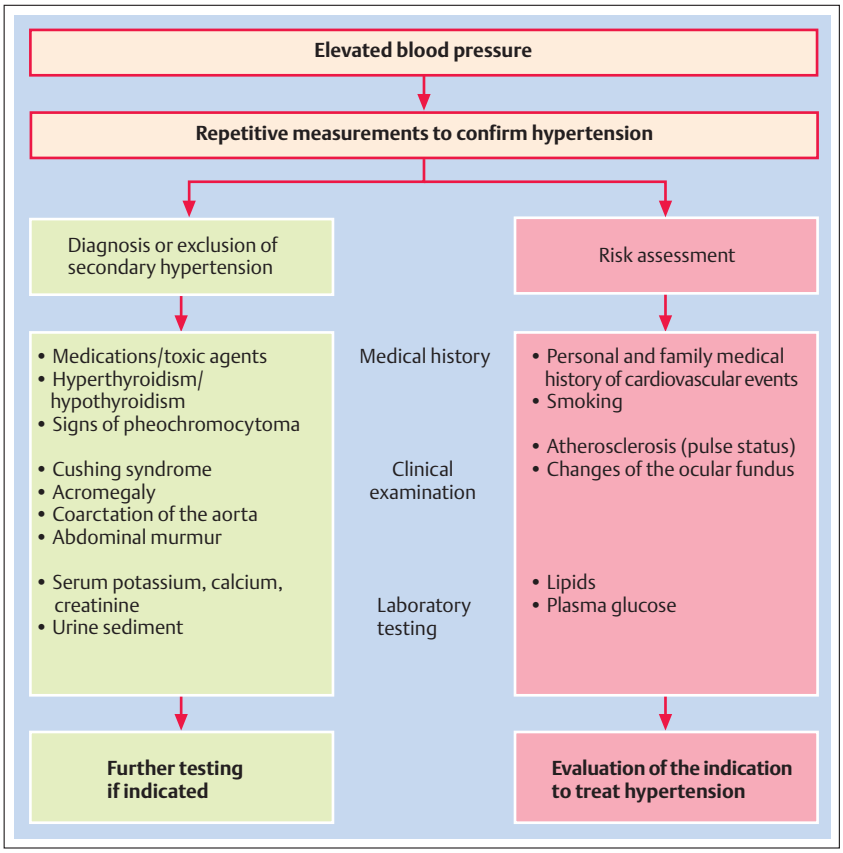

Fig. 23.**1** Management of elevated blood pressure values.

The diagnostic effort to exclude secondary hypertension must be weighed in a useful manner against the prevalence of the suspected hypertension form.

Preliminary Analysis. A great majority of secondary hypertension forms can be suspected or diagnosed by accurate evaluation of the history, clinical examination, and routine laboratory tests (Fig. 23.**1**).

Medical history should include the following:
- ➤ weight changes, sleep history (daytime sleepiness?)
- ➤ medications (hormone replacement therapy, contraceptives, nonsteroidal anti-inflammatory drugs, etc.)
- ➤ stimulants (alcohol, etc.)
- ➤ signs of hyperthyroidism and hypothyroidism
- ➤ signs of pheochromocytoma (p. 741).

Clinical examination may reveal signs of the following entities:
- ➤ Cushing syndrome (p. 742)
- ➤ acromegaly (p. 745)
- ➤ aortic coarctation (p. 747)
- ➤ renal artery stenosis. Always look for bruits of the renal artery.

Table 23.**2** Primary and secondary hypertension

Primary hypertension	92–96 %
Secondary hypertension	4–8 %
– renal	3–5 %
– renovascular	0.5–1 %
– endocrine	0.5–1 %
– other	< 0.5 %
Curable forms	1–2 %

Laboratory tests should include:
- ➤ serum creatinine, potassium, and calcium levels
- ➤ urine analysis.

Further Diagnostic Studies. If the results of the primary analysis indicate that one or the other form of secondary hypertension may be present then further diagnostic testing is usually indicated. For example, an abdominal ultrasound examination may be useful when renal causes of hypertension are suspected, or hormonal testing or imaging modalities may be required to diagnose endocrine forms of secondary hypertension. In the majority of cases, the primary analysis will reveal normal findings and antihypertensive therapy can be initiated according to risk assessment. It is important to note that

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Table 23.**3** Risk assessment in hypertension: end-organ damage and cardiovascular disease

Organ	End-organ damage	Cardiovascular disease
Heart	Left ventricular hypertrophy	Angina pectoris, myocardial infarction, congestive heart failure
CNS	Atherosclerotic plaques in arteries that supply the brain (as seen using ultrasound)	Ischemic stroke, hemorrhagic stroke, transient ischemic attack
Kidney	Microalbuminuria	Renal failure
Peripheral arteries	Atherosclerotic plaques (as seen using ultrasound)	Peripheral arterial disease
Retina		Retinopathy, loss of vision

even in younger patients, and in those with severe hypertension, primary (idiopathic) hypertension remains the most frequent form of hypertension.

Further testing may also be indicated in patients with refractory hypertension, which is difficult to control with adequate antihypertensive therapy. In these patients, further testing often reveals renal artery stenosis or primary aldosteronism.

Risk Assessment

Risk assessment is based on severity of hypertension and the presence of additional risk factors, including a positive family history, dyslipidemia, diabetes mellitus, and smoking. In addition, it is important to determine whether cardiovascular disease is present (Tab. 23.**3**). Risk assessment is simple and straightforward. The *medical history* should focus on personal and family history of cardiovascular events, particularly myocardial infarction and stroke. The *clinical examination* should include a meticulous examination of the vascular system, including palpation of peripheral pulses and auscultation of vascular regions for detecting signs of atherosclerosis. *Laboratory testing* must include glucose and lipid values. In some cases further testing may be indicated for accurate risk assessment, including echocardiography for detecting left ventricular hypertrophy, Doppler ultrasound for detecting arterial stenosis, etc.

23.2 Primary (Idiopathic) Hypertension

Pathogenesis. Idiopathic hypertension is present in more than 90% of patients with hypertension (Tab. 23.**2**). The underlying pathology is unknown. There are, however, several hereditary forms of hypertension (e. g., cellular ion channel defects) and acquired forms (e. g., obesity and high sodium intake) that contribute, at least in part, to the development of hypertension.

Classification. Severity of idiopathic hypertension is classified according to the World Health Organization (see Tab. 23.**1**). Mild forms of hypertension may not necessarily require antihypertensive therapy. The risk of cardiovascular events should be assessed for each patient individually to determine optimal management of hypertension.

Isolated systolic hypertension of the elderly requires special attention. Increased systolic blood pressure levels are caused by diminished distensibility of arterial walls, particularly the aortic wall. *Isolated systolic hypertension* is also associated with an increased risk of cardiovascular events.

Clinical Features. Most patients with idiopathic hypertension have no symptoms. Some patients complain of unspecific symptoms, such as headache, dizziness, impaired vision, or dyspnea. In patients with longstanding and untreated hypertension, symptoms from hypertensive damage to organs and tissues are common:

- *cerebrovascular system:* transient ischemic attack, ischemic stroke, hemorrhagic stroke
- *heart:* angina pectoris, myocardial infarction, congestive heart failure
- *kidneys:* nephrosclerosis with proteinuria and renal failure
- *peripheral vasculature:* atherosclerotic stenosis and occlusion, peripheral vascular disease.

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23.3 Secondary Hypertension

In Tab. 23.**4**, secondary causes of hypertension are summarized. As already mentioned, these causes account for less than 10% of hypertension cases (Tab. 23.**2**). In the following paragraphs the most important entities, including renal, endocrine, and cardiovascular causes of secondary hypertension, are discussed. Conditions that occur with main symptoms other than hypertension are described in other chapters of this book.

Table 23.**4** Secondary hypertension

Renal hypertension
- bilateral renal disease
  - acute and chronic glomerulonephritis
  - chronic interstitial nephritis
  - cystic kidney disease
  - diabetic nephropathy
  - collagen–vascular disorders
- unilateral renal disease
  - congenital hypoplasia
  - vesicoureteral reflux
  - unilateral hydronephrosis
  - postradiation nephritis
- renovascular disease (unilateral or bilateral)
  - atherosclerotic renal artery stenosis
  - fibromuscular dysplasia
  - rare causes
- renin-producing tumor
- kidney transplantation

Endocrine hypertension
- Cushing syndrome
- mineralocorticoid hypertension
- pheochromocytoma
- hyperthyroidism
- hypothyroidism
- primary hyperparathyroidism
- acromegaly
- neuroendocrine tumor (carcinoid)

Cardiovascular hypertension
- coarctation of the aorta
- increased cardiac output

Neurogenic hypertension
- increased intracranial pressure
- sleep apnea syndrome
- acute porphyria
- lead intoxication

Hypertension in pregnancy

Toxic agent-induced and drug-induced hypertension
- contraceptives
- nonsteroidal antiinflammatory drugs (NSAIDs)
- sympathicomimetics
- erythropoietin
- cyclosporine
- alcohol
- amphetamine
- cocaine
- anabolic steroids

Renal Hypertension

Bilateral Renal Disease

Renal disease is the most common cause of secondary hypertension and accounts for approximately 5% of hypertension cases. The primary analysis may reveal an elevated serum creatinine level, proteinuria, or abnormal urine analysis. Further diagnostic tests according to nephrologic criteria often include abdominal ultrasound, additional laboratory testing, or renal biopsy. The various kidney diseases are discussed in Chapter 29.

Hypertension following *kidney transplantation* deserves particular attention. In these patients, the cause of hypertension often is multifactorial including the underlying hypertension, transplant failure, fluid retention, cyclosporine, or stenosis of the transplant artery.

Unilateral Renal Disease

Unilateral renal disease, including congenital hypoplasia, or recurrent kidney infections in patients with vesicoureteral reflux, can cause hypertension. In these patients, serum creatinine or urine analysis may be normal, and diagnosis usually is confirmed by ultrasound (see Chapter 29).

Renovascular Hypertension

Renovascular hypertension is the most common, curable form but accounts for less than 1% of hypertension cases. Therefore, recommendations differ as to which imaging modality is best used in which

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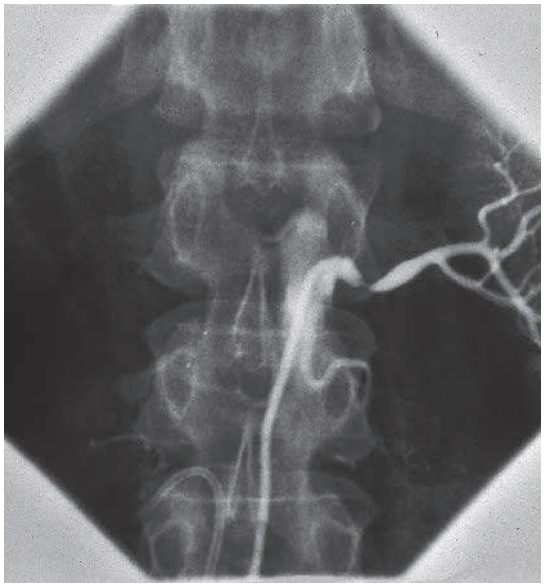
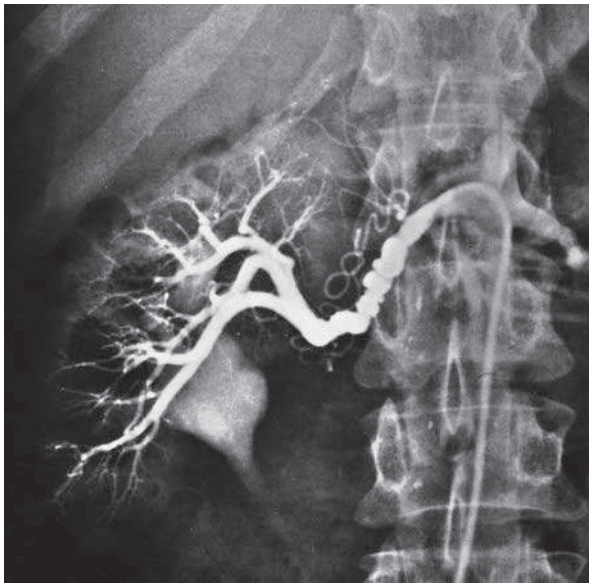


a



b

Fig. 23.**2** Angiography of the renal arteries.
a Atherosclerotic stenosis of the left renal artery.
b Fibromuscular dysplasia of the right renal artery, demonstrating the "beaded string" sign.

hypertension cases to search for renovascular hypertension.

Types. Angiographic criteria help differentiate between the following diagnoses (Tab. 23.**5**):
- ➤ atherosclerotic stenosis
- ➤ fibromuscular dysplasia
- ➤ rare causes.

Atherosclerotic stenosis is often located at the origin of the renal artery from the abdominal aorta and in the proximal part of the artery (Fig. 23.**2a**). In many patients, renal artery stenosis coincides with atherosclerotic lesions of the aorta and iliac arteries.

Fibromuscular dysplasia is more common in women. The right renal artery is involved more often than the left renal artery, and typical lesions are found in the middle and distal part of the renal artery. Angiographically, the "beaded string" sign helps to establish the diagnosis. The typical angiographic appearance reflects dysplasia and proliferation of the fibromuscular components of the media (Fig. 23.**2b**). Discrete fibromuscular stenosis or long and smooth lesions are less common. Fibromuscular dysplasia is not only seen in the renal arteries but similarly in carotid, mesenteric, or iliac arteries.

Table 23.**5** Causes of renovascular hypertension

Atherosclerotic stenosis	60–70 %
Fibromuscular dysplasia	30–40 %
Rare causes – renal artery embolism – renal artery aneurysm – arteriovenous fistula – arteriitis – coarctation of the abdominal aorta – neurofibromatosis	< 1 %

Table 23.**6** Screening methods in suspected renal artery stenosis

– Doppler and color-coded vascular ultrasound
– Multislice Computed Tomography (CT) angiography
– Magnetic Resonance (MR) angiography
– Nuclear imaging (with or without captopril)
– Captopril test (with measurement of renin activity)

Diagnosis. Several findings from the medical history and clinical examination may raise the suspicion of renal artery stenosis:
- ➤ acute or subacute onset of hypertension
- ➤ generalized atherosclerosis
- ➤ periumbilical or epigastric murmur.

However, none of these findings is specific enough to confirm the diagnosis. For example, murmurs can also be heard in approximately 10 % of patients with primary hypertension. Since primary hypertension is so much more common than renovascular hypertension, the predictive value of auscultation is limited.

Screening tests help to confirm or exclude a renal artery stenosis (Tab. 23.**6**). Definitive diagnosis is obtained, however, from conventional angiography using selective injection of contrast medium into the renal arteries. None of the screening tests is superior to the

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other, and all imaging modalities have advantages and disadvantages. In routine practice, the experience and availability of the various imaging modalities vary among health care facilities and, therefore, determine the diagnostic approach of suspected renal artery stenosis.

Color-coded Doppler ultrasound combines direct vessel wall and luminal imaging (Fig. 23.**3**) with flow measurements obtained from Doppler signals (Fig. 23.**4**). This allows both localization and exact hemodynamic determination of the degree of stenosis. However, this examination is time consuming, technically difficult, especially in obese and obstipated patients, and requires experience.

Multislice computed tomography (CT) angiography permits imaging of the renal arteries by means of intravenous injection of iodine contrast material and has a low interobserver variability. Disadvantages include radiation exposure and the need for a large amount of contrast medium. *Magnetic resonance (MR) angiography* is the imaging modality of choice for patients with severe renal failure because it requires no iodine contrast dye. *Scintigraphic imaging* or the *Captopril test* are only infrequently used in special circumstances.

Because of the low prevalence of renal artery stenosis, screening should be performed only when at least one of the *following criteria* is present:

- refractory hypertension despite adequate, antihypertensive combination therapy and despite good patient compliance
- worsening renal function that cannot be explained otherwise
- renal dysfunction induced by ACE inhibitors or angiotensin II receptor blockers
- unilaterally shrunken kidney, usually diagnosed by chance.

> Conversely, if none of the above mentioned criteria is present in a patient with hypertension, pretest probability is low and screening for renal artery stenosis is not justified.

Conventional angiography remains the "gold standard" for diagnosing or excluding renal artery stenosis.

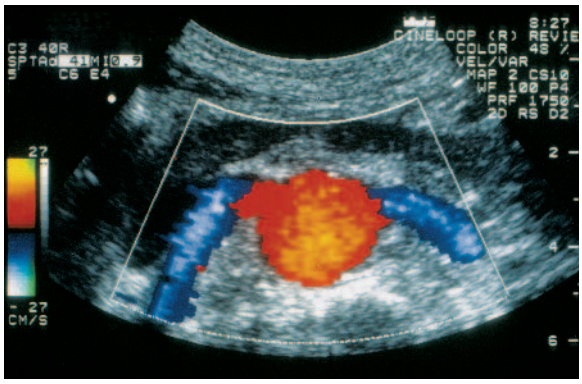

Fig. 23.**3** Color-coded Doppler ultrasound of the aorta and two normal-appearing renal arteries (cross-section).

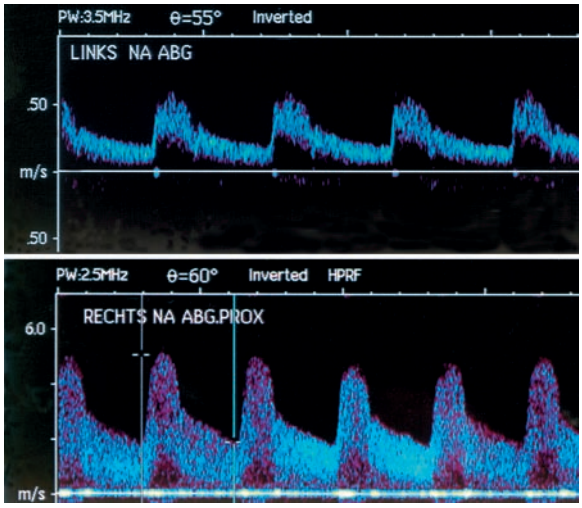

Fig. 23.**4** Pulse-wave Doppler ultrasound. Upper panel: normal signal. Lower panel: increased systolic and diastolic velocity and spectral broadening of the signal indicating hemodynamically significant right renal artery stenosis.

(Fig. 23.**2**). Many authors primarily use angiography as a stand alone test because of the drawbacks of the aforementioned noninvasive imaging tests.

Endocrine Hypertension

Several endocrine disorders are associated with systemic arterial hypertension. *Metabolic syndrome* is common and is characterized by insulin resistance (often combined with impaired glucose tolerance or diabetes mellitus type 2), obesity, dyslipidemia, endothelial dysfunction, and hypertension. Testing includes measurement of abdominal waist circumference (at the umbilical level), body mass index (BMI), blood pressure, and laboratory tests, such as glucose, lipids (triglycerides, HDL–cholesterol), uric acid, and urine analysis for the presence of microalbuminuria. Metabolic syndrome is discussed elsewhere in this book. Sleep apnea syndrome is also often associated with hypertension and discussed elsewhere.

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Endocrine Disorders Associated with Hypertension

In three rare endocrine disorders—*primary aldosteronism*, *pheochromocytoma*, and *Cushing syndrome*—arterial hypertension is often the presenting symptom. If one of these disorders is suspected, special screening tests are indicated. Each of these disorders is characterized by specific signs and symptoms: the typical medical history of pheochromocytoma, the characteristic clinical signs of the Cushing syndrome, and hypokalemia in primary aldosteronism.

Acromegaly is associated with hypertension in half of cases. It is almost always present in patients with long-standing disease who exhibit the typical features of acromegaly.

Furthermore, psychosocial factors, such as stress or depression, may have an unfavorable effect on the cardiovascular system through increased release of catecholamines or glucocorticoids. In these cases insulin resistance, hyperinsulinemia, and hypertension potentially increase the cardiovascular risk. In general however, endocrine imbalance from stress or depression can easily be differentiated from primary disorders of the endocrine system.

Mineralocorticoid Hypertension

In general, high levels of mineralocorticoids cause systemic arterial hypertension. The zona glomerulosa of the adrenal cortex may produce an excess of aldosterone, or the entire adrenal cortex may secrete high levels of mineralocorticoids, without an increase in angiotensin II levels (and without activation of the renin–angiotensin–aldosterone system). In contrast, high levels of mineralocorticoids cause suppression of active renin and angiotensin via negative feedback.

Conversely, systemic hypertension often is associated with secondary aldosteronism, with increased renin activity. Typically, the renin–angiotensin–aldosterone system is activated in patients with primary hypertension who are treated with diuretics, in patients with renovascular hypertension, and with other forms of secondary hypertension. The renin–angiotensin–aldosterone system is also activated in patients with vomitus, diarrhea, or other losses of gastrointestinal fluid. These patients usually are not hypertensive, but may have hypokalemia or hypokaluria.

Primary Aldosteronism (Conn Syndrome)

Clinical Features. Primary aldosteronism or Conn syndrome is defined as "autonomous," excessive production of aldosterone by one or both adrenal glands. It is associated with hypertension in the majority of cases and often with hypokalemia and metabolic alkalosis. Hypertension in primary aldosteronism is sometimes difficult to treat. Hypokalemia may be absent in patients with low sodium intake and in those on ACE inhibitor or angiotensin-receptor blocker therapy. The medical history should include a meticulous exploration of prior blood pressure values and changes in serum potassium levels. Hypertension can trigger headache and other symptoms. Chronic hypertension may cause symptoms of end-organ damage, particularly of the eyes, heart, and kidneys. Hypokalemia may be responsible for fatigue, weakness, polyuria, polydipsia, paresthesia, or neuromuscular hyperexcitability (to be differentiated from hyperventilation, hypocalcemia, and hypomagnesemia).

Diagnosis. If the serum potassium level is persistently low, potassium levels should be obtained from *24-hour urine* or *fasting spot urine samples*. Diuretics should be discontinued for a few days prior to urine collection. In patients with Conn syndrome, hypokalemia is accompanied by hyperkaluria.

Complex hormonal testing may not necessarily be required to initiate screening for primary aldosteronism. Diagnosis is confirmed by evidence of elevated plasma or urine aldosterone levels that cannot be suppressed by high sodium intake (> 200 mmol/day [> 12 g NaCl/day]). The diagnosis is also supported by decreased plasma renin activity, which remains suppressed in the upright position and with diuretic therapy. The current standard test is to look for the plasma aldosterone/renin activity ratio, which is quite reliable but also affected by most antihypertensive medications. Therefore, interpretation of results of these tests must take the influence of the antihypertensive therapy into account. For example, beta-blockers decrease, and diuretics increase, renin activity and the active renin levels. Regarding the *plasma aldosterone/renin activity (or active renin) ratio*, it has to be kept in mind that low levels of renin often are unreliable due to assay-related imprecision for lower range values. Therefore, it may be difficult to differentiate between primary hyperaldosteronism and "low renin hypertension," especially if plasma aldosterone levels are not clearly elevated. This also explains the variability in the estimated prevalence of mineralocorticoid hypertension, with an observed range from a few permille to several percent.

Localization. If primary aldosteronism is confirmed by laboratory testing, it is important to differentiate between adenoma (often unilateral) and hyperplasia (often bilateral). An accuracy of > 95 % is achieved with aldosterone measurements from blood samples obtained during selective catheterization of each vein of the adrenal glands. CT or MR imaging are helpful in dia-

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gnosing large adenomas, but often are equivocal. Incorrect interpretation of these imaging tests may result in unnecessary, surgical excision, also because "incidentalomas" of the adrenal glands are much more common than aldosterone-producing adenomas.

Nuclear imaging of the adrenal glands is another option to localize excessive aldosterone production. This is often performed in combination with dexamethasone suppression. A postural stimulation test may be helpful, whereby repetitive measurements of aldosterone, renin, and cortisol at rest (early morning) and after four hours of walking, are performed. In patients with adenoma, aldosterone and cortisol levels usually decrease because of ACTH dependence. In contrast, aldosterone and angiotensin II levels increase in patients with bilateral hyperplasia because of renin–angiotensin–aldosterone system dependence.

Other Forms

Glucocorticoid-suppressible aldosteronism or familial aldosteronism type I (autosomal dominant) is a rare cause of mineralocorticoid excess. Here, ACTH stimulates the enzyme that catalyzes the last step of aldosterone synthesis (see Tab. 23.**10**).

Some forms of minerlocorticoid hypertension are not caused by aldosterone but by an elevation of *other mineralocorticoids*. For example, some adenomas may primarily produce an excess of deoxycorticosterone (DOC).

DOC may also induce hypertension in patients with a *defect of 11β-hydroxylase*. This defect is rare but represents the second most common cause of congenital adrenal hyperplasia (CAH)/adrenogenital syndrome after 21-hydroxylase deficiency. Both defects can be diagnosed by neonatal screening of 17α-hydroxyprogesterone levels. 11β-Hydroxylase deficiency causes hypertension and low renin activity.

Another potential cause of low-renin hypertension is the *intake* of nonaldosterone mineralocorticoids, for example fludrocortisone.

In patients with *apparent mineralocortcoid excess* (see Tab. 23.**10**), cortisol and not aldosterone induces both hypertension and hypokalemia. A similar pattern is found in patients with excessive intake of liquorice. Liquorice is an additive in various foods, candies, botanical drugs, and chewing gums. The active component is glycyrrhizinic acid that inhibits inactivation of cortisol to cortisone through 11β-hydroxysteroid dehydrogenase. Excessive cortisol binds to the renal mineralocorticoid receptor and supresses both renin and aldosterone.

Several other forms of *excessive cortisol production* are associated with insufficient conversion of cortisol to cortisone, as is the case in some forms of cancer with ectopic production of ACTH. In these patients, hypokalemia, adynamia, and muscle weakness are dominant clinical features in contrast to the typical Cushing syndrome in which skin atrophy and redistribution of the subcutaneous tissue are important findings. Urine cortisol is substantially elevated.

In patients with Liddle syndrome, severe hypertension, hypokalemia, and low renin activity are not caused by excess of mineralocorticois but by a *genetic defect of the kidneys* (see below).

Differential Diagnosis. As already mentioned, forms of secondary hyperaldosteronsim are more common than the primary forms. Secondary hyperaldosteronism may be found in patients with hypertension and hypokalemia but characterized by high renin activity, and is often caused by diuretics, oral contraceptives, or renovascular hypertension, etc.

Pheochromocytoma

Pheochromocytomas produce, store, and secrete *catecholamines* and are usually localized in the adrenal medulla. In addition, catecholamine-producing tumors may origin from extra-adrenal chromaffin cells (paragangliomas), e. g., from the glomus caroticum, and in postganglionic sympathetic neurons (ganglioneuromas).

Clinical Features. In almost all patients with pheochromocytoma hypertension is the *cardinal symptom*, or one of the main signs of the disease.

> However, pheochromocytoma is the cause of hypertension in less than one in every thousand patients with hypertension.

Blood pressure values may be continuously elevated. In one-third of the patients, typical hypertensive attacks may occur exclusively, or additionally. Typical symptoms include headaches, palpitations, profuse perspiration, and anxiety. In severe forms, proteinuria, retinopathy, or encephalopathy may occur. In addition, tremor, chest or abdominal pain, nausea, or vomitus can accompany the attacks. Facial color can abruptly change, and both flushes and pallor are common. In addition, angina pectoris with or without ECG changes, myocardial infarction, pulmonary edema, or seizures may occur. In contrast to hyperventilation syndrome, panic attacks are not the trigger but the consequence of excessive catecholamine secretion.

Differential Diagnosis. Palpitation, dyspnea, paresthesia, tremor, light-headedness, neuromuscular hyperexcitability, and anxiety are unspecific symptoms and are found in various conditions such as: *hyperventilation*, hyperthyroidism, seizure disorders, migraine, coronary artery disease, congestive heart failure, hypocalcemia, hypomagnesemia, hypokalemia, and intake of *cocaine or other sympathetic stimulants*. Hypoglycemia can be accompanied mainly by sympathetic symptoms. The

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absence of neuroglycopenic symptoms should raise the suspicion of a reactive hypoglycemia rather than an insulinoma.

Diagnosis. Pheochromocytoma may be present in patients with refractory hypertension that is difficult to treat or in those with recurrent hypertensive attacks, often combined with elevated serum glucose levels, or in patients with adrenal incidentaloma. Screening is performed by measuring epinephrine/norepinephrine and metanephrine/normetanephrine from acidified 24-hour urine samples. These markers can also be measured in plasma samples in specialized laboratories.

Localization. If an excess of catecholamines is confirmed, imaging tests are required to localize the site of hormone production. Ultrasound may be used because tumors are often large. CT, however, is the routine imaging modality. MR imaging is advantageous because it helps in the differential diagnosis of adrenal tumors. Nuclear imaging is helpful for identifying extra-adrenal tumors or metastases. Approximately 15 % of pheochromocytoma cases are familial, often they are bilateral, at multiple sites, and 10 % are malignant. Genetic forms are listed in Tab. 23.**7**.

Incidentaloma. If an adenoma of the adrenal gland is accidentally diagnosed by an imaging test (incidentaloma), a pheochromocytoma should be considered. There is no way to exclude the diagnosis of pheochromocytoma by clinical criteria. Blood pressure should be monitored carefully (24-hour blood pressure monitoring), and laboratory screening may be justified.

According to older reports, pheochromocytoma was often found first at autopsy and the diagnosis was not established while the patient was alive. Due to the availability of contemporary imaging tests, incidentalomas are now diagnosed more often. If further testing reveals pheochromocytoma, surgery is often performed even in the absence of hypertension. Therefore, the prevalence of hypertension in patients with pheochromocytoma is less than the initially described rate of 90 %. Importantly, MR imaging is helpful in excluding pheochromocytoma in patients with adenoma on CT scan, and thus in avoiding unnecessary surgery.

Cushing Syndrome

Excessive adrenal production of glucocorticosteroids is the cause of the Cushing syndrome or hypercortisolism.

Iatrogenic Cushing Syndrome. In contrast to the endogenous Cushing syndrome, which has a prevalence of two in 100 000, the more common iatrogenic form *less frequently causes systemic arterial hypertension*. In iatrogenic Cushing syndrome other signs are, however, equally common, such as change in the psyche, increase in body weight, skin atrophy, osteoporosis, osteonecrosis, diabetes mellitus, or cataract. The reason for the difference in endogenous to iatrogenic Cushing syndrome is that most antiinflammatory or immunosuppressive corticosteroid drugs are compounds that strongly target the glucocorticoid receptor and to a lesser extent the mineralocorticoid receptor.

Clinical Features. Systemic arterial hypertension is found in 80 % of patients with the endogenous Cushing syndrome.

Excessive corticosteroid production may be due to increased pituitary or ectopic production of adrenocorticotropic hormone (ACTH), or due to ACTH-independent, adrenal cortisol production. In general, symptoms are caused by corticosteroids and not by ACTH and are therefore similar for both entities. However, excessive production of androgens, e. g., testosterone, can trigger symptoms in women. Furthermore, occasionally mineralocorticoid-related symptoms, such as hypokalemia, are present due to the mineralocorticoid effect of the cortisol (see Mineralocorticoid Hypertension, above).

Several signs are particularly common in patients with Cushing syndrome (Tab. 23.**8**). These signs are: *facial plethora, the "moon-shaped" face* (Fig. 23.**5**), *central obesity, and psychologic changes*. Patients and their rela-

Table 23.**7** Hereditary forms of pheochromocytoma

Multiple endocrine neoplasia type 2 (A or B) – *Ret* proto oncogene mutation (chromosome 10): receptor-type activation of tyrosine kinase	– in addition, C-cell hyperplasia or medullary thyroid carcinoma (calcitonin increased) – 2A: occasionally Lichen amyloidosus – 2B: dysmorphia and skin tumors
von Hippel–Lindau disease – tumor suppressor gene	– in addition, vascular malformations of the eyes (angioma of the retina) and brain (hemangioblastoma) – cystic malformations – often renal carcinoma
Neurofibromatosis type 1	– typical skin lesions
Succinate dehydrogenase complex – SDH-B, -C, -D mutation	– often extra-adrenal tumors (paraganglioma)

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tives may notice dramatic changes in mood and behaviour. Signs and symptoms include fatigue, loss of libido, emotional instability, irritability, nervousness, mnemonic and attention deficit, sleep disturbance, cognitive changes, psychosis, increase in body weight or supraclavicular or nuchal subcutaneous tissue, rubeosis, ecchymosis, striae rubrae (Fig. 23.**6**), easy bruising (Fig. 23. **7**), skin atrophy, muscle weakness, osteoporosis, kidney stones, diabetes, or thrombosis.

Diagnosis. In patients with typical symptoms, diagnosis is confirmed by measurement of *substantially elevated levels of cortisol* from 24-hour urine samples. In contrast, many patients with hypertension, increase in body weight, diabetes, or depression (e.g., from alcoholism) have slightly elevated cortisol levels but do not have Cushing syndrome. The excessive cortisol production is not the cause but the consequence of the disorder (pseudo-Cushing syndrome). Screening for endogenous hypercortisolism is especially useful in patients with typical signs, including typical redistribution of subcutaneous tissue, obvious padding in temporal and subclavicular depressions, as well as nuchally, skin atrophy, or muscle weakness. Excessive corticosteroid production should also be excluded in patients with refractory hypertension and in those with adrenal incidentaloma.

A meticulous evaluation of the medical history is crucial, including assessment of changes in the psyche and changes in facial expression (using old photographs).

Although more demanding for the laboratory than plasma cortisol testing, measurement of free cortisol from a 24-hour urine sample is the "gold standard" for the diagnosis of Cushing syndrome. Urine creatinine levels should be obtained simultaneously to estimate completeness of urine collection. Moderately elevated urine cortisol levels are also found in pseudo-Cushing syndrome or in patients with excessive polyuria. Overactivation of the hypothalamic–pituitary–adrenal axis is found in alcoholism, depression, anxiety disorder, anorexia, bulimia, severe obesity, sleep apnea, uncontrolled diabetes, severe infections, such as endocarditis or encephalitis, or renal failure. In patients with suspected Cushing syndrome, laboratory testing and not an imaging modality should be performed initially.

> Pituitary and adrenal incidentalomas are much more common than the endogenous Cushing syndrome.

Screening. Apart from measurement of 24-hour urine cortisol levels, screening may also be performed using dexamethasone inhibition, which includes intake of 1 mg of dexamethasone at midnight and measurement of the serum cortisol level at 0800 the next morning. Cortisol testing from a blood sample at midnight is an option in the hospitalized patients. In outpatients, cortisol in saliva can be assessed at midnight, if this laboratory method is available. At midnight, cortisol levels are low in healthy, unstressed individuals. In patients with the pseudo-Cushing syndrome all these tests may occasionally be falsely positive. Where lower assay cutoff values are used, the increase in specificity is accompanied by a decrease in sensitivity.

Fig. 23.**5** Plethora and "moon-shaped" face in a patient with Cushing syndrome.

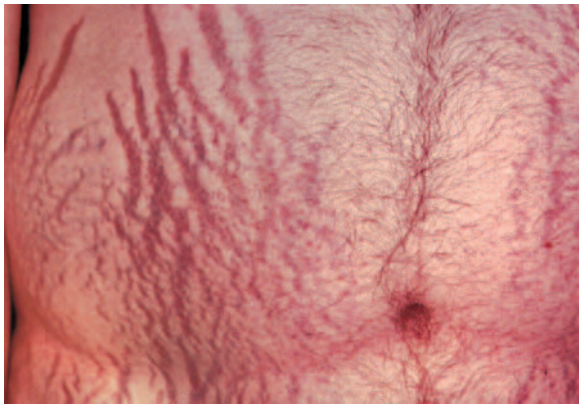

Fig. 23.**6** Striae rubrae.

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Fig. 23.**7** Ecchymosis in a patient with Cushing syndrome.

Table 23.**8** Common signs and symptoms in patients with Cushing syndrome

Symptom	Frequency
Facial plethora	90 %
Increased body weight, central obesity	70 %–90 %
Fatigue, muscle weakness	60 %
Skin atrophy, easy bruising	60 %
Hypertension	80 %
Headache	50 %
Decreased libido, disturbed menstrual cycle	90 %
Neuro-psychiatric symptoms, (emotional instability, depression)	70 %–90 %
Back pain, osteoporosis	40 %–60 %
Diabetes mellitus, impaired glucose tolerance	30 %–80 %
Kidney stones	20 %

ACTH-Dependent Cushing Syndrome

In this form, both adrenal glands produce an excess of corticosteroids and the origin of excessive ACTH secretion needs to be identified.

Cushing Disease. ACTH-secreting adenomas in the anterior lobe of the pituitary gland account for 75 % of the patients with ACTH-dependent Cushing syndrome. Quite often these tumors are too small to be detected by noninvasive imaging tests, such as MR imaging. On the other hand, MRI often reveals clinically, nonrelevant tumors. Accidentally diagnosed pituitary tumors are more common than ACTH-secreting tumors. Therefore, bilateral blood samples from the left and right cavernosus and/or petrosus inferior sinus are obtained by *invasive catheterization* to measure ACTH levels before and after corticotropin releasing factor (CRF) stimulation prior to planned (transsphenoidal) neurosurgery.

Paraneoplastic Cushing Syndrome. Ectopic production of ACTH in cancer patients (e. g., small-cell lung cancer) may be a cause of Cushing syndrome. These patients may have a known malignancy and recent onset of symptoms, including profound muscle weakness, hypokalemia, and excessive cortisol levels (see also Mineralocorticoid Hypertension, above). Carcinoid tumors rarely produce ectopic ACTH (or CRF) and may cause Cushing syndrome. The clinical course often is protracted, and diagnosis may be challenging, including the clinical differential diagnosis versus Cushing disease.

ACTH-Independent Cushing Syndrome

Adrenal glands autonomously produce an excess of corticosteroids. As a consequence, ACTH levels are low, and imaging modalities of the adrenals (CT, MRI) are indicated.

Exclusion of Cushing Syndrome in Patients with Adrenal Incidentaloma. Adrenal tumors rarely can be found during clinical examination (palpation). In most cases, these tumors are accidentally diagnosed by CT or MRI which was performed for reasons other than excess of adrenal hormones. *Prevalence of incidentaloma* is 2–4 % in CT series and 4–8 % in autoptic series of adults. The prevalence increases with age. Only a minority of the patients with incidentaloma has an active endocrine tumor and less than one per thousand patients has adrenal carcinoma. Therefore, a functional test should always precede the imaging test if an endocrine tumor is suspected. If a cortisol-producing adenoma is suspected, dexamethasone inhibition is helpful to exclude Cushing syndrome.

Diagnosis. In patients with ACTH-independent Cushing syndrome, a high dose (8 mg) of oral dexamethasone at midnight will not suppress excessive production of cor-

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Table 23.**9** Examples of hereditary forms of adrenal tumors

Multiple endocrine neoplasia type 1 (MEN 1) – menin mutation (chromosome 11) – tumor suppressor gene mutation	– often inactive, corticoadrenal adenoma – primary hyperparathyroidism (leading tumor in MEN1; hypercalcemia?) – neuroendocrine gastroenteropancreatic tumors, pituitary adenoma, skin tumors (angiofibroma, collagenoma)
Congenital adrenal hyperplasia (CAH)/adrenogenital syndrome – CYP21B, CYP11B1	– impaired sexual maturation – 17α-hydroxyprogesterone ↑ – hypotension or hypertension
Carney complex – PRKAR1A Li–Fraumeni syndrome – p53	– myxoma (often atrial), schwannoma, lentigines, nevi – breast cancer – thyroid carcinoma – glioma, sarcoma
McCune–Albright syndrome (MAS) – $G_s\alpha$-(GNAS1-) mutation	– osteopathy: fibrous dysplasia – dermatopathy: café–au–lait spots – endocrinopathy: pubertas precox, hyperthyroidism

tisol at 0800. In most cases, unilateral adrenal adenoma is then diagnosed by *CT or MR imaging*. There are however, bilateral forms, including rare genetic forms (Tab. 23.**9**), e. g., Carney complex syndrome, which is associated with atrial myxoma, or forms of Cushing syndrome due to ectopic adrenal receptors, an aberrant regulation by arginine vasopressin (AVP), gastric inhibitory polypeptide (GIP), luteinizing hormone (LH), human chorionic gonadotropin (hCG), etc., which may stimulate the adrenal glands despite low levels of ACTH.

Acromegaly

Acromegaly is caused by excessive production of growth hormone in adults. In contrast, gigantism occurs prior to the termination of bone maturation and puberty (often protracted due to secondary hypogonadism). Growth exceeds the anticipated genetic potential which can be estimated by asking for the height of the parents. Acromegaly is rare; the prevalence is approximately five in 100 000. The diagnosis may be missed for several years, and it may take years to cure acromegaly.

Clinical Features. In one-half of the patients, *systemic hypertension* is present at the time of diagnosis. Hypertension is more common among the elderly in whom small, slow-growing tumors are found. It is less common in younger patients who usually have developed symptoms more recently, and tumors often are large and fast-growing. Typically, *acral enlargement* is present in the face (supraorbital bulging, nose, chin), hands (digits, rings do not fit), and feet (increase in shoe size). Specialized physicians, including ophthalmologists, dentists, neurologists, or rheumatologists may be consulted by the patient for the following additional signs and symptoms:

- subcutaneous swelling, visceromegaly, macroglossia, skin thickening, hyperhidrosis
- arthropathy, neuropathy, carpal tunnel syndrome
- snoring, sleep apnea (with increased sleepiness during the day) in half of the patients, often obstructive form, but central sleep apnea is possible
- insulin resistance, hypertriglyceridemia, hyperglycemia (diabetes mellitus)
- cardiomegaly, cardiomyopathy (often associated with hypertension)
- abnormal menstruation, decreased libido
- headaches, neuro-ophthalmologic symptoms, including decrease in visual field and acuity, loss of vision
- thyroid enlargement, prostate hyperplasia, polyps of the colon.

Macroangiopathy in patients with acromegaly is similar to the metabolic syndrome, causing increased morbidity and mortality from *cardiovascular diseases*. Although profound *insulin resistance* is common in acromegalic patients, the characteristic increase in body weight is due to an increase in lean body weight and increase in body fluid, and not due to an increase in subcutaneous tissue.

> Acromegaly is rare but can be diagnosed clinically. Old photographs are often helpful to detect facial changes over time.

In most cases, diagnosis is suspected because of the signs and symptoms related to excessive growth hormone (GH) production. The diagnosis is less often made because of local tumor growth or pituitary failure.

Diagnostic Tests. The diagnosis is confirmed by elevated levels of GH and insulinlike growth factor 1 (IGF-1). The most reliable screening test is for IGF-1 and is also helpful to assess disease activity. GH levels after oral glucose tolerance testing are used to confirm the diagnosis. IGF-1 levels can occasionally be low despite

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Table 23.**10** Examples of genetic forms of hypertension

Liddle syndrome – sodium channel mutation, β- or γ-subunits, MIM 177 200	– increased reabsorption of sodium – loss of potassium, hypokalemia, alkalosis – renin ↓, aldosterone ↓ – responsive to amiloride
Glucocorticoid (dexamethasone)-suppressible aldosteronism – (GRA/GSA) = familial hyperaldosteronism type 1 – chimeric gene (promotor, proximal CYP11B1; distal CYP11B2)	– ACTH–dependent production of 11β-hydroxylase and aldosterone – aldosterone ↑, 18-hydroxycorticosterone ↑, plasma renin ↓ – responsive to dexamethasone
Apparent mineralocorticoid excess (AME) – HSD11B2 (AME): 11β-hydroxysteroid dehydrogenase deficiency type 2, MIM 218 030 (also with excessive liquorice intake: glycyrrhicinic acid inhibits the enzyme)	– impaired inactivation from cortisol to cortisone – potassium ↓, plasma renin ↓, aldosterone ↓
Pseudohypoaldosteronism type 2 (at least three forms) (Gordon syndrome)	– increased reabsorption of sodium – hyperkalemia – renin ↓, aldosterone ↓ – responsive to thiazides
Pregnancy-induced hypertension – stimulation of the mineralocorticoid receptor	– progesterone stimulates mineralocorticoid receptor
Certain forms of CAH – 11β-hydroxylase deficiency (CYP11B1) 17α-hydroxylase-17,20-lyase deficiency (CYP17)	– impaired sexual maturation – DOC ↑, 17α-hydroxyprogesterone ↑, renin activity ↓
PPAR-γ mutation	– insulin resistance, hyperinsulinemia

the presence of acromegaly, when its production is affected by decreased hepatic synthesis, due to liver cirrhosis, uncontrolled diabetes mellitus, primary or secondary hypothyroidism, severe malnutrition, or infectious disease. In these disease states the liver can no longer increase IGF-1 secretion in response to increased, growth hormone levels, as would normally be the case.

In general, *oral glucose testing* causes increased plasma glucose levels in patients with acromegaly and, in contrast to healthy individuals, GH cannot be suppressed. If the clinical diagnosis of acromegaly is confirmed by laboratory testing, MRI reveals a pituitary adenoma in most cases. Ectopic production of GH is exceedingly rare. In rare circumstances, acromegaly is caused by excessive hypothalamic or pancreatic production of growth hormone releasing factor (GRF).

Genetics of Hypertension and Rare Monogenetic Forms

Primary Hypertension. Systemic hypertension is hereditary, at least in part, which is supported by studies of twins. Several polymorphisms are suspected as putative hypertension genes. Heredity is polygenetic rather than monogenetic and remains unclear in most cases. Currently, routine genetic testing is not available, nor recommended, in patients with hypertension. The family history is often positive in patients with primary hypertension and metabolic syndrome.

Monogenetic Forms. There are, however, several rare, monogenetic forms of hypertension. One example is *glucocorticoid-suppressible aldosteronism* or familial hyperaldosteronism type I (see Mineralocorticoid Hypertension, above). In addition, there are several forms of congenital adrenal hyperplasia (CAH)/adrenogenital syndrome, such as *11β-hydroxylase deficiency* or excessive production of deoxycorticosterone (DOC), as well as Liddle syndrome.

Liddle syndrome is based on a mutation and activation of the β- or γ-subunits of epithelial sodium channels, resulting in increased reabsorption of sodium and severe refractory hypertension. Renin and angiotensin levels are low. Kidney transplantation could potentially correct the underlying disorder.

There are *hereditary forms of pheochromocytoma and Cushing syndrome*, as well as other rare genetic forms of hypertension (Tab. 23.**10**). In general, the type and amount of adrenal hormones that activate the mineralocorticoid receptor are of paramount importance regarding regulation of blood pressure. Not surprisingly, most of the genetic forms listed in Tab. 23.**10** involve the kidneys or adrenal glands. Moreover, observations in patients with renal transplantation have confirmed that the kidney plays a dominant role in high blood pressure.

One exceptional genetic form is caused by a *mutation of the PPAR-γ receptor*, known for the regulation of insulin sensitivity. In contrast to patients with insulin receptor defects, these patients have not only profound insulin resistance and hyperinsulinemia, but also systemic hypertension and endothelial dysfunction. In addition, they often have polycystic ovaries, hirsutism, and acanthosis nigricans.

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Cardiovascular Hypertension

Typical cardiovascular forms of hypertension include coarctation of the aorta and hypertension due to increased cardiac output. Systolic hypertension of the elderly also has cardiovascular origin (aortic sclerosis) but often is classified as primary hypertension because it is managed medically, and not surgically, as is the case in patients with coarctation.

Coarctation of the Aorta

Coarctation is a congenital, cardiovascular malformation and is classified depending on the localization of stenosis in relation to the ductus arteriosus: *preductal form* in infants and postductal form in adults. The preductal form is severe in most cases and causes symptoms in infants and toddlers. The postductal form usually is diagnosed in adults.

Clinical Findings. P*ostductal stenosis* occurs in adults. Hypertension is present in vascular regions that are localized proximal to the coarctation, and hypotension is present, distal to the coarctation.

> Severity of hypertension depends on the degree of stenosis, on the presence of collaterals, and on contractility of the left ventricle.

If the origin of the left subclavian artery is involved in the coarctation, elevated blood pressure values (using an upper arm cuff) are found on the right arm only. Coarctation often is associated with other congenital abnormalities, including bicuspid aortic valve, aortic stenosis, patent ductus arteriosus, and aneurysms of cerebral arteries.

Diagnostic Tests. Coarctation is one of the few secondary hypertension forms that can be diagnosed clinically. The physical examination must include a search for typical clinical signs, particularly in young patients with hypertension. In patients with suspected coarctation, the diagnosis is then confirmed by imaging modalities.

The *clinical examination* often reveals the following:

- *bilateral pulse palpation:* strong pulses of the upper extremities and diminished or missing pulses of the lower extremities (femoral and pedal pulses)
- *blood pressure measurement:* hypertensive values of the upper extremities and hypotensive values of the lower extremities; occasionally, hypotension is also present in the left arm.
- *auscultation:* systolic or systolo-diastolic murmur that is interscapular and often left of the thoracic spinal column; occasionally other murmurs depending on additional congenital abnormalities.

The following imaging modalities are useful:

- chest radiograph: costal notching due to the presence of collaterals; occasionally notching of the descending aorta
- echocardiography
- three-dimensional MR angiography (Fig. 23.**8**).

Hypertension Due to Increased Cardiac Output

Aortic regurgitation and *complete atrioventricular block* can cause increased cardiac output and hypertension. The diagnosis can be established clinically using the clinical examination, an electrocardiogram, and echocardiography.

Fig. 23.**8** Three-dimensional MR angiography (lateral view) in a 36-year-old man with coarctation of the aorta (arrow).

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Hypertension in Pregnancy

If elevated blood pressure values occur during pregnancy, one must differentiate between pregnancy-induced hypertension and chronic preexisting hypertension. Urine analysis should include quantification of protein, and is of paramount importance. Evaluation and management of the various forms of hypertension (Tab. 23.**11**) should be performed interdisciplinarily, involving internal medicine specialists and obstetricians.

Table 23.**11** Classification of hypertension in pregnancy

Hypertension	Findings
Pregnancy-induced hypertension	diastolic pressure > 90 mmHg after 20th week of gestation
Pregnancy-induced proteinuria	proteinuria > 0.5 g/24 hours after 20th week of gestation
Pregnancy-induced hypertension and proteinuria	preeclampsia
Chronic hypertension with preeclampsia	chronic hypertension plus proteinuria
Nonclassifiable hypertension	no blood pressure measurements prior to 20th week of gestation available

Toxic Agent-Induced and Drug-Induced Hypertension

In patients with hypertension, the medical history should include information on *drugs and toxic agents* which can induce hypertension. Several medications and toxic agents can induce hypertension through various mechanisms (see Tab. 23.**4**). A common scenario is hypertension from *nonsteroidal antiinflammatory drugs* (NSAIDs). NSAIDs can cause an increase in intravascular volume via inhibition of prostaglandin synthesis. *Oral contraceptives* can induce hypertension by stimulation of the renin–angiotensin–aldosterone system. Often, substitution of the NSAID with another analgetic medication or introduction of an alternative form of contraception solves the problem.

Toxic agents, including *alcohol, amphetamines, and cocaine*, can induce hypertension. The mechanism is sympathetic overactivation. Cocaine is particularly dangerous because it can induce profound hypertensive attacks and vasospasm that may cause myocardial infarction and stroke.

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24 Systemic Arterial Hypotension

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24.1 Primary (Idiopathic) Hypotension 750

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Introduction

In contrast to hypertension, *systemic arterial hypotension* is not clearly defined by blood pressure values. In routine clinical practice, however, a systolic arterial pressure of 100 mmHg has been identified as a useful cut-off point for diagnosing hypotension. In patients with *orthostatic hypotension*, the decrease in blood pressure values, which correspond to the change from a supine to a standing position rather than absolute blood pressure values, are important (see Chapter 31). As in hypertension, hypotension is also classified into *primary* and *secondary forms* (Tab. 24.**1**). In secondary forms, hypotension is caused by underlying conditions involving the adrenal glands, kidneys, heart, or the nervous system. Severity of the hypotension must be interpreted in the context of blood pressure values prior to the onset of the underlying condition. For example, in a patient with previous hypertension, symptoms of hypotension may occur despite preserved blood pressure values. *Shock* is a special form of hypotension, defined as reduced tissue and organ perfusion, resulting in decreased oxygen supply, end-organ damage, multisystem organ failure, and often death. The various forms of shock (hypovolemic, cardiogenic, septic, anaphylactic, etc.) are discussed in separate chapters of this book.

Table 24.**1** Secondary forms of hypotension

Endocrine hypotension
– Adrenocortical insufficiency
– Primary (Addison disease)
– Secondary (hypopituitarism)
– Other underlying endocrine disorders
– Genetically determined forms
Renal hypotension
Cardiac hypotension
– Congestive heart failure
– Arrhythmia (tachycardia, bradycardia)
– Impaired filling of the left ventricle
– Aortic stenosis
Neurogenic hypotension
– Primary autonomous dysfunction
– Secondary autonomous dysfunction
Hypovolemic hypotension
– Dehydration
– Bleeding and loss of plasma
Toxic and drug-induced hypotension
– Antihypertensives
– Nitrates
– Phosphodiesterase 5 inhibitors
– Sedatives
– Hypnotics
– Dopaminergic drugs

24.1 Primary (Idiopathic) Hypotension

Primary or idiopathic hypotension is diagnosed by excluding secondary forms of hypotension. It is more common among young, lean individuals, primarily females. Hypotension typically is found in both the supine and upright positions. Patients can be asymptomatic or may have profound orthostatic symptoms. In routine clinical practice, disturbing orthostatic symptoms, not the finding of a low blood pressure, often provoke diagnostic and occasionally therapeutic interventions. The pathology and the clinical presentation are discussed in detail in Chapter 31.

24.2 Secondary Hypotension

Endocrine Hypotension

Hypotension from Endocrine Disorders

Iatrogenic Hypotension. Common endocrine disorders are rarely associated with hypotension. Iatrogenic hypotension, however, can cause problems in patients with preexisting disorders, e. g., hip fracture after a fall in a patient with osteoporosis, or orthostatic symptoms in a diabetic patient with hypertension. Particularly elderly patients, who are treated for systolic hypertension with certain medications, are at high risk (see Tab. 24.**1**, Toxic and drug-induced hypotension). In elderly patients, orthostatic hypotension is associated with the occurrence of myocardial infarction.

Diabetes Mellitus. Diabetes mellitus (type 2) often is associated with hypertension through the metabolic syndrome. Late stages of diabetes (type 1 and 2) often cause

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Table 24.**2** Adrenocortical hormones

Origin of production	glomerulosa zone	fasciculosa zone
Hormone	aldosterone	cortisol
Effect	mineralocorticoid: – renal reabsorption of sodium ↑ – secretion of potassium ↑, H^+ ↑	glucocorticoid: – gluconeogenesis ↑ – protein catabolism ↑ – anti-inflammatory – immunosuppressive
Important in cases of	salt deficiency	stress
Stimulated by	angiotensin II potassium	ACTH
Dependent on	sodium intake body position	time of the day
Deficiency: laboratory findings	aldosterone ↓ potassium ↑ sodium ↓ (ADH ↑) metabolic acidosis	cortisol ↓ (DHEAS-S ↓) glucose ↓ eosinophilia lymphocytosis
Primary insufficiency: laboratory findings	plasma renin activity ↑	ACTH ↑

hypertension via renal dysfunction. In these patients, hypotensive blood pressure values often are iatrogenic. Occasionally, hypotension may be due to severe hyperglycemia and hypovolemia. Refractory orthostatic hypotension may also be caused by an autonomous neuropathy, which can be missed more easily than other complications, such as retinopathy or peripheral neuropathy. Hypotension may also be found in patients with hyporeninemic hypoaldosteronism, which is characterized by hyperkalemia without activation of the renin–angiotensin–aldosterone system.

Thyroid Disorders. Thyroid disorders are less often associated with hypotension than with hypertension. Hyperthyroidism usually causes systolic hypertension, high cardiac output and tachycardia. In contrast, hypothyroidism can cause diastolic hypertension from increased systemic resistance and bradycardia. Hypotension in a patient with a primary thyroid disorder is often caused by end-stage congestive heart failure. The autoimmune polyendocrinopathy syndrome type 2 (APS 2) may cause hypotension via adrenocortical insufficiency (Addison disease). Early morning plasma cortisol measurement, among other tests (see below), are helpful in the diagnosis of this condition. Plasma free thyroxine (fT_4) measurement is recommended in patients with suspected secondary (central) hypothyroidism, and adrenocorticotropic hormone (ACTH)/cortisol testing for suspected pituitary failure.

Hyperparathyroidism and Pheochromocytoma. Hypotension may occasionally be found in patients with primary hyperparathyroidism due to diminished plasma volume from hypercalcemic dehydration. It can also occur in patients with pheochromocytoma due to catecholamine-induced vasoconstriction and decrease in plasma volume. Once catecholamine receptors are down-regulated, a decrease in catecholamine production can cause severe symptomatic hypotension.

Adrenocortical Insufficiency. Adrenocortical insufficiency presents the classical cause of endocrine hypotension, which should be diagnosed and treated immediately. In most cases, severe deficiency of glucocorticoids or mineralocorticoids causes systemic hypotension (Tab. 24.**2**).

The *primary form* is localized in the adrenal glands (Addison disease). Low cortisol levels cause an increase in ACTH levels, and often an activation of the renin–angiotensin–aldosterone system, particularly if significant loss of sodium has occurred due to decreased production of aldosterone. In the *secondary form*, deficiency of cortisol is not accompanied by an appropriate increase in ACTH. While the stimulus for the inner zone of the adrenal cortex is missing, angiotensin-dependent and potassium-dependent production of aldosterone in the zona glomerulosa is preserved. The *secondary* and *tertiary forms* are localized in the pituitary gland or hypothalamus (pituitary failure).

Primary adrenocortical insufficiency has a prevalence of one in 10000 and should be distinguished from central (secondary or tertiary) adrenocortical insufficiency, which has a prevalence of two in 10000.

Primary Adrenocortical Insufficiency (Addison Disease)

Clinical Features. Primary adrenocortical insufficiency causes symptoms via diminished production of glucocorticoids, mineralocorticoids, and, rarely, via androgen deficiency (particularly in women who have reduced gonadal production of androgens). Additional symptoms are the result of increased production of ACTH.

In most cases, *profound fatigue* and *weakness* are present. Adynamia, muscular weakness, tiredness that worsens during the day, reduced exercise capacity, and stress intolerance are common.

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Fig. 24.**1** Typical skin pigmentation in a 49-year-old man with Addison disease.

Table 24.**3** Common symptoms in patients with Addison disease

Weakness, decreased exercise capacity	100 %
Loss of body weight	90–100 %
Increasing skin pigmentation	90–100 %
Hypotension	80–90 %
Nausea, loss of appetite	80–90 %
Abdominal pain	30–40 %
Hypoglycemia	30–40 %
Salt appetite	20 %

Usually, *loss of appetite* and a *decrease in body weight* occur. Common symptoms also include nausea, vomitus, abdominal pain, and diarrhea. Decreased levels of cortisol are responsible for loss of appetite via disturbed metabolic pathways: storage of glycogen and lipids, insulin secretion, gluconeogenesis, glycogenolysis, and lipolysis. *Loss of sodium* and *dehydration* can aggravate hypotension resulting in a decrease in body weight and may result in increased salt appetite, orthostatic hypotension, and nocturia. Occasionally, hypoglycemic, sympathetic, or neuroglycopenic symptoms are present. Hyponatremia from increased hypovolemia-induced secretion of antidiuretic hormone (ADH/AVP) is common, less frequently hypercalcemia may be found.

A long-standing *increase in ACTH levels* may result in *pigmentary abnormalities* of the skin and mucous membranes (Figs. 24.**1**, 24.**2**). An increase in pigment may be present in skin areas that are exposed to light or pressure, skin folds, fresh scars, genitals (spotted, bluish-brown), oral mucosa, gums, or tongue. Additional stress factors may induce a life-threatening adrenocortical (Addison) crisis. Common symptoms of Addison disease are summarized in Tab. 24.**3**.

> Profound fatigue, weakness, loss of appetite, decrease in body weight, pigmentary abnormalities, and systemic arterial hypotension are common symptoms in patients with Addison disease.

Differential Diagnosis. *Decrease in body weight* and *weakness* may also be found with anorexia nervosa, myasthenia gravis, thyrotoxicosis, polymyalgia, alcoholism, drug abuse, tuberculosis, diabetes mellitus (insulin deficiency), celiac disease, or cancer.

Pigmentary abnormalities are also seen in pregnancy, with oral contraceptives, hemochromatosis, liver cirrhosis, chronic interstitial nephritis from nonsteroidal anti-inflammatory drugs, or myelofibrosis.

Diagnosis. Addison disease is confirmed by low levels of plasma cortisol. Cortisol measurement should be performed without prior exposure of glucocorticoids and in the early morning hours (between 0600 and 0800) where peak levels are found in healthy individuals. ACTH is consistently elevated in Addison disease and should be measured simultaneously. Stimulation with synthetic ACTH (e. g., Synacthen, 0.25 mg intravenous) can be also used. Cortisol is measured at baseline and 60 minutes after injection. There are numerous modifications of adrenocortical stimulation tests. In case of primary adrenocortical insufficiency, complex analyses are usually not required.

Causes. *Tuberculosis* was the most common cause of primary adrenocortical insufficiency until several decades ago. In industrialized countries, Addison disease is more often caused by *autoimmune-mediated degeneration of the adrenal glands* in which the adrenal cortex slowly is destroyed without clinically apparent inflammation. Antibodies against 21-hydroxylase are often positive. Other causes are summarized in Tab. 24.**4**.

Isolated deficiency of mineralocorticoids is rare. In the *primary form*, aldosterone levels are low and cannot be stimulated. Systemic arterial hypotension, hyperkalemia, metabolic acidosis, and increased plasma renin activity are typical.

Isolated secondary (low renin) hypoaldosteronism is more common than the primary form and is occasionally observed in patients with autonomous diabetic neuropathy, renal disease, nervous system disorders, or amyloidosis. This condition may also be idiopathic and is characterized by hypotension, hyperkalemia, and hypochloremic metabolic acidosis.

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Fig. 24.**2** Pigmentation of palmar skin folds in Addison disease.

Secondary Adrenocortical and Anterior Pituitary Insufficiency

Iatrogenic Secondary Adrenocortical Insufficiency. Prior to discussing the various forms, it has to be mentioned that in case of isolated secondary adrenocortical insufficiency, i. e., acquired selective ACTH deficiency, *previous pharmacotherapy with corticosteroids and their abrupt termination* should be considered, particularly if clinical signs of Cushing syndrome are also present.

Anterior Pituitary Insufficiency. In patients with secondary adrenocortical insufficiency, *anterior pituitary insufficiency* should be considered (Tab. 24.**5**). In the acquired forms, local tumor growth may be responsible for headaches, visual field defects, or loss of vision. In case of *posterior pituitary involvement*, hypernatremia, polydipsia, or polyuria may be present. ADH deficiency causes central diabetes insipidus rather than systemic hypotension.

Typically, deficiencies of growth hormone or gonadotropins are more common than a deficiency of ACTH or thyroid-stimulating hormone (TSH). Deficiency of prolactin is extremely uncommon, but may result in agalactia (e. g., typical in Sheehan disease, which is characterized by postpartal infarction of the anterior pituitary gland). In men, *prolactin deficiency* is less often diagnosed because there are no obvious symptoms. However, measurement of prolactin in men may be helpful to detect disturbances of the hypothalamic–pituitary axis. Substantially elevated levels of prolactin are often diagnostic for prolactinoma, whereas moderately elevated levels may reflect disturbed dopaminergic inhibition of prolactin producing cells.

Clinical Features. In contrast to patients with Addison disease, patients with pituitary insufficiency are markedly pale due to deficiency of ACTH, melanotropic hormone, and due to diminished skin perfusion. This paleness often involves the entire skin and cannot be explained by concomitant anemia, which often is mild in patients with pituitary insufficiency (Fig. 24.**3**).

Body mass index varies and is often normal. Occasionally, obesity is related to hypothalamic damage or to deficiency of growth hormone, gonadotropins, or TSH. Cachexia may be found in patients with severe deficiency of ACTH.

Blood pressure values may also vary in patients with anterior pituitary insufficiency. Hypertension due to increased systemic resistance is more common and is often associated with obesity and atherosclerosis. Deficiency of growth hormone, gonadotropins or TSH can cause premature atherosclerosis. Systemic hypotension is less common and is usually caused by deficiency of ACTH and cortisol.

Table 24.**4** Causes of primary adrenocortical insufficiency

- Autoimmune disorder
  - isolated
  - APS 1 (in addition, mucocutaneous candidiasis, hypoparathyroidism, autoimmune hepatitis, etc.)
  - APS 2 (in addition, autoimmune hypothyroidism, diabetes mellitus type 1, autoimmune gastritis/pernicious anemia, celiac disease, vitiligo, etc.)
- Bilateral adrenocortical tuberculosis
- Adrenoleukodystrophy (X-linked), *ABCD1* mutation, accumulation of long-chain (> 24 C) fatty acids
- Fungi: histoplasmosis, cryptococcosis, blastomycosis (therapy with ketoconazole)
- AIDS: CMV, HIV
- Metastatic cancer: lung, breast, kidney, lymphoma
- Drugs: mitotane, aminoglutethimide, etomidate, ketoconazole, suramine
- Acute adrenocortical insufficiency: hemorrhage, necrosis, thrombosis, antiphospholipid antibody syndrome, meningococcal sepsis
- Congenital forms e. g., DAX-1 (hypogonadotropic hypogonadism), StAR mutation (lipoid CAH)

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Table 24.**5** Symptoms and diagnosis of anterior pituitary insufficiency

Hormone	Symptoms from deficiency	Diagnosis
Growth hormone (GH)	– diminished growth in children – decrease in body fluid (lean body mass ↓) – adipose tissue ↑ – fatigue ↑, exercise capacity ↓, endurance ↓, attention ↓, quality of life ↓	IGF-1 ↓ (especially in young patients) GH ↓ (inappropriate response to stimulation)
Gonadotropic hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	– body and pubic hair ↓ – loss of lateral eyebrows – skin thickness and consistence ↓ (skin folds ↑) – depression – infertility, loss of libido – women: amenorrhea, dyspareunia, breast atrophy – men: erectile dysfunction, loss of potency, testicular atrophy, lean body weight ↓ – premature osteoporosis	estradiol ↓ (women), testosterone ↓ (men), without increase in gonadotropic hormones
Thyroid-stimulating hormone (TSH)	– intolerance of cold temperatures – dry skin, perspiration ↓, skin thickness ↑ – body weight ↑, obstipation – fatigue, need for sleeping ↑, lethargia, depression – bradycardia, hypertension	fT_4 ↓, fT_3 ↓ without adequate increase in TSH (TSH normal, slightly elevated or decreased)
Adrenocorticotropic hormone (ACTH)	– paleness – weakness, adynamia, fatigue, apathy – abdominal pain, nausea, stress-induced vomitus, loss of appetite, loss of body weight, hypoglycemia – dizziness, hypotension	cortisol ↓ without adequate increase in ACTH

In patients with anterior pituitary insufficiency, hypotension is less common than in those with primary adrenocortical insufficiency because aldosterone production is preserved in the latter patients.

Causes. Causes and consequences of anterior pituitary insufficiency are summarized in Tabs. 24.**5** and 24.**6**. In general, magnetic resonance imaging (MRI) of the head and pituitary gland are diagnostic; in most cases a tumor is found.

Isolated deficiency of ACTH without panhypopituitarirism often is caused by medications, as already mentioned above, e. g., glucocorticoids, opioids. Occasionally, an autoimmune disorder of the pituitary gland is diagnosed, which typically is associated with other autoimmune disorders.

Fig. 24.**3** Facial abnormalities in a patient with hypopituitarism; paleness, loss of pigmentation, alabaster-like skin folds, loss of lateral eyebrows.

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Diagnosis. In patients with pituitary and other cerebral disorders, including head trauma and neurosurgery for brain tumor, measurement of electrolytes may indicate a disturbed production of ADH and natriuretic peptides. In addition, measurement of early morning cortisol (with or without stimulation with synthetic ACTH) and fT_4 are helpful. Complex stimulation tests, such as insulin-induced hypoglycemia, are sophisticated and not without risk, e. g., in patients with seizure disorder or coronary artery disease. Various stimulation tests aim to explore the different pituitary axes and often are available in specialized facilities only.

Table 24.**6** Causes of pituitary insufficiency

- Pituitary tumor (macroadenoma, i. e., tumor size > 10 mm)
- Pituitary infarction
- Neurosurgery
- Head trauma
- Head irradiation
  - peripituitary tumors: craniopharyngioma, germinoma, meningioma, glioma, ependymoma, chordoma, cysts, empty sella
- Infiltrative disorders (granuloma, infection, inflammation, storage disease)
  - histiocytosis, sarcoidosis
  - tuberculosis, mycosis, Whipple disease, abscess
  - hemochromatosis
  - lymphocytic autoimmune disease
- Metastases, particularly breast and lung cancer, often diabetes insipidus
- Congenital forms
  - various forms, malformations, gene mutations, onset often in childhood

Disorders with Associated Endocrine Disturbances

Many diseases and syndromes affect endocrine systems, and systemic hypotension may only occasionally be present. The conditions discussed in this chapter are relatively common but should not be considered as entities in which an endocrine disorder is the primary cause of the clinical problem. Hypotension only rarely occurs as a main finding.

Chronic Fatigue Syndrome and Posttraumatic Stress Disorder. Patients often consult various specialists because of unexplained fatigue, weakness, stress intolerance, reduced exercise performance, attention deficit, or sleep disturbance. These symptoms commonly occur after viral infection (Epstein–Barr virus), traumatic experience or events, or abuse. These common disorders are difficult to diagnose and define. Neurasthenia was a frequent diagnosis at the beginning of the 20th century. Currently, they are now summarized as chronic fatigue syndrome (CFS) and posttraumatic stress disorder (PTSD). Several of the symptoms could be explained by cortisol deficiency. Although abnormalities in the various hypothalamic–pituitary axes may be found (such as relative cortisol deficiency), they are not the cause but the consequence of the entity. Primary or secondary forms of adrenocortical insufficiency are not present, and, therefore, adrenocortical hormone therapy is often associated with transient improvement only.

Anorexia Nervosa. The main symptoms in patients with anorexia nervosa are *forced excessive weight loss*, *hyperactivity*, and *hypogonadotropic hypogonadism*, the latter causing amenorrhea in women. Anorexia nervosa is more often diagnosed in women who are typically extremely lean. Electrolyte abnormalities (hypokalemia) are often aggravated by abuse of diuretics and laxatives. In contrast to weight loss in patients with ACTH or cortisol deficiency due to panhypopituitarism, willpower to lose weight and activation of ACTH and cortisol are common in patients with anorexia nervosa, stress, and depression. Plasma cortisol levels may be normal or even elevated.

Genetic Forms of Hypotension

These entities are rare, with the exception of *congenital adrenal hyperplasia (CAH)* caused by 21-hydroxylase deficiency. Some other molecular defects were discovered in recent years.

Monogenetic Hypotension. The monogenetic forms of hypotension are similar to the monogenetic causes of hypertension (Tab. 24.**7**). Genetic defects involve production and effector organs of the adrenocortical hormones, as well as genetic defects of ion channels and transporters that are expressed in the kidneys.

Although the abuse of diuretics represents the most common cause of hypotension and hypokalemia, these findings may occasionally be caused by a genetic defect. *Gitelman syndrome* and *Bartter syndrome* are both congenital tubulopathies characterized by hypokalemia and alkalosis. Gitelman disease is more common than Bartter disease and involves the thiazide-sensitive sodium cotransporter of the distal tubulus (SLC12A3), causing hypocalciuria. The phenotype is occasionally mild, and the diagnosis may be established in adolescence or adulthood. The occurrence of neuromuscular symptoms may prompt laboratory testing, which reveals a profound *hypokalemia*. Typically, hypomagnesemia and chondrocalcinosis are found. In these entities, secondary hyperaldosteronism and activation of the renin–angiotensin–aldosterone system may compensate hypotension, but at the price of worsening hypokalemia.

Hypotension may also be caused by defective production or effectiveness of aldosterone, as is the case with *pseudohypoaldosteronism* and certain *defects in corticosteroid biosynthesis* (congenital adrenal hyperplasia [CAH], adrenogenital syndrome [AGS]).

Severe *catecholamine deficiency* is a rare cause of hypotension that is often associated with orthostatic

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Table 24.7 Examples of genetic forms of hypotension

Gitelman syndrome – MIM 263 800 – sodium chloride cotransporter, NCCT	– potassium ↓, alkalosis – plasma renin activity ↑, aldosterone ↓ – magnesium ↓, hypocalciuria – SLC12A3 mutation
Bartter syndrome – at least five forms, prenatal manifestation: polyhydramnios, postpartal: severe volume loss, in addition, deafness	– potassium ↓, alkalosis – plasma renin activity ↑, aldosterone ↓ – prostaglandin E_2 ↑ – hypercalciuria
Pseudohypoaldosteronism type 1 – two forms: MIM 177 735, MIM 264 350 – mutation of the mineralocorticoid receptor – ENaC mutation	– aldosterone ↑ – potassium ↑, acidosis
Aldosterone synthetase deficiency	– aldosterone ↓
Certain forms of CAH – most common: 21-hydroxylase deficiency – rare: 3β-hydroxysteroid dehydrogenase deficiency, lipoid hyperplasia	– aldosterone ↓ (salt loss) – hydroxyprogesterone ↑ – CYP21A2 mutation
Dopamine β-hydroxylase deficiency – orthostatic hypotension	– epinephrine ↓, norepinephrine ↓, in plasma and urine

problems. In contrast to adrenalectomized patients, who have a good quality of life while on corticosteroid substitution, and in whom an isolated deficit in epinephrine is not relevant, patients with dopamine β-hydoxylase deficiency produce neither epinephrine nor norepinephrine and suffer from severe symptoms.

Renal Hypotension

Renal disease (see Chapter 29) often causes systemic arterial hypertension. In rare cases, renal disorders are responsible for systemic arterial hypotension. Low blood pressure values may be due to excessive loss of protein and fluid in patients with *nephrotic syndrome*. Loss of sodium and intravascular fluid may also be found in patients with chronic interstitial nephritis. Hypotension may also occur in patients with uremic pericarditis. Uremic polyneuropathy can cause hypotension via dysfunction of the autonomous nervous system.

Cardiac Hypotension

Primary reduction in cardiac output results in various degrees of systemic arterial hypotension, and depends on the dynamics of the development of the underlying cardiac condition. Cardiac hypotension may be completely asymptomatic or may cause dizziness or syncope. It is observed with the following cardiac diseases:

- reduction of myocardial contractility in congestive heart failure
- tachyarrhythmias and bradyarrhythmias
- impaired filling of the left ventricle due to pericardial effusion, acute pulmonary embolism, chronic cor pulmonale, or mitral stenosis
- severe aortic stenosis.

The clinical presentation and differential diagnosis of the various cardiac conditions are discussed in detail in Chapters 20 and 22.

Neurogenic Hypotension

Vascular regulation during positional change, disturbance of this regulation (orthostatic hypotension), and the various neurological disorders that may cause orthostatic hypotension are discussed in Chapter 31.

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Hypovolemic Hypotension

Dehydration and loss of blood or plasma can be accompanied by systemic arterial hypotension. Dehydration can be caused by:

- vomiting, diarrhea
- loss of sodium and fluid into the third space in peritonitis or ileus
- renal loss of sodium and fluid from diuretic medication, osmotic diuresis, and certain renal disorders (particularly, chronic interstitial nephritis).

Bleeding (particularly, acute gastrointestinal hemorrhage) may cause rapid arterial hypotension and hypovolemic shock. *Loss of plasma* (peritonitis, pleuritis, pancreatitis, etc.) may also cause hypotension over time.

Toxic and Drug-Induced Hypotension

Antihypertensive medications are the most common drugs that are associated with systemic arterial hypotension. With exception of additional comorbidities, blood pressure values may be normal both in the supine and upright positions. Symptomatic orthostatic hypotension is more important, and is especially common among the elderly on antihypertensive medications.

Other drugs that can cause orthostatic hypotension are nitrates, sedatives, hypnotics, and dopaminergic drugs (common medications in patients with Parkinson disease).

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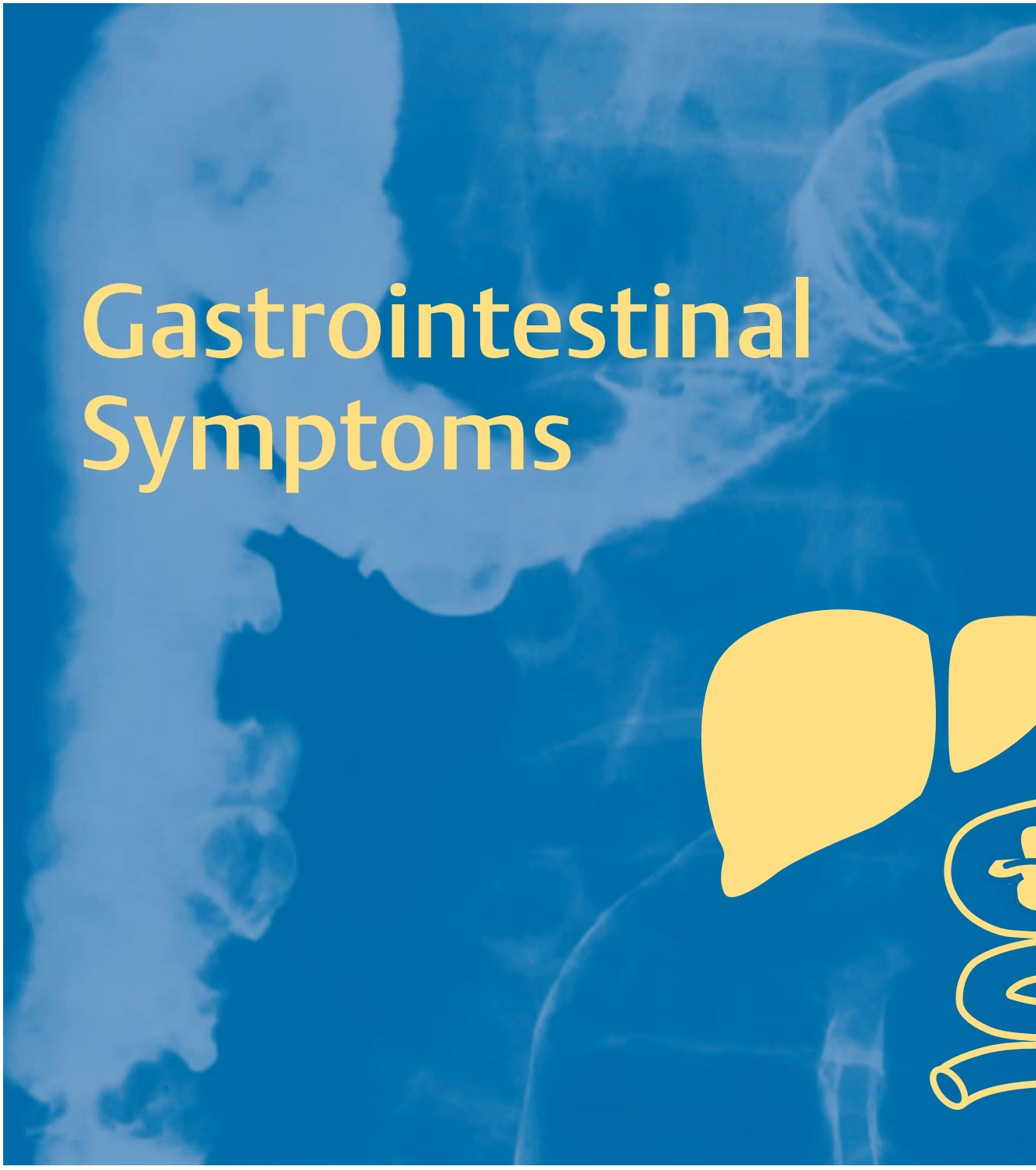
Gastrointestinal Symptoms



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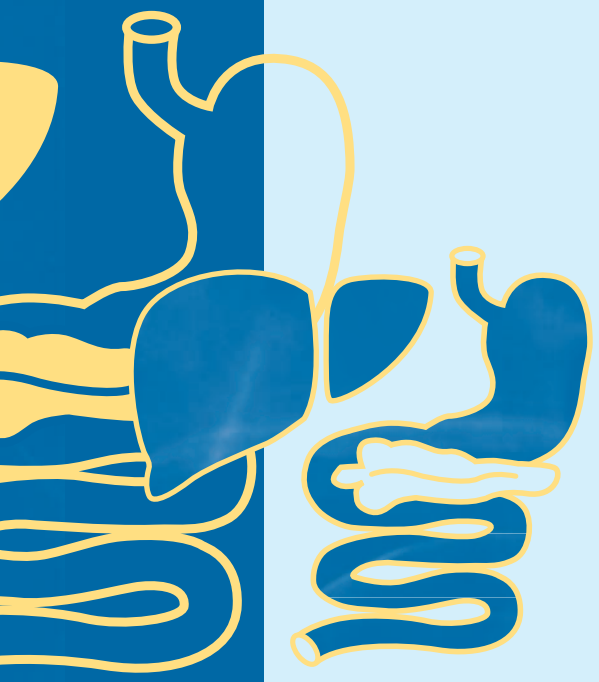

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25 Jaundice

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25.1 General Differential Diagnosis of Jaundice

Definition, Bilirubin Metabolism

Definition. Jaundice is defined as yellowing of body fluids and tissues due to an increase in *bilirubin*. Yellowing of sclerae (see Fig. 3.**67**) is visible at serum concentrations > 2.0–2.5 mg/dL (34–43 μmol/L) and of the skin at levels > 3.0–4.0 mg/dL (51–68 μmol/L).
The yellowish-red discoloration of the skin following excessive carrot or tomato intake, etc. can be distinguished from jaundice by the absence of yellowing of the sclerae. The same applies to drug-induced yellowing of the skin (e. g., as seen with mepacrine or busulfan).

Bilirubin Metabolism. The classification of jaundice and the correct interpretation of laboratory findings are based on bilirubin metabolism (Fig. 25.**1**). Bilirubin primarily is formed (80 %) in the reticuloendothelial system (RES) by the *degradation of hemoglobin* released by senescent red blood cells (RBCs). Other sources of bilirubin are myoglobin, cytochromes, other heme-containing enzymes, and a small pool of free heme. Approximately 300 mg (0.5 mmol) of bilirubin are formed daily. The so-called "shunt bilirubin" originates from hemoglobin of erythrocytes and erythrocytic precursors that prematurely degrade in the bone marrow. This normally small fraction markedly increases in the event of ineffective erythropoiesis (dyserythropoiesis).
In blood bilirubin is bound to albumin. Only a small quantity is free. Following hepatocellular uptake, bilirubin is bound to bilirubin-binding proteins (Y protein [= ligandin = glutathione S-transferase] and Z protein), and made water soluble by conjugation with glucuronic acid by microsomal bilirubin UDP-glucuronyl transferase. Secretion of bilirubin diglucuronide into the bile canaliculi occurs primarily via the MRP2 (multidrug resistance-associated protein 2) pump. Bilirubin diglucuronide excreted in the bile cannot be absorbed in the gall bladder or the intestine. In the terminal ileum and colon, bilirubin diglucuronide is converted into urobilinogen by bacterial enzymes and subsequently oxidized to urobilin and stercobilin. Urobilinogen is absorbed in the terminal ileum and colon, transported via the portal vein to the liver, and re-excreted in the bile (*enterohepatic circulation*). Small quantities of urobilinogen escape hepatic extraction and are excreted via the kidneys.

Pathophysiology of Jaundice

Hyperbilirubinemia and the clinical symptoms of jaundice are caused by defects at different stages of bilirubin metabolism that can also occur in combination.

Increased Bilirubin Production

Hemolysis is the most frequent cause of this type of jaundice. Hemolytic jaundice is generally mild. An additional hepatobiliary disease should be suspected if serum bilirubin levels exceed 4–5 mg/dL (68–86 μmol/L). Jaundice is due to *unconjugated bilirubin*. Bilirubinuria is absent, while urinary urobilinogen levels are often increased. Laboratory parameters indicate hemolysis (e. g., reticulocytes = ↑, LDH = ↑, haptoglobin = ↓, and possibly Hb = ↓). Liver function tests are normal.

Extensive hematomas (e. g., trauma, lung infarction) occasionally lead to transient hyperbilirubinemia.

An increase in *shunt bilirubin* is observed in *hematologic diseases* with premature degradation of erythrocyte precursors in the bone marrow (dyserythropoiesis, e. g., with pernicious anemia, lead poisoning, myelodysplastic syndrome). The clinical symptoms are marked by anemia secondary to impaired erythrocyte maturation. In contrast to hemolytic jaundice, the reticulocytes are normal or low and haptoglobin are normal.

Displacement of Bilirubin from Albumin Binding

Various endogenous (e. g., long-chain fatty acids) and exogenous substances (primarily drugs, e. g., sulfonamides, ampicillin, indomethacin), which are bound to albumin, can displace bilirubin from albumin.

Reduced Hepatic Bilirubin Uptake

Reduced circulation through the sinusoids (e. g., portosystemic anastomoses, portacaval shunt or transjugular intrahepatic portosystemic shunt) can result in the reduced uptake of bilirubin in liver cells. Bilirubin uptake can also be competitively inhibited by various endogenous (e. g., bile acids) and exogenous substances (e. g., quinidine, ajmalin, indocyanine green). Bilirubin uptake in liver cells is also reduced in some cases in Gilbert syndrome (see below).

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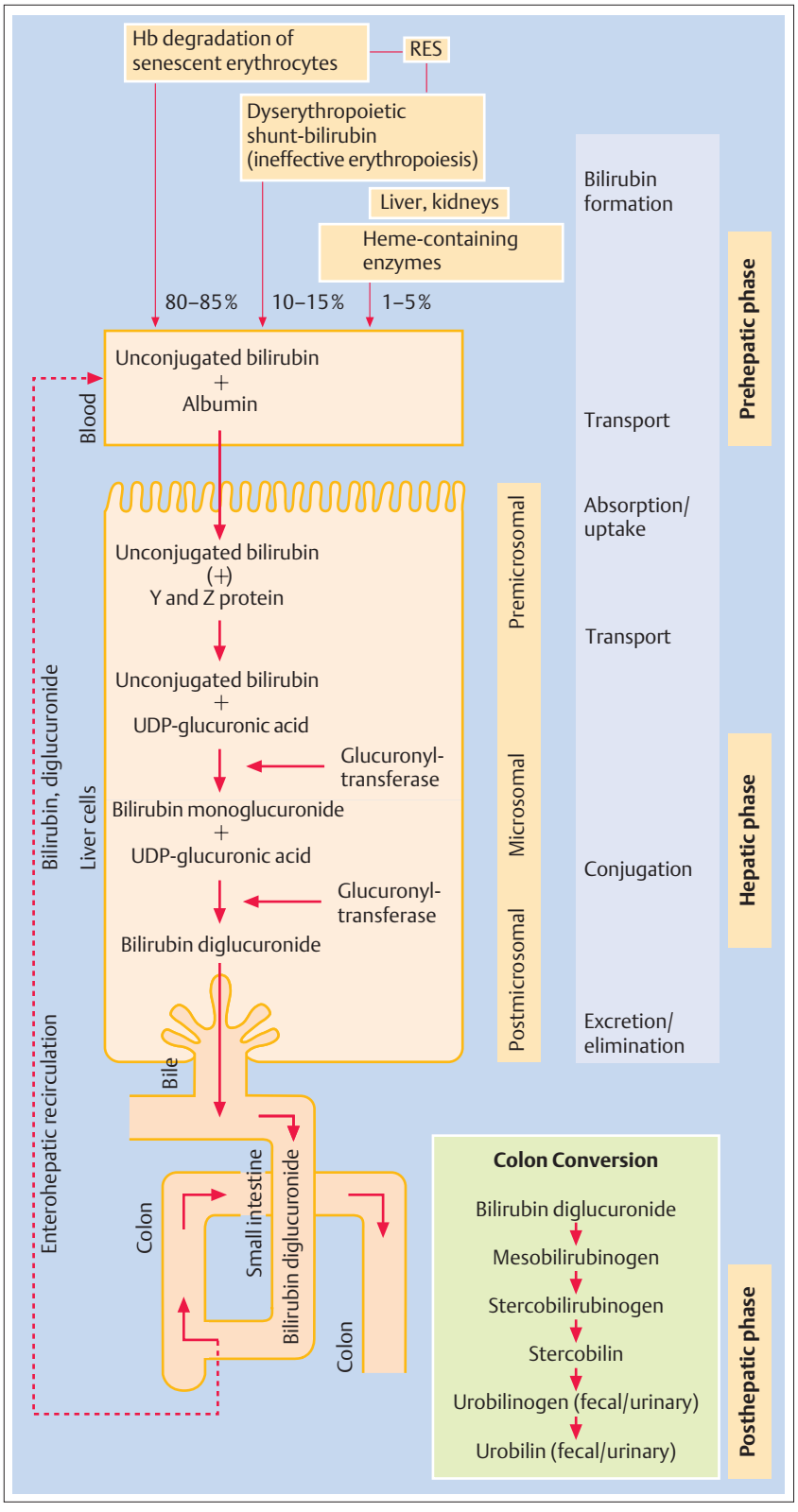

Fig. 25.**1** Bilirubin metabolism.

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Reduced Hepatic Bilirubin Storage

Various endogenous (e. g., long-chain fatty acids) and exogenous substances (e. g., indocyanine green, radiographic contrast media) can compete for binding to intracellular bilirubin-binding proteins. A genetic defect of intrahepatic bilirubin-binding proteins probably causes Rotor syndrome.

Impaired Glucuronidation of Bilirubin

Bilirubin conjugation can be impaired by enzyme inhibition or hereditary enzyme defects. Bilirubin conjugation can be reduced by exogenous (e. g., ethinyl estradiol, chloramphenicol) and endogenous substrates (e. g., thyroid hormones in hyperthyroidism), which either compete for or inhibit glucuronyl transferase. Bilirubin conjugation is also impaired in neonatal jaundice and *breast milk jaundice*. The pathogenesis of these forms of jaundice is complex. Typical genetic enzyme defects underly Crigler–Najjar syndrome types I and II, and Gilbert syndrome.

Impaired Bilirubin Secretion

The secretion of bilirubin from liver cells into the bile canaliculi is the limiting step in bilirubin metabolism, while the glucuronidation of bilirubin is a relatively stable function with a high reserve capacity. Jaundice from *hepatocellular damage* in acute and chronic liver diseases is, therefore, characterized by a rise in conjugated bilirubin levels. The urine is dark brown secondary to conjugated bilirubinuria. The stool color depends on the extent of hepatocyte damage, i. e., the greater the damage, the lighter the stool.

Intrahepatic and extrahepatic cholestasis also belong to this group. Biliary obstruction results in conjugated hyperbilirubinemia. In complete bile duct obstruction, the stool is acholic and urobilinogen cannot be detected in the urine. If only the right or left bile duct is obstructed in an otherwise normal liver, bilirubin levels are normal due to increased bilirubin secretion by the opposite side. Genetic defects of bilirubin excretion at the canalicular membrane cause Dubin–Johnson syndrome or Rotor syndrome. Both syndromes are rare. The liver function tests are normal and the clinical course is benign.

Clinical Classification of Jaundice

Based on the pathophysiology, jaundice can be clinically classified as (Tab. 25.**1**):

- hemolytic (prehepatic)
- hepatocellular (intrahepatic)
- cholestatic (posthepatic).

Central to diagnosis is the determination of indirectly and directly reacting bilirubin in serum by the diazo reaction. Indirect bilirubin is approximately equivalent to unconjugated bilirubin and direct bilirubin to conjugated bilirubin.

Table 25.**1** Main causes of jaundice

Hemolytic jaundice

Hepatocellular jaundice
- isolated, nonhemolytic hyperbilirubinemias
  - unconjugated hyperbilirubinemia (Crigler–Najjar syndrome types I and II, Gilbert syndrome, Meulengracht syndrome)
  - conjugated hyperbilirubinemias (Dubin–Johnson syndrome, Rotor syndrome)
- viral and other infectious forms of hepatitis
  - acute hepatitis A, B, C, D, E
  - chronic hepatitis B, C, D
  - Epstein–Barr virus infection, cytomegalovirus infection, parvovirus B19 infection
  - leptospirosis, Q fever, etc.
- autoimmune hepatitis
- toxic and drug-induced liver diseases
  - e. g., alcohol, *Amanita phalloides* poisoning
  - INH, etc.
- cirrhosis of the liver
  - hepatic
  - alcoholic
  - hemochromatosis, Wilson disease, α_1-antitrypsin deficiency, etc.
- hepatovenous causes
  - congested liver
  - Budd–Chiari syndrome, veno-occlusive disease

Cholestatic jaundice
- intrahepatic cholestasis
  - hepatocellular (e. g., viral or alcohol-induced hepatitis)
  - drug-induced (e. g., chlorpromazine)
  - intrahepatic pregnancy-related cholestasis
  - familial recurrent benign cholestasis
  - primary or secondary biliary cirrhosis
  - primary or secondary sclerosing cholangitis
  - sepsis
  - postoperative jaundice
- extrahepatic cholestasis
  - cholelithiasis
  - tumor (bile duct carcinoma, papillary carcinoma, head of pancreas carcinoma)
  - postoperative or postinflammatory stricture
  - pancreatitis (possibly with pseudocysts)
  - parasites (*Fasciola hepatica*, *Ascaris lumbricoides*, *Clonorchis sinensis*, *Opisthorchis viverrini*)
  - bile duct anomalies (atresia, megacholedochus, etc.)

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Unconjugated Hyperbilirubinemias. In predominantly unconjugated hyperbilirubinemia, *hemolytic jaundice* should be ruled out. Anemia occurs only in case of inadequate compensation of a reduced erythrocyte lifespan.

Dyserythropoiesis-mediated jaundice is a rare form of unconjugated hyperbilirubinemia.

A diminished hepatic bilirubin uptake results in unconjugated hyperbilirubinemia and is usually caused by spontaneous surgical or nonsurgical *portacaval shunts*. *Gilbert syndrome* is the most common cause of unconjugated hyperbilirubinemia in adults. The diagnosis is primarily based on the exclusion of other causes of unconjugated hyperbilirubinemia.

Crigler–Najjar syndrome type II with reduced bilirubin glucuronidation and otherwise normal liver function is extremely rare in adults.

Conjugated Hyperbilirubinemias. Conjugated hyperbilirubinemias are mostly caused by *hepatobiliary diseases*. In this situation, the most important diagnostic step is to distinguish between *obstructive* and *nonobstructive* cholestasis.

In cases of obstructive cholestasis, generally caused by obstruction of the extrahepatic bile ducts, invasive (endoscopic, radiologic, or surgical) measures are indicated to relieve the mechanical obstruction.

Diagnosis is based on medical history, clinical examination, and laboratory parameters (e. g., AST, ALT, AP, γ-GT; see below). Ultrasound examination, usually identifies dilatation of the extrahepatic bile ducts in cases of obstructive cholestasis. Endoscopic, retrograde cholangiopancreaticography (ERCP), or if this cannot be done, percutaneous transhepatic cholangiopancreaticography (PTC) or magnetic resonance cholangiopancreaticography (MRCP) allow identification of the causes of obstruction (mostly stone versus tumor). With ERCP or PTC, biopsies and therapeutic procedures (papillotomy, insertion of endoprostheses or drainage) can be performed.

Genetic disorders of bilirubin excretion rarely occur in adults: *Dubin–Johnson syndrome* and *Rotor syndrome*. Marked conjugated hyperbilirubinemia associated with normal liver function tests is typical. Liver histology is also normal apart from the appearance of a brownish-black pigment in Dubin–Johnson syndrome.

Foreign substances, primarily *toxins and drugs*, can affect several steps of bilirubin metabolism and result in unconjugated or conjugated hyperbilirubinemias. Diagnosis is generally based on a complete history (especially with respect to drug use and environmental factors [occupational exposure]). Freqently jaundice regresses following elimination of the foreign substance.

Clinical Symptoms

Medical History. Important aspects in medical history are blood transfusions or the administration of blood products prior to anti-HCV screening (hepatitis C), intravenous drug use (hepatitis B, C, and D), sexual contacts (hepatitis B and D), stays in countries of low socioeconomic standards (hepatitis A and E, amebic abscess), alcohol use, and exposure to toxins or drugs.

Acute abdominal pain is particularly characteristic for cholelithiasis. Severe pain can also be due to acute liver congestion or liver metastases with infiltration of the liver capsule. A feeling of pressure to moderately severe pain is observed with liver abscess, cholangitis, hepatitis, or echinococcosis. Painless jaundice suggests extrahepatic tumor obstruction.

Palpation. Palpation of the lower edge of the liver, and percussion of the liver–lung border allows determination of the size of the liver. Hepatomegaly is present when the liver span exceeds 9–12 cm. The liver consistency and surface can also be determined given favorable physical conditions. A palpable enlarged gallbladder suggests tumor obstruction (*Courvoisier sign*). Palpable splenomegaly is often present in hemolytic and hepatocellular, but not cholestatic, jaundice. An enlarged liver and spleen (hepatosplenomegaly) is observed in liver diseases with portal hypertension, in systemic reticuloendothelial, hematologic or lymphatic disease, in sepsis and various viral infections.

Palpation of the liver and spleen allows determination of their approximate size. *Ultrasonography* allows precise assessment of the liver and spleen including differentiation between diffuse and focal alterations.

Fever. Fever is a noncharacteristic symptom. In hepatitis and other infectious forms of jaundice, it often develops before, or with, the onset of jaundice. Drug-induced jaundice occasionally also begins with fever, and cholangitis frequently causes intermittent fever.

Ascites. Ascites can occur in all forms of jaundice, except hemolytic jaundice. It is most common in liver cirrhosis. Ascites < 1 L is difficult to detect by clinical examination. Ultrasonography detects as little as 100–200 mL. Ascites can be difficult to detect in pregnancy and in patients with large ovarian cysts, urinary retention, abdominal fat, and meteorism.

Pruritus. Itching is a typical sign of intrahepatic or extrahepatic cholestasis and can precede jaundice for a prolonged period (e. g., in primary biliary cirrhosis). It can be severe and greatly affect the patient's general state of health. The extremities, soles of the feet, and

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palms of the hand are affected most by pruritus. The trunk, face and genitals are usually little affected. Cutaneous hemorrhage and infections can result from scratching.

Excretions. Acholic stools are characteristic for total bile duct obstruction. Increased renal bilirubin excretion results in dark colored urine.

General Symptoms. As with influenza, general symptoms including lethargy, headaches, and arthralgia before onset of jaundice are typical for hepatitis. Noncharacteristic, general physical diseases of long duration (i. e., several weeks) or increasing frequency, accompanied by loss of appetite and weight loss, suggest tumor obstruction.

Skin Changes. In acute hepatitis, *exanthems* can develop in 5–20% of patients in the prodromal stage. These take the form of urticarial exanthems or exanthems resembling measles or scarlet fever exanthems. Immune complexes and cryoglobulins can lead to vasculitis, e. g., purpura in hepatitis B and C. During childhood and especially in children 2–4 years of age, hepatitis B can be accompanied by *acrodermatitis papulosa eruptiva* (*Gianotti–Crosti syndrome*), mostly associated with marked liver and lymph node swelling, but no jaundice.

Chronic liver diseases are frequently accompanied by different types of skin changes (see Liver cirrhosis, below). Star-shaped teleangiectasias (*spider nevi*) are very typical and are mainly located in light-exposed areas (i. e., face, forearms, backs of hands, neck, and upper anterior chest wall). The teleangiectasias disappear upon targeted compression of the central arterioles. Spider nevi are not only observed in liver diseases but also in pregnancy and after administration of oral contraceptives, as well as in healthy individuals.

Vascular skin changes also include *palmar erythema*, which mainly affects the thenar and hypothenar eminences, as well as the fingers, excluding the palms. Palmar erythema can, for example, also occasionally develop during pregnancy, oral contraceptive administration, and hyperthyroidism in persons without liver disease.

Trophic skin changes are also typical for chronic liver diseases. They manifest as "paper-thin" skin with loss of subcutaneous fatty tissue, marked fold formation, and the finest markings of teleangiectasia.

Hypotrichosis. *Hair growth pattern changes* occur in patients with chronic liver diseases, especially in liver cirrhosis. This is frequently manifested by loss of hair from the chest, abdomen, armpits, and pubic regions. This is probably due to changes in hormone status, leading also to *gynecomastia.*

Nail Changes. Nail changes are common in chronic liver diseases: whitish striation of the nails, opaque nails with a thin nail fold, coilonychia in hemochromatosis, or bluish coloration of the lunulae of the fingers in Wilson disease. Watch-glass nails and clubbed fingers also develop with chronic liver diseases.

Muscular Atrophy. Examination of patients with chronic liver disease frequently reveals muscular atrophy, especially of the extremities. This contrasts with an increase in ascites-induced abdominal distension.

Hemorrhagic Diathesis. Clinical signs of hemorrhagic diathesis are frequent in patients with severe acute and chronic liver diseases.

Other Liver-Specific Symptoms. Some skin changes are typical for a specific liver disease: grayish-brownish hyperpigmentation in hemochromatosis, *xanthelasma* in primary biliary cirrhosis with marked hypercholesterolemia, and porphyric dermatosis, mainly in porphyria cutanea tarda. The appearance of dilated veins on the anterior abdominal wall is a key feature of portal hypertension (*caput medusae*).

Many liver diseases also affect other organs or organ systems and, vice versa, many extrahepatic diseases (e. g., right ventricular failure and systemic hematologic or lymphatic diseases) can affect the liver. Clinical signs and symptoms should, therefore, always be assessed in the context of a complete clinical examination.

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Laboratory Parameters

The many available clinical and laboratory tests should be rationally selected to make the correct diagnosis (Tabs. 25.**2**, 25.**3**).

Hepatocellular Damage

The most important markers of hepatocellular damage are:

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)

While AST is localized in the cytoplasm and mitochondria, ALT is localized in the cytoplasm only. Glutamate dehydrogenase (GLDH) is is located in mitochondria only. Extrahepatic causes (e. g., myocardial infarction, muscular disorders, trauma) must be ruled out in the case of elevated transaminase levels, especially AST. GLDH, on the other hand, is very liver-specific. The AST : ALT ratio is typically > 1 in alcohol-induced liver disease and < 1 in liver diseases of viral origin. The highest transaminase levels are found in acute hepatitis (AST and ALT > 10 x upper limit of normal [ULN]). In obstructive jaundice, transaminase levels always rise, but generally remain at levels < 10 x ULN. Slightly to moderately elevated transaminase levels can indicate various liver diseases (e. g., alcoholic or drug-induced liver diseases, chronic viral hepatitis, liver cirrhosis, liver congestion).

Table 25.**2** Clinical–chemical diagnosis in hepatobiliary diseases

Clinical Features	Laboratory parameters
Hepatocellular integrity	AST, ALT
Biliary integrity	Alkaline phosphatase, γ-GT
Hepatocellular synthesis	Coagulation factors, PTT, serum albumin, cholinesteras

AST = aspartate aminotransferase; ALT = alanine aminotransferase; γ-GT = γ-glutamyl transpeptidase

Cholestasis

Alkaline phosphatase (AP) and γ-*glutamyltranspeptidase* (γ-GT) serve as laboratory parameters for cholestasis. Unlike γ-GT, AP also originates from organs other than the liver (AP isoenzymes, mainly osteoblasts, i. e., elevated values in children and adolescents [e. g., in bone metastases, Paget disease, hyperparathyroidism]) .

> γ-GT thus facilitates differentiation between hepatobiliary and bone-related causes of elevated AP levels.

The determination of AP isoenzymes is possible but rarely required. Simultaneously increased AP and γ-GT levels make a hepatobiliary disease very likely, while an

Table 25.**3** Laboratory findings in different liver diseases

Liver disease	Serum bilirubin	Transaminases	Alkaline phosphatase	PTT	γ-Globulins
Gilbert syndrome	unconjugated	normal	normal	normal	normal
Dubin–Johnson syndrome	conjugated	normal	normal	normal	normal
Acute hepatitis	mainly conjugated	↑ ↑ ↑	↑	normal – ↑ ↑ ↑	normal
Chronic hepatitis	mainly conjugated	↑ – ↑ ↑	normal – ↑	normal – ↑	normal – ↑ ↑ ↑
Liver cirrhosis	mainly conjugated	normal – ↑	normal – ↑	normal – ↑ ↑ ↑	↑ ↑
Cholestasis	mainly conjugated	↑ – ↑ ↑	↑ ↑ ↑	normal – ↑ ↑ (normal after intravenous vitamin K)	normal
Space-occupying lesions	mainly conjugated	normal – ↑	↑ ↑	normal – ↑ (late)	normal

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elevated AP level with normal γ-GT excludes a hepatobiliary cause. High serum AP levels are detected in obstructive jaundice and bacterial cholangitis.

Moderate increases occur in virtually all hepatocellular diseases (e. g., acute and chronic hepatitis, fatty liver, and liver cirrhosis). In addition, increased AP values are found in space-occupying liver lesions (e. g., metastases, hepatocellular carcinoma, hepatic abscess) and infiltrating or granulomatous liver diseases (e. g., sarcoidosis, miliary tuberculosis).

γ-GT is an extremely sensitive but less specific cholestasis parameter; higher values are often difficult to interpret.

Serum cholesterol levels may rise considerably with cholestasis. This typically is associated with xanthelasma formation in primarily biliary cirrhosis.

Hepatocellular Synthesis

The following are useful parameters for evaluating hepatocellular synthesis:

- coagulation factors
- serum albumin
- cholinesterase

Coagulation factors are particularly suitable parameters in acute liver diseases given their liver-specific synthesis and their short serum half-life. Determination of the prothrombin time (Quick test) or partial thromboplastin time (PTT) is generally sufficient. PTT can be prolonged in vitamin K deficiency (e. g., in obstructive jaundice). In this case, PTT normalizes within 12–24 hours after intravenous administration of 5–10 mg vitamin K. Absence of normalization indicates serious hepatocellular damage (e. g., severe hepatitis or liver cirrhosis).

Liver Screening

The evaluation of 3 parameters is generally sufficient for liver screening (see Tab. 25.**2**):

- AST or ALT (hepatocellular integrity)
- AP or γ-GT (biliary integrity)
- PTT (hepatocellular synthesis)

If all 3 parameters are normal, a clinically relevant hepatobiliary disease can, in all probability, be ruled out. Important exceptions are patients with inactive advanced liver cirrhosis or the early stages of metabolic liver diseases.

Urinary Findings

Conjugated bilirubin can be detected in the urine in conjugated hyperbilirubinemias, (i. e., in hepatocellular or cholestatic jaundice) and with the rare Dubin–Johnson or Rotor syndromes. Bilirubinuria rules out hemolysis as the only cause of jaundice. If urobilinogen is negative in the face of positive bilirubin in urine, complete biliary obstruction must be assumed.

Immunoglobulins

Liver cirrhosis, as well as chronic hepatitis with active inflammation (especially in autoimmune hepatitis), are associated with a polyclonal γ-globulin increase.

Quantitative Liver Function Tests

Quantitative liver function tests are used to assess the metabolic capacity and the blood supply-dependent liver clearance. These function tests are indicated in selected cases only. Examples include the *MEGX test*, which is based on the metabolism of lidocaine by oxidative de-ethylation into monoethylglycinexylidide (MEGX), and *indocyanine green* (ICG) *clearance*. Plasma ammonia as a parameter of hepatic urea metabolism is not sufficiently specific in many cases and does not correlate with the degreee of hepatic decompensation or encephalopathy.

Tumor Markers

In patients with focal liver lesions, tumor markers may be of importance:

- α-fetoprotein (AFP)
- carcinoembryonic antigen (CEA)
- carbohydrate antigen 19–9 (CA 19–9)

α-Fetoprotein (AFP). Normal values for AFP are below 10 μg/L. Levels of up to 500 μg/L are detected in pregnancy, in acute and chronic hepatitis and in liver cirrhosis. Levels > 500 μg/L are diagnostic for hepatocellular carcinoma (HCC) or tumors producing β-human chorionic gonadotropin (β-HCG). Apart from clearly elevated AFP levels, a continuous rise in AFP, even with values below 100 μg/L, suggests HCC und warrants further diagnostic steps. AFP is increased in approximately 70 % of patients with HCC.

Carcinoembryonic Antigen (CEA). CEA is a marker for colorectal carcinoma. As with most tumor markers, its

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value lies in the monitoring of the clinical course (e. g., following surgical resection of the tumor or after therapy in metastasizing colorectal carcinoma).

Carbohydrate Antigen (CA 19–9). Elevated CA 19–9 levels are frequent in pancreatic carcinoma, but also nonspecifically in cholestasis.

Autoantibodies

Immunologic tests allow differentiation of primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) from viral and toxic liver diseases. The following autoantibodies are clinically important (Tab. 25.**4**):

- *Antimitochondrial antibodies (AMA):* High-titer AMA, primarily IgG class, can be detected in >95% of patients with PBC. AMA have different antigen-specific characteristics; the AMA in PBC are typically directed against the M2 antigen (E2 subunit of mitochondrial pyruvate dehydrogenase). Various chronic liver diseases, such as primarily sclerosing cholangitis (PSC), sarcoidosis, other granulomatous liver diseases, and drug-induced cholestatic hepatitis can clinically mimic PBC but are AMA negative.
- An atypical perinuclear antineutrophil cytoplasmic antibody (*pANCA*) is frequently (80%) found in primary sclerosing cholangitis.
- *Antinuclear antibodies (ANA):* Different cell nucleus structures have been identified as ANA targets. ANA are typically markedly raised in systemic lupus erythematosus or in combined collagen disease (Sharp syndrome). A high-titer ANA, often in conjunction with a smooth muscle antibody (SMA) or liver cell membrane antibodies (LMA) is characteristic of AIH type I, previously termed "lupoid hepatitis." Various liver diseases (e. g., chronic viral hepatitis) are also associated with low-titer ANA.
- *Anti-smooth muscle antibodies (SMA):* Detection of high-titer anti-SMA IgG antibodies, especially with specificity for the smooth muscle actin, are useful for the diagnosis of AIH. SMA are often associated with other autoantibodies (e. g., ANA, low-titer SMA, AMA) and are found to a variable degree in many chronic liver diseases, as well as in viral infections, malignant tumors, collagenoses, and chronic inflammatory bowel diseases.
- *Liver–kidney microsome (LKM) antibodies:* A distinction is made between 3 subgroups of LKM antibodies:
  - *LKM 1 antibodies* are present in type II AIH, which is occasionally associated with hepatitis C virus (HCV) infection. Type II HCV-negative AIH has specific clinical characteristics that suggest a unique etiology and pathogenesis. In addition to onset at an early age (50% in childhood) and primarily monospecific autoimmunity against a specific epitope on cytochrome P450 2D6, this disease is characterized by a poor prognosis and a particularly frequent association with autoimmune diseases of other organs.
  - *LKM 2 antibodies* specifically occur in hepatitis induced by diuretic ticrynafen (tielinic acid).
  - *LKM 3 antibodies* are present in up to 20% of patients with chronic hepatitis D.

Other antibodies detected in association with autoimmune hepatitis include anti-soluble liver cell antigen (SLA) antibodies, anti-liver–pancreas (ALP) antibodies, anti-liver microsomal (ALM) antibodies and anti-asialoglycoprotein receptor (AASGPR) antibodies.

Hepatitis Serology

See Viral Hepatitis, below.

Table 25.**4** Autoantibodies in primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH)

PBC	AMA (M2)
PSC	pANCA
AIH type I	ANA (possibly + SMA, LMA)
AIH type II	LKM 1
AIH type III	SLA/LP
Ticrynafen-induced hepatitis	LKM 2
Hepatitis D-related AIH	LKM 3

AMA = antimitochondrial antibodies; pANCA = perinuclear anti-neutrophil cytoplasmic antibodies; ANA = antinuclear antibodies; SMA = smooth muscle antibodies; LMA = liver cell membrane antibodies; LKM = liver–kidney microsome antibodies; SLA = soluble liver cell antibodies; LP = liver–pancreas antibodies

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Imaging Techniques

- *Ultrasound* is the method of choice in the diagnosis of cholelithiasis, acute cholecystitis, extrahepatic cholestasis, circumscribed space-occupying lesions in the liver and pancreas, and small quantities of ascites.
- *Computed tomography* (CT) is useful for differentiating liver lesions (metastases, HCC, abscess, hemangioma, focal nodular hyperplasia, adenoma). Both methods are less informative in diffuse parenchymal liver diseases, i. e., normal findings do not exclude diffuse liver metastases or a micronodular, cirrhotic liver.
- *Duplex sonography* is particularly useful in the diagnosis of portal hypertension, portal vein thrombosis, Budd–Chiari syndrome, and veno-occlusive diseases It is also useful to assess the function of portosystemic shunts, TIPS and the patency of the hepatic artery after liver transplantation.
- *Magnetic resonance imaging* detects typical findings in hemochromatosis ("black liver"), but also contributes primarily to the diagnosis of focal liver lesions and the assessment of the biliary system (MRCP).
- *Laparoscopy* or ultrasound-guided *liver biopsy* allow assessment of the grade (degree of inflammation) and stage (degree of fibrosis) of liver diseases. Fibroscan may, in the future, replace biopsy for diagnosis of diffuse liver diseases and may become the method of choice for staging.
- *Endoscopic retrograde cholangiopancreaticography* (ERCP), percutaneous transhepatic cholangiography (PTC), and magnetic resonance cholangiography (MRC) have proved useful in the differential diagnosis of biliary diseases, especially in extrahepatic cholestasis. Apart from diagnosis, ERCP and PTC also allow therapeutic intervention.
- *Liver angiography*, among other methods, is relevant for the detection of hypervascularized liver tumors. In addition to duplex sonography, this technique is also useful in the diagnosis of hemobilia. Considerable significance is attributed to angiography in technical catheterization procedures, e. g., *transarterial chemoembolization* (TACE) and *transjugular intrahepatic portosystemic shunt* (TIPS).

Liver Biopsy

Tissues for histologic examination can be obtained through ultrasound-guided or CT-guided liver biopsy (Menghini technique), laparoscopy, or via the transjugular route. In many diffuse or granulomatous liver diseases the diagnosis can be established histologically only, particularly in early stages of liver cirrhosis. Other important indications for liver biopsy include an unexplained elevation in liver function tests, grading and staging of chronic hepatitis B and C, and suspected nonalcoholic steatohepatitis (NASH).

25.2 Special Differential Diagnosis of Jaundice

Isolated, Nonhemolytic Hyperbilirubinemias

Isolated, nonhemolytic hyperbilirubinemias are hereditary diseases with a benign clinical course, except for Crigler–Najjar syndrome type I. These can be subdivided into unconjugated and conjugated hyperbilirubinemias (Tab. 25.**5**).

Unconjugated Hyperbilirubinemias

Crigler–Najjar Syndrome Type I. This is due to a complete defect in the bilirubin UDP-glucuronyl transferase. The symptoms appear shortly after birth and prognosis is very unfavorable (kernicterus), if untreated.

Crigler–Najjar Syndrome Type II. The activity of bilirubin UDP-glucuronyl transferase is reduced. Jaundice usually appears in the first year of life but sometimes not until the second decade of life. Most patients are asymptomatic. Neurologic and intellectual defects can occur in some patients.

Gilbert Syndrome (Meulengracht Intermittent Juvenile Jaundice). The pathogenesis of this syndrome is complex and has not been fully elucidated. It is caused in part by reduced bilirubin UDP-glucuronyl transferase activity. Bilirubin levels fluctuate and generally do not exceed 3–4 mg/dL (51–68 μmol/L). Fasting can aggravate hyper-

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Table 25.**5** Differential diagnosis of hereditary isolated nonhemolytic hyperbilirubinemias

	Crigler–Najjar syndrome type I	Crigler–Najjar syndrome type II	Gilbert syndrome	Dubin–Johnson syndrome	Rotor syndrome
Serum bilirubin	↑ ↑ ↑, unconjugated 340–860 μmol/L 20–50 mg/dL	↑ ↑, unconjugated < 340 μmol/L < 20 mg/dL	↑, unconjugated < 68 μmol/L < 4 mg/dL	↑, conjugated 34–86 μmol/L 2–5 mg/dL	↑, conjugated 34–86 μmol/L 2–5 mg/dL
UGT activity	0	↓ ↓ (< 10 %)	↓ (60 %–70 %)	normal	normal
Acquired	AR	AR	AR	AR	AR
Age of onset	shortly after birth	first year of life to the second decade of life	postpuberty, mostly in men	extremely variable, mostly during the second decade of life	variable, mostly during childhood
Prognosis	very unfavorable (kernicterus)	generally good	very good	good	good
Prevalence	rare	rare	frequent (2–7 %)	rare	rare
Histology	normal	normal	normal (lipofuscin)	brownish-black pigment	normal

AR = autosomal recessive; UGT = bilirubin UDP-glucuronyl transferase

bilirubinemia. In most cases, the jaundice is detected by chance. Carriers are asymptomatic. Liver function tests and liver histology are normal, except for an increased lipofuscin deposit. The prognosis is good and no treatment is required.

Conjugated Hyperbilirubinemias

Dubin–Johnson Syndrome. Dubin–Johnson syndrome is an autosomal-recessive disease associated with an increase in conjugated bilirubin to 2–5 mg/dL (34–86 μmol/L) due to impaired hepatic bilirubin excretion (mutation of the *MRP2* gene). All other liver functions are normal. The syndrome is usually a chance finding during puberty. Pregnancy or oral contraceptives can trigger the disease. A brownish-black pigment in liver histology is characteristic.

Rotor Syndrome. The symptoms of Rotor syndrome largely correspond to those of Dubin–Johnson syndrome. However, no pigment is found in liver histology. The syndromes can be differentiated by oral cholecystography (gall bladder implicated in Rotor syndrome but not in Dubin–Johnson syndrome).

Viral Hepatitis

Differential Diagnosis. The differential diagnosis between viral, autoimmune, and toxic or drug-induced hepatitis is most important in patients with primarily hepatocellular diseases. While toxic liver damage is clinically very similar to hepatitis, drug-induced liver disease either takes a hepatitislike or a cholestatic course. Among all toxins, *chronic alcohol use* plays by far the most important role. In clinical practice, alcohol-induced liver diseases must be distinguished from nonalcohol-induced liver disease. The broad spectrum of alcohol-induced liver diseases (asymptomatic fatty liver, alcohol-induced hepatitis, alcohol-induced liver cirrhosis) with the variable clinical and biochemical findings must be considered.

Chronic Hepatitis: Definition and Classification. Chronic hepatitis is defined as hepatitis having a duration of at least 6 months. The previous classification system for chronic hepatitis in chronic persistent hepatitis and chronic active or aggressive hepatitis was replaced by a new classification system based on the etiology, inflammatory activity (grading), and degree of fibrosis (fibrosis, cirrhosis → staging) (Tab. 25.**6**).

Hepatitis Viruses. Currently, 5 different hepatitis viruses have been identified: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV) (Tab. 25.**7**). In addition to these primary hepatotropic viruses, various non-

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Table 25.**6** Classification of chronic hepatitis based on etiology

Type of hepatitis	HBsAg	anti-HCV (HCV RNA)	anti-HDV (HDV RNA)	Autoantibodies
B	+	–	–	–
C	–	+	–	2–10 % anti-LKM 1
D	+	–	+	10–20 % anti-LKM 3
Autoimmune hepatitis Type I Type II Type III	 – – –	 – (+) –	 – – –	 ANA (possibly + SMA, LMA) LKM 1 SLA/LP
Drug-induced	–	–	–	some: ANA, LKM, LM
Unknown	–	–	–	–

Table 25.**7** Hepatitis A–E

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Screening procedure	anti-HAV	HBsAg or anti-HBc	anti-HCV	anti-HDV	anti-HEV
Transmission	enteral	parenteral, sexual, perinatal	parenteral	parenteral	enteral
Incubation period (days)	15–49	25–160	21–84	60–110	10–56
Acute hepatitis	+	+	+	+	+
Fulminant hepatitis	very rare	rare (approx. 1 %)	very rare	occasional	rare (20 % during pregnancy)
Chronic hepatitis [%]	–	1–10	55–85	2–7 in coinfection, > 70 in superinfection	–
Cirrhosis in chronic hepatitis [%]	–	approx. 20–30	approx. 4–20	approx. 30–60	–
HCC	–	+	+	+	–

primarily hepatotropic viruses exist that can trigger concomitant hepatitis within the scope of a systemic infection, (e. g., cytomegalovirus [CMV], Epstein–Barr virus [EBV], herpes simplex virus [HSV], coxsackieviruses, measles virus).

Transmission. HAV and HEV infections are transmitted enterally. Most infections are associated with acute icteric hepatitis and all resolve. HBV, HCV, and HDV are transmitted parenterally and frequently lead to chronic hepatitis with the potential to progress to liver cirrhosis and HCC.

Hepatitis A

Pathogen, Transmission, and Epidemiology. HAV is a small RNA virus belonging to the Picornaviridae family. HAV infection is mostly transmitted enterally (fecal–oral) through contaminated water or food, or through contact with HAV-infected persons. Hepatitis A is particularly endemic in countries with a low socioeconomic standard. In these regions, children are mostly infected. In Western countries, hepatitis A is increasingly contracted during adulthood and a typical travel-related disease.

Serology. The diagnosis of hepatitis A is based on the detection of anti-HAV antibodies. The presence of anti-HAV IgM indicates acute hepatitis A. As hepatitis A resolves, anti-HAV IgM disappears, anti-HAV IgG levels rise, and generally persist for life, protecting against reinfection (Fig. 25.**2**; Tab. 25.**8**).

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Table 25.**8** Hepatitis viruses: interpretation of serologic and molecular findings

Virus	Marker	Interpretation
HAV	anti-HAV IgM	acute HAV infection
	anti-HAV IgG	resolved HAV infection and immunity against reinfection or, vaccination response
HBV	HBsAg	HBV infection
	HBeAg	replicative HBV infection
	anti-HBc IgM	acute or chronic HBV infection
	anti-HBc IgM + IgG	chronic HBV infection
	anti-HBc IgG	active or resolved HBV infection
	HBsAg + anti-HBe	nonreplicative HBV infection, replicative infection with HBV mutants
	anti-HBs + anti HBe	resolved HBV infection, anti-HBV immunity
	anti-HBs	resolved HBV infection and immunity against reinfection or, vaccination response
	HBV DNA	replicative HBV infection
HCV	anti-HCV	active or resolved HCV infection
	HCV RNA	replicative HCV infection
HDV	anti-HDV IgM	acute HDV infection
	anti-HDV IgM + IgG	chronic HDV infection
	anti-HDV IgG	resolved HDV infection
	HDV RNA	replicative HDV infection
HEV	anti-HEV	acute or resolved HEV infection
	HEV RNA	replicative HEV infection

Clinical Features. Hepatitis A is mostly an acute disease that rarely takes a protracted clinical course and never becomes chronic. Similarly, there is no asymptomatic carrier status. In children, HAV infection is generally asymptomatic or mild. In adults, after an incubation period of 25 days on average (15–49 days), clinically symptomatic, acute hepatitis is frequent. Apart from fatigue, lethargy, headache, loss of appetite, nausea, and vomiting, the first and most common clinical signs are dark urine, acholic stools and generalized jaundice. The clinical signs and symptoms generally regress within 2–3 weeks. A protracted or recurring clinical course is occasionally observed. From a clinical perspective however, these are mostly mild and patients always recover. Hepatitis A can also take a predominantly cholestatic course with jaundice and pruritus persisting for months with only moderately elevated transaminase levels. Fulminant clinical courses of hepatitis A are very rare and are observed mainly in drug users and elderly patients.

Hepatitis B

Pathogen, Transmission, and Epidemiology. HBV is a small DNA virus belonging to the Hepadnaviridae family. The prevalence of HBV infection shows marked, geographic differences. The disease is particularly prevalent in China, Southeast Asia, and parts of Africa. Intermediate prevalence rates are recorded in Central, Eastern, and Southern Europe, the Middle East, Japan, and Southern Asia. The prevalence rate is relatively low in North America and Western Europe (< 1%). In regions with high prevalence rates, HBV infection is mostly transmitted during the perinatal period or early childhood. In North America and Western Europe, the infection is parenterally or sexually transmitted. Intravenous drug users and homosexuals are particularly at risk.

Serology. HBsAg is the most important serologic marker of acute and chronic HBV infection (see Fig. 25.**2**; Tab. 25.**8**).

HBsAg alone establishes the diagnosis of HBV infection and is the screening test of choice in patients presenting with clinical or laboratory findings of hepatitis.

Anti-HBc screening is also appropriate in the rare cases of HBV infection with negative HBsAg (e. g., in fulminant hepatitis B with rapid viral elimination and seroconversion to anti-HBs, or in the case of HDV-superinfection, with transient suppression of HBV infection) and for epidemiologic studies because all subjects with active or past HBV infection are anti-HBc-positive.

HBsAg appears in *acute hepatitis B* shortly before clinical disease. Elevated transaminases, anti-HBc IgM and subsequently IgG can be detected. HBeAg indicates high viral replication and an early phase of the disease. As clinical symptoms regress and transaminase levels normalize, HBeAg and HBsAg disappear followed by seroconversion to anti-HBe and anti-HBs. Persistent hepatitis and HBV DNA positivity despite the loss of HBeAg or seroconversion to anti-HBe indicates infection by a HBV mutant that no longer produces HBeAg (so-called precore stop codon mutant).

The serologic constellation of anti-HBc, anti-HBe, and anti-HBs defines *resolved hepatitis B*, and reflects immunity against reinfection. Highly sensitive molecular analyses, however, show that HBV DNA can persist

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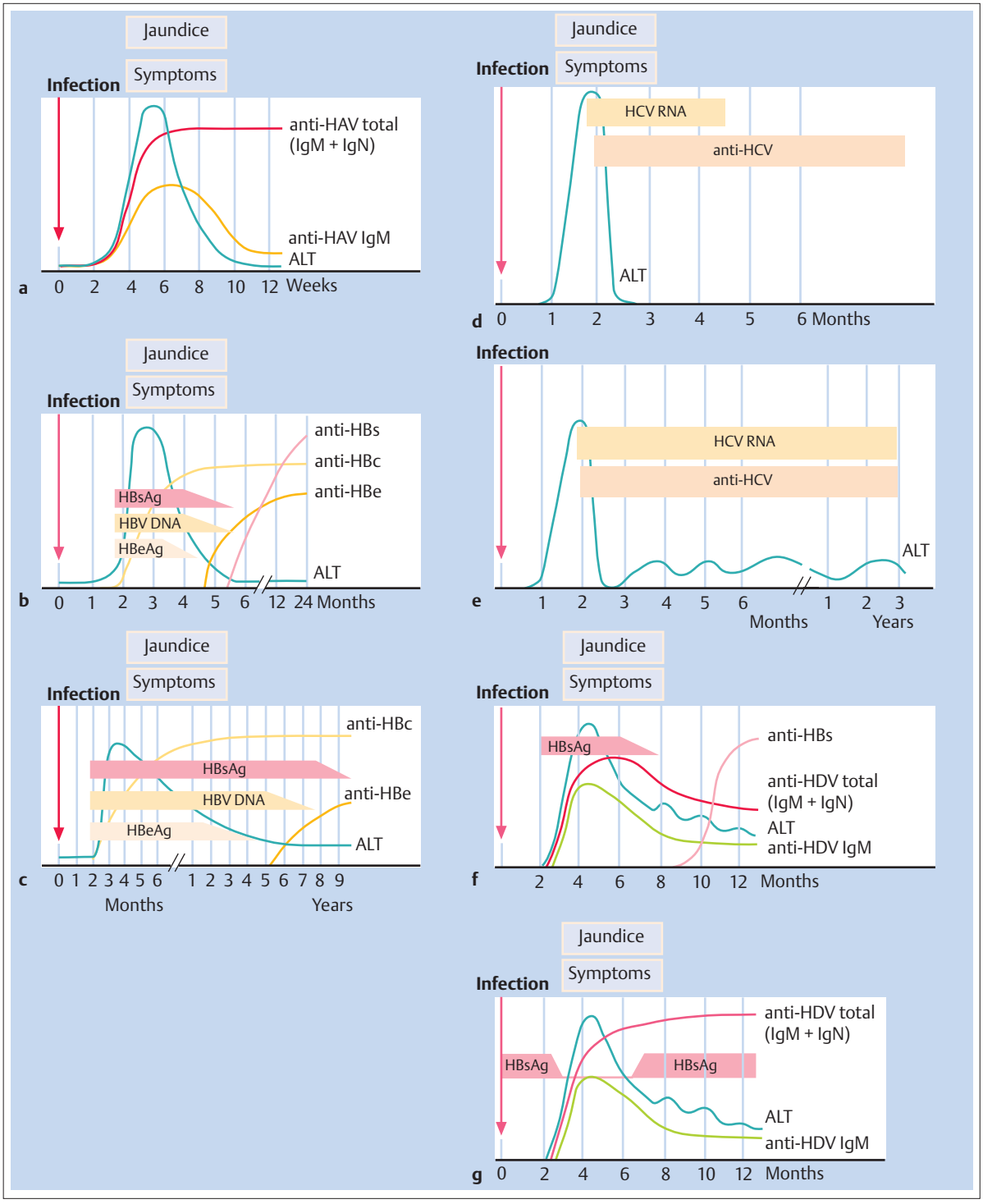

Fig. 25.**2** Clinical, laboratory, and virologic course of hepatitis A, B, C, and D (jaundice, transaminase levels, virus serology, and DNA/RNA).

a Hepatitis A
b Acute hepatitis B
c Chronic hepatitis B
d Acute hepatitis C
e Chronic hepatitis C
f HBV/HDV coinfection
g HBV/HDV superinfection

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in serum for several months or even years after clinical and serologic resolution of acute hepatitis B.

In chronic HBV infection, HBsAg generally persists for years or decades, with and without seroconversion from HBeAg to anti-HBe. Transaminase levels can be normal ("inactive HBsAg carrier") or elevated (chronic hepatitis B).

Following hepatitis B vaccination, anti-HBs is the only serologic marker indicating *vaccination response*.

Molecular Screening Methods. HBV DNA can be detected using signal amplification following *molecular hybrid capture* or branched DNA assay or *DNA target amplification* → polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The limit of detection using hybrid capture methods and PCR are 10^5–10^6 genome copies/mL and approximately 10^2 genome copies/mL, respectively.

Based on current knowledge and for practical reasons (infection, hepatitis activity, determination of therapeutic success during/after antiviral therapy), the result of a hybrid capture method is relevant with a limit of detection of 10^5 genome copies/mL. Molecular detection methods currently play a key role in the diagnosis and therapeutic monitoring of chronic HBeAg-negative/anti-HBe-positive hepatitis B. These tests are also relevant in the management of HBV-infected patients with or without immune suppression or to detect resistance to antivirals. The *HBV-genotype* (A–H) is of no clinical relevance at present.

Clinical Features. The clinical course of HBV infection depends, among other factors, on the age of the patient at the time of infection. In neonates or children, HBV infection is mostly asymptomatic but results in a carrier status in >90% of cases. In adults, by comparison, HBV infection is often symptomatic but acute hepatitis B spontaneously resolves in > 90% of patients. In patients with chronic hepatitis B, however, liver cirrhosis with a high HCC risk frequently develops.

In adults, clinically symptomatic, acute hepatitis frequently develops after an incubation period of approximately 75 days (25–160 days). The clinical symptoms and signs generally regress within 3–6 weeks.

Inactive HBsAg carrier status is a special course of chronic HBV infection frequently observed after perinatal or early childhood infection. It is characterized by positivity for HBsAg without any clinical, laboratory, or histologic evidence of hepatitis. The clinical course is generally favorable.

Clinically, it can be difficult to distinguish between acute hepatitis B and an *exacerbation of chronic hepatitis B*, because anti-HBc-IgM can be positive in both. The anti-HBc-IgM titers are usually higher in acute hepatitis B than in exacerbation of chronic hepatitis B. However, no quantitative tests have been validated or are routinely available.

Acute hepatitis B occasionally can take a fulminant clinical course (approximately 1% of cases), and is the most common viral cause of acute liver failure. Co-infection with HDV frequently occurs, especially in intravenous drug users.

Fibrosing cholestatic hepatitis is another special course of hepatitis B that develops mostly in patients with reinfection after liver transplantation. It generally leads to transplant failure within approximately one year.

Extrahepatic Manifestations. Extrahepatic manifestations of HBV infection are found in acute and chronic hepatitis B (e. g., a syndrome similar to serum sickness with fever, arthralgia and urticaria), hemolytic changes (aplastic anemia), vasculitis (e. g., panarteriitis nodosa), glomerular nephritis, and peripheral polyneuropathies.

Hepatitis C

Pathogen, Transmission, and Epidemiology. HCV is an enveloped RNA virus belonging to the Flaviviridae family. HCV infection is parenterally transmitted. Before anti-HCV screening, HCV was mainly transmitted through blood transfusions of or blood products. Currently, intravenous drug use is the main known route of transmission. Compared with HBV infection, mother–child and sexual transmission are rare. So-called sporadic cases with no known source of infection are common in clinical practice (approximately 50%).

Serology. Sensitive and specific third generation *enzyme immunoassays* (EIA) are currently available for the diagnosis of hepatitis C (see Fig. 25.**2**; Tab. 25.**8**). The *recombinant immunoblot assay* (RIBA) as a serologic confirmation test is recommended only in special situations (e. g., EIA positivity without evidence of hepatitis or anti-HCV positivity and negative HCV RNA).

Anti-HCV is positive on average seven to eight weeks after infection. In *acute hepatitis C*, anti-HCV can be detected in only 50–70% of patients. Therefore, if acute hepatitis C is suspected, HCV RNA should be determined by RT-PCR. HCV RNA can be detected one to two weeks after acute hepatitis C infection (Fig. 25.**2 d**).

Anti-HCV antibodies can persist for a long time or slowly disappear after successful treatment of HCV infection. Anti-HCV antibodies are always present in patients with *chronic hepatitis C*. Third-generation EIA can, very rarely, test negative in HCV-infected patients with severe immunosuppression or in dialysis patients. HCV RNA determination is key to detect HCV infection in these patients.

Molecular Detection Methods. The detection of HCV RNA by RT-PCR confirms the diagnosis of *chronic hepatitis C* and is central to assessing the *therapeutic results*. HCV genotype analysis and quantification by quantitative RT-PCR or bDNA assay are important for planning and monitoring treatment.

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Clinical Features. Acute hepatitis C with an incubation period of approximately 50 days (21–84 days) is, in most cases, asymptomatic. Jaundice is present in only about 25%. Acute hepatitis C develops into a chronic infection in 55–85% of patients. Within 20 years, approximately 4–20% of patients with chronic hepatitis C develop liver cirrhosis and then frequently a HCC. Hepatitis C very rarely takes a fulminant clinical course. Extraphepatic manifestations include combined cryoglobulinemia, glomerular nephritis, keratoconjunctivitis sicca similar to Sjögren syndrome, and B-cell non-Hodgkin lymphoma.

Hepatitis D

Pathogen, Transmission, and Epidemiology. HDV is an RNA viroid that replicates only in the presence of HBV. HDV infection is parenterally transmitted, mostly through blood or blood products and, rarely, through sexual contact. It is endemic in the Mediterranean region where 20–30% of HBsAg-positive subjects are anti-HDV positive. HDV infection is also frequently observed in high-risk groups such as intravenous drug users and hemophiliacs.

Serology. Diagnosis is based on the detection of anti-HDV in HBsAg-positive individuals (see Fig. 25.**2**; Tab. 25.**8**).

Clinical Features. Acute hepatitis D develops either as *co-infection* with an inoculum containing HBV and HDV, or as *superinfection* with HDV of a patient with chronic HBV infection.

The natural clinical course of HBV-HDV co-infection and HDV superinfection differs considerably. The clinical symptoms of acute hepatitis D appear after an incubation period of approximately 70 days (60–110 days). Following *acute HBV–HDV co-infection*, the clinical signs and symptoms regress within 2–10 weeks in 90–95% of patients. In 20–30% of patients, however, the clinical course is biphasic with a second rise in transaminase levels. The second phase can be very severe in some patients, leading to fulminant hepatitis D. Chronic hepatitis D develops in only 2–7% of patients after HBV-HDV coinfection.

HDV superinfection takes a fulminant or subfulminant course in 10–20% of patients. The rapid and high-titer anti-HDV positivity together with anti-HBc-positivity and frequently transient, undetectable HBsAg is key to diagnosis. Unlike coinfection, superinfection takes a chronic clinical course in 70–95%. In chronic hepatitis D liver cirrhosis is more common and of earlier onset than in patients with chronic hepatitis B only.

Hepatitis E

Pathogen, Transmission, and Epidemiology. HEV is a small RNA virus. The diagnosis of HEV infection is based on the serologic detection of anti-HEV antibodies (see Tab. 25.**8**). In Europe and North America, anti-HEV testing is indicated in patients originating or coming from HEV-endemic areas, with clinical and laboratory findings of acute icteric hepatitis and who are anti-HAV-IgM negative or anti-HAV IgG-positive.

Clinical Features. The clinical course of HEV infection is generally acute and self-limiting. Symptomatic acute hepatitis usually develops after an incubation period of 10–56 days. The clinical signs and symptoms normally regress within two to three weeks. HEV infection, can however, take a fulminant course, especially in women in the third trimester of pregnancy, with a mortality rate of 10–20%. Chronic HEV infection or an asymptomatic HEV carrier status are unknown.

Other viruses

In addition to the hepatitis viruses A–E, another parenterally transmitted virus, closely related to HCV, has been identified known as hepatitis G virus (HGV) or GB virus C (GBV-C). HGV or GBV-C, however, is not hepatotropic and no causal relationship with acute or chronic hepatitis has been demonstrated to date. The same applies for the TT virus (TTV), which was initially identified in a Japanese patient with the initials TT.

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Autoimmune Hepatitis

Pathogenesis. Autoimmune hepatitis (AIH) generally takes a chronic clinical course. Autoimmune processes play a major role in the pathogenesis. The disease mainly occurs in women and is often associated with autoimmune diseases of other organs.

Immunologic Diagnosis. Various autoantibodies are used to classify AIH (see Tab. 25.**4**). Whether this classification has etiologic, therapeutic, or prognostic significance is not known to date.

- ANA, possibly with SMA and LMA, are typical for *AIH type I*.
- *AIH type II* is characterized by LKM 1 antibodies directed against cytochrome P4502D6.
- Cytosolic autoantibodies such as anti-SLA and anti-LP are typical for *type III AIH.*
- Certain forms of *drug-induced hepatitis* (ticrynafen, dihydralazine, carbamazepine) are immune-mediated and are frequently positive for autoantibodies, e. g., ANA, LKM (LKM 2 with ticrynafen-induced autoimmune hepatitis) and LMA.

Clinical Features. AIH generally begins insidiously. Women are affected four times more often than men. The disease occurs mostly between the ages of 15–24 or between 45–55 years of age. Fatigue, upper abdominal pain, and oligomenorrhea or amenorrhea are the initial clinical signs and symptoms. Transaminase levels are always elevated and can reach levels > 10 x ULN in symptomatic patients. Elevated ESR and polyclonal hypergammaglobulinemia are cardinal symptoms. High ANA, SMA, or LKM 1 autoantibody titers confirm the diagnosis. The diagnosis of AIH is very important because immunosuppressive therapy is required, while chronic viral hepatitis B and C are treated, among others, with pegylated interferon-α, for example. Interferon-α, however, is contraindicated in AIH while immunosuppressants result in exacerbation of viral hepatitis.

Toxic and Drug-Induced Liver Diseases

Toxic and drug-induced liver diseases are frequent and have a broad range of clinical presentations. Typical examples of drug-mediated liver diseases are listed in Tab. 25.**9**. A detailed drug history, including herbal drugs (e. g., *Chelidonium majus*, greater celandine) and others is most important. Alcohol plays the major role among toxins

Alcohol-Induced Liver Diseases

The spectrum of alcohol-induced liver diseases includes fatty liver, hepatitis, and liver cirrhosis.

Alcoholic Fatty Liver

Clinical Features and Diagnosis. Fatty liver is the earliest and most common liver pathology following excessive alcohol consumption. In general, it is clinically asymptomatic and presents with hepatomegaly. Rarely, the liver is painful upon palpation; loss of appetite, nausea, and vomiting may occur. Severe liver dysfunction is very rare. Laboratory analyses show relatively high γ-GT levels compared to AP. Transaminase levels are usually only slightly raised. The liver is soft upon palpation, provided that no fibrosis or cirrhosis is present. Ultrasound shows an enlarged liver with signs of steatosis (white liver, Fig. 25.**3**). Alcohol-induced fatty liver generally reverses within a few weeks following alcohol abstinence. With continued alcohol use, fatty liver can develop into cirrhosis without any signs of hepatitis. Perivenular fibrosis is a typical precirrhotic lesion in these patients.

Differential Diagnosis. Differential diagnosis of *macrovesicular*, liver steatosis includes, in addition to alcohol, nonalcoholic fatty liver (NAFL) typically associated with obesity, diabetes mellitus and hyperlipidemia. Macrovesicular steatosis can also occur with endogenous or exogenous glucocorticoid excess, protein-deficient diets, prolonged fasting, total parenteral nutrition and with certain drugs (e. g., tamoxifen, amiodarone). This should be distinguished from *microvesicular* steatosis that can present as an acute, life-threatening liver disease (e. g., Reye syndrome, acute fatty liver during pregnancy [see below] or certain drugs [valproate and intravenous tetracycline]).

Alcohol-Induced Hepatitis

Clinical Features and Diagnosis. Alcohol-induced hepatitis is characterized by painful hepatomegaly, jaundice, fever, and leukocytosis. Liver failure (ascites, hepatic encephalopathy, gastrointestinal hemorrhage) may ensue in severe cases. Laboratory tests show raised

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Table 25.**9** Drug-induced liver diseases

Liver pathology	Clinical presentation	AST/ALT	AP	Examples
Hepatocellular				
Inflammation	acute: acute hepatitis	↑ – ↑ ↑ ↑	↑	INH, diclofenac, paracetamol
	chronic: AIH	↑ – ↑ ↑	↑	nitrofurantoin, methyldopa
Steatosis	acute (microvesicular): Reye syndrome			intravenous tetracycline, valproate
	chronic (macrovesicular): alcohol-induced fatty liver	↑	↑ – ↑ ↑	methotrexate, glucocorticoids
Cirrhosis				methotrexate, amiodarone
Cholestasis				
Canalicular		normal	↑ – ↑ ↑ ↑	anabolic and contraceptive steroids
Hepatocanalicular	primary biliary cirrhosis	↑	↑ – ↑ ↑ ↑	chlorpromazine, ajmaline, erythromycin
Ductal	primary sclerosing cholangitis	↑	↑ – ↑ ↑ ↑	intra-arterial 5-fluorouracil
Granuloma				sulfonamides, allopurinol, amiodarone
Vascular				
Peliosis hepatis		↑	↑ ↑	anabolic and contraceptive steroids
Budd–Chiari syndrome	liver congestion	↑ – ↑ ↑	variable	oral contraceptives
Veno-occlusive disease				high-dose chemotherapy in conjunction with bone marrow transplantation
Portal hypertension				vitamin A intoxication
Hepatic tumors				
Adenoma				oral contraceptives, alkylated steroids
HCC				alcohol; aflatoxin B1
Malignant hemangioendothelioma				vinyl chloride, estrogens

transaminase levels combined with elevated cholestasis parameters. The AST : ALT ratio is frequently > 2. Hyperlipidemia and a macrocytosis of erythrocytes, possibly anemia, are characteristic features. Thrombocytopenia may also be present. Acute alcohol-induced hepatitis may be life-threatening. Subacute–chronic disease advances to liver cirrhosis in many patients but has a good prognosis if alcohol use is stopped.

Zieve syndrome is a special form of acute alcohol-induced hepatitis, characterized by hyperlipidemia (primarily triglycerides, cholesterol), jaundice, and hemolytic anemia.

Differential Diagnosis. Findings similar to alcoholic steatohepatitis can occur in patients suffering from obesity, diabetes mellitus, hyperlipidemia, or following jejunum–ileum bypass surgery (*nonalcoholic steatohepatitis*, NASH). NASH belongs to the so-called nonalcoholic fatty liver diseases (NAFLD) and, following the exclusion of alcohol use and hepatitis C, is currently one of the most common causes of elevated liver enzymes. NASH can develop into liver fibrosis, cirrhosis and HCC.

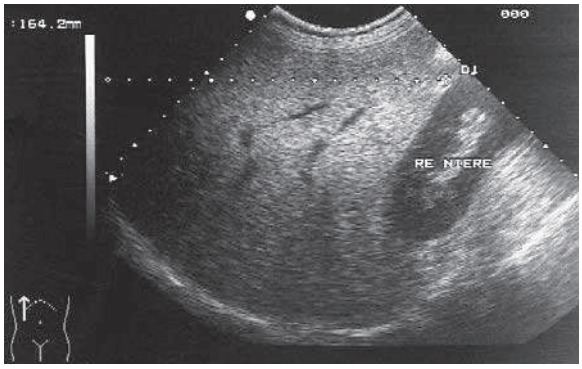

Fig. 25.**3** Ultrasound pattern in fatty liver. Enlarged liver with a dense echo pattern (white liver) as compared to renal parenchyma.

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Alcohol-Induced Liver Cirrhosis

See Liver cirrhosis, below.

Liver cirrhosis

Definition and Pathogenesis. Liver cirrhosis results from chronic liver diseases, independent of etiology.

Common criteria are necrosis of the liver parenchyma, nodular regeneration, and fibrosis with ensuing structural and vascular alterations of the liver (Fig. 25.**4**). The clinical spectrum ranges from asymptomatic patients, signs of chronic liver disease to acute life-threatening complications. Causes of liver cirrhosis are listed in Tab. 25.**10**. Viral hepatitis and alcohol use are the most important etiologic factors. Morphologically, macronodular and micronodular cirrhosis can be distinguished, without clear etiologic correlation, however.

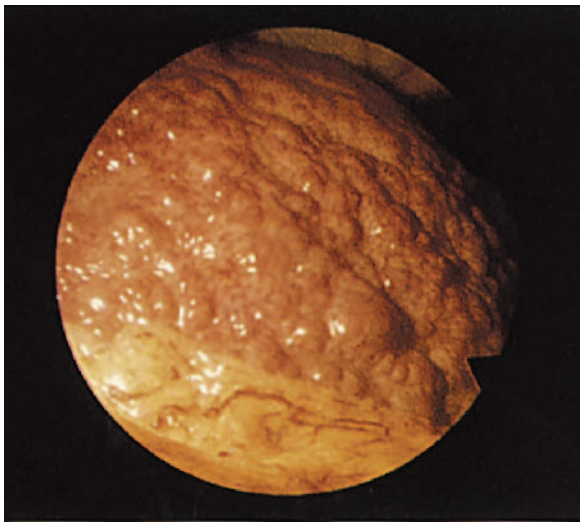

Fig. 25.**4** Laparoscopic findings in cirrhosis of the liver. Reproduced from Gerok W, Blum HE, eds. Hepatologie. 2nd ed. Munich: Urban and Schwarzenberg; 1995.

Table 25.**10** Etiologies of liver cirrhosis

- Drugs and toxins
  - e. g., alcohol, methotrexate, amiodarone
- Chronic hepatitis B, C, D
- Nonalcoholic steatohepatitis
- Autoimmune hepatitis
- Biliary diseases
  - primary and secondary biliary cirrhosis
  - primary and secondary sclerosing cholangitis
  - vanishing bile duct syndrome
- Hereditary metabolic disorders
  - hemochromatosis
  - Wilson disease
  - α_1-antitrypsin deficiency
  - glycogen storage disease types I and IV
  - galactosemia
  - hereditary fructose intolerance
  - cystic fibrosis and others
- Circulatory disorders
  - chronic right ventricular failure, pericarditis constrictiva, pericardial effusion
  - veno-occlusive disease
  - Budd–Chiari syndrome
- Idiopathic

Classification. The early stages of cirrhosis can be clinically asymptomatic. Clinically, cirrhosis can be *active* with signs of liver cell damage and necrosis (elevated transaminase and γ-globulin levels, jaundice, fever, weight loss, etc.) or *inactive*. The term *decompensated cirrhosis* refers to the presence of sequelae of the disease that are generally not spontaneously reversible (ascites, gastrointestinal hemorrhage, hepatic encephalopathy, hepatorenal or hepatopulmonary syndrome).

Clinical Features. In early stages of the disease symptoms are usually uncharacteristic: reduced fitness, fatigue, and diffuse abdominal discomfort. The liver is often enlarged.

In *compensated cirrhosis*, diagnosis is based on clinical symptoms, laboratory tests, and signs of portal hypertension. Examination reveals typical symptoms and skin changes (Figs. 25.**5**–25.**7**). A firm, nontender liver is found on palpation. Splenomegaly is often present. Most patients are anicteric or are only slightly jaundiced. Transaminase levels are normal or only a little elevated. AP levels, however, can be slightly to moderately raised. Serum protein electrophoresis usually shows a polyclonal hypergammaglobulinemia and, at advanced stages, hypalbuminemia.

The *decompensated stage* is characterized by portal hypertension. Ascites and meteorism, which occur earlier but also result from portal hypertension, dominate the clinical picture. The liver becomes smaller and is often no longer palpable due to ascites (Fig. 25.**8**, 25.**9**). The spleen is enlarged. Venous collaterals can be seen in marked cases as periumbilical *caput medusae* and endoscopically as esophageal varices. Hemorrhoids develop in some patients. Complications of portal hypertension (hemorrhage from the esophageal varices), terminal liver failure, and HCC are frequent causes of death.

Hepatic encephalopathy with confusion, stupor, and *flapping tremor*, frequently develops and can persist or fluctuate for a long time before progressing to coma. See Hepatic Encephalopathy, below, for trigger factors.

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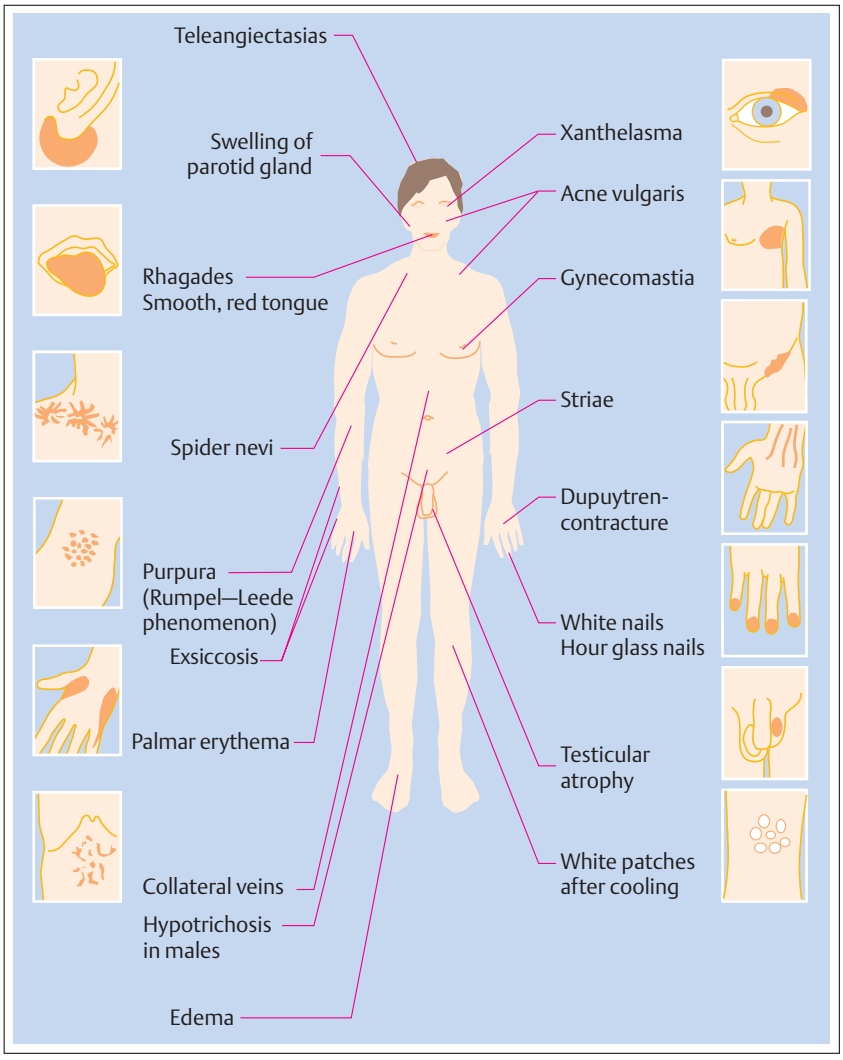

Fig. 25.**5** Clinical signs of liver cirrhosis.

a

b

Fig. 25.**6** Skin alteration in liver cirrhosis.
a Spider nevus (vascular spider, star nevus) with typical, central arterioles from which the vessels form a star pattern.
b Disappearance of spider nevus following central arteriole compression.

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Fig. 25.**7** Skin alterations in liver cirrhosis. Palmar erythema.

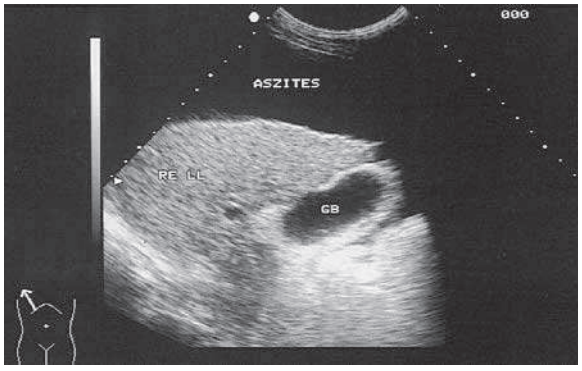

Fig. 25.**8** Ultrasound pattern in decompensated liver cirrhosis with ascites. Small liver with raised, uneven surface.
RE LL = right liver lobe; GB = gallbladder.

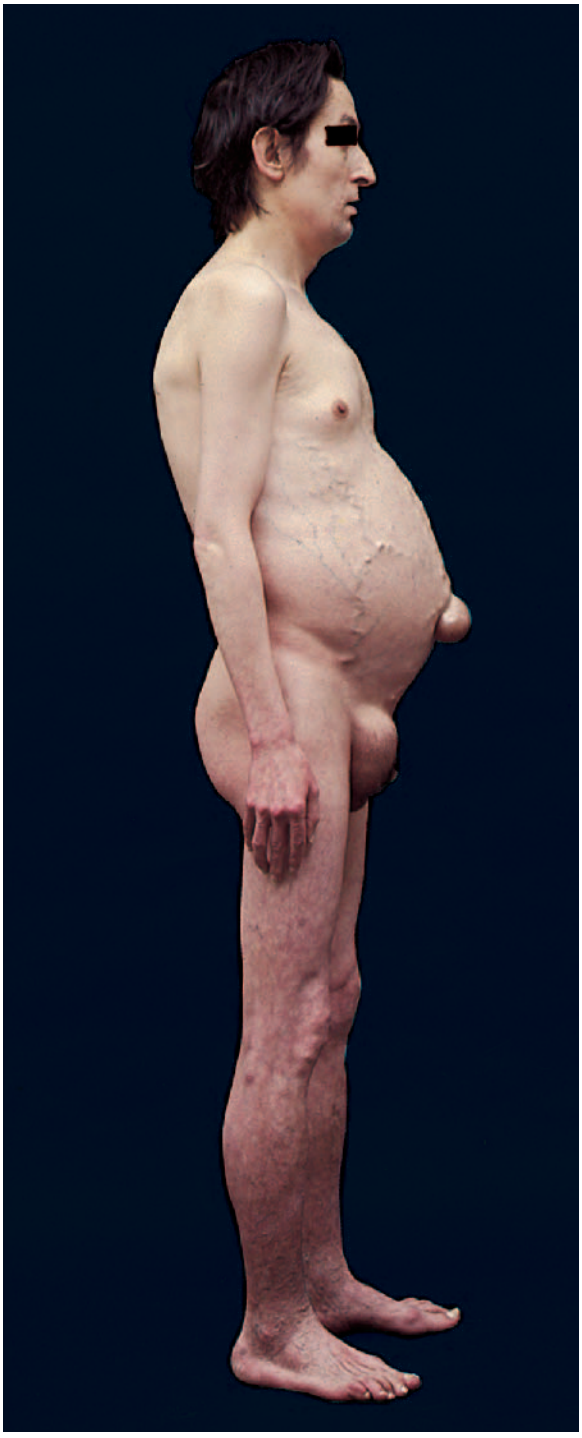

Fig. 25.**9** Patient with liver cirrhosis: ascites, umbilical hernia, inguinal hernia, venous collaterals, gynecomastia, absence of masculine secondary hair. ▷

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Other *frequent complications* include infections (spontaneous bacterial peritonitis, sepsis, tuberculosis), hypoglycemia, renal failure, hypersplenism, gastric and/or duodenal ulcers, and cholelithiasis (pigment stones).

Classification Depending on Severity. Liver cirrhosis is classified according to Child–Pugh, taking hepatic synthesis (albumin, PTT), biliary excretion (bilirubin), and clinical parameters into account (Tab. 25.**11**).

Table 25.**11** Child–Pugh classification of liver cirrhosis

Points	1	2	3
Albumin g/dL	> 3.5	2.8–3.5	< 2.8
Bilirubin mg/dL (μmol/L)	< 2.0 (< 34)	2.0–3.0 (34–51)	> 3.0 (> 51)
Quick %	> 70	40–70	< 40
Ascites	none	moderate	massive
Encephalopathy	none	grade I–II	>grade II

Child A: 5–6 points; Child B: 7–9 points; Child C: 10–15 points.

Ascites

Ascites is generally a symptom of advanced (liver) disease. Massive ascites can result in dyspnea, abdominal pain, immobility, and hernias.

Causes of ascites are listed in Tab. 25.**12**. The main causes are liver cirrhosis and malignant tumors.

Table 25.**12** Causes of ascites

Ascites in portal hypertension
- prehepatic: mainly portal vein thrombosis (generally no or little ascites)
- intrahepatic: liver cirrhosis
- posthepatic: Budd–Chiari syndrome and veno-occlusive disease

Ascites from liver congestion
- right ventricular failure (cor pulmonale)
- pericarditis constrictiva
- pericardial effusion

Malignant ascites
- peritoneal carcinomatosis
- intra-abdominal tumors (HCC, liver metastases, mesothelioma, malignant lymphoma, etc.)

Inflammatory ascites
- spontaneous bacterial peritonitis
- secondary bacterial peritonitis
- tuberculous peritonitis
- collagenoses
- genital infections (*Chlamydia*)

Pancreatogenic ascites
- acute or chronic pancreatitis (pseudocysts)

Rare causes of ascites
- severe hypalbuminemia (nephrotic syndrome, Ménétrier disease, etc.)
- mesenterial venous thrombosis
- uremia
- hypothyroidism
- chylous ascites
- hemoperitoneum (e. g., trauma)
- Meigs syndrome, etc.

Clinical Features.

- *Splenomegaly* indicates liver cirrhosis and portal hypertension.
- *Pleural effusions* are frequent in patients with ascites, regardless of etiology, due to defects in the diaphragm. It mostly occurs in cardiac congestion, liver cirrhosis (hepatic hydrothorax), collagenoses, (polyserositis in systemic lupus erythematosus), malignant tumors with diffuse metastases, and in *Meig syndrome* (benign ovarian tumor with ascites and pleural effusion).
- Ascites and *peripheral edema* indicate cardiac congestion or hypalbuminemia from different etiologies.

Spontaneous Bacterial Peritonitis (SBP). SBP develops in patients with ascites. Unlike secondary bacterial peritonitis, there is no perforation in the gastrointestinal tract. The symptoms range from asymptomatic to the characteristic, full-blown picture of peritonitis. SBP must be considered primarily when the patient's general condition deteriorates for unexplained reasons or when ascites no longer responds to a low-salt diet and diuretics. Other clinical signs of peritonitis such as fever, pain, or tenderness to palpation are unreliable and frequently absent. The detection of > 500 leukocytes/μL or > 250 polymorphonuclear leukocytes/μL is diagnostic for SBP. In addition to SBP, HCC, portal vein thrombosis, or tuberculosis must be considered in patients with known liver cirrhosis and ascites that become refractory to treatment.

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Analysis of Ascites

Ascites should be analyzed for protein concentration, cell count (including differentiation), infectious agents and, if indicated, cytology, which allows the differentiation of the cause of ascites (Tab. 25.**13**).

Transudate Versus Exudate. A distinction can be made between transudate and exudate based on the protein concentration. *Transudate* (protein content < 30 g/L, specific weight 1.005–1.018, serous) suggests cardiac congestion or portal hypertension. A serum–ascites–albumin gradient of 11 g/L also indicates portal hypertension.
Exudate (protein content > 30 g/L, specific weight > 1.018, cell-rich) indicates a malignant tumor, an infection, collagenoses, or pancreatogenic ascites. Exudates can be serous, fibrinous, hemorrhagic, or chylous. Hemorrhagic exudate is mostly due to malignancy, and sometimes to tuberculosis, trauma, or pancreatitis.

Malignant and Infectious Ascites. Malignant ascites is diagnosed by detection of malignant cells in the ascites fluid. Culturing for infectious agents is very important in infectious ascites, even though they are usually negative, especially in SBP. Pancreatogenic ascites can be diagnosed by its high amylase concentration.

Chylous Ascites and Pseudochylous Ascites. *Chylous ascites* is due to obstruction of the lymph flow through the thoracic duct. This is either idiopathic or occurs secondary to neoplasia, inflammation, tuberculosis, or trauma. In tropical regions, filariasis is another etiologic factor.
A distinction is made between genuine chylous ascites and *pseudochylous ascites*. The latter is characterized by a turbid, milky appearance and a lower triglyceride content (e. g., ruptured ovarian cysts).

Mucinous Ascites (Accumulation of Gelatinous Masses in the Abdominal Cavity). This occurs primarily with pseudomyxoma peritonei, extending from the appendix (mucoceles) or from ovarian cysts.

Table 25.**13** Differential diagnosis of ascites

	Macroscopy	Protein (g/L)	Leukocytes (μL)	Additional analyses
Liver cirrhosis	straw-colored or icteric	< 30	< 250 particularly mesothelial	
Spontaneous bacterial peritonitis	straw-colored, icteric, turbid	< 30	> 500 > 250 PMN	bacteriology
Secondary bacterial peritonitis	turbid or purulent	> 30	> 1000 predominantly PMN	bacteriology
Malignant ascites	straw-colored, hemorrhagic, mucinous, or chylous	> 30	> 1000	cytology
Tuberculous ascites	clear, turbid, hemorrhagic, or chylous	> 30	> 1000 mostly lymphocytes (> 70 %)	laparoscopy, peritoneal biopsy, bacteriology, PCR
Pancreatogenic ascites	turbid, hemorrhagic, or chylous	variable, often > 30	variable mostly < 1000	amylase activity

PMN = polymorphonuclear leukocytes.

Portal Hypertension

Clinical Features. The cardinal symptoms of portal hypertension are:
- ascites
- splenomegaly
- venous collaterals

Symptoms vary greatly, depending on the site of impaired portal flow. Collaterals in the abdomen (caput medusae, Fig. 25.**10**), the stomach, the esophagus (varices) and the rectum (hemorrhoids), are observed in all forms (Figs. 25.**11**; 25.**12**). A venous hum may be heard over the umbilical vein (*Cruveilhier-von-Baumgarten* sign).

Ascites is particularly marked in liver cirrhosis and in Budd–Chiari syndrome. In portal vein thrombosis, ascites is absent or occurs as a late complication.

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Fig. 25.**10** Caput medusae in a patient with chronic Budd–Chiari syndrome.

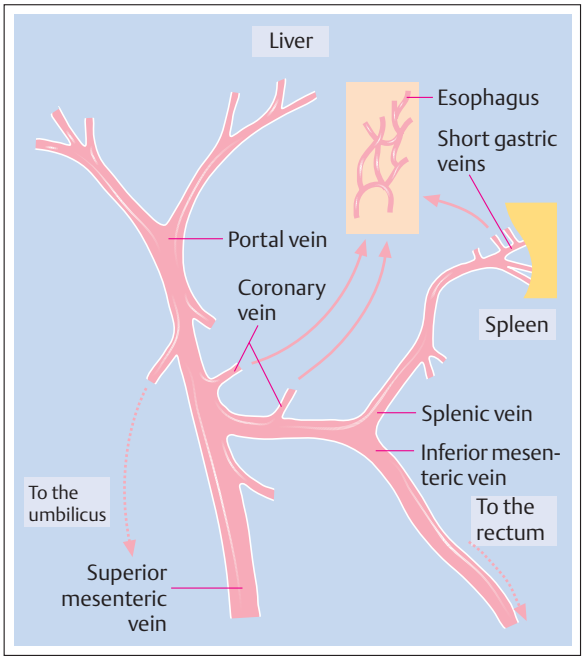

Fig. 25.**11** Diagram illustrating the major collaterals in portal hypertension.

Pathogenesis and Diagnosis. Portal hypertension classification according to the location of the venous flow impairment is illustrated in Fig. 25.**13**. Portal hypertension can result from impairment of the flow in the portal vein (prehepatic), liver (intrahepatic), or hepatic veins (posthepatic). The sinusoids of the hepatic lobule are the focal point for classification. Portal hypertension and its cause can usually be detected by duplex ultrasonography. Angiography (indirect splenoportography or mesentericoportography) or invasive hemodynamic measurements (normal and blocked hepatic vein pressure, portosystemic pressure gradient) are rarely required. The main diseases associated with portal hypertension are summarized in Tab. 25.**14**.

Prehepatic Causes. *Portal vein thrombosis* is the most common cause of portal hypertension. It can result from a neonatal umbilical vein infection, infection or inflammation in the abdominal region (appendicitis, pancreatitis, ulcerative colitis, Crohn disease, etc.), liver cirrhosis, HCC, pancreatic carcinoma, myeloproliferative syndrome, collagenoses, retroperitoneal fibrosis, trauma, disorders with hypercoagulability, or surgery (e. g., post-splenectomy).

Portal vein thrombosis should be suspected in patients with (bleeding) esophageal and/or gastric fundus varices without known liver disease. In prehepatic portal hypertension, caused by thrombotic obstruction of the portal vein, liver function is not or only slightly affected because the reduced portovenous flow is compensated by an increased arterial flow. In partial portal vein thrombosis, intrahepatic portal collaterals (so-called *cavernous transformation*), that ensure partial compensation, are formed.

Intrahepatic Causes. In intrahepatic venous flow obstruction, the block can be at the presinusoidal, sinusoidal, and postsinusoidal level.

Increased *intrahepatic presinusoidal resistance* is usually caused by granulomas or infiltrates with secondary fibrosis of the periportal regions (*sarcoidosis, systemic hematologic and lymphatic diseases, collagenoses*). In some countries, schistosomiasis is the main cause of presinusoidal portal hypertension. The parasite eggs, which are laid in the portal regions, induce granuloma and scar formation, resulting in impaired presinusoidal

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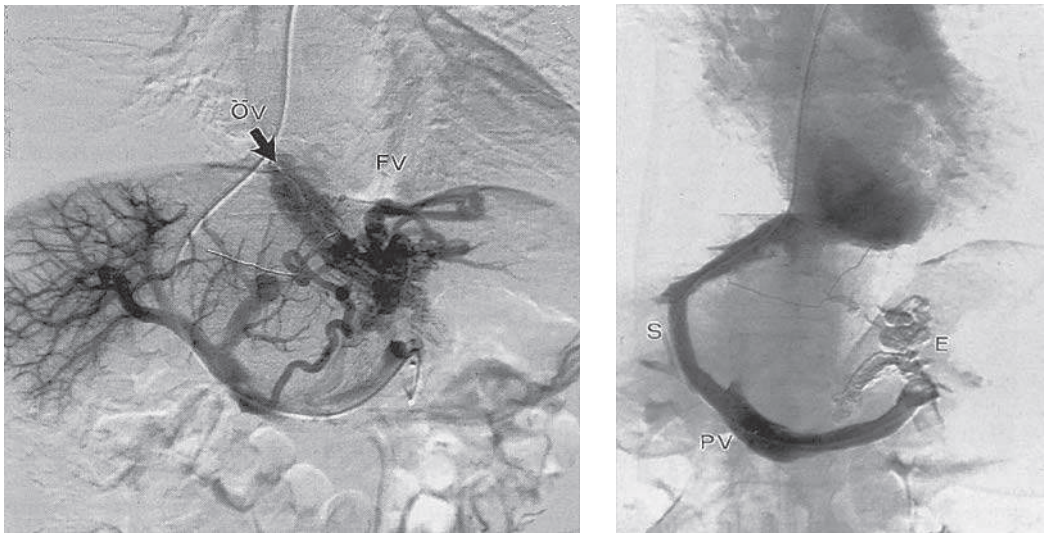

a b

Fig. 25.**12** Angiography of the portal system before and after TIPS implantation.

a Image illustrating varices originating from the left gastric vein. ÖV = esophageal varices; FV = fundus varices.

b Following TIPS implantation, the varices are no longer perfused. The hepatic portal circulation is substantially reduced by the stent shunt(s). PV = portal vein; S = stent shunt; E = collaterals embolized with histoacryl.

Reproduced from Gerok W, Blum HE, eds. Hepatologie. 2nd ed. Munich: Urban and Schwarzenberg; 1995.

Table 25.**14** Diseases with portal hypertension

Site of Flow Impairment	Frequent Diseases	Rare Diseases
Prehepatic	portal vein thrombosis	arterioportal fistula
Intrahepatic		
– presinusoidal	primary biliary cirrhosis	schistosomiasis sarcoidosis lymphoproliferative diseases congenital liver fibrosis idiopathic portal hypertension nodular regenerative hyperplasia
– sinusoidal	liver cirrhosis alcohol-induced liver disease	
– postsinusoidal	liver cirrhosis alcohol-induced liver disease	veno-occlusive disease Budd–Chiari syndrome
Posthepatic	right ventricular failure tricuspid (valve) failure constrictive pericarditis pericardial effusion	compression or thrombosis of hepatic veins by Budd–Chiari syndrome or tumor

flow. In *congenital liver fibrosis* (microcystic liver), the presinusoidal flow is obstructed by fibrosis of the periportal regions. Diagnosis can be suspected in patients with renal cysts and normal liver function. Diagnosis is confirmed by liver biopsy. Presinusoidal portal hypertension can also develop with *nodular regenerative hyperplasia*, which can be associated with collagenosis and lymphoproliferative diseases, among others, and with drugs (anabolic steroids and chemotherapeutic agents). *Idiopathic portal hypertension* is common in India and Japan and is characterized by elevated portal vein pressure with splenomegaly and collateral formation with patent portal veins, a normal liver structure, and function. Histology reveals periportal fibrosis and portal vein sclerosis.

An increased *intrahepatic sinusoidal resistance* is the most frequent cause of portal hypertension in liver cirrhosis.

Intrahepatic postsinusoidal portal hypertension is caused by impaired flow in intrahepatic veins.

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Posthepatic Causes. Elevated central venous pressure due to right-sided heart failure is the most common cause of posthepatic portal hypertension. In *pericarditis constrictiva*, portal hypertension can often be detected before cardiac symptoms (pulsus paradoxus), suggesting the diagnosis. The early formation of ascites (ascites praecox), generally accompanied by hypalbuminemia, dominates the clinical picture.

In patients with ascites without peripheral edema and with normal liver function, constrictive pericarditis should always be considered. This can be successfully treated by surgery.

Liver Failure

Liver failure can occur in any form of severe, diffuse liver disease. It is characterized by deterioration of all liver functions and is accompanied by hepatic encephalopathy.

A rapid deterioration of the physical condition, loss of appetite, apathy, confusion, tremor, foetor hepaticus, and hypovolemia indicate liver failure. Jaundice quickly progresses, transaminase levels decrease and PTT increases. Vitamin K therapy has no impact.

The main causes of acute liver failure are viral, toxic and drug-induced.

Hepatic Encephalopathy

Definition. Hepatic encephalopathy (HE) is characterized by an altered state of consciousness due to advanced liver disease.

Pathogenesis. The pathogenesis of HE is only partially understood. Toxic substances from the intestinal tract, which are no longer detoxified by the liver, or which bypass the liver via the collateral circulation or shunts, enter the brain and contribute to HE. A high-protein diet, gastrointestinal hemorrhage, electrolyte imbalance (hypokalemia [diuretics]), hypovolemia, and the administration of sedatives can trigger HE in patients with advanced liver disease.

Clinical Features. Depending on the grade of HE, it can present as reduced intellectual functions, lack of concentration, delirium, and coma. *Flapping tremor* is a typical feature. Writing tests are useful for monitoring HE. The EEG shows typical changes. Delirium tremens, alcohol-induced hallucination, and subdural hematoma must be ruled out in alcoholics. Generally, patients with delirium tremens are more active and apprehensive, have less general tremor, well-structured conversation, and less stupor. In addition, severe liver dysfunction is not typical in delirium tremens.

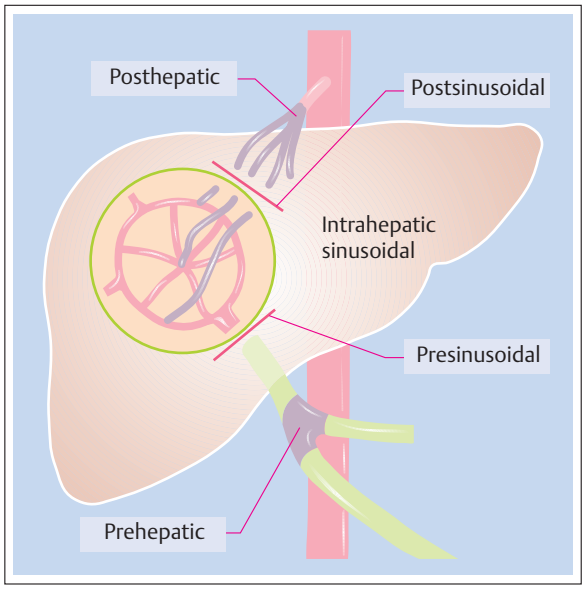

Fig. 25.**13** Diagram illustrating the locations of venous flow impairment in various forms of portal hypertension; (1) prehepatic, (2) intrahepatic–presinusoidal, (3) intrahepatic–sinusoidal, (4) intrahepatic–postsinusoidal, (5) posthepatic.

Hepatorenal Syndrome

Definition. Hepatorenal syndrome (HRS) is defined as progressive oliguric renal failure in patients with severe liver disease and portal hypertension and without clinical, laboratory, or pathologic–anatomic evidence for other causes of renal failure.

Pathogenesis. Renal vasoconstriction plays a central role in the pathogenesis of HRS. Oliguria with excretion of virtually sodium-free urine occurs in the face of marked water and sodium retention. In contrast to prerenal failure, expansion of the plasma volume does not improve renal function in HRS.

Hepatopulmonary Syndrome

If in patients with liver cirrhosis arterial hypoxemia cannot be explained by a lung or heart disease, pleural effusion or ascites, a hepatopulmonary syndrome (HPS) should be considered, analogous to HRS.

Pathogenesis. Intrapulmonary arteriovenous shunts and a pathologic ventilation–perfusion ratio contribute to the development of HPS. Cyanosis and clubbing of the fingers are frequent. However, most patients have no marked pulmonary symptoms. Reduced blood oxygen saturation on standing (orthodeoxia) or platypnea (dyspnea in upright position that improves in supine

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position) are typical but not specific and can also occur in other pulmonary or cardiac diseases. The cause is attributed to increased perfusion of the dilated blood vessels in the poorly ventilated, basal sections of the lung in the upright position, resulting in an increase in shunt volume. Intrapulmonary shunts can be detected by contrast medium echocardiography or lung perfusion scintigraphy.

Metabolic Liver Disorders

Several hereditary metabolic disorders can lead to liver cirrhosis (see Tab. 25.**10**). Hereditary hemochromatosis, Wilson disease, and α_1-antitrypsin-deficiency are the most frequent clinical entities.

Hemochromatosis

Definition and Epidemiology. *Hereditary hemochromatosis* (HH) is an autosomal-recessive inherited disorder of iron metabolism caused in many cases by a mutation of the *HFE* gene. With a prevalence of homozygotic gene carriers of 1:400 and a disease manifestation in 1:500 to 1:4000, HH is the most frequent hereditary liver disease in caucasians. Secondary forms of iron overload in the liver as in chronic hemolytic anemia, chronic viral hepatitis, or alcohol use should be distinguished from HH.

Pathogenesis. Increased intestinal iron absorption, leading to iron overload of various organs, especially the liver, pancreas, and heart, plays a key role in the pathogenesis of HH. Early diagnosis is of major importance because timely therapy by phlebotomy can prevent irreversible organ damage and lead to normal life expectancy.

Clinical Features. The disease is more prevalent in men than in women, and becomes symptomatic between 40–60 years of age. Symptoms are nonspecific and include fatigue, lethargy, abdominal discomfort, joint pain, and impotence. Among the various organs affected, *pancreatic involvement*, results in diabetes mellitus during the early stages. Liver cirrhosis and *osteoarthropathy* frequently occur. Hypophyseal insufficiency is occasionally observed. Advanced stages are characterized by *cardiomyopathy with arrhythmias* and heart failure. Testicular atrophy is particularly marked. Grayish-brownish hyperpigmentation of the skin (bronze diabetes) and of the mucosa with a typical smoky gray discoloration of the palms of the hands are typical for HH. The HCC risk is approximately 40 times higher than in the general population.

Table 25.**15** Iron indices in hereditary hemochromatosis

	Normal	Hereditary hemochromatosis
Serum iron (μg/dL)	60–160	> 160
Transferrin saturation (%)	< 45	> 60
Serum ferritin (μg/dL)	< 300	> 700
Iron content of the liver (mg/g [μmol/g] dry weight)	< 1.7 (< 30)	> 4.5 (> 80)
Liver iron index	< 1	> 2

Liver iron index = iron content of the liver (μmol/g dry weight)/age.

Diagnosis. An *elevated transferrin saturation* of > 60% (> 80% = diagnostic) and *increased serum ferritin* levels (> 700 μg/dL; Tab. 25.**15**) are characteristic of HH. Ferritin is an acute phase protein and can also be nonspecifically elevated. An increased liver iron content (> 4.5 mg/g [> 80 μmol/g] dry weight; liver iron index = μmol/g dry weight/age > 2.0) suggests HH.

Liver iron content is also increased in secondary hemosiderosis. A liver iron index of > 2.0, however, distinguishes HH from secondary hemosiderosis.

Mutations in the disease-causing *HFE* gene can be detected by PCR: approximately 85% of patients are homozygous for the C282Y mutation. Most of the other patients are heterozygous for the C282Y and H63D mutation (so-called compound heterozygotes) or have a mutation in another gene involved in iron metabolism.

Wilson Disease

Definition and Pathogenesis. Wilson disease (WD) is an autosomal-recessive inherited disease of the copper metabolism resulting in toxic copper deposits in various organs, especially liver and central nervous system. This is caused by mutations of the copper-transporting P-type ATPase (*ATP7B* gene on chromosome 13), which is involved in biliary copper excretion.

Clinical Features. The clinical symptoms vary greatly. WD, therefore, must be considered in any unclear liver disease, especially in younger patients. The brownish-greenish *Kayser–Fleischer corneal ring*, which can often be detected only using a split lamp, is pathognomonic (Fig. 25.**14**).

WD generally becomes symptomatic between the ages of five and 30. A typical patient presents with *chronic liver disease and/or neurologic or neuropsychiatric symptoms*. Cerebral copper accumulation damages

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the basal ganglia as well as the thalamus, resulting in extrapyramidal, cerebellar, and pseudobulbar symptoms, such as tremor, dysarthria, and ataxia. Fulminant liver failure, which is characteristically accompanied by Coombs-negative hemolysis, is rare, but common in patients with WD who interrupt therapy. Additional symptoms include sunflower cataract, renal dysfunction, cardiomyopathy, osteoporosis, osteomalacia, and hyperpigmentation.

Diagnosis. Diagnosis is established by:
- detection of the Kayser–Fleischer corneal ring
- reduced serum ceruloplasmin (< 200 mg/L)
- reduced serum copper levels (< 3 μmol/L) and increased free copper (> 3.9 μmol/L)
- elevated urinary copper (> 100 μg/24 h), especially following administration of D-penicillamine (1500–3000 μg, 6 hours after administration)
- increased copper levels in the liver (> 250 μg/g dry weight)

The Kayser–Fleischer corneal ring is seen in all patients presenting with neurologic symptoms and in 55–70 % of patients with liver disease only. It can also be seen in chronic cholestasis accompanied by copper accumulation (e. g., primary biliary cirrhosis).

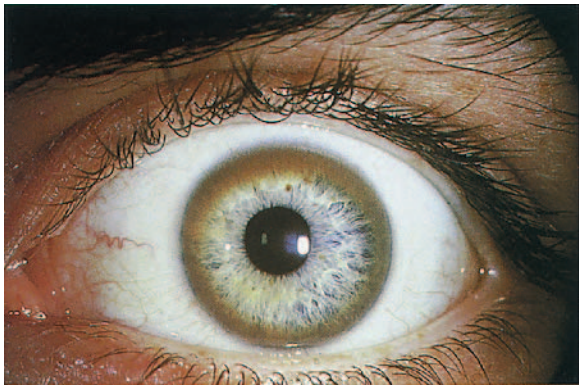

Fig. 25.**14** Kayser–Fleischer corneal ring in Wilson disease. Reproduced from Gerok W, Blum HE, eds. Hepatologie. 2nd ed. Munich: Urban and Schwarzenberg; 1995.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is a rare disease that presents primarily in children as liver disease and obstructive pulmonary disease. In adulthood, the disease becomes symptomatic as liver cirrhosis and its complications, including HCC. More than 60 biochemical variants of α_1-antitrypsin have been identified to date. The most common types are the protease inhibitor variants (Pi) M, S, and Z. The disease occurs in the homozygous form, PiZZ, and less frequently in the heterozygous form, PiSZ. The probability of a liver disease varies considerably. In adults the PiZZ genotype leads to liver cirrhosis in approximately 15 % of patients. Chronic obstructive pulmonary disease is the most common clinical sign of α_1-antitrypsin deficiency.

Absent or reduced α_1-globulins in serum electrophoresis suggest α_1-antitrypsin deficiency. Isoelectric focusing is used to differentiate between the various types, which can also be defined by molecular techniques.

Hepatovenous Causes of Liver Diseases

Hepatovenous causes of liver diseases include liver congestion, Budd–Chiari syndrome, and veno-occlusive disease.

Congested Liver

Liver congestion and liver cirrhosis must be distinguished. In patients with heart failure, it is often difficult to decide whether liver enlargement is due to heart failure, or vice versa, whether heart failure is the consequence of a coexisting heart and liver disease. Liver and heart disease is common in alcoholics (e. g., alcohol-induced cardiomyopathy). On the other hand, chronic right-sided heart failure can cause liver cirrhosis.

The *acutely congested liver* is often painful, especially upon palpation, and enlarged. Transaminase levels can rise significantly. Clinical signs of right-sided heart failure (congested neck veins, dilatation of the hepatic veins on ultrasound examination, absence of an inspiratory collapse of the inferior vena cava) suggest the correct diagnosis. Echocardiography is frequently helpful.

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Budd–Chiari Syndrome

Pathogenesis and Diagnosis. Massive hepatomegaly, extremely painful on palpation and accompanied by rapidly developing ascites, is typical of Budd–Chiari syndrome (BCS) with partial or complete obstruction of the hepatic veins or the inferior vena cava between the hepatic veins and the right atrium due to thrombosis, tumor, or a venous web. A distinction can be made between acute and chronic BCS.

Duplex ultrasonography is generally diagnostic. Acute right ventricular insufficiency and pericarditis constrictiva must be ruled out.

Clinical Features. In *acute BCS* venous obstruction affects the splanchnic system, resulting in fulminant hypoxic liver failure and rapidly developing ascites, and sometimes ileus.

In *chronic BCS* centrolobular necroses gradually extend and lead to cirrhosis. The clinical symptoms are dominated by massive ascites rather than liver cell insufficiency. Chronic BCS can occasionally be oligosymptomatic or even asymptomatic.

Causes. BCS occurs in patients with myeloproliferative syndrome (especially polycythemia vera), and coagulation disorders with hypercoagulability, in patients taking oral contraceptives, paroxysmal nocturnal hemoglobinuria, antiphospholipid antibody syndrome, pregnancy, infections (amebic abscess and echinococcosis), or tumors (HCC, renal cell carcinoma). Frequently, the cause remains unclear (idiopathic BCS).

Veno-Occlusive Disease

In hepatic veno-occlusive disease (VOD, endophlebitis, hepatica obliterans), the small draining veins are constricted or obstructed by thrombi. VOD is a frequent cause of liver dysfunction following high-dose chemotherapy in preparation for bone marrow transplantation. It occurs within 3 weeks, but mostly within the first few days after transplantation. Clinical symptoms include jaundice, right-sided upper abdominal pain due to hepatomegaly, and sudden weight gain due to ascites. Duplex ultrasonography is generally diagnostic. Among other conditions, VOD also occurs after liver irradiation and in myeloproliferative syndrome.

Cholestatic Jaundice

Cholestatic jaundice is classified as *nonobstructive* (mostly intrahepatic) and *obstructive* (mostly extrahepatic) cholestasis, which require different therapeutic strategies (Tab. 25.**16**).

Intrahepatic Cholestasis

This term refers to cholestasis *originating in the liver* that is caused by impaired elimination of conjugated bilirubin due to diseases at different levels (postmicrosomal, i. e., following conjugation to bilirubin glucuronide), the bile capillaries, bile ductules, or larger intrahepatic bile ducts (Fig. 25.**15**).

Apart from the intracellular form (Dubin–Johnson syndrome), common features are clinical (pruritus) and biochemical signs of cholestasis (elevated AP, γ-GT, and possibly cholesterol levels). In contrast to extrahepatic cholestasis, pain, cholangitis, and above all, dilatation of the extrahepatic bile ducts are absent.

Jaundice During Pregnancy

If jaundice develops during pregnancy, pregnancy-specific causes must be distinguished from the more frequent diseases associated with jaundice (e. g., viral or drug-induced hepatitis, cholelithiasis). In pregnancy serum albumin levels decrease secondary to an elevation of the plasma volume and an increase in AP levels originating from the placenta. Spider nevi and palmar erythema can occur, but disappear following delivery.

Pregnancy-Specific Causes. Hyperemesis gravidarum, intrahepatic pregnancy-related cholestasis, acute pregnancy-related fatty liver, (pre)eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) are the major causes of pregnancy-specific jaundice (Tab. 25.**17**).

- The clinical picture of *hyperemesis gravidarum* is dominated by nausea and vomiting. Mild hyperbilirubinemia is frequently observed, but usually disappears on normal caloric intake.
- *Intrahepatic pregnancy-related cholestasis* typically manifests with pruritus during the third trimester of pregnancy. Jaundice can appear 1–4 weeks later but is often absent. Pruritus and jaundice disappear immediately after delivery, but are likely to recur during subsequent pregnancies.
- *Acute pregnancy-related fatty liver* is a rare disease characterized by microvesicular fatty liver. It develops towards the end of pregnancy and has a very severe prognosis. Nausea, vomiting, and upper abdominal pain are followed within one to two

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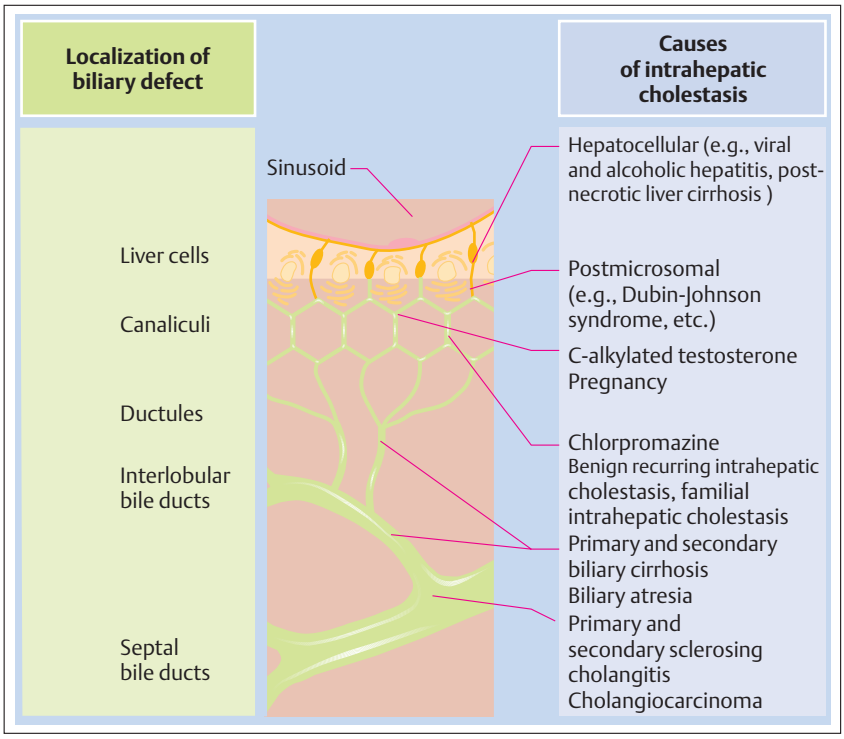

Fig. 25.**15** Classification of intrahepatic cholestasis based on localization of biliary defect.

Table 25.**16** Differential diagnosis of cholestasis

Obstructive cholestasis	Nonobstructive cholestasis

– Extrahepatic obstruction
  – cholelithiasis
  – cholangiocarcinoma
  – papillary carcinoma
  – carcinoma of the head of the pancreas
  – pancreatitis, pancreatic pseudocysts
  – parasitosis (e. g., fasciolosis, ascariasis)
  – primary sclerosing cholangitis
  – duodenal diverticulosis
  – bile duct atresia
  – Mirizzi syndrome
– Intrahepatic obstruction
  – intrahepatic tumors or metastases
  – intrahepatic gallstones (Caroli syndrome)
  – primary sclerosing cholangitis
  – inflammation or fibrosis of portal regions
  – cholangiocarcinoma
	– Drugs and other substances (estrogens, phenothiazine, commercial toxins, etc.)
	– Severe bacterial infections (sepsis)
	– Intrahepatic pregnancy-related cholestasis
	– Familial intrahepatic cholestasis (Byler syndrome, Alagille syndrome)
	– Acute and chronic forms of hepatitis
	– Primary biliary cirrhosis
	– Other forms of liver cirrhosis
	– Postoperative jaundice
	– Total parenteral nutrition
	– Granulomatous and infiltrative liver lesions (sarcoidosis, malignancies)
	– Benign recurrent intrahepatic cholestasis
	– Intrahepatic biliary atresia

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Table 25.**17** Pregnancy-specific causes of jaundice

Disease	Jaundice	Trimester	Frequency
Hyperemesis gravidarum	mild	1 (or 2)	0.3%–1.0%
Intrahepatic pregnancy-related cholestasis	frequently only pruritus	2 or 3	0.1%–0.2%
Acute pregnancy-related fatty liver	frequent	3	0.008%
(Pre)eclampsia	rare, late	2 or 3	5%–10%
HELLP syndrome	rare, late	3	0.1%

weeks by jaundice. Untreated, fulminant liver failure frequently develops, and is often fatal. Immediate termination of pregnancy is mandatory.

- *(Pre)eclampsia* is characterized by the triad comprising edema, proteinuria, and hypertension (EPH gestosis) occurring late in the second or third trimester. The clinical picture is dominated by EPH and neurologic symptoms. Liver infarctions, subcapsular hematomas, and liver failure are rare complications.
- *HELLP syndrome* is a complication of severe preeclampsia. The syndrome can be attributed to microangiopathic hemolytic anemia with elevated transaminase levels and thrombocytopenia. Changes become apparent in the third trimester and are most marked in the first 2 days after delivery. Jaundice occurs only rarely.

Postoperative Jaundice

The potential causes and pathogenetic factors of postoperative jaundice are complex and include, among others, increased bilirubin levels from degradation of transfused erythrocytes, hematoma resorption, drugs, and hemodynamic factors. Benign, postoperative jaundice in general develops within three days after major surgery, reaching a peak of conjugated hyperbilirubinemia of 5–25 mg/dL (86–428 μmol/L) eight to 10 days after surgery, subsequently normalizing within 14–18 days. Transaminase levels are normal to moderately raised and AP levels are slightly to moderately increased.

Intrahepatic Cholestasis with Severe Infectious Diseases

Severe bacterial infections (e. g., sepsis, pneumonia, leptospirosis, salmonellosis) can be accompanied by cholestatic jaundice. The symptoms are dominated by the underlying diseases and jaundice is merely an accompanying symptom.

Drug-Induced Cholestatic Liver Diseases

Numerous drugs can lead to intrahepatic cholestasis. A mild *canalicular* form can be distinguished from a *hepatocanalicular* (cholangiolitic) form. Pure cholestasis is the cardinal symptom of the canalicular form, typically caused by estrogens, especially ethinyl estradiol, contraceptives, and C17-alkylated anabolic steroids. Portal inflammation with elevated transaminase levels is observed in the hepatocanalicular form. Typical causes are phenothiazines, especially chlorpromazine, ajmaline, thyreostatic drugs, and erythromycin. In contrast to the canalicular form, drug-induced cholestatic liver disease is usually dose-independent and starts within 4 weeks of treatment. The prodromal stage is short and mild. Febrile temperatures are frequent at onset. Jaundice is generally self-limiting once the causative drug has been discontinued but can, occasionally, last for several months.

Primary Biliary Cirrhosis

In *biliary cirrhosis* a primary and a secondary form can be distinguished. Biliary cirrhosis can be secondary to any intrahepatic or extrahepatic cholestasis and differs from primary biliary cirrhosis (PBC).

Definition. PBC is a chronic cholestatic liver disease of unknown etiology characterized by the destruction of *small intrahepatic bile ducts*, presumably caused by autoimmune processes. Women between 35–70 years of age are primarily affected.

Clinical Features. Difficult-to-treat pruritus is often the first symptom, many years before any other symptoms. Clinically, hepatomegaly, elevated AP levels, and the pathognomonic *antimitochondrial antibodies* with M2 specificity, which are detected in 95% of cases, characterize the patient with PBC. Fatigue, brown pigmentation of light-exposed skin (melanosis), skeletal pain (osteoporosis), and arthralgia frequently occur. Jaundice is a sign of advanced PBC.

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Diagnosis. The laboratory findings are characterized by elevated cholestasis parameters, hypercholesterolemia, and, in advanced disease, hyperbilirubinemia. Xanthelasmas and skin xanthoma develop in patients with severe, long-term hypercholesterolemia. Raised immunoglobulin levels, especially IgM, are frequently observed. PBC is often associated with other autoimmune diseases such as Sjögren syndrome, scleroderma, or CREST syndrome. Liver histology is helpful.

Primary Sclerosing Cholangitis

Definition. Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease of unknown etiology characterized by segmental inflammation and fibrosis of the *intra- and/or extrahepatic bile ducts*. It leads to secondary biliary cirrhosis via stenoses, inflammation and obliteration of the affected bile ducts.

Epidemiology. 70% of patients are men and the average age at onset is 40 years. Between 50–75% have coexisting chronic, inflammatory bowel disease, predominantly ulcerative colitis. Conversely, PSC is detected in 2–4% of patients with ulcerative colitis.

Clinical Features. The onset of the disease is generally insidious. Fatigue, pruritus, jaundice, and hepatomegaly may be present. AP levels are raised, but can fluctuate during the clinical course. *Perinuclear antineutrophilic cytoplasmic antibodies* (pANCA) develop in 70–85% of patients. Endoscopic retrograde cholangiography (ERC) typically revealing disseminated intrahepatic and extrahepatic bile duct strictures, is central to diagnosis (Fig. 25.**16**). Cholelithiasis frequently occurs. Recurrent cholangitis is a typical complication. The incidence of cholangiocarcinoma is increased.

Differential Diagnosis. Differential diagnosis includes PBC, cholangiocarcinoma, bile duct strictures following intra-arterial chemotherapy with 5-fluorouracil, cholangiopathy in HIV infection, and *secondary sclerosing cholangitis*, (e. g., due to postoperative strictures or congenital structural changes of the bile ducts).

Vanishing Bile Duct Syndrome. PBC and PSC can develop in the so-called *vanishing bile duct syndrome* (VBDS). This etiologically and pathogenetically heterogeneous syndrome is characterized by destruction of the small intrahepatic bile ducts with abnormal dilatations or fibrotic changes. Various inherited disorders and acquired disorders belong to this group. *Caroli disease* is characterized by dilatations of the large, segmental, intrahepatic bile ducts with formation of sludge and stones. In *Caroli syndrome*, dilatation of the major bile ducts is associated with portal fibrosis, resulting in portal hypertension. Acquired VBDS occurs in rejection following liver transplantation, in graft-versus-host disease, sarcoidosis, cystic fibrosis, cytomegaly virus infection (especially in immunosuppression), cryptosporidiae infection in AIDS, histiocytosis X, Hodgkin disease, and various drugs (e. g., chlorpromazine), in addition to PBC and PSC.

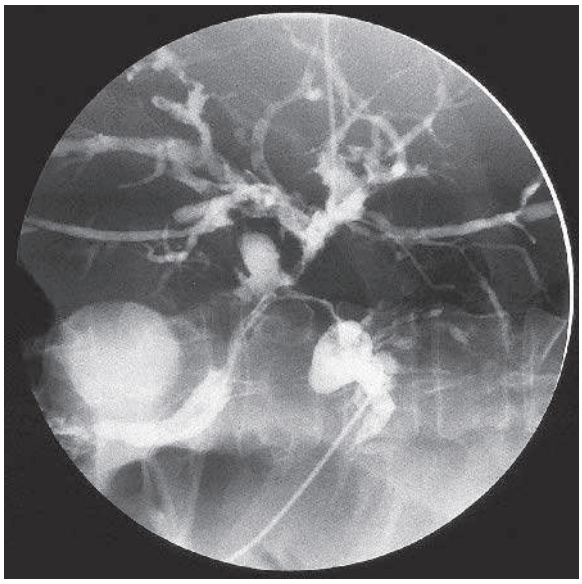

Fig. 25.**16** Percutaneous transhepatic cholangiography in a 40-year-old man with primary sclerosing cholangitis. The intrahepatic bile ducts show multiple stenoses and dilated segments.

Extrahepatic Cholestasis

Clinical Features. Bile flow is compromised by obstruction in the bile ducts. The liver is often enlarged and painful upon palpation, while the spleen is normal in size. Laboratory findings indicate cholestasis: elevated alkaline phosphatase, γ-GT, and bilirubin levels. Transaminase levels are usually only slightly elevated. A clear distinction between intrahepatic and extrahepatic cholestatis is often impossible by laboratory analyses and liver biopsy. In total obstruction, urinary bilirubin is positive and urobilinogen negative. The stool is acholic.

Diagnosis. Ultrasound examination is central to diagnosis of bile duct obstruction (Fig. 25.**17**; 25.**18**) together with ERC(P) or PTC (Fig. 25.**19**).

Stone Obstruction

Obese, multiparous, and diabetic women over 40 years of age frequently have gallstones. *Choledocholithiasis* is frequently accompanied by *cholecystitis*. Fever and chills suggest cholangitis. In gallstone obstruction, jaundice follows the initial pain or chills within 12–24 hours. In contrast to tumor obstruction, obstruction by gallstones is rarely complete over a prolonged period, and the stool

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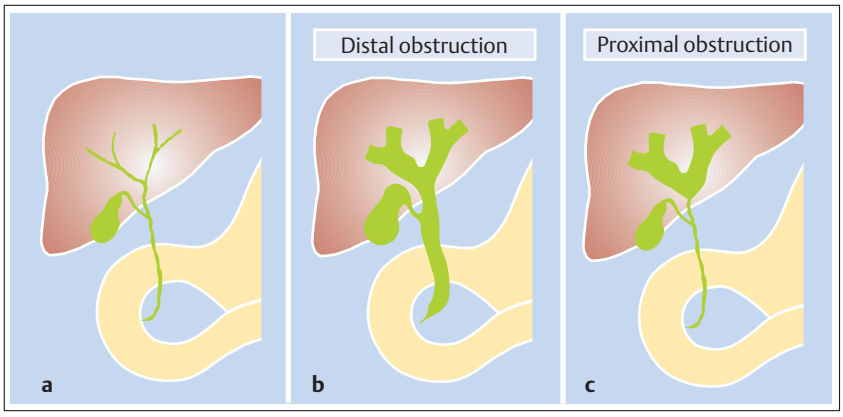

Fig. 25.**17** Diagram illustrating site of obstruction in
a Intrahepatic cholestasis
b, c Extrahepatic cholestasis

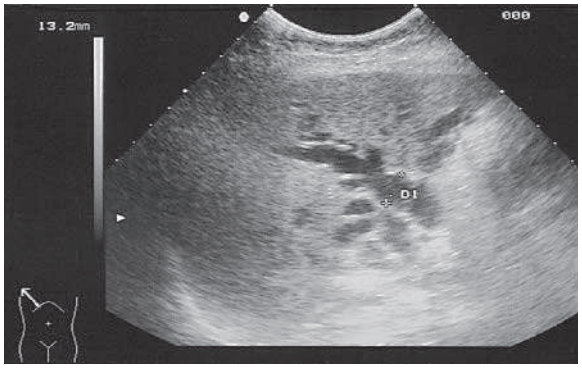

Fig. 25.**18** Extrahepatic obstructive jaundice. Ultrasound findings with dilated bile ducts in an 85-year-old woman with Klatskin tumor.

is only transiently acholic. Serum bilirubin levels do not reach excessive values.

Tumor Obstruction

Carcinoma of the head of the pancreas, the papilla Vateri, or the bile duct can lead to obstructive jaundice at early stages of the disease. It is generally painless.

If the gallbladder is palpable this is typically due to tumor obstruction (*Courvoisier sign*). In stone obstruction the Courvoisier sign is usually absent because the gallbladder, altered by recurrent cholecystitis, can no longer expand.

Other Causes of Obstructive Jaundice

- *Bile duct strictures* can be a complication of biliary surgery and can result in recurrent cholangitis.
- *Papillary stenosis*, usually in patients with cholelithiasis or after surgery, can result in intermittent cholestasis, and sometimes recurrent pancreatitis.
- Other less common causes include *congenital alterations* of the ductus choledochus or the papilla vateri (e. g., megacholedochus, choledochoceles, duodenal diverticula).
- Cholestasis is often observed in acute *pancreatitis* (compression of the distal, intrapancreatic ductus choledochus).
- *Obstruction by parasites* can occur (e. g., *Fasciola hepatica* [occurring worldwide and particularly in Latin America, Mexico, and the USA], *Ascaris lumbricoides* [worldwide and mainly in tropical countries], *Clonorchis sinensis* [China, Japan, and Southeast Asia], and *Opisthorchis viverrini* [Thailand]).

Cholangitis

Pain, chills, and jaundice (*Charcot triad*) are the cardinal symptoms of cholangitis. Pain may be absent. Bacterial cholangitis especially in patients with extrahepatic bile duct obstruction by gallstones or strictures, is less frequent in tumor obstruction. Parasites rarely cause cholangitis.

Laboratory findings indicate cholestasis and a bacterial infection. Transaminase levels are only moderately raised. The liver is enlarged and painful upon palpation. Cholangitis resolves within a few days after antibiotic therapy, but recurs if the cause of the obstruction is not eliminated. Complications of cholangitis are liver abscess formation, sepsis, and *secondary biliary cirrhosis* in patients with a chronic clinical course.

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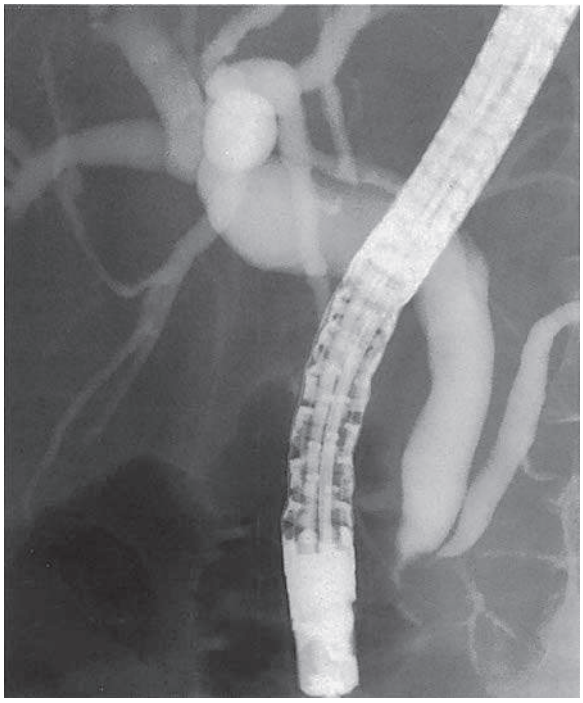
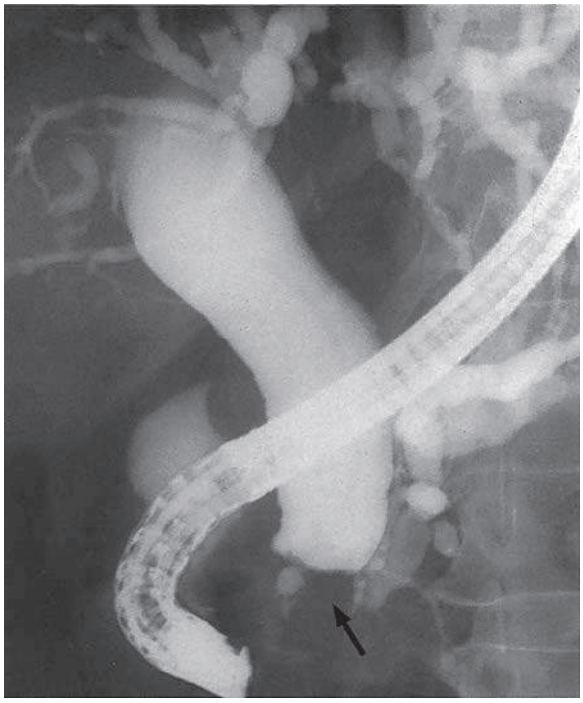


a



b

Fig. 25.**19** Extrahepatic obstructive jaundice

a Papillitis stenosans with conical obstruction of the papilla and marked dilatation of the intrahepatic and extrahepatic bile ducts and the ductus pancreaticus (ERCP).

b Papillary carcinoma with complete obstruction (arrow) and marked dilatation of the intrahepatic and extrahepatic bile ducts and the ductus pancreaticus.

Taken from Gerok W, Blum HE, eds. Hepatologie. 2nd ed. Munich: Urban and Schwarzenberg; 1995.

Space-Occupying Liver Lesions

Pathogenesis. Most focal liver lesions can lead to a *partial or complete bile duct obstruction* depending on their localization and size. Obstruction of both hepatic branches results in total obstruction with elevated bilirubin and cholestasis parameters. The obstruction of one hepatic branch or of subbranches causes partial obstruction with normal bilirubin and elevated cholestasis parameters.

Causes. Liver metastases (particularly from colorectal carcinoma, lung, breast, and stomach cancer, malignant melanoma, carcinoid tumors), liver infiltration by a malignant lymphoma or leukemia, HCC, liver abscesses, and echinococcal cysts, all can cause complete or partial obstruction.

In patients with liver metastases and a partial or complete obstruction, symptoms from the primary tumor may be absent (e. g., in pancreatic, stomach, and colorectal carcinoma). However, liver metastases often are a late manifestation of a known malignancy.

Diagnosis. *Elevated AP levels* are typical. Transaminase levels can be slightly raised. Jaundice is evident only in patients with extensive metastases. Space-occupying lesions can generally be detected by ultrasound, CT or MRI, and ultrasound-guided biopsy is usually diagnostic.

Liver Tumors

Liver tumors are either primary (HCC, cholangiocarcinoma) or secondary (metastases, Fig. 25.**20**). Occasionally, the liver can be infiltrated by an extrahepatic tumor (e. g., gallbladder carcinoma).

Benign Tumors. Liver cell adenoma, focal nodular hyperplasia (FNH), and cavernous hemangioma are common benign tumors.

Adenomas and FNH are mainly detected in women between 20–45 years of age, frequently taking oral contraceptives. Whereas liver cell adenoma can develop into HCC, FNH is not considered a premalignancy. Nevertheless, FNH can regress following the withdrawal of oral contraceptives, but, in contrast to adenoma, the causal relationship between FNH and oral contraceptives is controversial. The diagnosis of adenoma and

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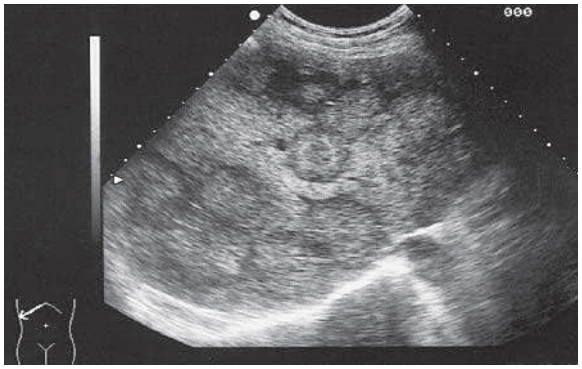

Fig. 25.**20** Multiple liver metastases of a non-small cell lung cancer in a 58-year-old man (ultrasound).

FNH can generally be established only on histologic examination.

Cavernous hemangioma is the most common benign liver tumor and is generally detected by chance. Oral contraceptives should be stopped. Only large, symptomatic tumors require therapy. Extensive hemangioma can occasionally lead to thrombocytopenia and hypofibrinogenemia (*Kasabach–Merritt syndrome*).

Malignant Tumors. *Hepatocellular carcinoma* (HCC) is the most frequent malignant liver tumor. Men are more frequently affected than women. Liver cirrhosis is present in 60–90%. Known risk factors include chronic hepatitis B, C, or D, exposure to aflatoxins, alcohol use, and hereditary metabolic disorders such as hemochromatosis and α_1-antitrypsin deficiency. HCC rarely develops in Wilson disease, PBC, and autoimmune hepatitis. The clinical presentation of HCC is nonspecific. Patients occasionally report a feeling of pressure in the right upper abdomen, loss of appetite and weight, as well as fatigue. HCC-induced portal vein thrombosis with hemorrhage from varices, ascites of recent onset, and other signs of decompensated liver cirrhosis can be the first symptoms. Jaundice indicates a poor prognosis.

> In order to detect HCC at an early, potentially curable, stage, ultrasound examination and AFP determinations must be done at six-month intervals in patients at risk.

In addition to ultrasound examination, contrast-enhanced CT typically shows an early contrast medium uptake (Fig. 25.**21**). Diagnosis should be confirmed histologically in patients with no significant increase in AFP levels.

Hepatoblastoma occurs in children under 3 years of age.

Cholangiocarcinoma (CC) develops either in the small or larger bile ducts intrahepatically or in the extrahepatic bile ducts (bile duct carcinoma, Klatskin tumor). CC is most prevalent in the sixth decade of life. It is occasionally associated with PSC and bile duct infestation by liver flukes especially in Asia (*Clonorchis sinensis*, *Opisthorchis viverrini*). Gallbladder carcinoma is usually diagnosed only in advanced stages.

Malignant hemoangioendothelioma (hemangiosarcoma) is rare and develops, among other situations, after exposure to thorium dioxide (thorotrast, used as a radiographic contrast medium between 1930 and approximately 1955), arsenic, and vinyl chloride monomers (plastic industry).

Echinococcosis

Pathogens, Transmission, and Epidemiology. Two types of echinococcosis must be distinguished:

- *Echinococcus granulosus* (cystic echinococcosis)
- *Echinococcus multilocularis* (alveolar echinococcosis).

E. granulosus is more frequent than *E. multilocularis* and occurs primarily in livestock-rearing areas. The dog is the primary host. Intermediate hosts are sheep, pigs, cattle, foxes, red deer, and humans. *E. multilocularis* is endemic in areas of Southern Germany and Eastern Switzerland, as well as in Canada, the USA, Russia, China, and Japan. The fox is the primary host, and occasionally, the dog. Field mice are intermediate hosts. Humans can also be infected as intermediate hosts. Transmission to humans occurs through contact with egg-containing feces or saliva from infected dogs (*E. granulosus*) or consumption of contaminated berries or vegetables (*E. multilocularis*).

Clinical Features. Both echinococcus infections form cysts in the liver and in other organs (e. g., lungs, brain, spleen). The cysts grow slowly over many years before they become clinically symptomatic. Symptoms and local complications depend on the location and size of the cysts. *E. granulosus* grows expansively. *E. multilocularis* forms numerous small cysts that grow by infiltrating and metastasizing.

Diagnosis. *E. granulosus* and *E. multilocularis* can be distinguished by imaging (ultrasound, CT [Fig. 25.**22**]), and serology. Percutaneous biopsy carries the risk of an anaphylactic reaction and dissemination.

Hepatic Abscesses

Hepatic abscesses are most frequently caused by *amebiasis* and *bacterial cholangitis*. Fever and pain are the first symptoms. The liver is enlarged and painful on palpation and percussion. Transaminase and AP levels are only slightly elevated, associated with leukocytosis and an increased ESR. Diagnosis is confirmed by ultrasound or CT (Fig. 25.**23**). Amebiasis can be diagnosed by serology. Ultrasound-guided aspiration and drainage is frequently indicated. Amebic enteritis may precede abscess formation in 50% of patients.

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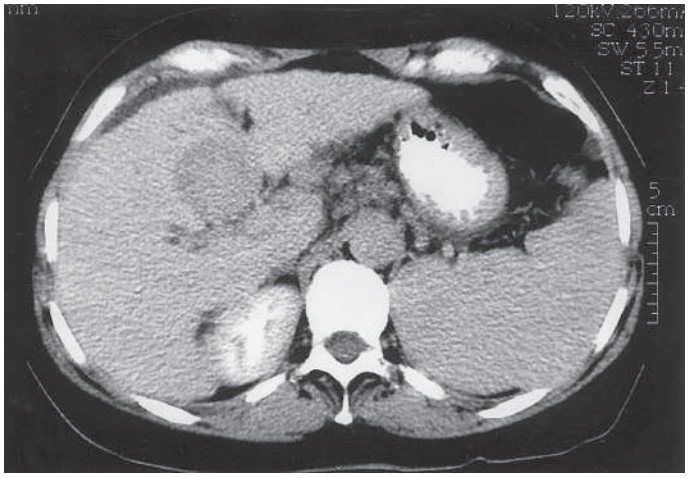

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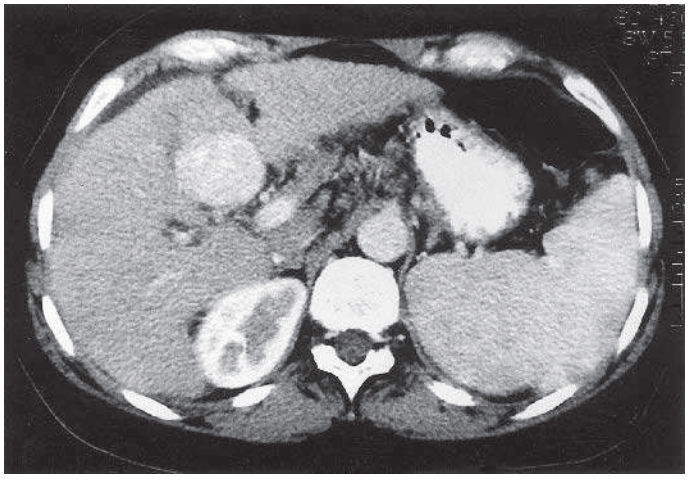

b

Fig. 25.**21** Hepatocellular carcinoma in a 70-year-old patient with chronic hepatitis C and liver cirrhosis.
a Native CT: hypodense lesion.
b Contrast-enhanced CT: early uptake of contrast medium.

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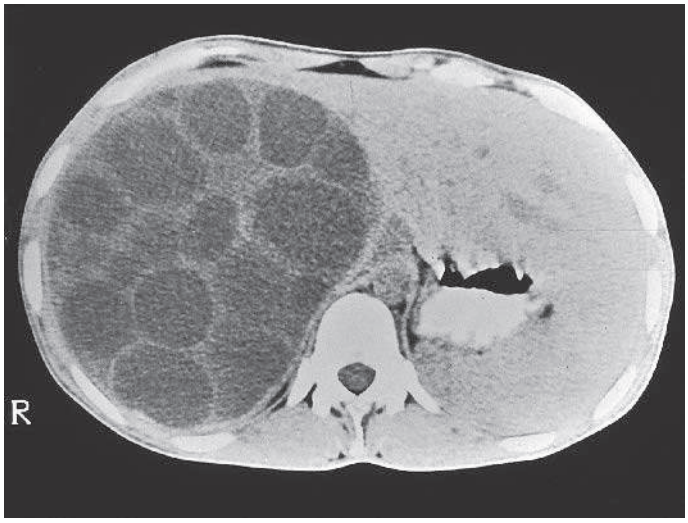

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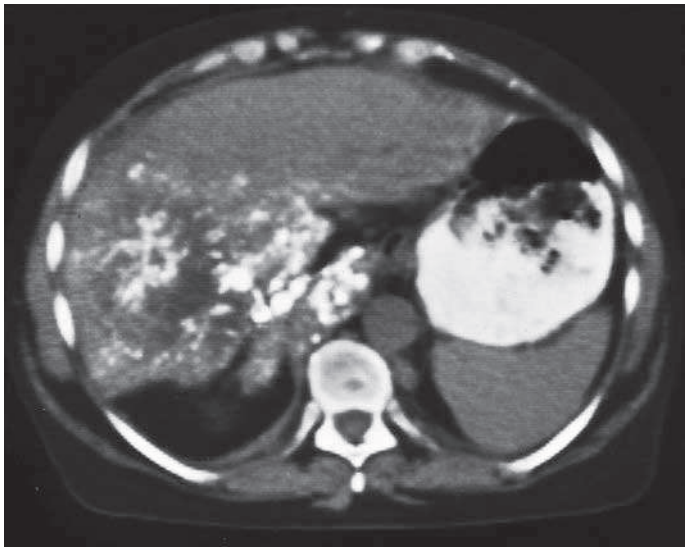

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Fig. 25.**22** Echinococcosis seen on CT
a *Echinococcus granulosus*
b *Echinococcus multilocularis*; tumorlike expansion into the right hepatic lobe and calcifications

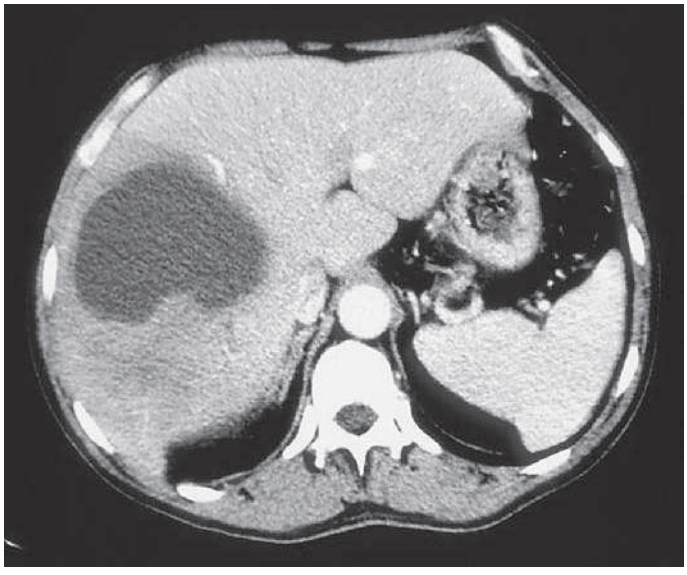

Fig. 25.**23** Amebic abscess seen on CT

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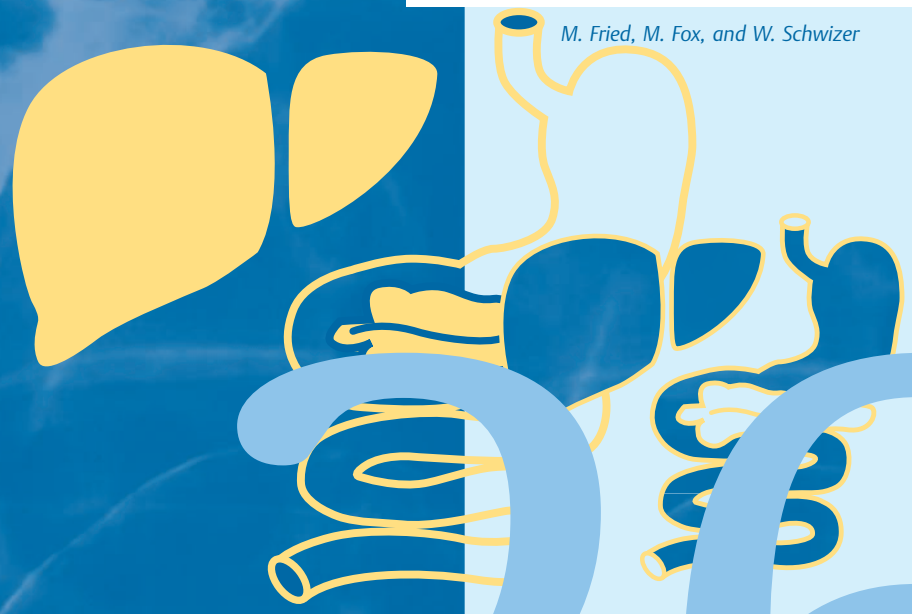
26 Dysphagia

M. Fried, M. Fox, and W. Schwizer



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General Classification, Clinical Terms

The following symptoms can be distinguished in patients with swallowing problems:

- *Oropharyngeal ("transfer") dysphagia:* failure to initiate swallowing and/or propel the bolus from the pharynx to the esophagus, often combined with choking, cough, and aspiration or nasal regurgitation (most common in the presence of underlying neurological or muscular disease).
- *Esophageal ("transport") dysphagia:* failure to transport the bolus through the esophagus to the stomach, often combined with retching, regurgitation, and aspiration; esophageal dysphagia is an alarm symptom that requires immediate investigation.
- *Odynophagia:* pain on the passage of a bolus through the esophagus (most common in the presence of esophageal ulceration or trauma).

These symptoms are to be distinguished from:

- *"Sore throat":* pain on swallowing with or without the presence of a bolus (most common in the presence of pharyngitis or tonsillitis).
- *Globus sensation (globus "hystericus"):* foreign body sensation ("ball") in the back of the throat that is neither related to swallowing, nor combined with dysphagia or odynophagia.

Investigation of Esophageal Dysphagia. The principle causes of esophageal dysphagia are detailed in Fig. 26.**1**. For patients presenting with esophageal dysphagia the clinical history provides essential information that allows the various forms of swallowing difficulties to be classified and the likely causes to be identified. The cardinal questions required for the following classification are detailed in Fig. 26.**1**. Patients with severely disturbed bolus transport and stasis frequently experience regurgitation and aspiration at night (e. g., Zenker diverticulum, achalasia). Chronic cough and recurrent chest infection often accompany these symptoms. These problems may be the presenting complaint and can be more troublesome than the esophageal symptoms.

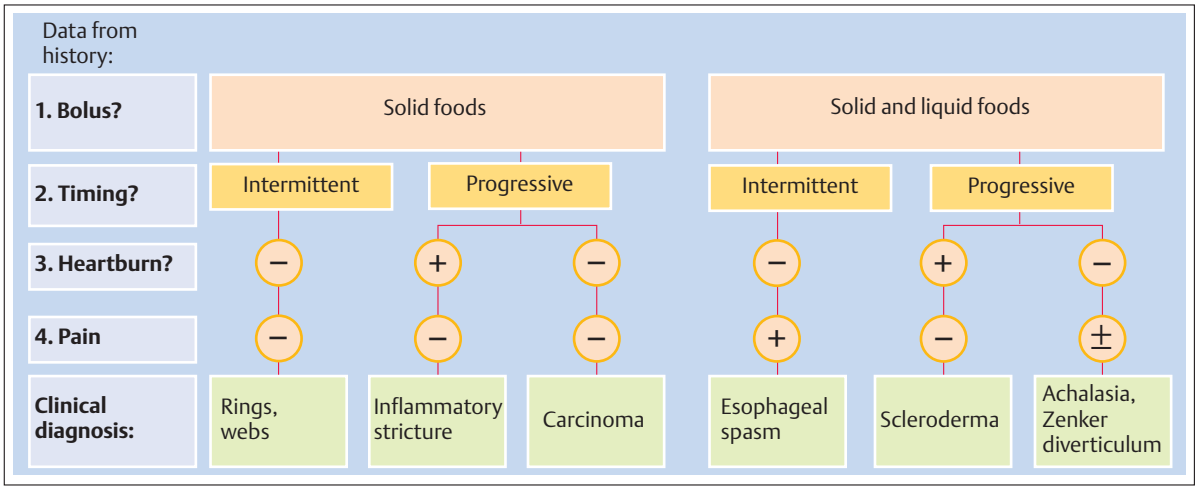

Fig. 26.**1** Differential diagnosis of dysphagia: four essential questions in the clinical history.

26.1 Structural Lesions

Esophageal Tumors

Esophageal Carcinoma. Many cases of esophageal carcinoma are recognized on the basis of a typical clinical presentation (rapidly progressive dysphagia, initially for solid food and then for fluids; anorexia, weight loss, and anemia). Squamous cell carcinoma tends to occur in heavy smokers and drinkers, whereas adenocarcinoma is most common in elderly men (> 60 years) with a long history of gastroesophageal reflux disease. On endoscopy, squamous cell carcinoma is found in the proximal esophagus, whereas adenocarcinoma occurs in the distal esophagus. Tumors in the gastric cardia (gastric adenocarcinoma) may present in a similar fashion to esophageal carcinoma if direct extension of the tumor involves the gastroesophageal junction.

Every presentation of dysphagia is suspicious of cancer and should be investigated by endoscopy.

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Endoscopy is the most important investigation (Fig. 26.**2**). Biopsies obtained at endoscopy establish the diagnosis by histology. Radiologic investigations are insensitive, especially at early stages of the disease. At later stages, further symptoms may be caused by local invasion of neighboring organs:

- *hoarseness and aphonia* (recurrent laryngeal nerve)
- *Horner syndrome* (sympathetic chain, cervical ganglion)
- *dyspnea* (tracheal compression, esophago–tracheal fistula, metastases).

Leiomyoma. Esophageal leiomyoma also presents with swallowing difficulties. In contrast to esophageal carcinoma, these rare tumors progress slowly and general health is usually preserved. Endoscopy reveals a smooth swelling in the esophagus, often without a break in the mucosa, consistent with the presence of a submucosal lesion.

Mediastinal Conditions

Mediastinal processes such as malignant disease (e. g., lung cancer) and *anomalous blood vessels* (e. g., aortic aneurysm, arteria lusoria) are rare causes of dysphagia. Dysphagia caused by thyroid goiter is suggestive of malignancy or massive retrosternal extension.

Inflammatory Stenosis

Peptic Stenosis. The most common form of inflammatory stenosis is a complication of *gastroesophageal reflux disease* (GERD). Dysphagia caused by peptic stricture is most common in elderly men and is usually preceded by a long (many years) history of heartburn, acid regurgitation, and other reflux-related symptoms. The stenosis develops as a consequence of chronic scarring in patients with severe inflammation, often associated with a large, sliding hiatus hernia. This cause of dysphagia is uncommon because only 30–40 % of GERD patients have esophagitis (the majority suffer from nonerosive reflux disease [NERD]), and only those with untreated, severe ulcerative disease are likely to develop a peptic stricture at the gastroesophageal junction.

Barrett Esophagus. Columnar cell metaplasia in the lower esophagus (Barrett esophagus) is a complication of GERD. It used to be believed that these changes represented a progression from reflux esophagitis after many years of acid damage. However, recent observations suggest that Barrett esophagus can develop within a short period of time (< 1 year) and may represent a distinct phenotypic response to acid exposure in the lower esophagus. Barrett esophagus is a premalignant condition with an incidence rate of 1–3 % per year for the development of dysplasia and 0.5 % per year for adenocarcinoma. Ulceration and stenosis within Barrett esophagus often indicates the presence of dysplasia or carcinoma. Regular surveillance endoscopy and biopsy is recommended at two to three year intervals and more frequently in the presence of ulceration, stenosis, or histologically confirmed dysplasia.

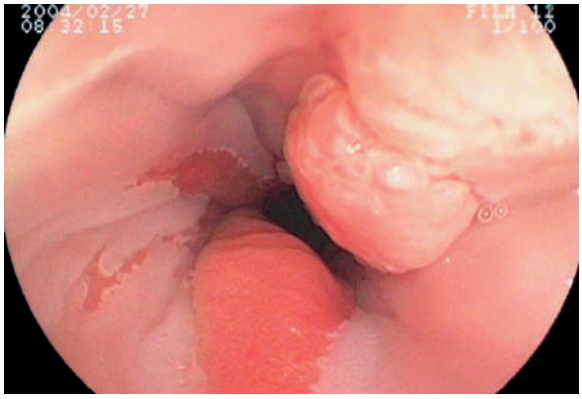

Fig. 26.**2** Esophageal adenocarcinoma with stenosis in a 62-year-old man with a long history of gastroesophageal reflux disease.

Rare Causes. Other rare causes of inflammatory stenosis are:

- *Trauma* (e. g., chemical injury, especially strong alkali), impacted tablets (e. g., nonsteroidal anti-inflammatory medications (NSAIDs), radiotherapy).
- *Postsurgical* (e. g., gastroesophageal anastomosis, acid damage following Heller myotomy for achalasia without prophylactic antireflux procedure).
- *Dermatological disease* with esophageal involvement (e. g., pemphigus vulgaris, epidermiolysis bullosa hereditaria).
- *Scleroderma* with esophageal involvement (aperistalsis, weak lower esophageal sphincter) with severe GERD and secondary peptic stenosis.

Diagnostic Tests. Endoscopy (Fig. 26.**3**) and radiological investigation are required to identify the position, severity, and probable cause of inflammatory stenosis.

Esophageal Membranes and Rings

Esophageal rings are circular stenosis found in the lower esophagus comprising either mucosal tissue (e. g., Schatzki ring) or muscular tissue. *Esophageal membranes* (webs) are semicircular, eccentric mucosal lesions found in the upper esophagus (e. g., Plummer–Vinson syndrome). Esophageal rings cause intermittent dysphagia for solid food, whereas patients with esophageal membranes are usually asymptomatic. The etiology of these lesions is not always clear, but may be congenital (muscular rings) or develop in the presence of GERD (Schatzki ring) or iron-deficiency anemia (Plummer–Vinson syndrome).

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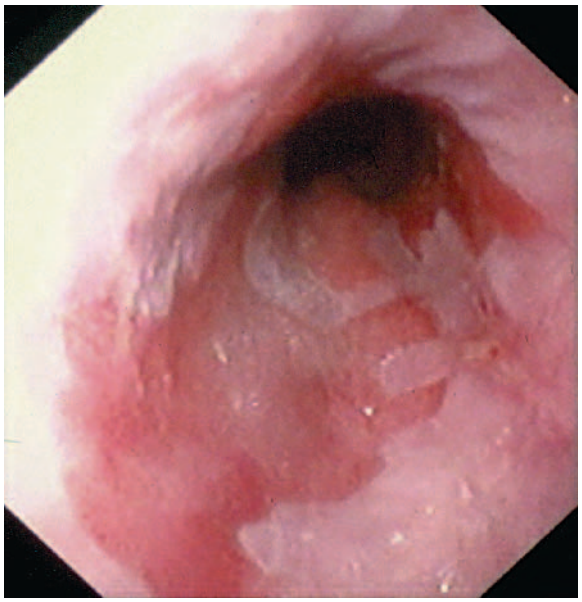

Fig. 26.**3** Barrett esophagus in a 64-year-old man with salmon-colored epithelium (gastric metaplasia) in the lower esophagus.

Fig. 26.**4** Large Zenker diverticulum in the posterior pharyngeal wall in a 73-year-old man.

Diverticulum

Zenker diverticulum is an "out-pouching" of mucosa above the cricopharyngeal muscle at a point of relative weakness in the posterior muscle wall of the hypopharynx. Small diverticulae of this type tend to cause dysphagia, whereas larger diverticulae cause regurgitation of food, occasionally complicated by aspiration. Gurgling in the throat on swallowing and halitosis may be present. In contrast to *pulsion diverticulae* (e. g., Zenker), *traction diverticulae* are found in the mid to lower esophagus and rarely cause symptoms. Traction diverticulae are most commonly observed in patients with esophageal dysmotility, increased contraction pressure, and a thickened esophageal muscle wall. Both forms of diverticulae are recognized by characteristic appearance on radiological investigation (Fig. 26.**4**).

26.2 Esophageal Motility Disorders

Achalasia

Achalasia is a rare disease (incidence 1:100 000) that usually occurs in the third to sixth decade, affecting men and women equally. The dysphagia caused by achalasia is due to failure of the lower esophageal sphincter to relax upon swallowing (i. e., functional obstruction). In general, this leads to aperistalsis and dilation of the tubular esophagus (megaesophagus), although uncoordinated contractions are observed in a minority of patients (vigorous achalasia).

Pathophysiology. The precise etiology is unknown. However, the primary lesion appears to be an *inflammatory degeneration of the inhibitory neurons* that mediate lower esophageal sphincter relaxation, with secondary changes in the esophageal muscle wall. Chagas disease is a related condition that occurs in Latin America caused by *Trypanosoma cruzi*, in which complete destruction of the intramural ganglion cells leads to failure of lower esophageal sphincter relaxation and megaesophagus.

Clinical Features and Diagnosis. In both conditions, dysphagia for solid food and liquids is the main presenting symptom, together with regurgitation of undigested food and weight loss. Retrosternal pain is not unusual and may be described as "heartburn." The diagnosis is suggested by the presenting symptoms, typical radiological findings, and endoscopy (to exclude structural lesions). The diagnosis is established by manometry (Fig. 26.**5**). Classical findings include raised lower esophageal sphincter pressure, failure of lower

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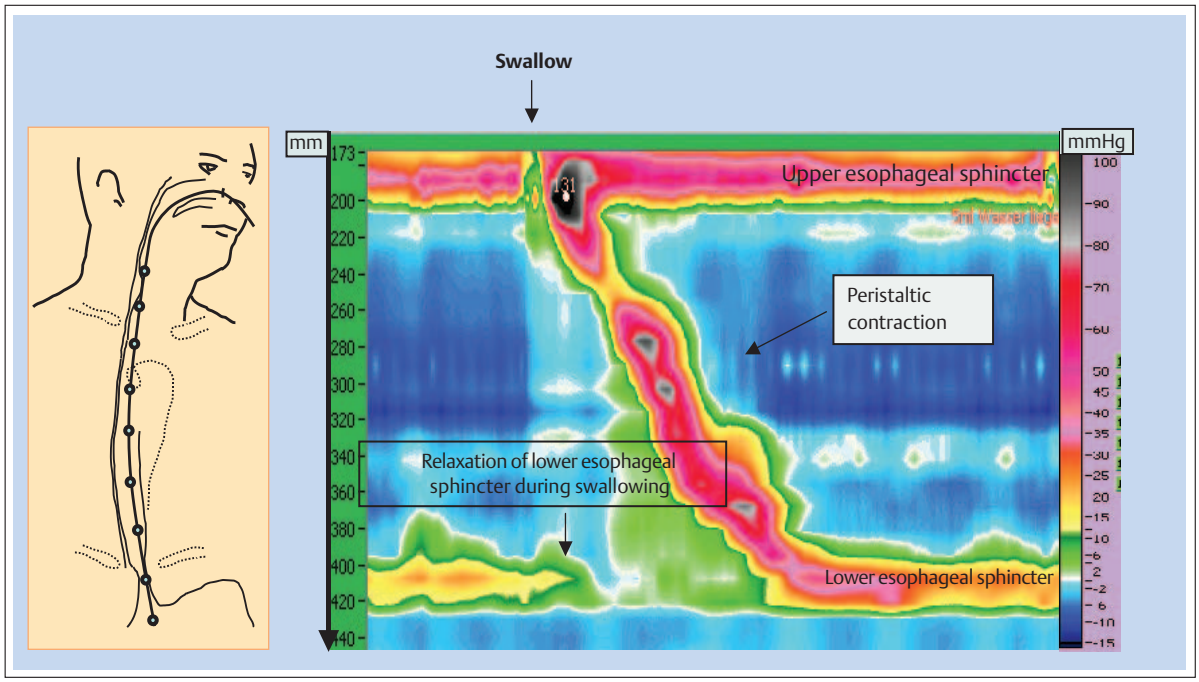

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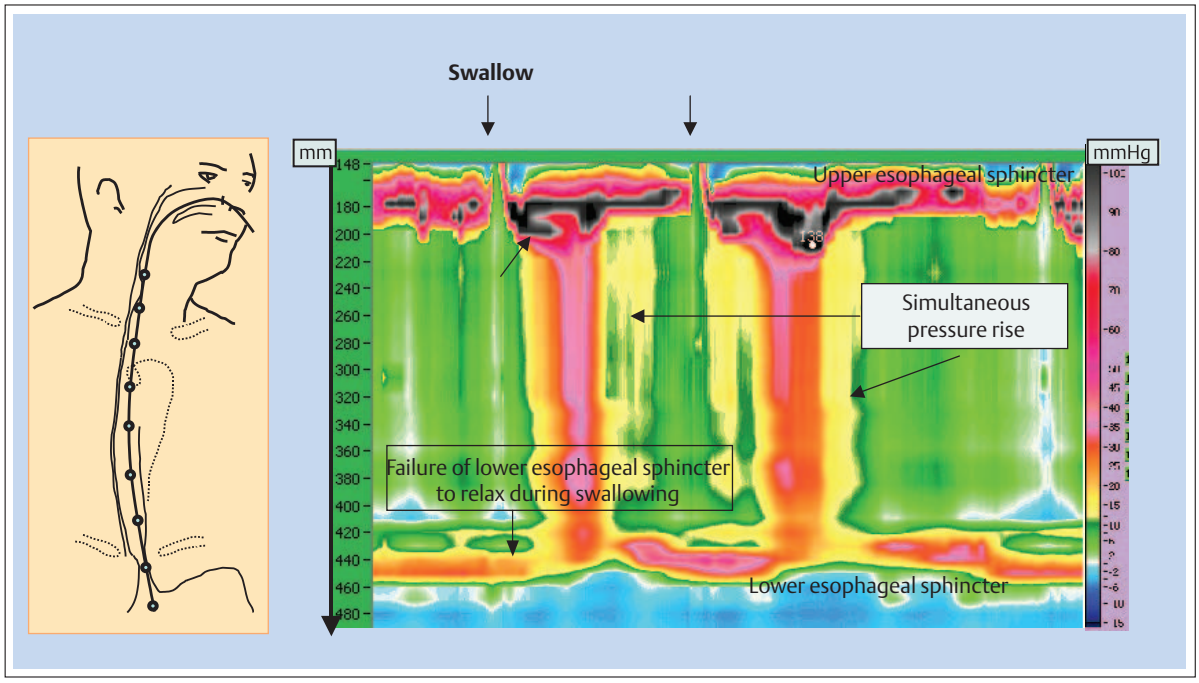

b

Fig. 26.**5** High resolution (32-pressure sensor) manometry of a normal water swallow.

a The spatiotemporal plot displays time on the x axis and distance from the nares on the y axis. Pressure is indicated by color and shading (see color bar [right axis]; low-pressure light blue–green, high pressure dark red–black). The upper and lower esophageal sphincters open at the same time on swallowing, allowing the bolus to be transported through the tubular esophagus into the stomach by peristaltic contraction without resistance.

b High resolution manometry of a water swallow (spatiotemporal plot) in a 35-year-old man with achalasia presenting with an 18-month history of dysphagia to solid food and liquids. The upper esophageal sphincter opens on swallowing, the lower esophageal sphincter fails to relax. The bolus remains in the mid-esophagus and simultaneous, low-amplitude pressure changes are observed in the tubular esophagus (this "common cavity effect" indicates esophageal dilation).

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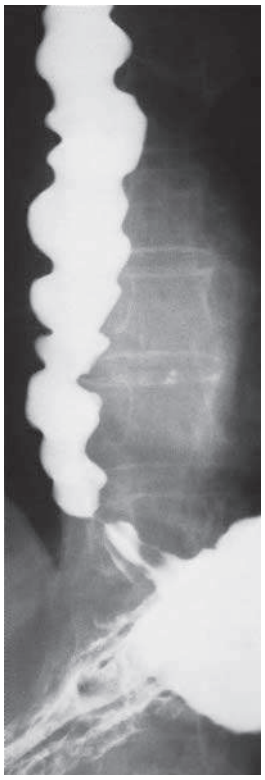

Fig. 26.**6** Tertiary (nonperistaltic) esophageal contractions in a 73-year-old man with dysphagia and regurgitation. Pseudodiverticulae are seen between the contractions ("corkscrew" esophagus).

esophageal sphincter relaxation on swallowing, and aperistalsis.

The diagnosis must be confirmed by manometry, because endoscopy may be normal with unimpeded passage into the stomach and radiology is frequently nonspecific.

Medical treatment of achalasia is usually unsatisfactory. Relief of symptoms is achieved by weakening the lower esophageal sphincter by pneumatic dilation, intrasphincteric injection of *Clostridium/botulinum* toxin, or Heller myotomy.

Diffuse Esophageal Dysmotility

Dysphagia for solid food and liquids can be caused by "diffuse esophageal spasm" (DES). Hypertensive, peristaltic esophageal contractions ("nutcracker" esophagus) and hypertensive lower esophageal sphincter pressure rarely cause dysphagia, but are associated with atypical chest pain. This "noncardiac chest pain" can be severe and occur between meals (also at night). It is important to differentiate these symptoms from angina pectoris (e. g., lack of association with exercise, normal electrocardiogram). Although, esophageal and coronary artery spasm can occur in the same patients. Esophageal spasm and pain can be triggered by various stimuli (acid reflux, hot or cold food, stress). The diagnosis of esophageal dysmotility is established by manometry. In DES a simultaneous, segmental rise in distal esophageal pressure occurs on swallowing, whereas in "nutcracker" esophagus peristalsis is preserved but contraction pressures in the distal esophagus are greatly elevated (> 180 mmHg). Typical radiological findings of DES are multiple, nonprogressive, tertiary ("corkscrew") contractions with "pseudodiverticulae" between the rings of contraction (Fig. 26.**6**). However these appearances may be intermittent and of short duration and are not sensitive for diagnosis. Radiological findings of "nutcracker" esophagus are generally normal.

26.3 Mucosal Disease (Odynophagia)

Esophageal Ulceration

The sudden onset of odynophagia is suggestive of esophageal ulceration caused by *caustic material or medication* ("drug-induced ulcer," commonly tetracycline, NSAIDs, anticholinergics, iron and potassium preparations). The ingestion of tablets before bed or without adequate fluid can lead to prolonged contact of irritating medicinal compounds with the esophagus and local damage to the mucosa. The diagnosis is confirmed by endoscopy. Healing is facilitated by acid suppression and is usually successful within a week.

Esophageal Trauma. Odynophagia can be caused by mucosal damage following the ingestion of foreign objects (e. g., fish bones). Short-lasting odynophagia is common after endoscopic procedures, especially sclerotherapy of varices.

Esophagitis

Gastroesophageal reflux disease is by far the most common cause of esophagitis. However, odynophagia is uncommon, except in the most severe cases. Dysphagia is often reported by patients with GERD, either as a consequence of primary esophageal dysmotility or more commonly, secondary to the effects of acid exposure on the esophagus. Acid suppression often improves these symptoms. In contrast, infectious causes of esophageal

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ulceration often cause odynophagia with or without dysphagia. Common agents include *Candida*, herpes viruses, and *Cytomegalovirus* (most common in immunosuppressed patients, e. g., HIV infection). Esophagitis with or without "sore throat" (indicating pharyngeal involvement) can also be caused by radiotherapy and chemotherapy.

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27 Diarrhea

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Introduction

Definition. In patients presenting with diarrhea it is important to distinguish:

- "true diarrhea," i. e., too frequent, too fluid, too much volume (over 250–300 g/day)
- "false diarrhea," i. e., too frequent, too fluid, but without an increase in stool volume, often caused by fecal impaction in the distal colon (either due to anorectal dysfunction or colorectal stenosis), secondary dissolution and passage of liquid stool
- increased frequency of essentially normal, formed stool (e. g., irritable bowel syndrome, proctitis).

All three problems may be referred to as "diarrhea" by patients. Targeted clinical questioning is required to differentiate these conditions because "false diarrhea" suggests acute constipation as the underlying cause and requires specific management (see Chapter 28). Similarly, the final group represents either functional variation within the normal physiological range, or indicates the presence of distal colorectal disease. Finally, diarrhea must be distinguished from fecal incontinence (uncontrolled evacuation of rectal contents), a common and often unrecognized problem.

Pathophysiology. The most important causes of diarrhea are detailed in Tab. 27.**1**. The distinction between acute and chronic diarrhea is established in clinical practice and serves as the basis for the following summary. The causes of diarrhea can be further divided into five groups on the basis of pathophysiology (Tab. 27.**1**), although in many cases several pathological processes can be operating simultaneously.

Location of Disease. Diarrhea can also be categorized on the basis of which part of the gastrointestinal tract is affected. Diarrhea is a common symptom of colonic disease that, if persistent, is usually simple to diagnose by endoscopy, e. g., ulcerative colitis, Crohn disease, carcinoma. The assessment and classification of diarrhea caused by small bowel disease is more difficult. Small bowel diarrhea can occur either due to increased passage of ileal effluent (most commonly secretory diarrhea, Tab. 27.**1**) or the presence of osmotically active substances in the stool such as excess bile acid, laxatives, or undigested nutrients (e. g., lactose, free fatty acid; osmotic diarrhea, Tab. 27.**1**). In both cases diarrhea occurs only if the ability of the colon to absorb water and form stool is exceeded.

Duration of Disease. In clinical practice physicians make the distinction between acute (days to weeks) and chronic or chronic, recurrent (more than three weeks) diarrhea, although the three-week cut-off is arbitrary.

Table 27.**1** Pathogenic mechanisms of diarrhea

Osmotic
(diarrhea ceases during fasting)
– intestinal disaccharidase deficiency (e. g., lactose intolerance)
– primary–genetic (children); acquired–idiopathic (adults)
– secondary, e. g., infectious–inflammatory, with celiac disease, postgastrectomy, blind loop syndrome
– monosaccharide malabsorption, e. g., glucose–galactose malabsorption, secondary to childhood infectious diarrhea
– artificial sweetener, e. g., sorbitol, mannitol
– laxatives, e. g., lactulose, magnesium salts, phosphate salts
Secretory
(diarrhea persists during fasting)
– microbial enterotoxin, e. g., *E. coli*, *Vibrio cholera*, *Rotavirus, Norwalk virus, Cryptosporidium*, *Staphylococcus*, *Clostridium perfringens*
– chemical–noxious, e. g., caffeine, theophylline, diuretics, certain laxatives, alcohol
– hormones, e. g., gastrin (Zollinger–Ellison), VIP (Verner–Morrison), serotonin (carcinoid), prostaglandin/calcitonin (medullary thyroid carcinoma)
– endogenous noxious, e. g., dihydro-bile acids (ileal resection and/or disease), free fatty acids
– tumor, secretory villous adenoma
Exudative
– mucosal damage
– bacterial–parasitic, e. g., *Shigella*, *Salmonella*, *Amoeba*, *Giardia*, HIV/AIDS
– inflammatory, e. g., antibiotic-associated diarrhea, celiac disease, Crohn disease, Whipple disease, ulcerative colitis, ischemia
– congenital, e. g., diarrhea due to chloride transporter deficiency
– chemical–noxious, e. g., chemotherapeutic agents
Sensorimotor dysfunction
– irritable bowel syndrome
– postvagotomy
– cholinergics
– hyperthyroidism
– diabetic enteropathy, carcinoid syndrome
Miscellaneous
– intestinal obstruction
– intestinal distension
– portal hypertension

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27.1 Acute Diarrhea

General Considerations on Practical Management

Symptomatic Therapy. There are many different causes of acute diarrheal illness and infective, parasitic, toxic, allergic, and iatrogenic causes must be considered (Tab. 27.**1**). Acute diarrhea is common, but generally mild and self-limiting. An important question to consider in the management of acute diarrhea is whether immediate investigation is required, or alternatively empirical, symptomatic treatment followed by investigation if the condition does not respond. This decision is based on the severity, type, and duration of symptoms, as well as the general condition of the patient.

Primary Investigation. Immediate investigation is only required for acute diarrhea in *exceptional circumstances*:

- bloody stool
- severe systemic upset, most commonly high fever, dehydration, collapse
- high-volume diarrhea
- severe underlying disease
- recent travel in the Tropics
- employment in the catering industry
- epidemic diarrheal illness
- infants and young children
- recent antibiotic therapy (see below).

Infectious and Parasitic Diarrheal Disease

Classification. Acute diarrhea caused by *infective agents* is divided into two groups:

- *noninflammatory causes* (e. g., mediated by toxins), "choleric"
- *inflammatory causes* (e. g., mediated by invasive infection), "dysentery".

Noninflammatory Causes. The *small bowel* is most commonly affected. Typical signs of noninflammatory acute diarrheal disease include high volume, watery diarrhea that can rapidly lead to hypotension, acidosis, and shock, usually without causing a fever. Important causes include *Vibrio cholera*, enterotoxigenic *E. coli* (ETEC), *Rotavirus*, and *Norwalk virus*. *Giardia* and *Cryptosporidium* are common parasitic causes and produce a similar, although less acute, presentation of the disease. This form of diarrheal disease is mediated by *enterotoxins* and *leukocytes* in the stool are *not observed*.

Inflammatory Causes. The *colon* is most commonly affected. Inflammatory causes of acute diarrheal disease generally produce smaller volumes of stool than toxic diarrheal disease. The stool is often bloody and purulent containing *large numbers of leukocytes*. Abdominal pain and high fevers often accompany the diarrheal illness. Common causes include *Shigella* species, *Campylobacter jejuni*, *Salmonella*, enteroinvasive *E. coli* (EIEC), and *Clostridium difficile* (usually after antibiotic therapy as an inpatient). *Entamoeba histolytica* must be considered in patients returning from the Tropics. Diarrhea associated with fever, arthritis, and erythema nodosum is typical for *Yersinia enterocolitica* infection.

Food Poisoning. Acute vomiting and diarrhea in a group that shared food, often within six hours of ingestion, strongly suggests food poisoning caused by food *contaminated by toxin-producing bacteria* (e. g., *Staphylococcus aureus*, *Clostridium perfringens*, *Bacillus cereus*).

Investigation. The infective agent can be identified in only 40–60% of patients with infectious diarrhea. In Europe the average incidence of acute, infectious diarrheal disease includes 14% *Salmonella*, 14% *Campylobacter*, 4.3% *Clostridium difficile*, 3.4% *Rota virus*, 2.5% *Shigella*, and 2.5% parasitic. However, marked regional differences exist, and in patients returning from the Tropics and in immunocompromised patients (including AIDS) the prevalence of pathogenic protozoal infection is much higher. A summary of parasitic infections that can be associated with diarrhea is provided in Tab. 27.**2**.

Antibiotic-Associated Diarrhea (Pseudomembranous Colitis)

Between 5–25% of patients treated with broad spectrum antibiotics develop a diarrheal illness two to 20 days after starting therapy. The most common infectious cause of antibiotic-associated diarrhea are the toxins (A and B) produced by *Clostridium difficile*, a bacterium that proliferates when normal gut flora are suppressed. The severity of the clinical illness and its duration is very variable; severe disease with fatal outcome can occur. The endoscopic findings (80% in the left hemicolon) vary between diffuse mucosal erythema and severe ulcerative disease with pseudomembrane formation. The diagnosis is confirmed by the detection of *C. difficile* toxin in the stool.

Diarrhea Caused by Toxins

Diarrhea can be caused by endogenous and exogenous toxins.

Endogenous Toxins. *Uremia* is the most common endogenous toxic cause of diarrhea. This is an important

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Table 27.2 Diarrhea caused by parasitic diseases

	Distribution	Route of infection
Parasites that frequently cause diarrhea		
Protozoa		
Entamoeba histolytica	predominantly Tropics	fecal–oral
Giardia duodenalis	ubiquitous	fecal–oral
Isospora belli	Tropics	fecal–oral
Balantidium coli	ubiquitous	fecal–oral
Trematode worms		
Schistosoma mansoni	predominantly Africa, South America	percutaneous
Schistosoma japonicum	Far East	percutaneous
Nematode worms		
Trichirus trichiura	ubiquitous	fecal–oral
Strongyloides stercoralis	Tropics, subtropics	percutaneous
Parasites that predominantly cause diarrhea in patients with AIDS		
Cyclospora	ubiquitous	fecal–oral
Cryptosporidium	ubiquitous	fecal–oral
Microsporidium	ubiquitous	fecal–oral
Parasites that occasionally cause diarrhea		
Protozoa (*Coccidia*), *Plasmodium falciparum* (*malaria tropica*)		
Trematode worms (Far East: distomatose, bandworms, most commonly *Hymenolepsis nana*, *Taenia saginata*, *Taenia solium*, *Diphyllobothrium latum*)		
Nematode worms (*Ascaris lumbricoides*, *Ankylostoma duodenale*, *Trichinella spiralis*)		

mechanism contributing to diarrhea, which is commonly seen in *severe infection* and other systemic diseases.

Exogenous Toxins. *Arsenic* and *mercury* are exogenous toxins that cause severe diarrhea. If the possibility of *arsenic intoxication* is raised, the diagnosis can be established by chemical analysis of the arsenic content in the hair and nails. In acute poisoning the green color and garlic odor of the vomitus and diarrhea suggest the diagnosis. *Mercury intoxication* most commonly presents acutely with large volume, frequently bloody diarrhea, stained black by the presence of mercury salts (e. g., HgS). Only oral ingestion of mercury salts causes disease; in contrast to the inhalation of mercury vapor, the presence of metallic mercury in the gastrointestinal tract is harmless.

Fungal Poisoning. Mushroom or toadstool poisoning should be considered in patients presenting with acute vomiting and diarrhea. If the symptoms present within three hours of ingestion, this is usually a (generally mild) food poisoning caused by rotten fungi, or rarely trehalose intolerance (a complex carbohydrate found in fungi). Life-threatening poisoning by *Amanita phalloides* occurs six to 10 hours after ingestion with vomiting, abdominal colic, and diarrhea often followed by a brief symptomatic recovery before an acute, usually fatal, liver failure supervenes.

Medications. Many drugs can cause diarrhea (e. g., iron preparations, magnesium-containing antacids, colchicine, chemotherapeutic agents, biguanide hypoglycemics).

The possibility of covert laxative use must always be considered. Paradoxically, laxatives are a frequent cause of diarrhea in individuals seeking medical attention for diarrhea. Patients may also create factitious diarrhea by the addition of water or urine to the stool.

Food Allergy. Similar to other organs, the bowel can be affected by allergic reactions. However, this is an uncommon cause of diarrhea. Diarrhea of sudden onset and brief duration, shortly after exposure to a particular foodstuff is typical (e. g., shellfish, eggs, strawberries); with recurrent episodes of gastrointestinal symptoms after repeated exposure. Allergic phenomena affecting other organs are frequent, most commonly the skin (e. g., angioedema, urticaria). Diagnosis is based on a suggestive clinical history and resolution of symptoms with an exclusion diet sometimes confirmed by trial exposure and skin tests. An allergic etiology for eosinophilic gastroenteritis has been proposed. Abdominal pain, followed by bloody diarrhea, may also occur as a gastrointestinal manifestation of Henoch–Schönlein purpura.

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27.2 Chronic Diarrhea

General Considerations. Chronic diarrhea (lasting more than 3 weeks) is rarely caused by infectious disease.

> Chronic diarrhea is a common symptom with many potential underlying causes.

A classification of the more important causes of chronic diarrhea, based on practical clinical considerations, is presented in Tab. 27.**3**. In general, a focused clinical history provides an initial assessment and provisional segregation of patients with functional (common) and organic (relatively rare) disorders (Tab. 27.**4**).

Chronic diarrhea that occurs at night, as well as during the day, and is associated with weight loss or rectal bleeding always requires urgent investigation to exclude organic disease. Functional diarrhea is likely in patients < 40 years old with a long history of symptoms, in good general and nutritional health. The provisional diagnosis is supported if colonoscopy and laboratory tests (full blood count, renal and liver biochemistry, inflammatory indices, stool microscopy) are normal.

Table 27.**3** Causes of chronic diarrhea (categorized by pathogenesis)

Functional disorders
– mainly irritable bowel syndrome
Organic causes
– inflammatory disease (mainly ulcerative colitis, Crohn disease, ischemia, tuberculosis)
– neoplasia (mainly colon carcinoma; often alternating with constipation)
– malassimilation syndrome (malabsorption and maldigestion)
– endocrine–hormonal causes (e. g., hyperthyroidism, carcinoid, islet cell tumor, diabetes)
– miscellaneous (e. g., parasitic infection, laxatives, lactose intolerance, AIDS)

Table 27.**4** Causes of chronic diarrhea (categorized by clinical presentation)

History	Functional diarrhea	Organic diarrhea
Duration	years, often intermittent	usually weeks to months
Frequency	mainly morning and postprandial	day and night
Weight	stable	falling
Stool consistency	loose, watery; sometimes with mucous	bloody, mucopurulent or voluminous–fatty

Diseases with Abnormal Findings on Endoscopy

Ulcerative Colitis

Clinical Features. The first presentation of ulcerative colitis can be difficult to distinguish from infectious gastroenteritis (e. g., *Campylobacter jejuni*, *Salmonella* species, *Clostridium difficile*), because both can present with bloody, mucopurulent diarrhea with intermittent fevers. Repeated stool microscopy and culture for pathogenic organisms and parasites is required. At later stages the diagnosis becomes less difficult. The disease often "begins" at a relatively young age, between 15 and 50 years, and there is a slight predisposition in women. The diarrhea is usually painless, although anorectal inflammation may cause tenesmus. *Rectal bleeding* is a common symptom, often mixed with a mucopurulent discharge, with or without the passage of stool. In ulcerative proctitis (no colonic involvement) diarrhea may not occur. In such cases, formed stool is passed with blood on the surface of the stool. The diagnosis must not be mistaken for hemorrhoids! Microcytic, hypochromic (iron-deficiency) anemia with a leukocytosis (left shift), and raised inflammatory indices are common (less so in isolated proctitis).

Clinical Course and Complications. Ulcerative colitis is a *chronic relapsing*, and *remitting* disease. As well as an acute form with sudden onset of severe diarrhea and systemic upset, relatively mild forms exist in which these features are not present and in which mucopurulent or bloody rectal discharge are the only symptoms. *Local complications* include severe bleeding, toxic dilation (megacolon), and perforation. Extra-intestinal complications of ulcerative colitis affect the eyes (e. g., uveitis, episcleritis), skin (erythema nodosum, pyoderma gangrenosum), joints (polyarthralgia, sacroiliitis), blood vessels (vasculitis), and bile ducts (pansclerosing cholangitis).

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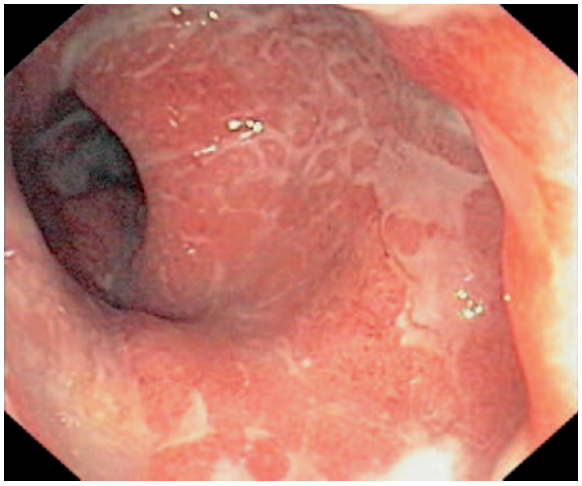

Fig. 27.**1** Ulcerative colitis with extensive superficial rectal ulceration in a 73-year-old man.

Diagnosis. The most important investigation in ulcerative colitis is colonoscopy, in particular, examination of the rectum and sigmoid colon. Endoscopy reveals an erythematous, granular mucosa without the normal vascular pattern with contact bleeding on light touch. Larger mucosal lesions (erosions and ulcers) are more commonly observed in the colon than the rectum. The extent of the disease process can also be established at endoscopy. In contrast to Crohn disease, the distal colorectum is always affected, mucosal disease in the affected bowel is continuous and evenly distributed. With increasing duration of ulcerative colitis there is progressive scarring and shrinkage of the diseased bowel with narrowing and shortening of the affected bowel (drain pipe colon).

Increased Risk of Malignant Disease. The risk of colonic carcinoma is significantly raised in ulcerative colitis, particularly in patients with pancolitis and over 10 years, history of disease (5–8% risk of carcinoma at 15 years, disease duration, 12% risk at 20 years).

> In patients with chronic pancolitis (8–10 years) regular colonoscopic surveillance with systematic biopsy is recommended for the early diagnosis of dysplasia and carcinoma.

Toxic Megacolon. In a patient with severe ulcerative colitis the presence of toxic megacolon is indicated by systemic upset, dilated abdomen, and ileus, together with massive colonic dilation (> 8 cm) on the plain abdominal radiograph. This life-threatening complication has a high risk of perforation and immediate surgical management should always be considered.

Differential Diagnosis. The diagnosis of ulcerative colitis is based on:

- typical clinical history
- characteristic endoscopic findings
- exclusion of other conditions with a similar clinical and endoscopic findings including:
  - Crohn disease
  - chronic infectious enterocolitis (*Entamoeba histolytica*, tuberculosis)
  - ischemic colitis
  - radiation colitis
  - pseudomembranous colitis
  - venereal proctitis (*Neisseria gonorrhoeae*, *Chlamydia*, herpes simplex virus), differentiation from ulcerative proctitis can be difficult on clinical grounds
  - collagenous colitis and microscopic colitis, endoscopy normal in these conditions.

"Conventional" infectious gastroenteritis (e. g., *Campylobacter jejuni*) may cause a temporary, self-limiting hemorrhagic colitis.

Together with the clinical history and examination, the appearance, distribution, and histology of mucosal lesions on endoscopy and biopsy differentiate ulcerative colitis from Crohn disease (Fig. 27.**2**). On occasion, it is difficult to differentiate these conditions and overlapping syndromes are known (indeterminate colitis).

Venereal Diseases of the Anorectum

The primary manifestation of sexually transmitted disease in the anorectum is not rare, particularly in homosexual men. The majority of these conditions are not specific to this anatomical location, e. g., herpes simplex virus, *condylomata accuminata*, *molluscum contagiosum*. Syphilis can present as perianal condylomata lata. *Chlamydia* and *Neisseria gonorrhoeae* cause hemorrhagic proctitis that can be diagnosed by rectal swab and culture. In homosexual men (also patients with HIV) sexual transmission of pathogens such as protozoa and fungi must be considered (e. g., *Amoeba*, *Cryptosporidium*, *Candida*).

Lymphogranuloma venereum causes an ulcerative proctitis limited to the rectum that if not diagnosed and treated appropriately has a tendency to cause scarring with the formation of a rectal stricture 4–5 cm above the anal canal. Mucosal biopsy demonstrates a nonspecific granulomatous inflammation.

The differential diagnosis includes carcinoma, Crohn disease, and tuberculosis. The diagnosis is established by rectal swab and culture, or evidence of chlamydial disease on serology.

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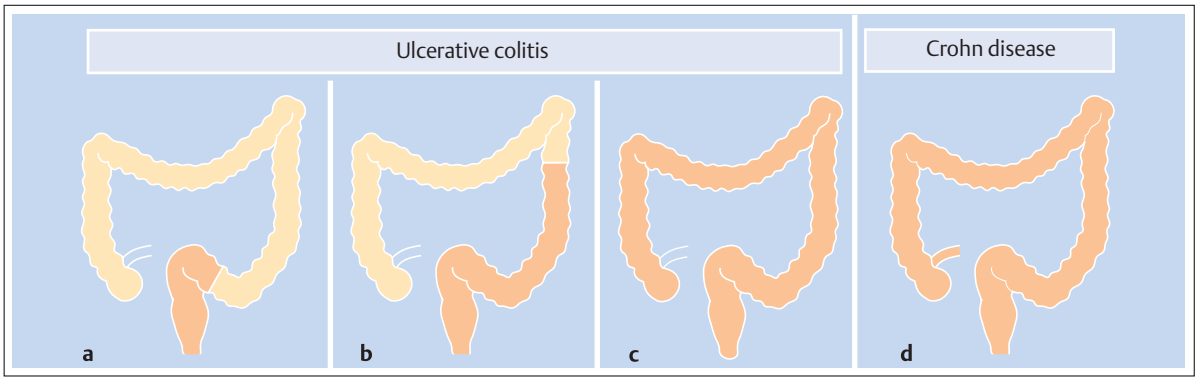

Fig. 27.**2** Typical distribution of disease and clinical presentation of ulcerative colitis and Crohn disease.
a Blood on the surface of formed stool.
b, **c** Blood mixed with loose stool, in the case of **c** frequently with evidence of inflammation (high erythrocyte sedimentation rate (ESR), leukocytosis with left shift, occasionally fevers).
d "Skip lesion;" diarrhea usually without rectal bleeding, evidence of inflammation (high ESR, leukocytosis with left shift, occasionally fevers).

Ischemic (Entero)Colitis

Pathogenesis. Bloody diarrhea is also observed in ischemic (entero)colitis (Fig. 27.**3**). This condition is a consequence of either an *obliterative angiopathy* of blood vessels serving the bowel (e. g., thromboembolism, vasculitis) or reduced perfusion through patent mesenteric vessels (e. g., shock, myocardial infarction, cardiac failure). The location and extent of affected bowel depends on the regional anatomy of the mesenteric blood supply (celiac trunk, superior mesenteric artery, inferior mesenteric artery). The splenic flexure, descending and sigmoid colon are the most commonly affected segments. The diagnosis of ischemic bowel is suggested if symptoms present during or immediately *after an episode of cardiovascular shock* or if a clear history of *postprandial abdominal pain* (mesenteric angina) is present.

Ischemic colitis has been described after vascular graft surgery for aortic or aorto-iliac disease in which the inferior mesenteric artery is sacrificed and the blood supply through the remaining vessels is insufficient. An *aorto-iliac steal syndrome* has also been described. Ischemic colitis has been observed in patients with coagulation disorders, women taking the contraceptive pill, systemic vasculitis, and even in long-distance runners. Mesenteric ischemia can also occur proximal to stenotic lesions (e. g., cancer) in the sigmoid and rectum.

Isolated ulcers at the splenic flexure, descending or sigmoid colon may indicate ischemia.

Fig. 27.**3** Ischemic colitis; deep sharply delineated colonic ulceration in an 87-year-old woman.

Crohn Disease (Segmental Granulomatous Ileocolitis)

Clinical Features. The presentation of Crohn disease is similar to ulcerative colitis; with the important difference that bloody diarrhea is less common and abdominal pain, fever, and weight loss are more common. The condition is a chronic inflammatory bowel disease of unknown etiology. The inflammatory process involves the full thickness of the bowel wall and can affect any part of the gastrointestinal tract; most commonly the right colon and terminal ileum. Patchy segmental in-

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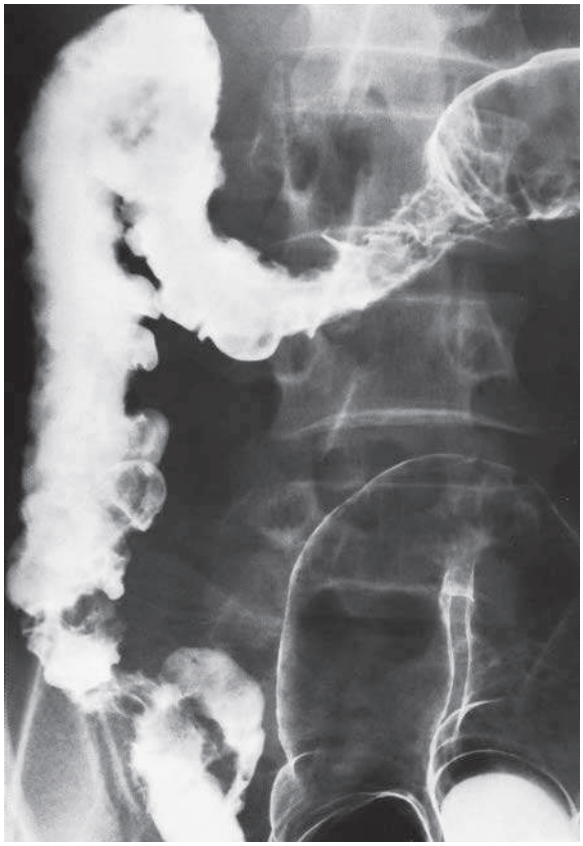

Fig. 27.**4** Crohn disease with segmental involvement of the right colon and of the terminal ileum. Deep intramural fissuring of the transverse colon with apparent pseudodiverticular dilation of a healthy segment of ascending colon between the affected segments.

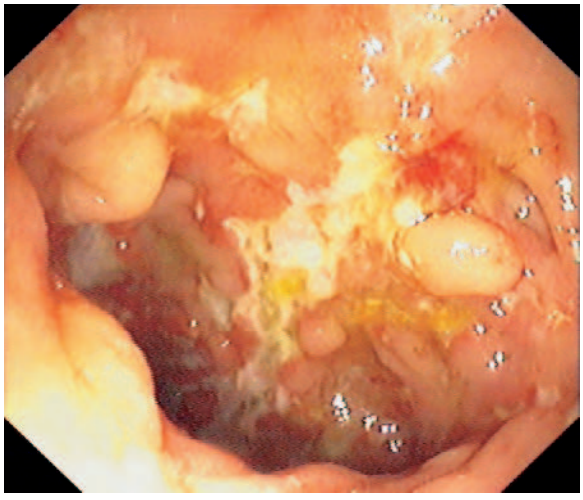

Fig. 27.**5** Crohn disease in a 17-year-old girl with a long history of recurrent abdominal colic and persistent diarrhea; deep linear ulceration with occasional fissuring in the transverse colon with deformation of the lumen.

volvement is typical with areas of macroscopically normal and inflamed mucosa observed on endoscopy. The small bowel is affected in 30–35%, the terminal ileum and right colon in 40–45%, and the left colon in 15–20% (see Figs. 27.**2d**, 27.**4**). In contrast to ulcerative colitis, the distal colon and rectum are often spared (i.e., normal sigmoidoscopy). However, perianal complications, commonly fistula, are present in 30–35%. Laboratory tests usually reveal a mild to moderate anemia and leukocytosis with toxic granulation. Thrombophilia and raised inflammatory indices are common. Low albumin, as a result of the inflammatory enteropathy, is often observed. Evidence of malabsorption (e.g., steatorrhea, vitamin B12 deficiency) may be present in ileal disease.

Clinical Course and Complications. Crohn disease typically follows a chronic course over years with exacerbations and long remissions. Acute, severe exacerbations are rare compared to ulcerative colitis and life-threatening complications such as severe bleeding and free perforation are exceptional. Rather, stenotic disease with recurrent episodes of obstruction is common, especially in small bowel disease. Transmural fistulae with local abscess formation are also observed. Systemic complications also occur, most commonly affecting the joints (e.g., polyarthralgia), skin (e.g., erythema nodosum), and eyes (e.g., uveitis). In contrast to ulcerative colitis, postoperative complications are common following bowel resection for Crohn disease, with local recurrence at the anastomosis occurring in over 50% of cases.

Diagnosis. The diagnosis of Crohn disease is based on typical endoscopic (Fig. 27.**5**) and radiological findings (Fig. 27.**2d**) demonstrating segmental, discontinuous distribution of disease with areas of deep transmural, linear, and polymorphic ulceration resulting in a cobblestone appearance of the affected bowel.

Differential Diagnosis. The clinical, endoscopic, and radiological findings of Crohn disease may also occur in chronic infections of the gastrointestinal tract (e.g., actinomycosis, tuberculosis, *Yersinia*, *Campylobacter*) as a consequence of medications (e.g., nonsteroidal anti-inflammatory agents), in malignant lymphoma, diverticulitis, or intestinal ischemia. As a result, the diagnosis of Crohn disease should be made with caution if presenting for the first time with an acute episode.

Gastrointestinal Tuberculosis

Clinical Features. The *ileocecal region* is the most common site for gastrointestinal tuberculosis causing *diarrhea*, *abdominal pain*, and *weight loss*. Gastrointestinal tuberculosis rarely presents as a primary disease in Western populations; it often occurs as a complication of severe disseminated pulmonary disease. In immi-

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grants to Western countries the most common cause is local reactivation of disease, usually with evidence of old pulmonary tuberculosis on chest radiography. Clinical examination sometimes reveals a fullness in the right iliac fossa on palpation; fecal blood loss is common. Anemia and evidence of chronic infection are rarely absent on laboratory testing.

Investigation. In addition to typical changes on chest radiography and the presence of acid-fast bacilli in the sputum, gastrointestinal endoscopy and radiology reveal infiltration, ulceration, and deformation of the cecum and ascending colon (Fig. 27.**6**). The differential diagnosis for these findings is that of inflammatory bowel disease. *Histology* and evidence of tuberculosis on culture of biopsy specimens are diagnostic.

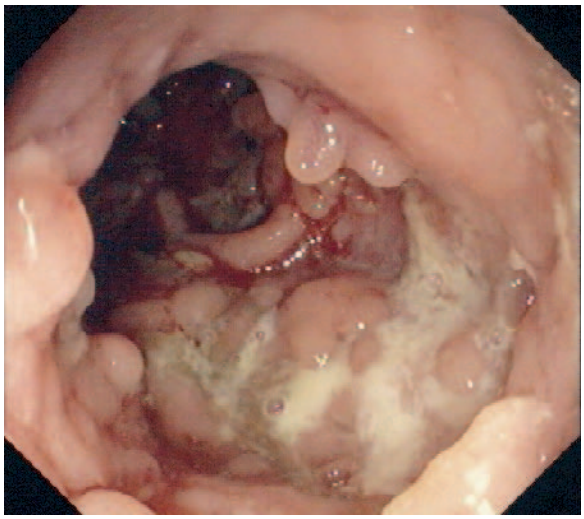

Fig. 27.**6** Ileocecal tuberculosis; pus laden ulceration and multiple pseudopolyps in the ileum in a 42-year-old man from Tibet, erroneously diagnosed with Crohn disease several years prior.

Malignant Small Bowel Tumors

Epidemiology. Small bowel malignancy is very rare. When it occurs, small bowel adenocarcinoma is most often seen in the duodenum, becoming less common in the jejunum and ileum. This contrasts with *lymphoma*, which is more common in the distal small bowel. *Carcinoid tumors* (see below) and gastrointestinal stromal tumors (GIST) are other potentially malignant tumors of the small bowel.

Clinical Features. Malignant and benign small bowel tumors become symptomatic when their size and location leads to partial or complete bowel obstruction with postprandial colic, nausea, and vomiting. Tumors that are not obstructive are usually asymptomatic or present with nonspecific abdominal symptoms, which are difficult to associate with the tumor. Malignant small bowel tumors also cause bleeding (often occult anemia) and perforation. Diarrhea occurs in association with hormone-secreting, neuroendocrine small bowel tumors.

Small bowel lymphoma sometimes cause diarrhea, anemia, and B-symptoms (fever, night sweats, weight loss) before bowel obstruction occurs.

In patients with HIV, Kaposi sarcoma must also be considered as a cause of altered bowel habit, gastrointestinal bleeding, and more rarely, bowel obstruction.

Diagnosis. In patients with bowel obstruction, radiological investigations (computed tomography [CT] or abdominal radiography) demonstrate *ileus* (dilated bowel, multiple fluid levels) above the stenosis caused by the tumor. Only for duodenal tumors can conventional upper gastrointestinal endoscopy be used to demonstrate and perform biopsies. In patients with abdominal symptoms without obstruction, in whom a small bowel tumor is suspected, the following investigations can be applied: radiological investigations of the small bowel (classic double-contrast studies of the small bowel, CT, or magnetic resonance imaging [MRI] small bowel imaging), enteroscopy, and capsule endoscopy. *Radiologic investigations* are diagnostic only for relatively large tumors. Push *enteroscopy* can detect and biopsy lesions in the proximal one-third of the small bowel. A more complete, noninvasive visual representation of the complete small bowel is possible with *double balloon enteroscopy* or *capsule endoscopy*. Radiology and capsule endoscopy provide a provisional diagnosis. However, histological confirmation is not possible. In this situation surgery provides definitive diagnosis and therapy.

Benign Small Bowel Tumors

More than half of all small bowel tumors, including *adenoma*, *leiomyoma*, *lipoma*, and *angioma*, are benign. In most cases these are asymptomatic and are chance findings at surgery or autopsy. Symptoms only occur when these lesions cause small bowel obstruction.

Colorectal Carcinoma

Epidemiology. Colorectal carcinoma is the second or third most common malignant disease in Western populations. The lifetime risk of developing colorectal cancer is approximately 5%. The incidence increases with age in a linear fashion.

Clinical Features. Most colorectal cancers remain asymptomatic until the disease is at an advanced stage. Good general health does not exclude underlying colorectal carcinoma; abdominal pain independent of defecation is rarely present. The most common presentation is a

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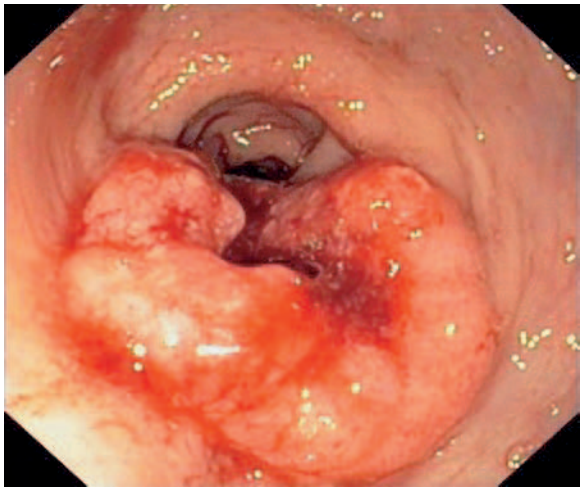

Fig. 27.**7** Exophytic colonic carcinoma in the sigmoid colon (pT3N1) in a 58-year-old woman with a three-month history of rectal bleeding.

change in bowel habit. Large tumors can occasionally be palpated on abdominal examination. *Bleeding* can occur from the surface of the tumor leading to *anemia* or overt rectal bleeding.

Anemia of unknown cause and/or rectal bleeding must always raise the suspicion of colorectal carcinoma and must be investigated by urgent endoscopy.

Occult blood loss may be present before other symptoms develop and can be used for early detection of colorectal carcinoma (fecal occult blood test). This investigation is only appropriate as a screening test in asymptomatic patients. Those patients with anemia or overt rectal bleeding must be investigated by endoscopy. Fecal occult blood testing is superfluous in this situation.

Advanced colon carcinoma occasionally causes large bowel obstruction. Complete obstruction causes an acute abdomen, nausea, and vomiting with dilated large and small bowel above the stenosis. This acute presentation is usually preceded by a change in bowel habit and stool consistency with alternating constipation and diarrhea, bloating, and abdominal colic. Rectal carcinoma rarely causes obstruction and presents with tenesmus and continence problems (involuntary passage of stool with wind), although these symptoms are nonspecific.

The possibility of colorectal carcinoma must be considered in all patients with a change in bowel habit, especially those above the age of 40.

Occasionally, the first presentation of colorectal carcinoma is as a consequence of metastatic liver disease (e. g., hepatomegaly, jaundice, weight loss). In these cases imaging by ultrasound, CT, or MRI (with guided liver biopsy) is crucial to establish the diagnosis. Fever and sepsis may also be the first manifestation of colorectal carcinoma; probably because the tumor facilitates the translocation of bacteria into the blood stream from the bowel.

Diagnosis. If alarm symptoms (e. g., change of bowel habit, rectal bleeding, anemia) raise suspicion of colorectal carcinoma a colonoscopy must be performed (Fig. 27.**7**). Conventional radiology (e. g., barium enema) has an auxiliary role in patients with narrow stenosing lesions that the endoscope cannot pass. So-called "virtual colonoscopy" (CT or MRI colonoscopy) may be available if colonoscopic examination is incomplete. Only deep-seated rectal tumors can be detected by digital examination and this is not a reliable screening test in any circumstances because so few lesions can be palpated.

Serological carcinoembryonic antigen (CEA) assessment and fecal occult blood testing (a screening test in asymptomatic patients) are not appropriate investigations for the diagnosis of colorectal cancer.

Colorectal Polyps

Epidemiology. Almost 50% of individuals in Western populations will develop a colorectal polyp in their lifetime (Fig. 27.**8**). Colorectal polyps can be divided into two main groups based on histology:

- nonneoplastic, hyperplastic polyps that very rarely carry a risk of malignant change
- neoplastic, adenomatous polyps (tubular, villous, or tubulo-villous adenoma); approximately 10% of these polyps will develop into colorectal carcinoma in a period of five to 10 years and are considered to be precancerous lesions.

Juvenile polyps (hamartoma) are a further, very rare polypoid lesion of the large bowel.

Clinical Features. Colorectal polyps are usually asymptomatic. Similar to colorectal carcinoma, rectal bleeding and obstructive symptoms (e. g., change in bowel habit) only occur with large lesions. However, villous adenoma occasionally presents with the passage of rectal mucous and diarrhea, rarely with secondary hypokalemia. The diagnosis of colorectal polyps is usually made at colonoscopy. The indications for investigation are usually symptoms that are not associated with the presence of polyps (e. g., abdominal pain). Because of the high prevalence of precancerous colorectal polyps many countries recommend screening investigations for asympto-

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matic individuals above 50 years. Patients in whom a colorectal polyp has developed are at an increased risk of developing further polyps and should be entered into a colonoscopic surveillance program.

Diagnosis. The majority of colorectal polyps are asymptomatic. Therefore, most of these lesions are incidental findings at *colonoscopy*. Most polyps can be completely resected during the same investigation. This provides a histological diagnosis that is important for prognosis.

Colorectal adenoma are precancerous and their removal at endoscopy can reduce the incidence of colorectal carcinoma by up to 80%.

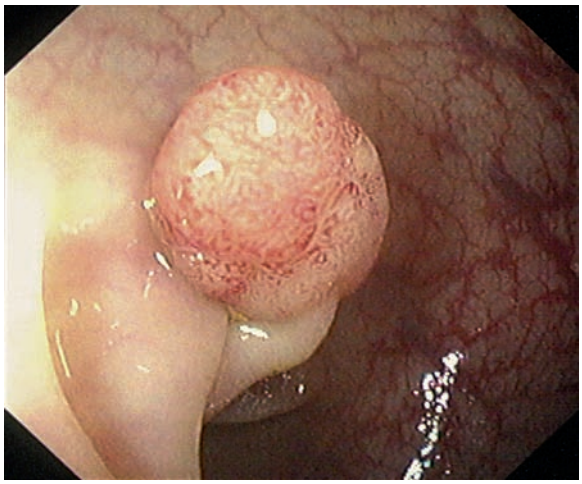

Fig. 27.**8** Pedunculated adenomatous sigmoid polyp.

Hereditary Colorectal Carcinoma

A variety of genetic mutations can increase the risk of colorectal polyps and carcinoma (Fig. 27.**9**). The presentation of patients with these conditions and the investigation of their symptoms are similar to those with sporadic polyps and carcinoma.

Hereditary nonpolyposis colorectal carcinoma (HNPCC) or *Lynch syndrome* is the most common of these rare syndromes (3–5%). This condition is inherited in an autosomal dominant manner. Colorectal carcinoma usually develops in affected individuals after the age of 45. The incidence of other malignancies is increased by the same mutation (e. g., endometrial, urogenital, ovarian, gastric, etc.).

The second most common form (0.5–1%) of hereditary colorectal carcinoma is *familial adenomatous polyposis* (FAP). The cause is a mutation on the adenomatous polyposis coli *(APC)* gene on chromosome 5 and is also inherited in an autosomal dominant manner. Patients develop hundreds to thousands of colorectal polyps during adolescent years and always develop cancer. For this reason *prophylactic panproctocolectomy* is recommended to these individuals at a young age.

A variant of FAP is *Gardener syndrome*, a condition defined by the presence of colorectal polyps with mesenchymal neoplasms including osteoma, fibroma, and desmoid tumors. From around 45 years of age a proportion of FAP patients develop a malignancy at the ampulla of Vater; usually presenting with extrahepatic jaundice.

Turcot syndrome (adenoma combined with brain tumors), *Cronkite–Canada syndrome* (hamartoma with alopecia and nail dystrophia), and *Peutz–Jeghers syndrome* (hamartoma throughout the gastrointestinal tract with perioral pigmentation) are further hereditary syndromes that are associated with increased incidence of colorectal carcinoma.

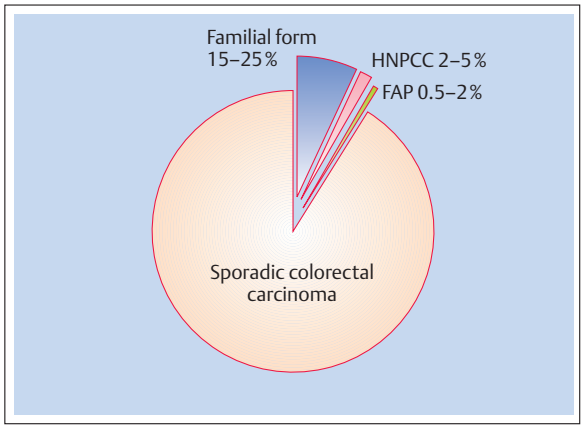

Fig. 27.**9** Hereditary syndromes associated with colorectal cancer.

The possibility of hereditary colorectal carcinoma should be considered in all patients that develop colorectal polyps under age 50. Always obtain a family medical history.

In the two most prevalent hereditary colorectal cancer syndromes (HNPCC, FAP) genetic testing reveals typical mutations in most patients. Upon detection of a hereditary cancer syndrome in a patient, first degree family members should be offered appropriate screening.

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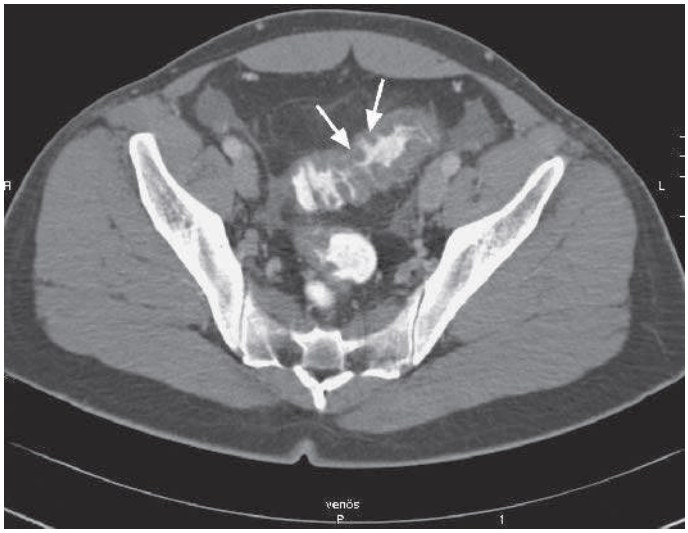

Fig. 27.**10** Sigmoid diverticulitis (CT image after administration of contrast media) in a 33-year-old man (unusually young) with a second presentation of acute diverticulitis; inflammation with thickening of the bowel wall and obstruction of diverticular orifice.
Image courtesy of S. Wildermuth, Institute of Diagnostic Radiology, University Hospital of Zürich.

Diverticulosis and Diverticulitis

Epidemiology. A large proportion of Western populations develop large bowel diverticula with prevalence increasing with age. There is no gender predisposition. At least 1 % of these patients develop diverticulitis.

Clinical Features. Diverticulosis is asymptomatic. The condition is often an incidental finding on colonoscopy and is most common in the sigmoid colon. There is an epidemiological association between diverticulosis and *constipation*, although the pathological link is unclear.

Diverticulitis is a *local bacterial infection*, which is probably the result of a local perforation in the region of a diverticulum. The severity of diverticulitis, localization, and extent of abdominal pain depends on the site of disease, degree of peritoneal irritation, and spread of infection. On occasion, extensive perforation occurs with diffuse peritonitis and abscess formation. Most commonly, diverticulitis causes local, usually left-sided, abdominal pain, sometimes termed a "left-sided appendicitis."

Complications. Other complications of diverticulosis include diverticular *bleeding* and a portion of patients develop large bowel stenosis (usually in the sigmoid colon); probably as a result of muscle wall thickening and recurrent diverticulitis. Stenosis can cause a change in bowel habit with alternating constipation and diarrhea. More severe narrowing causes partial bowel obstruction with abdominal colic and bloating.

Rare complications of diverticulitis include dysuria caused by an inflamed diverticulum in close proximity to the bladder and even fistula formation between the bowel and the bladder. In the latter case bowel gas can pass with the urine (pneumaturia). Similarly, left-sided hydronephrosis has been reported as a complication of sigmoid diverticular disease.

Diagnosis. Uncomplicated diverticulosis is often an incidental finding at colonoscopy or barium enema. However, the diagnosis of diverticulitis is not established at endoscopy but rather by CT (Fig. 27.**10**). Ultrasound or MRI are alternative diagnostic techniques. The condition is recognized by the presence of thickened colonic wall and, if present, local abscess formation.

Diseases Without Abnormal Findings on Endoscopy

Lactase Deficiency

The possibility of lactase deficiency should be considered in patients with diarrhea of unknown cause. Congenital lactase deficiency has been described in infants.

Acquired lactase deficiency and milk intolerance can develop in adults (very frequent in noncaucasians). In acquired lactase deficiency (i. e., milk tolerated in childhood) diffuse abdominal discomfort, bloating, flatulence, and diarrhea develop after ingestion of milk. The diagnosis can be confirmed by a lactose tolerance test with assessment of hydrogen gas in the breath after a 50 g lactose test meal. A rise in hydrogen gas in expired air (to above 20 ppm) with the development of typical symptoms indicates lactase deficiency in the small

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bowel mucosa. Elimination of significant quantities of milk from the diet is therapeutic.

In addition to the idiopathic form, *secondary lactose intolerance* is frequently caused by a number of gastrointestinal diseases (e. g., infectious gastroenteritis, celiac disease, Crohn disease).

Further rare causes of disaccharidase deficiency include: sucrose-isomaltose intolerance in children (a congenital, autosomal recessive disease) and trehalose intolerance (following ingestion of certain fungi).

Psychogenic Diarrhea

Diarrhea is known to occur with *anxiety states*, such as fear of an upcoming event (e. g., examinations); an impressive demonstration of psychosomatic regulation. Affected individuals are usually those who react sensitively to external stressors. Upon direct questioning, a long history of variable bowel habit is often obtained and psychogenic diarrhea probably belongs to the same category of conditions as irritable bowel syndrome (although by definition abdominal pain is absent).

Malassimilation (Maldigestion and Malabsorption)

Introduction

Chronic diarrhea and weight loss are suggestive of a malassimilation syndrome if symptoms and signs of nutritional deficiency are present, e. g., macrocytotic (folate or vitamin B12 deficiency) or microcytic, hypochromic (iron-deficiency) anemia, peripheral edema (hypoproteinemia), tetany, bone pain (calcium and vitamin D deficiency), hemorrhagic diathesis (vitamin K deficiency), glossitis, and peripheral neuropathy (vitamin B deficiency).

Pathogenesis. Malassimilation can be caused by many different disturbances of the digestive process. The end effect of these conditions is the loss of essential nutrients from the diet with the stool. The causes of malassimilation can be divided into two main groups (maldigestion and malabsorption) and various subgroups (Tab. 27.**5**).

Maldigestion is caused by deficiencies of bile or digestive enzyme secretion (or action) resulting in impaired emulsification of fat or hydrolysis of carbohydrate, protein, or fat into smaller molecules.

Malabsorption is characterized by impaired uptake of the products of digestion from the lumen of the bowel into the blood and lymphatic systems. Causes include:

- *mucosal disease* (e. g., celiac disease, Crohn disease)
- *reduced absorptive surface* (e. g., small bowel resection, entero-enteric fistula)
- *reduced contact time* (e. g., carcinoid syndrome)
- *disturbed mesenteric blood supply* (e. g., mesenteric ischemia) or lymphatic drainage (e. g., tuberculosis, malignancy).

Clinical Features. The most reliable, objective sign of malassimilation is the presence of *steatorrhea*, i. e., stool fat excretion in excess of 7 g/day at a dietary intake of 100 g/day. However, steatorrhea is absent in the rare, inherited malabsorption conditions in which an isolated failure of the small bowel impairs digestion or absorption of particular nutrients (e. g., disacharidase deficiency, glucose–galactose transporter dysfunction, Hartnup disease, and other syndromes related to amino acid malabsorption). In contrast, steatorrhea is likely to be present in patients that present with oily, odiferous, high-volume diarrhea over 300 g/day.

Diagnosis. The investigation of malassimilation must address two questions:

- Is malassimilation present? (Biochemical evidence of nutritional deficiency or steatorrhea.)
- If yes, what is the cause? (Small bowel assessment by endoscopy and biopsy, radiology, assessment of pancreatic function.)

The blood count and "small bowel screen" are important for the diagnosis of malassimilation. *Anemia* is usually present in celiac disease and may be the only indication of disease in some patients. Typically, there is a polymorphic picture with evidence of iron, folate, and vitamin B12 malabsorption. Primary pernicious anemia is easily distinguished by the presence of gastric (not duodenal) atrophy and the presence antiparietal cell antibodies. In addition, 50 % of patients with celiac disease have Howell–Jolly bodies on the blood film indicative of splenic atrophy.

The "*small bowel screen*" should include important biochemical markers that are abnormal in malabsorption such as reduced albumin, urea, calcium, phosphate, iron, serum lipids, prothrombin, and raised alkaline phosphatase (osteomalacia). Abnormalities of blood count and "small bowel screen" are usually less marked in maldigestion.

Primary Malabsorption

Celiac Disease (Endemic Sprue)

Pathogenesis. Celiac disease in adults and children is caused by a gluten-sensitive, *immune-mediated enteropathy* (gluten or gliadin is a protein found in cereal

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Table 27.**5** Causes of malassimilation syndrome

Maldigestion
- gastric (e. g., postgastric resection)
- hepatobiliary (e. g., cholestatic)
- bile acid deficiency
- pancreatic (e. g., chronic pancreatitis)

Malabsorption
Primary[1]
- celiac disease (endemic sprue)[1]
- tropical sprue[1]

Secondary
- postoperative
  - short bowel syndrome
  - bowel diversion, e. g., gastrocolic fistula, gastroileostomy[2]
  - stricture[2]
  - blind loop syndrome[2]
- inflammatory or neoplastic disease affecting the colon or mesentery
  - Whipple disease[1]
  - Crohn disease[2]
  - infectious gastroenteritis (temporary)
  - parasitic disease
  - collagenous sprue[1]
  - radiation enteritis (radiotherapy)
  - eosinophilic (allergic) gastroenteritis[1]
  - malignant lymphoma or tuberculosis
- endocrine–hormonal (rare)
  - hyperthyroidism
  - diabetic enteropathy
  - Addison disease
  - carcinoid syndrome
  - Zollinger–Ellison syndrome
  - Verner–Morrison syndrome
  - medullary thyroid carcinoma
  - ganglion neuromatosis
  - generalized mastocytosis
- miscellaneous (very rare)
  - amyloidosis
  - scleroderma
  - small bowel diverticulosis[2]
  - abetalipoproteinemia[1]
  - hypogammaglobulinemia[1]
  - intestinal lymphangiectasia[1]
  - mesenteric ischemia
  - drugs (e. g., laxatives, colestyramine, neomycin, chemotherapeutic agents)
  - idiopathic intestinal pseudo-obstruction

[1] With typical findings on small bowel biopsy.
[2] With typical findings on small bowel imaging.

crops, including wheat, barley, and rye). In certain individuals (genetic predisposition) the presence of gluten in the diet triggers immune-mediated mucosal damage in the small bowel. This is usually reversible after exclusion of gluten from the diet. New methods of screening in Europe have shown that celiac disease is one of the most common genetic diseases with a prevalence of between 1:130 and 1:300. The probability that first degree relatives are affected lies between 10–20%. The disease affects both sexes with equal frequency and presents most commonly in middle age, with a tendency to abrupt changes in clinical course (e. g., occult to overt disease).

Clinical Features. The fully developed disease presents with *severe diarrhea*, *significant weight loss*, *general weakness*, and typical features of nutritional deficiencies that clearly point to the diagnosis. In this situation the diagnosis is quickly confirmed by specific investigations. In patients with a short history and severe disease the clinical differential includes underlying malignancy. The further differential diagnosis of celiac disease includes Crohn disease, hyperthyroidism, anorexia nervosa, severe laxative abuse, and Addison disease.

Atypical and *occult presentations* of celiac disease are up to 10 times more frequent than that of the fully developed clinical picture. Patients often present with mono- or oligosymptomatic disease. The diagnosis is often delayed in those with isolated iron deficiency anemia or osteomalacia until malabsorption is considered and appropriate investigations performed. In 5–10% of patients with celiac disease diarrhea is absent. There may even be a tendency to constipation. The most important complication of untreated celiac disease is the increased risk of intestinal malignancy, in particular T-cell lymphoma. This risk is particularly high in patients with refractory sprue, ulcerative jejunitis, and the rare collagenous sprue; all conditions that do not respond to the gluten-free diet.

In severe disease, physical examination may reveal, in addition to cachexia, a bloated "doughy" abdomen, peripheral edema, hypotonia, and increased skin pigmentation (without mucosal pigmentation in contrast to Addison disease). These findings are absent when the disease is controlled.

Diagnosis. The diagnosis of celiac disease is suggested by serological tests and confirmed by small bowel biopsy (Fig. 27.**11**). IgA and IgG antigliadin antibodies do not have sufficient specificity or sensitivity for diagnosis, indeed antigliadin IgA antibodies can be detected in up to 90% of healthy, elderly individuals. In contrast *antiendomysial antibodies* offer high diagnostic accuracy. The antigenic target for antiendomysial antibodies was recently discovered to be the enzyme tissue transglutaminase. The detection of specific IgA and IgG transglutaminase antibodies further increase the specificity and sensitivity of serological tests.

> The typical clinical presentation, positive serology, and typical changes on small bowel histology all suggest the diagnosis of celiac disease. Confirmation is provided if a gluten-free diet produces clinical remission, reduction in autoantibody titers, and normalization of small bowel histology.

This response is important because identical histology is found in tropical sprue and hypogammaglobulinemia with sprue. Similar changes are also found in a range of other intestinal disorders (e. g., gastric resection, parasitic infection, certain medications) although these tend to be localized rather than diffuse findings. In other causes of malassimilation small bowel histology is

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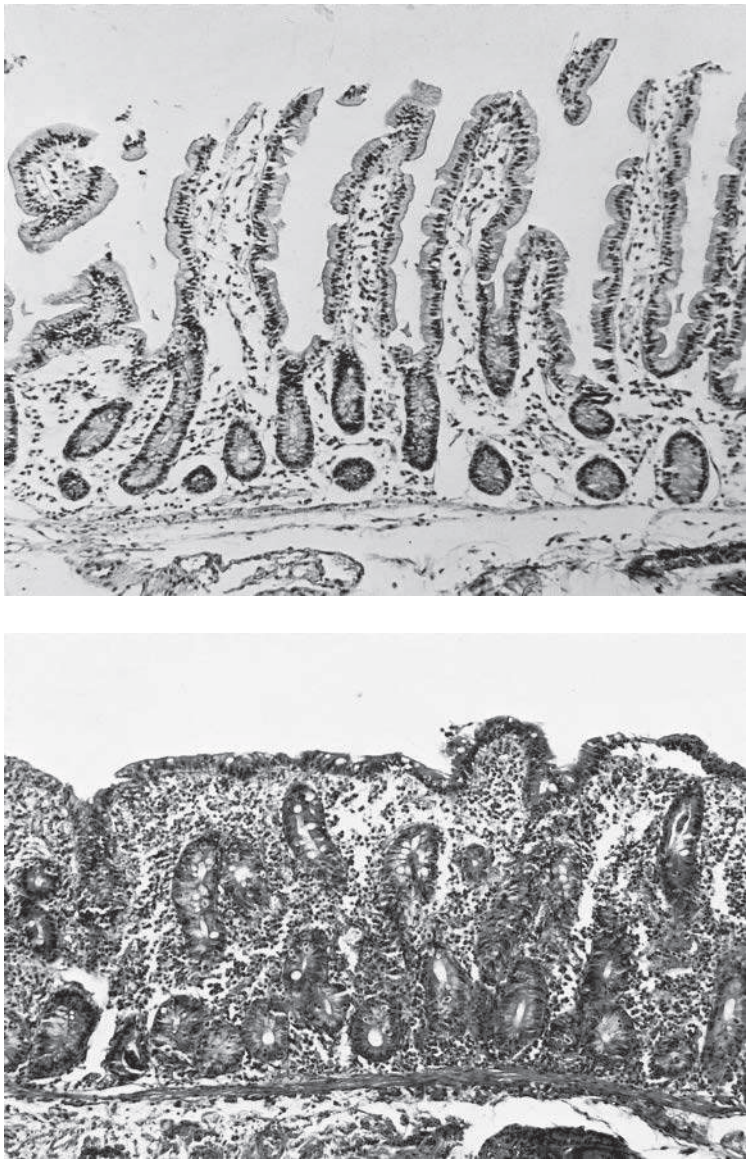

Fig. 27.**11** Small bowel histology
a Normal
b Untreated celiac disease; there is villous atrophy and increased intraepithelial lymphocytes.

either normal (e. g., maldigestion, postresection, endocrine–hormonal disease) or demonstrates changes diagnostic of other conditions (e. g., Whipple disease, amyloidosis, intestinal lymphangiectasia, abetalipoproteinemia).

Tropical Sprue

Tropical sprue is an infectious disease (unknown pathogen) that occurs primarily in the Far East, India, Central America, and Puerto Rico. The clinical presentation is similar to celiac disease. However, here the condition responds to antibiotics rather than dietary therapy.

Maldigestion and Secondary Malabsorption

Steatorrhea without abnormal small bowel histology suggests the presence of secondary malabsorption or maldigestion (see Tab. 27.**5**).

Steatorrhea caused by *obstruction of the biliary tract* is easy to recognize because of concurrent jaundice. Typical findings in pancreatic steatorrhea due to *chronic pancreatitis* include pancreatic calcification, exocrine pancreatic insufficiency, and an abnormal glucose tolerance test.

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Steatorrhea and Bile Acid Malabsorption

Pathogenesis, Enterohepatic Circulation. A precondition for fat absorption from the gastrointestinal tract is the emulsification of dietary fat by bile (formation of micelles). For this reason fat absorption is highly dependant on bile acid metabolism (Fig. 27.**12**). Bile acids are produced in the liver and secreted by the biliary tract into the duodenum. After facilitating fat digestion, bile acid is largely reabsorbed in the ileum. On average, the bile acid pool of about 4 g passes through this enterohepatic circulation 6 times per day. Physiological losses of about 0.5 g/day are replenished by hepatic synthesis.

Ileal disease or resection can cause bile acid malabsorption (e. g., Crohn disease). *Limited ileal resections* (< 100 cm) increase the amount of bile acid reaching the colon, with stimulant laxative effects, which can cause diarrhea. However, the liver compensates for increased losses by increasing bile acid synthesis, preserving the bile acid concentration needed for fat emulsification in the small bowel and only mild steatorrhea is observed (< 20 g fat/24 h; Fig. 27.**12b**; compensated bile acid malabsorption). After more *extensive ileal resection* (> 100 cm) or disease the liver cannot compensate for the loss of bile acid, the concentration falls below the level required for efficient fat digestion, leading to high-volume steatorrhea (Fig. 27.**12c**; treatment: medium-chain triglycerides [MCT] and substitution of fat-soluble vitamins). Ileal resection or disease is also associated with increased formation of gallstones (supersaturation by cholesterol due to reduced bile acid pool) and increased formation of renal stones (increased oxalate absorption due to calcium binding by unabsorbed free fatty acids in the colon). Maldigestion and steatorrhea also occurs with small bowel overgrowth (increased deconjugation of bile acid with impaired emulsification of fat). Antibiotic therapy is effective treatment for the latter condition (Fig. 27.**12d**).

Whipple Disease

Whipple disease is a rare condition that usually presents in a manner similar to celiac disease. Early recognition of this potentially lethal disease is important because effective treatment is available. Whipple disease most commonly affects middle-aged men. Rheumatic symptoms typically present before those of malassimilation, sometimes by several years. The diagnosis is based on the presence of pathognomonic *PAS-positive macrophages in the small bowel* biopsy. On ultrasound or at laparotomy, enlarged mesenteric lymph nodes are evident. The Gram-positive intracellular bacteria that causes Whipple disease, *Tropheryma whippelei*, has recently been identified and cultured. PCR techniques are now available allowing direct confirmation of the infectious agent. Prolonged antibiotic therapy can induce long-term remission and cure the disease.

Small Bowel Bacterial Overgrowth (SBO)

Pathogenesis. There are almost no bacteria in the proximal small bowel, but the level of colonization increases through the ileum although not to the levels observed in the colon. Small bowel bacterial overgrowth (SBO) is commonly present after ileocecal resection or formation of a blind-ending small bowel loop. Rare causes of SBO include small bowel diverticula, fistula, stenosis, or severe disturbances of small bowel motility (e. g., scleroderma). Increased bacterial colonization of the small bowel increases bile acid deconjugation leading to triglyceride malabsorption and steatorrhea. In addition, deconjugated bile acid has a direct toxic effect on small bowel mucosal function, inhibiting sodium resorption by the enterocytes. In addition, bacterial overgrowth impairs vitamin B12 absorption, although folate levels are increased (produced by bacterial metabolism).

Clinical Features. Patients with SBO may be asymptomatic or present with evidence of malabsorption. Common symptoms include diarrhea, steatorrhea, and vitamin B12 deficiency anemia.

Diagnosis. The diagnostic "gold standard" is quantitative bacterial culture of jejunal aspirates obtained at endoscopy; a population density of $> 10^5$ bacteria/mL is considered pathologic. Alternatively the diagnosis is suggested by a positive hydrogen breath test (75 g glucose test meal); a simple but nonspecific investigation.

The ideal treatment of SBO is management of the underlying condition. This is rarely possible and antibiotic therapy to reduce bacterial overgrowth is usually attempted. This can achieve several months of clinical remission in some patients, whereas relapse occurs in others within weeks.

Short Bowel Syndrome

Extensive small bowel resection causes secondary malabsorption (see Tab. 27.**5**) due to reduction in the absorptive area of the bowel, reduced gastrointestinal transit time, and bile acid malabsorption. Due to the remarkable capacity of the remaining bowel to adapt, if more than 100 cm of ileum remains it is usually possible to maintain adequate nutrition by mouth using careful nutrition and fluid management (especially if the colon is preserved). Milk products should be avoided as secondary lactase deficiency is common after small bowel resection. Supplements of fat-soluble vitamins are necessary because of steatorrhea. Replacement of vitamin B12 and trace elements is of particular importance after extensive ileal resection.

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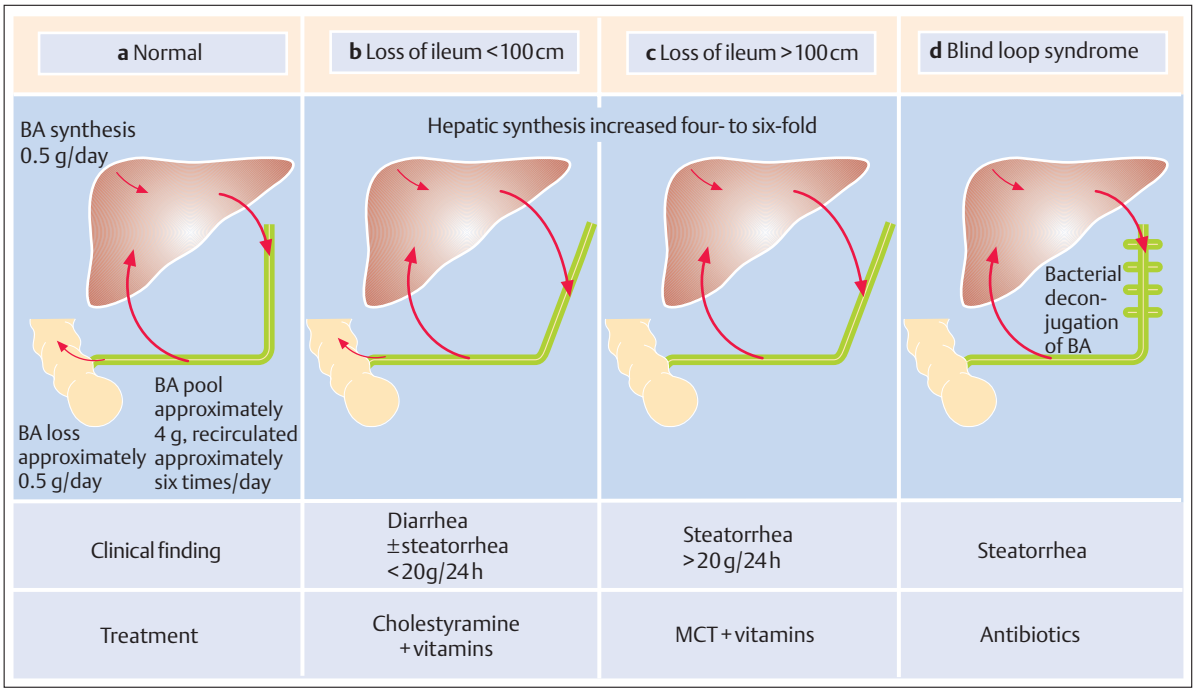

Fig. 27.**12** Schematic representation of the enterohepatic circulation of bile acid.
a Normal
b–d Various disease states (BA = bile acid, MCT = midchain triglycerides).

Intestinal Lymphangiectasia

Intestinal lymphangiectasia is caused by obstruction to the lymphatic drainage of the bowel. This condition can be congenital or acquired secondary to abdominal trauma, malignancy, chronic pancreatitis, and occasionally severe cardiac failure. As a consequence, the transport of chylomicrons and lipoproteins is impaired, leading to fat malabsorption and also a protein-losing state. The combination of steatorrhea, hypoalbuminemia, and lymphopenia is typical for intestinal lymphangiectasia. The diagnosis is established by small bowel biopsy. Treatment is directed against the underlying condition. Medium-chain triglycerides can reduce diarrhea and steatorrhea because these are not absorbed via the lymphatic system but directly into the blood stream.

Endocrine and Hormonal Causes of Diarrhea

Endocrine Disease

- *Hyperthyroidism* is a common cause of diarrhea mediated by an endocrine disease; steatorrhea is occasionally present.
- *Hypoparathyroidism* occasionally causes diarrhea. Note: celiac disease must always be excluded in patients presenting with diarrhea and hypocalcemia.
- *Adrenal insufficiency* (Addison disease) is occasionally accompanied by diarrhea.
- *Severe insulin-dependant diabetes mellitus* may cause diarrhea. This is not due to pancreatic exocrine insufficiency, but a diabetic neuropathy affecting the autonomic nervous system. Peripheral neuropathy, together with evidence of autonomic dysfunction in other visceral organs may be present (e.g., orthostatic hypotension, atonic bladder, impotence, abnormal sweating).
- *Diabetic autonomic neuropathy/dysfunction* is closely related to glucose control and the severity of the underlying disease. Pancreatic disease (chronic pancreatitis, pancreatic cancer) as a cause of both diabetes mellitus and steatorrhea must always be excluded.

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Hormone-Secreting Tumors

Diarrhea is a prominent symptom in several rare hormone-secreting tumors of the pancreas (gastrinoma [Zollinger–Ellison syndrome], VIPoma [Verner–Morrison syndrome]) and the gastrointestinal tract (neuroendocrine tumors, carcinoid syndrome). Common features of these conditions include:

- similar embryological origin (neural crest)
- typical morphological and histochemical features
- production of various polypeptide hormones by the same biochemical system (APUD = amino precursor uptake decarboxylation).

Carcinoid Syndrome

Clinical Features. *Diarrhea* is often the first symptom that occurs in carcinoid disease, often preceding other features by several years. In advanced disease it is present in > 75 % of cases. However, the possibility of carcinoid syndrome is usually considered by the examining doctor only when *flushing* occurs (Fig. 27.**13**). This vasomotor phenomenon is usually accompanied by diarrhea, abdominal colic, and respiratory symptoms, and can be triggered by alimentary (dietary) or emotional stimuli. This is a pathognomonic feature of carcinoid syndrome and is rarely missed. Another classic late symptom is endocardial fibrosis with valvular insufficiency or stenosis exclusively affecting the right heart (Hedinger syndrome).

Other patients with carcinoid syndrome present with prominent asthmatic symptoms.

Fig. 27.**13** Patient with metastatic carcinoid tumor during a flush.

Pathophysiology. Carcinoid syndrome is caused by hormone-secreting, metastatic neuroendocrine tumors (carcinoid) in the gastrointestinal tract, rarely by bronchial neuroendocrine tumors (when present, endocardial fibrosis affects the left heart), and gonadal neuroendocrine tumors (cystic ovarian and testicular teratoma with carcinoid tissue).

> Carcinoid symptoms may occur as part of a paraneoplastic syndrome caused by carcinoma of the lung, pancreas, stomach, or liver.

The most common site of the primary carcinoid tumor, single or multiple, is usually in the ileocecal region. Neuroendocrine tumors occasionally cause small bowel stenosis and present with acute obstruction, more rarely with bleeding. However in general, neuroendocrine tumors of the gastrointestinal tract present with characteristic symptoms, such as flushing, only after the development of liver metastases. Carcinoid syndrome presents most commonly in patients between 40 and 70 years of age, without sexual predisposition.

Diagnosis. The production of 5-hydroxytryptamine (serotonin) is important for diagnosis. The 5-hydroxytryptamine level in the plasma is usually raised. However, it is simpler and more reliable to assess the 5-hydroxyindole acetic acid (5-HIAA) level in the urine over 24 hours. 5-HIAA is an end product of serotonin metabolism that is almost always highly elevated in patients with carcinoid syndrome.

The differential diagnosis of carcinoid syndrome is limited. Diarrhea and occasionally steatorrhea can be observed in generalized *mastocytosis* probably as a result of increased histamine release in the small bowel mucosa.

Verner–Morrison Syndrome (VIPoma)

Diarrhea caused by rare, noninsulin-secreting pancreatic adenomas (Verner–Morrison syndrome) is caused by increased secretion of vasoactive intestinal peptide (VIP). The resulting disease is characterized by massive, watery diarrhea (often > 10 L/day) with gross electrolyte depletion and shock ("pancreatic cholera"). Similar to gastrinoma, one or several non-β-cell adenoma or a diffuse islet cell hyperplasia are present, the removal of which is curative. The tumors can be benign or malignant. It is simple to differentiate VIPoma from gastrinoma by the measurement of serum gastrin.

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Caution: diarrhea and hypokalemia are much more commonly caused by laxative abuse.

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28 Constipation

M. Fried, M. Fox, and M. Thumshirn

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Introduction, Clinical Terms

"Too infrequent, too little, too hard" are words with which patients that seek medical attention for constipation describe their bowel habit. In everyday clinical practice constipation can be defined as less than two bowel actions per week, usually passing hard stool, and associated with straining. However, when applying this definition it must be kept in mind that two to three bowel actions per week and small stool volumes may be physiological, depending on the volume and type of food ingested.

Classification. In the clinic it is important to distinguish
- acute constipation
- chronic constipation (duration more than three months).

Every lasting change of bowel habit with sudden onset should be classified as acute constipation and requires urgent investigation. This includes "paradoxical" or "overflow" diarrhea that follows fecal impaction in the distal colon and anorectum with secondary dissolution and passage of liquid stool.

Pathophysiology of constipation:
- mechanical obstruction, e. g., colorectal carcinoma, anal carcinoma, diverticular disease
- disturbed colorectal motor function, e. g., slow transit, pregnancy, hypothyroidism, porphyria, hypokalemia, hypercalcemia, medication (opiate, tricyclics), toxin (lead)
- disturbed neurological function (peripheral or central), e. g., Hirschsprung disease, major psychiatric disease (depression, psychosis), irritable bowel syndrome
- disturbed toileting behavior, e. g., anismus, painful defecation (anal fissure, thrombosed hemorrhoid), change of routine (work, travel), hospitalization
- miscellaneous, e. g., dietary factors (poor fluid intake, low-fiber), anorexia nervosa, underlying systemic disease.

Alarm symptoms must be sought in all patients presenting with constipation, especially those with a change in bowel habit over age 45, with rectal bleeding, weight loss, or a family history of bowel cancer. These features increase the risk that the patient has an underlying colorectal cancer or colitis.

28.1 Acute Constipation

Patients presenting with constipation of sudden onset, especially in older age, must be investigated to exclude a colonic stenosis such as *carcinoma* or *diverticular disease* (muscle wall thickening and/or inflammation). Abdominal pain and increasing bloating are further indications of a mechanical bowel obstruction. Polyps can cause similar symptoms, either due to obstruction or by acting as a focus for intussusception. Intraintestinal problems such as inflammatory strictures (e. g., Crohn disease) or ingested foreign bodies may cause acute constipation, as may extraintestinal disease (especially urogenital tumors). Further causes of acute constipation can be identified by detailed questioning. These include anal disease (e. g., anal fissure), drugs (e. g., opiate, tricyclics, anticholinergics, calcium antacids), sudden changes in lifestyle (e. g., travel), diet (e. g., low fiber) or activity (e. g., hospitalization).

28.2 Chronic Constipation

Chronic constipation is very common and may be the result of a number of pathophysiological mechanisms, including colonic motor and neurological dysfunction, abnormal toileting behavior and dietary problems; several of which may be present in any one patient. Constipation is often associated with "*slow transit*" of the stool through the colon. Colonic transit time can be assessed, and the severity of any disturbance quantified by the passage of radio-opaque markers through the gastrointestinal tract (Fig. 28.**1**). Chronic constipation may also be caused by *disorders of anorectal function* (e. g., functional outlet obstruction).

Pathogenesis. The passage of stool through the bowel proceeds in a stepwise fashion by phasic contraction of the colonic musculature and mass movement of luminal contents, which occur at discrete intervals during the day. The transit time from cecum to anus is normally 12–24 hours. Mass movements are often initiated by visceral events, such as the gastrocolic reflex after eat-

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ing. Contraction of the distal colon and the passage of stool into the rectum trigger the urge to defecate. Should this important signal be *suppressed on a regular basis*, the sensation of urgency can be lost and this may lead to fecal loading and slow colonic transit. Other factors that lead to chronic constipation by reducing fecal volume or inhibiting normal colonic function include *reduced fluid intake*, *low-fiber diet*, *reduced physical activity*, and the effects of a stressful (but sedentary), modern lifestyle. It is often difficult to identify a single cause of chronic, functional constipation in an individual. Constipation predominant irritable bowel syndrome is distinguished from functional constipation by the presence of abdominal pain relieved by defecation. Abdominal wind and bloating, as well as occasional episodes of loose stool and diarrhea (irritable bowel syndrome with alternating constipation/diarrhea), may also be prominent in this condition.

Therapy. For best effect, the treatment of constipation often needs to address several factors simultaneously: management of abnormal toileting behavior, improvement of stool volume and consistency by increasing fluid and fiber (also bulking agents and laxatives), and encouragement of physical activity.

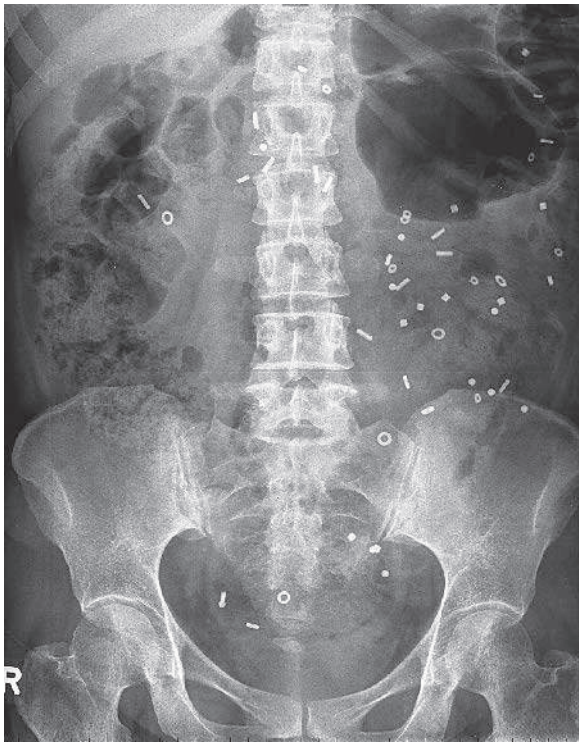

Fig. 28.**1** Colon transit time assessment by radio-opaque marker study. Severe constipation in this 44-year-old woman is indicated by the retention of 52/60 markers in the colon after six days.

28.3 Temporary Constipation

Chronic functional constipation can last for years. However, temporary problems with constipation can develop as a direct or indirect effect of underlying medical conditions:

- *Hormonal factors* are responsible for constipation associated with pregnancy and hypothyroidism and hyperparathyroidism.
- Visceral pain and inflammation associated with gallstones, renal colic, peptic ulceration, pancreatitis, and intra-abdominal infection may cause severe, resistant constipation.
- Major psychiatric conditions (especially depression), Parkinson disease, cerebrovascular disease, brain and spinal lesions are often associated with constipation.
- Constipation is prominent in patients affected by administration of *exogenous* (e. g., opiate abuse, lead poisoning) or the accumulation of *endogenous* (e. g., porphyria) toxins.
- Various *drugs* cause constipation (e. g., opiate analgesia, sedatives, anticholinergics, calcium-containing antacids, iron preparations, or ganglion blockers).

Intestinal Pseudo-Obstuction Syndrome. Pseudoobstruction is a syndrome that presents with symptoms and signs of colonic obstruction in the absence of an objective, mechanical lesion. It presents either acutely or as a chronic relapsing condition. The etiology may be primary (idiopathic) or secondary to a number of underlying diseases (neuromuscular disorders, scleroderma, endocrine conditions [e. g., hypothyroidism, hypoparathyroidism], retroperitoneal malignancy, severe psychiatric conditions, or drugs).

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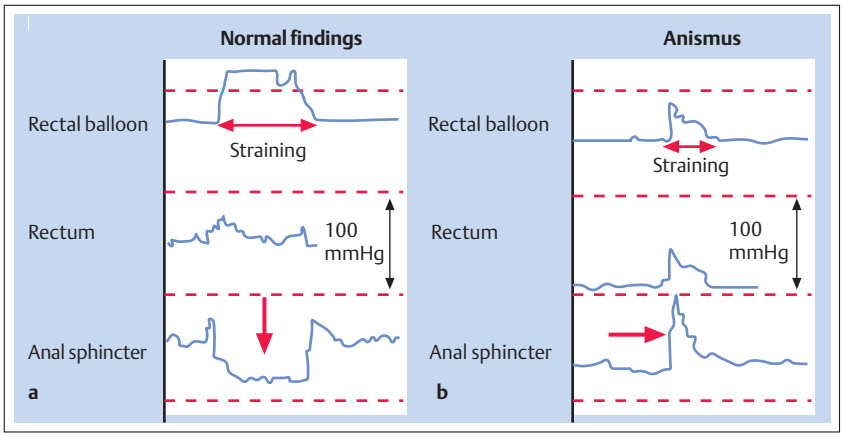

Fig. 28.**2** Anal manometry
a Normal findings
b Anismus in a 35-year-old woman. The patient with anismus demonstrates paradoxical contraction rather than relaxation of the anal sphincter on attempted defecation.

28.4 Anorectal Dysfunction

Functional obstruction of defecation can be the result of *anismus* (Fig. 28.**2**) or *pelvic floor dysfunction*. These problems can be identified only by investigation of anorectal function (proctoscopy at rest and on straining, anal manometry, defecography). In patients with anismus, the muscle of the anal sphincter contracts rather than relaxes during attempted defecation. In patients with weak pelvic musculature (most common in women with multiple vaginal deliveries), the normal descent of the pelvic floor on straining is exaggerated. The lack of effective support results in inefficient expulsion of stool on attempted defecation. Moreover, the normal anatomic relationship between rectum and anal canal is altered, such that the direction of forces on straining are no longer directed through the anal canal, resulting in a functional outlet obstruction.

28.5 Megacolon and Megarectum

Constipation is the most important symptom in megarectum. Congenital aganglionosis of the myenteric plexus (Hirschsprung disease) is to be differentiated from acquired megarectum in which the myenteric plexus is preserved. However, in both forms a massively dilated colon is seen on radiography.

Congenital Megacolon. Hirschsprung disease usually presents shortly after birth or in early childhood with abdominal distension, severe constipation, and signs of partial intestinal obstruction. The *cause* of this functional obstruction is the absence of ganglion cells in the myenteric plexus in the rectum and a variable length of distal colon. This pathology results in tonic contraction (spasticity) of the muscle wall and failure of the affected segment to accommodate and transmit stool. "Short-segment" Hirschsprung disease, affecting only the distal rectum, occasionally presents in adulthood. The diagnosis is established by the absence of the rectoanal inhibitory reflex on manometry and full thickness biopsy of the affected bowel.

Acquired Megacolon. Acquired megacolon or megarectum is characterized by gross chronic dilation of the rectum and colon without severe inflammation (toxic megacolon), and without a spastic, aganglionic segment of distal colon or rectum. In adults, megarectum and megacolon can be observed in association with various underlying diseases including degenerative neuromuscular conditions, scleroderma, Parkinson disease, amyloidosis, hypothyroidism, porphyria, and Chagas disease. However, the etiology of many cases remains uncertain.

> Every presentation of megarectum is suspicious of mechanical obstruction in the distal bowel and should be investigated by endoscopy to exclude an inflammatory or neoplastic stenosis.

Far more common than megacolon, many patients with chronic constipation have a long (undilated), tortuous colon. This so called "redundant colon" does not have clear pathological importance except when complicated by sigmoid or cecal (rare) volvulus.

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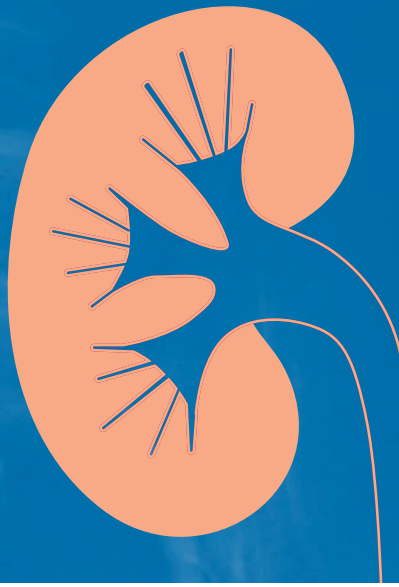
Nephrologic Symptoms



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30 Water, Electrolyte, and Acid–Base Disorders
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29 Abnormal Renal Function

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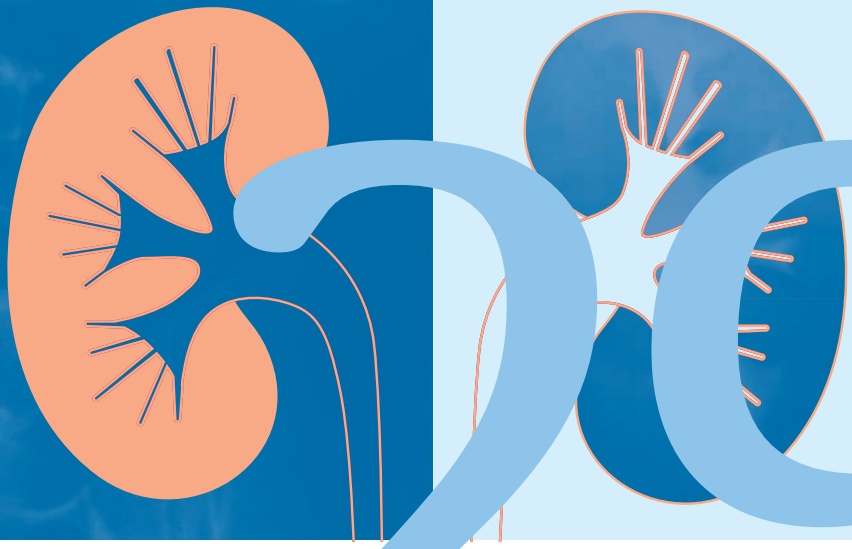

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Abbreviations used in this chapter:

ANA	antinuclear antibodies
ANCA	antineutrophilic cytoplasmic antibodies
ARF	acute renal failure
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CRF	chronic renal failure
GFR	glomerular filtration rate
GN	glomerulonephritis
HUS	hemolytic–uremic syndrome
NSAIDs	nonsteroidal anti-inflammatory drugs
PKD	polycystic kidney disease
RPGN	rapidly progressive glomerulonephritis
SLE	systemic lupus erythematosus

29.1 Symptoms and Signs of Altered Renal Function

Overview and Practical Diagnostic Procedures

The symptoms and signs of kidney diseases are extremely manifold. Since, in addition to the excretory function, the kidneys are responsible for many other functions in metabolism, kidney diseases manifest themselves in various ways. These can occur in isolation and manifest clinically as, for example nephrotic or nephritic syndromes, or in connection with systemic diseases, for example lupus erythematosus (lupus nephritis) or diabetes mellitus (diabetic nephropathy).

In Table 29.**1** the different nephrologic syndromes and their most important characteristics are described. Disturbances of the electrolyte and water balance are not considered here, but will be discussed in Chapter 30. Certain diseases of the kidney can have striking clinical symptoms, for example flank pain and colics in patients with kidney stones. In many cases, however, kidney diseases or diseases of the lower urinary tract manifest themselves only through pathologic urinary findings. In an insidious manner, certain slowly progressive chronic kidney diseases become manifest only at a late stage of advanced renal insufficiency. Often these patients, in spite of a decrease in the glomerular filtration rate (GFR) of $> 80\,\%$, show no, or only nonspecific, symptoms, for example increased weakness or inappetence.

Diagnostic Procedures. When examining patients with suspected nephrologic problems the following questions arise:

- What is the etiology of the renal disease (primary or secondary nephropathy)?
- Is it an acute or a chronic renal disease?
- Has the disease already led to an impairment of the kidney function?

These questions can often be answered by a detailed history, clinical examination, and simple laboratory findings.

In the possible presence of a renal disease a minimal standardized series of laboratory tests should be carried out. These should include, in particular, a detailed microscopic and chemical urine analysis. The blood analyses should comprise blood count, creatinine, blood urea nitrogen (BUN), uric acid, electrolytes, calcium, phosphate, alkaline phosphatase, total protein, albumin, and protein electrophoresis.

Only when one or more of these tests yield pathologic results are additional examinations required, which, depending on history and clinical examination, include the following:

- 24-hour urine collection (in particular proteinuria/albuminuria)
- microbiologic urine analysis
- pH measurement and analysis of blood gases when disturbances of the acid–base balance are presumed
- immunologic diagnosis (complement factors, antinuclear factors, antineutrophilic cytoplasmic antibodies (ANCA), antiglomerular basement membrane (anti-GBM) antibodies, rheumatoid factor, cryoglobulins)
- examination of renal function (creatinine clearance, other clearance determination methods)
- imaging methods (renal ultrasound and color duplex sonography, computed tomography (CT), magnetic resonance imaging (MRI), isotopic nephrogram, retrograde imaging of the lower urinary tract, digital subtraction angiography)
- renal biopsy (light microscopy, immunofluorescence, electron microscopy).

Serologic Examinations

Decreased complement factors (CH_{50}, C3, C4), in connection with glomerulonephritis (GN), are found in postinfectious glomerulonephritides (poststreptococcal GN, GN in endocarditis), membranoproliferative GN, cryoglobulinemic GN (frequently in connection with hepatitis C), and systemic lupus erythematosus.

Antinuclear factors are found in particular in systemic lupus erythematosus, Sjögren syndrome, and systemic sclerosis (scleroderma). In lupus nephritis anti-DNA antibodies are also identified. Antibodies against cytoplasmic elements of granulocytes (ANCA) in the presence of identified renal disease are suggestive of systemic vasculitis. cANCA directed against proteinase 3 are relatively specific for Wegener granulomatosis, whereas pANCA directed against myeloperoxidase are particularly characteristic for microscopic polyangiitis. Anti-GBM antibodies are typically suggestive of Goodpasture syndrome, a rare type of rapidly progressive glomerulonephritis (RPGN).

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Table 29.1 Principal nephrologic syndromes

Syndrome	Characteristics
Diseases of the kidneys	
Nephritic syndrome	Hypertension, edema, proteinuria, hematuria (dysmorphic erythrocytes, erythrocyte casts)
Nephrotic syndrome	Edema, proteinuria, hypoalbuminemia, lipiduria, hyperlipidemia, hypercoagulability
Rapidly progressive glomerulonephritis	Nephritic urinary sediment, hypertension, rapidly progressive renal failure
Uremic syndrome	Loss of appetite, fatigue, pruritus, nausea, vomiting, dysesthesias
Isolated pathological urine finding	Asymptomatic (hematuria, leukocyturia, proteinuria)
Diseases of the urinary tract	
Renal stones	Flank pain and colics, loin pain upon percussion, hematuria
Urinary tract infection	Cloudy urine, dysuria, pollakisuria, leukocyturia, bacteriuria; fever, chills, and flank pain in the case of pyelonephritis

Cryoglobulins can occur without an evident cause (essential cryoglobulinemia) or as a secondary consequence of various diseases (atypical pneumonias, lymphomas, hepatitis C) and induce glomerulonephritis and systemic vasculitis.

Evaluation and Measurement of the Glomerular Filtration Rate

The course of chronic renal diseases is often progressive. It is therefore important to observe the course of a chronic renal disease by means of the GFR. For this purpose, different methods of evaluation and measurement are available.

A consequence of chronic renal failure (CRF, see below) is the retention of different substances. Among these are typically creatinine, BUN, and the low molecular weight-protein cystatin C. The change of the renal function can best be followed by means of the serum creatinine. Creatinine is produced through the degradation of creatine from the muscles and through meat ingestion. In cases of constant creatinine production, the renal excretion is predominantly dependent on the GFR and, therefore, the creatinine value is an indicator of the renal function.

Creatinine Clearance. In practice, the Cockcroft–Gault formula is frequently used for the evaluation of the GFR. Thus, the creatinine clearance is calculated as follows:

$$Cl_{creatinine} = \frac{(140 - age) \times body\ weight\ (kg)}{serum\ creatinine\ (\mu mol/L)}$$

In women the calculated value is multiplied by the factor 0.85 because of lower muscle mass. This formula takes into consideration, in particular, the loss of renal function with age and can therefore be used for dosage adaptation of drugs in older patients. In very obese patients the ideal body weight should be used in the formula instead of the total weight.

In clinical routine, the creatinine clearance is frequently measured. For this, a 24-hour urine collection is required. For the determination of the creatinine clearance the following formula is applied:

$$Cl_{creatinine} = \frac{U \times V}{P}$$

V = urine volume in mL/min, U = concentration of creatinine in urine in μmol/L, P = concentration of creatinine in serum in μmol/L.

Standard values of creatinine clearance in adults are as follows:

- men: 95–140 mL/min
- women: 75–125 mL/min.

For reasons of comparability, clearance values are usually standardized to 1.73 m^2 of body surface.

When determining the creatinine clearance it has to be considered that creatinine is not only filtered, but, with decreasing renal function, it is also secreted. In advanced renal failure this leads to an overestimation of the GFR.

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29.2 Differential Diagnosis of Pathologic Urine Findings

Urinalysis is a well-established laboratory method that has lost none of its importance over time. While previously urinalysis was only possible by using the senses to evaluate color, cloudiness (turbidity), odor, and taste, numerous complex new methods of urinalysis have been developed, allowing precise diagnostic conclusions. Thanks to its methodologic simplicity and diagnostic reliability, the analysis of urine and urine sediment still holds a high importance in ambulatory and hospital medicine, since a careful urinalysis is often more informative than complicated and expensive technical examinations.

Collection and Processing of Urine Samples

Urine is continuously produced by the kidneys. In the glomeruli, approximately 180 L of primary urine per day are filtered from the plasma (ultrafiltrate). Glucose, electrolytes, amino acids, water, and other inorganic and organic substances are reabsorbed from this ultrafiltrate, resulting in a final urine volume of 1.0–2.5 L per day. Urine consists essentially of water and electrolytes as well as of organic substances resulting from protein degradation metabolism, e. g., urea. In addition, numerous organic structures are excreted in the urine, including erythrocytes, leukocytes, epithelial cells, casts, and crystals.

Spot Urine. Urine is either sampled as spontaneous urine in aliquots, or is collected as 24-hour urine. With regard to spontaneous urine, the *first morning urine* is particularly suited for bacteriologic analyses and for the detection of a low-grade proteinuria due to its concentration. In the *second morning urine*, cellular components, e. g., casts, can be far better evaluated, since they are less degraded than in the acidic and concentrated first morning urine. When sampling spot urine the so-called *middle stream technique* should be used in order to reduce contamination from the external genital organs. In practice, however, it is often difficult to obtain a sufficiently clean urine sample from the patients. The extent of genital contamination can best be estimated by determining the number of squamous epithelial cells in the urine sediment. When interpreting bacteriologic results, particular attention should be paid to ensure that the spontaneous urine sample is not contaminated.

24-Hour Urine. Collection of 24-hour urine is sometimes difficult in clinical practice. Due to insufficient instruction many patients collect 24-hour urine inaccurately. The 24-hour urine is used in particular to quantify a *proteinuria* and to determine the creatinine clearance, or to document a calciuria or uricosuria. If a 24-hour urine collection is not possible, the concentration of protein and creatinine can, alternatively, be measured in the spot urine in order to estimate the degree of proteinuria per 24 hours. To calculate the proteinuria in g/24 h, the following formula can be used:

$$\text{Proteinuria (g/24 h)} = \frac{\text{urine protein (g/L)}}{\text{urine creatinine (mmol/L)}} \times 11.3$$

Timely processing of urine is very important, since the urine used for the analysis should be as fresh as possible. When immediate processing is not possible, urine may be kept for several hours in the refrigerator at 4 °C. If urine is kept at room temperature, numerous changes may occur, including an increase in the pH value due to ammonia production from urea, a decrease of glucose content by bacterial degradation, volatilization of ketones, and disintegration of erythrocytes and erythrocyte casts.

Test Strips (Dipsticks). Urinalysis by means of test strips (dipsticks) has considerably simplified the technique of urine analysis. It has to be considered, however, that the test strip represents primarily a screening method that can be used for the rough identification of a proteinuria (except microalbuminuria and Bence Jones proteinuria), a (micro)hematuria, or an infection of the urinary tract (positive evidence of nitrite and leukocytes). Positive results require further investigation. This is true, in particular, when there is evidence of blood or leukocytes in urine.

Physical Urine Analysis

The physical properties of urine, including cloudiness, color, odor, volume, specific gravity, and pH value, reveal much important diagnostic information (Tab. 29.**2**). Normal urine is clear and transparent. When urine is left standing for a while, amorphous phosphates, urates, and carbonates can precipitate and lead to cloudiness. Pyuria, hematuria, bacteriuria, and lipiduria can also produce cloudiness. Shaking the urine usually results in the production of foam, which disappears after a short time. Persistent foam in pale yellow urine can be indicative of proteinuria.

Color of Urine

The normal *yellow* color of urine is caused by so-called urochromes. The excretion of these urochromes also remains constant with variable diuresis. Thus, in polyuria colorless or pale yellow urine is observed, in oliguria urine is dark yellow. *Red* or *brown* urine can be a consequence of hematuria, hemoglobinuria, or myoglobinuria. The differentiation is made after centri-

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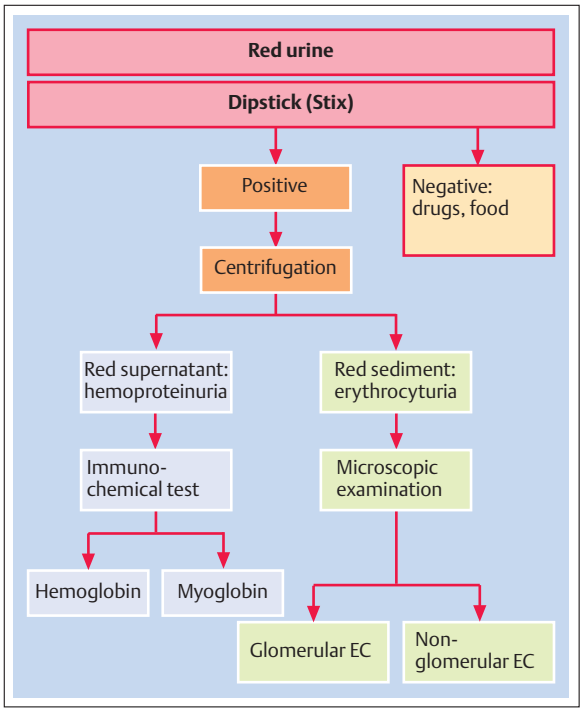

Fig. 29.**1** Differential diagnostic considerations and investigations for the occurrence of red urine. EC = erythrocytes.

fugation and microscopy (Fig. 29.**1**). Lack of erythrocytes in the sediment in positive strip tests is indicative of hemoglobinuria (color of serum is often reddish due to hemolysis) or myoglobinuria (normal color of serum, increased creatine kinase). Foods or drugs, e. g., beetroots, or rifampicin, can also induce a reddish color. Red urine could be a result of blood addition due to menstruation. *Pink*-colored urine can be caused by large quantities of amorphous urates. *Dark brown* or *yellow–orange* urine indicates bilirubinuria. *Black* urine is observed as a consequence of the excretion of melanin in metastatic melanoma or alcaptonuria (very rare). *Whitish* (and cloudy) urine can be indicative of pyuria, vaginal contamination with squamous epithelia and mucus, crystalluria, lipiduria, or chyluria (rare, e. g., in filariasis).

pH of Urine

The pH value of urine is a measure of proton concentration in urine, and lies normally between 5 and 6. By means of the dipstick test the pH value of urine can be measured in the range 4.5 to 8. It must be remembered, however, that only fresh urine should be analyzed, since urine spontaneously becomes alkaline at room temperature. A pH value $>$ 7.5–8.0 is strongly suggestive of a *urinary tract infection* caused by ureolytic bacteria (often also positive nitrite test). An alkaline pH is also found in *metabolic alkalosis*. In the presence of a *metabolic acidosis* the urine pH value should be $<$ 5. If the pH is higher, a disturbance of renal acid elimination, corresponding to a renal tubular acidosis, must be considered.

Urine Volume

Oliguria (less than 400 mL per day) and polyuria (more than 3 L per day) are indicative of numerous renal diseases. *Anuria* (lack of urine production) is observed in postrenal obstruction (bladder or prostate problems), as well as in bilateral interruption of the renal perfusion, e. g., due to aortic dissection. *Oliguria* is observed in the event of severe fluid or blood loss and dehydration, as well as in acute and advanced chronic renal failure. *Polyuria* is found in patients with diabetes mellitus, diabetes insipidus, and psychogenic polydipsia. The urine quantity can, in extreme cases, amount to up to 15 L per day.

Specific Gravity and Osmolality

Specific gravity and urine osmolality define the concentration functionality of the kidney. The *specific gravity* of urine can be determined by means of an urome-

Table 29.**2** Physical examination of the urine

Parameter	Normal value	Pathological findings
Turbidity	Clear	Turbid (infection, lipiduria, crystalluria)
Color	Slightly yellow	Red (hematuria) Dark brown (bilirubin)
Quantity	1000–2500 mL	$<$ 400 mL (oliguria) $>$ 3000 mL (polyuria)
Specific gravity	1.005–1.030	$<$ 1.005 (polydipsia; diabetes insipidus) $>$ 1.030 (exsiccation, prerenal kidney failure, radiocontrast agents)
pH value	5.0–6.0	$>$ 6.0 (urinary tract infection, renal tubular acidosis, metabolic alkalosis)

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ter, refractometer, or simply with a dipstick. Normally, the specific gravity varies between 1.005 (very diluted urine) and 1.030 (highly concentrated urine). Independent of the concentration degree, dense particles, e. g., glucose, protein, or radiologic contrast agents, can increase the specific gravity of urine. Isosthenuria is a condition in which the specific gravity of urine equals that of the blood, i. e., 1.010 (corresponding to 285 mOsm/kg H_2O). Isosthenuria is often found in patients with advanced chronic renal failure.

Urine osmolality, defined by means of an osmometer, varies from 50–100 mmol/kg, in the case of ample fluid supply with suppression of ADH release, and can amount to up to 1400 mmol/kg during a thirst period with subsequent maximal ADH release. Determination of the urine osmolality is required for the investigation of polyuric–polydiptic syndromes using a thirst test, for unclear hyponatremia, and for the differential diagnosis of acute renal failure.

Table 29.**3** Chemical examination of the urine by dipstick (stix)

Parameter	Normal value	Pathological findings
Glucose	Negative	+ to ++++ (diabetes mellitus, renal glucosuria)
Protein	Negative	+ to +++ (glomerular injury)
Acetone	Negative	+ to +++ (ketoacidosis, starvation)
Bilirubin	Negative	+ to +++ (hepatitis, cirrhosis, jaundice by obstruction)
Urobilinogen	Weakly positive	+ to ++++ (liver cell damage, hemolysis)
Nitrite	Negative	Positive (Gram-negative urinary tract infection)

Chemical Urine Analysis

Using test strips and chemical laboratory methods a large number of inorganic and organic substances can be measured in the urine. The semiquantitative or quantitative evaluation in the spontaneous or the 24-hour urine provides important diagnostic information on metabolic and renal diseases.

Dipsticks include up to 10 different analyses, which, besides the chemical parameters (glucose, protein, hemoglobin, ketones, bilirubin, urobilinogen, nitrite), are also suitable to evaluate the pH value, specific gravity, as well as blood and leukocytes (Tab. 29.**3**). The evaluation by means of dipsticks is *semiquantitative*. With automation the dipsticks can also be evaluated photometrically using specific equipment, but the evaluation remains semiquantitative.

A precise *quantitative* evaluation of the concentration of certain molecules can be carried out in the *spontaneous* as well as in the *24-hour urine*. In clinical routine the evaluation is simpler in spontaneous than in the 24-hour urine, but the reliability of the results is limited in so far as each concentration measured is dependent on the amount of water that is simultaneously excreted (and therefore on the urine volume). This factor can be corrected through collection of 24-hour urine.

Glucosuria

In the dipstick analysis, glucose is identified through *glucose oxidase*. This test is specific for glucose. A positive result indicates diabetes mellitus or renal glucosuria. Renal glucosuria can be caused primarily either by mutations in the Na^+-glucose transporter in the proximal tubulus or by tubular damage. In addition to the renal glucosuria a bicarbonaturia, phosphate diabetes, and aminoaciduria are also present in Fanconi syndrome (generalized functional disturbance of the proximal tubulus).

False-positive evidence of glucose in urine can be caused through peroxide-containing, or other strongly oxidizing, cleaning agents. False-negative results are caused by high doses of vitamin C. Currently, however, most dipsticks have eliminated the influence of ascorbic acid.

Ketonuria

The generic term ketones refers to the substances acetone, acetoacetate, and β-hydroxybutyric acid. Ketones result from the intermediate metabolism of fats. Normally, they are not present in urine. The test strip reaction with *nitroprusside* detects, in particular, acetoacetate and to a much lesser extent acetone, but not β-hydroxybutyric acid. Ketones are found in urine in diabetic and alcoholic ketoacidosis, in conditions of starvation, and in cases of chronic recurrent vomiting.

Proteinuria

Of the different proteins that can be found in urine, *albumin* represents the most important because of its significance in the early detection of renal diseases. The occurrence of a pathologic albuminuria is routinely detected by screening with test strips.

The GBM is a filter whose pores retain higher molecular weight proteins, e. g., albumin, transferrin, and immunoglobulins, due to a sieving effect, but conversely, are permeable for low molecular weight proteins, e. g., free light chains (κ or λ) or peptide hormones (Fig. 29.**2**). The sieving effect of the glomerular capillaries is dependent on molecular radius and charge of the respective proteins. The proteins advancing in the tubule lumen are reabsorbed and catabolized in the proximal tubular cells, so that proteinuria becomes

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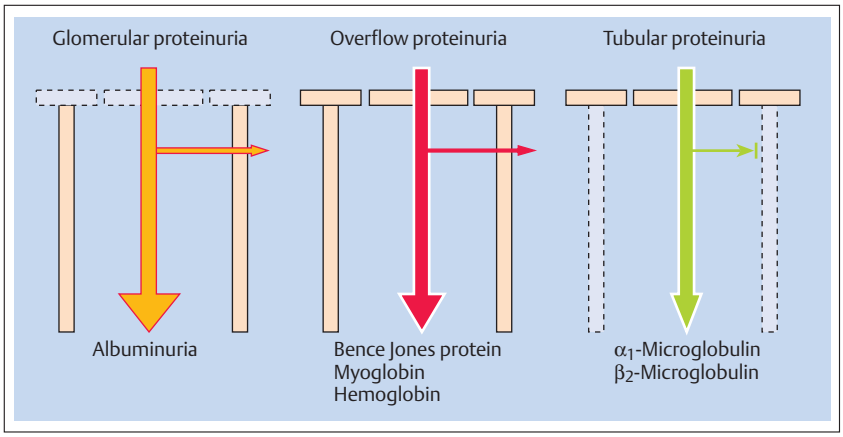

Fig. 29.**2** Schematic representation of the different types of proteinuria. Glomerular proteinuria occurs through damage to the glomerular filtration barrier. Overflow proteinuria is due to the excessive accumulation of low molecular weight proteins such as light chains, myoglobin, and hemoglobin in the blood. Tubular proteinuria is caused by reduced tubular reabsorption of normally filtered low molecular weight proteins (α_1-microglobulin, β_2-microglobulin).

manifest only after exceeding the reabsorption capacity of the proximal tubules.

Benign and Orthostatic Proteinuria. The normal (physiologic) total protein excretion in urine amounts to 40–150 mg/day. In physical effort or fever, this limit may occasionally be exceeded, but the rate should always be < 0.5 g/24 hours (*benign* proteinuria). So-called *orthostatic* proteinuria is occasionally observed in adolescents during their growth phase. The proteinuria occurs during the daytime due to a prolonged upright position and is not detected in nighttime urine. An orthostatic accentuation of protein excretion is also detectable in most patients with pathologic proteinuria (comparison of daytime and nighttime urine).

Table 29.**4** Classification of proteinuria by pathophysiologic criteria

Classification	Type of excreted proteins and pathophysiology
Glomerular proteinuria	Normal plasma proteins due to defective glomerular filter (mostly albumin)
Overflow proteinuria	Increased formation and filtration of low molecular weight proteins (e. g., monoclonal lightchains, myoglobin, hemoglobin), which appear in the urine when the tubular absorption rate is exceeded; kidneys primarily intact at structural and functional level
Tubular proteinuria	Normal, low molecular weight plasma proteins appear in urine due to a reduced tubular reabsorption capacity; kidneys structurally (e. g., interstitial nephropathy) or functionally (e. g., Fanconi syndrome) altered

Microalbuminuria. The regular test strip method is particularly able to detect larger quantities of albumins (> 300 mg/day). Microalbuminuria (albumin within the range of 30–300 mg/day) and the excretion of *immunoglobulins* (κ and λ light chains = Bence Jones proteins) are usually not detected by the test strip method. However, for the detection of microalbuminuria, a highly sensitive dipstick can be used. The albuminuria per 24 hours can be estimated on the basis of the ratio [albumin/creatinine] by means of additional creatinine measurement by dipstick. These special dipsticks can be very helpful in the early detection of a diabetic nephropathy, though the test must be repeated several times for confirmation.

Glomerular Proteinuria. The type and quantity of urinary proteins are of great clinical importance. Table 29.**4** and Fig. 29.**2** show the classification of proteinuria by pathophysiologic criteria. Glomerular proteinuria is caused by damage to the glomerular filtering system and is a frequent cardinal symptom in primary and secondary renal diseases.

The glomerular proteinuria can also be classified schematically into *selective* and *nonselective*. *Selective* means that predominantly anionic proteins of medium size with a molecular weight of 50 000–80 000 Da (e. g., albumin) are identified, an indication that the GBM is only minimally damaged, e. g., in minimal change glomerulonephritis (lipoid nephrosis). *Nonselective* means that, in addition to albumin, proteins with a molecular weight of $> 50\,000$–$80\,000$ Da are also found in the urine (e.g., IgG), which indicates more extensive damage of the glomeruli, e. g., in more inflammatory glomerulonephritides. The extent of proteinuria often reflects the degree of the glomerular damage (Tab. 29.**5**). Selective identification of low quantities of albumin in urine (microalbuminuria) in a diabetic patient indicates an early stage of diabetic nephropathy. Large nonselective quantities of protein (albumin and globulins) in the range of several g/24 h indicate more significant glomerular damage, such as

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membranous glomerulonephritis or a focal segmental glomerulosclerosis.

When the proteinuria is < 3.5 g/24 h, it normally produces no or only minimal clinical signs. When it is in the nephrotic range (> 3.5 g/24 h), the urine can become foamy. In addition, there can be lipiduria, which makes the urine milky and cloudy. In parallel with the extent of proteinuria patients develop a more or less distinctive edema. A severe nephrotic syndrome with massive edema, pleural effusions, and ascites (anasarca) accompanies an albuminuria > 10 g/day and a hypoalbuminemia < 20–30 g/L.

Overflow Proteinuria. An overflow proteinuria occurs without primary glomerular damage but in the presence of abnormal levels of proteins in blood, that are normally glomerularly filtered. When the filtration of these proteins (in particular Bence Jones protein, hemoglobin, and myoglobin) exceeds the tubular reabsorption capacity, an overflow proteinuria is produced.

A Bence Jones proteinuria has to be traced by specific methods, since it is frequently missed in strip tests. A positive sulfosalicylic acid turbidity test and a negative strip test are considered indicative of the presence of Bence Jones proteinuria, which should be verified by immunofixation/immunoelectrophoresis. Bence Jones proteinuria is found in the following diseases:

- multiple myeloma
- Waldenström disease
- AL amyloidosis
- light-chain deposition disease
- lymphoma
- Fanconi syndrome in adults.

Plasma cell dyscrasia can be accompanied by manifest albuminuria (up to a clinically distinct nephrotic syndrome) in cases of disturbed permeability of the glomerular basal membrane, which is caused by the deposition of light chains. This is predominantly observed in light chain deposition disease.

> Whereas a proteinuria of up to 3.5 g/day can have several causes, a proteinuria of more than 3.5 g/day is caused exclusively by glomerular proteinuria or overflow proteinuria.

The distinction can be made with *urine electrophoresis*, which allows the identification of Bence Jones proteinuria and provides an impression of the low and high molecular fractions involved in the proteinuria (Fig. 29.**3**).

Tubular Proteinuria. Tubular proteinuria results from an insufficient ability to resorb normal levels of glomerularly filtered protein. An increased amount of low molecular weight plasma proteins are found in the urine, e.g., α_1- and β_2-microglobulins. Underlying diseases are usually *interstitial nephropathies* or *Fanconi syndrome*.

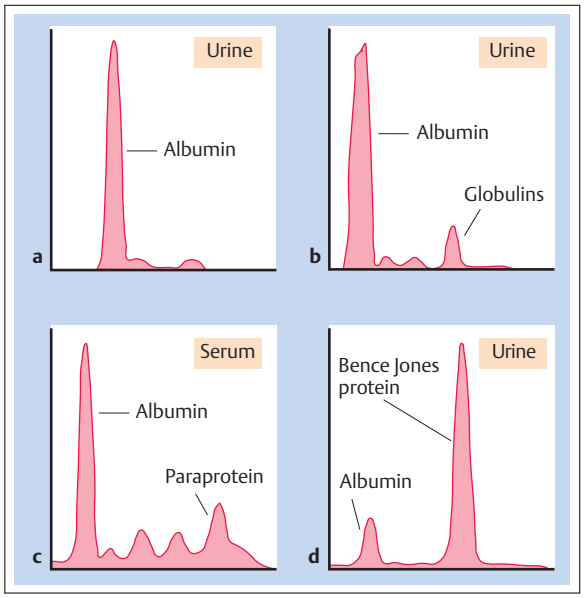

Fig. 29.**3** Urine and serum protein electrophoresis.
a Urine protein electrophoresis in the case of selective albuminuria.
b Urine protein electrophoresis in the case of nonselective proteinuria.
c Serum protein electrophoresis in a patient with Waldenström disease (monoclonal gammopathy type IgM κ).
d Urine protein electrophoresis for **c**; distinct microglobulinuria, Bence Jones type (light chains [κ]).

Identification of Bilirubin and Urobilinogen in Urine

If *bilirubin* is identified by means of the test strip, this indicates a raised serum level of conjugated (direct) bilirubin. This could be the first sign of liver disease and is frequently detected prior to clinical jaundice. Bilirubin is found in urine in hepatitis, liver cirrhosis, as well as in cholestasis. Bilirubin is rarely identified in the urine in cases of hemolytic jaundice, since unconjugated biliru-

Table 29.**5** Classification of albuminuria

Level	Spot urine		24-hour urine collection	
	mg/L	mg/mmol	mg/24 h	µg/min
Normalbuminuria	< 20	< 2	< 30	< 20
Microalbuminuria	20–200	2–20	30–300	20–200
Macroalbuminuria	> 200	> 20	> 300	> 200

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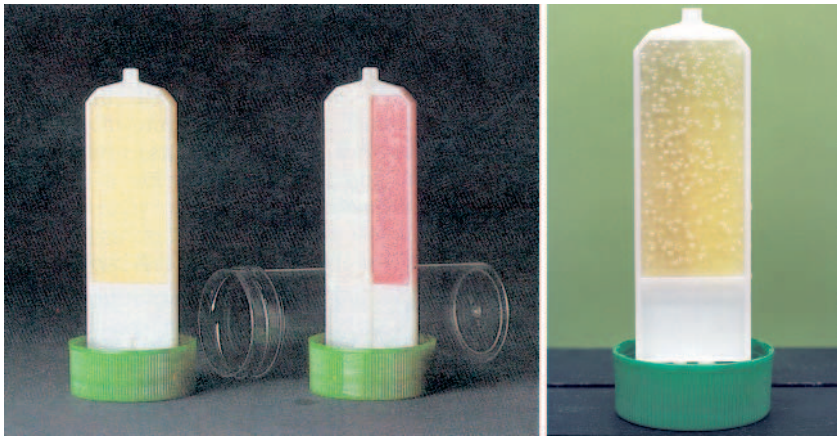

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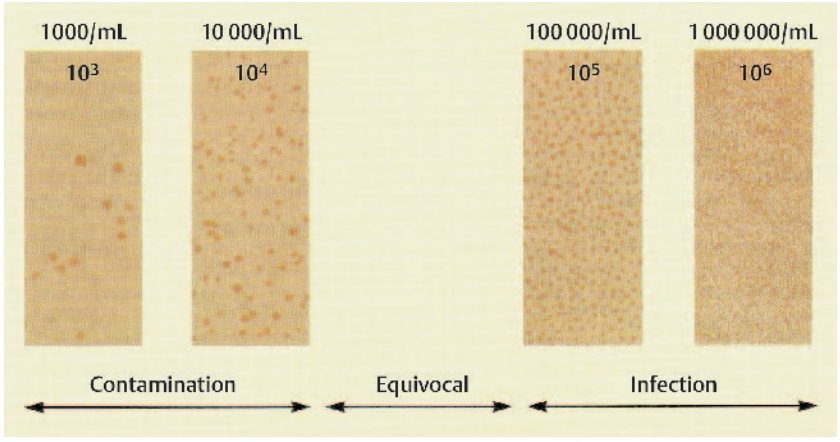

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Fig. 29.**4** Urine culture
a UriCult® paddle with different culture media on the front and rear sides.
b Positive culture result with 10^5 monomorphic whitish colonies.
c Diagrams for estimating the number of bacteria on a positive UriCult® paddle.

bin (due to hemolysis) is produced in the serum and is not filtered.
Urobilinogen is found in the bowel due to reduction of bilirubin, and is enterohepatically reabsorbed, and then excreted in the urine. Low quantities of urobilinogen are identified physiologically in urine. Increased values are observed in patients with liver injury and hemolytic anemia, but not, however, in obstructive jaundice. Therefore, a differentiation between obstructive jaundice and hepatic jaundice becomes possible.

Identification of Nitrite for the Diagnosis of Urinary Tract Infections

The identification of nitrite by means of a *test strip* is important in the diagnosis of bacterial urinary tract infections. The majority of Gram-negative bacteria can transform nitrate into nitrite. Gram-positive bacteria and *Candida* do not cause transformation of nitrate into nitrite. The reproduction of bacteria in urine that has been standing can lead to a positive nitrite test without the presence of an infection.

Microbiologic Urine Analysis. This analysis is performed to confirm a urinary tract infection. Currently, this is done almost exclusively by means of a paddle coated on both sides with solid agar immersion culture medium, on which the most significant bacteria can grow (Fig. 29.**4a, b**). The culture media are dipped in the urine sample. Usually the properly collected middle stream urine is analyzed. Dipping is followed by incubation at 37 °C for 24 hours. Details of the technique are provided in the instructions, which also contain diagrams by which the number of bacterial colonies can be estimated (Fig. 29.**4c**). Two-thirds of patients with urinary tract infections have 10^5 or more bacteria/mL in the urine. Lower numbers of bacteria are predominantly found in women with acute infections of the urinary tract. The simultaneous presence of a leukocyturia or pyuria also indicates an infection.

Causative Agents. In the majority of patients the infection is caused by a single species. The growth of several different bacterial colonies is suspicious of a contamination. Mixed cultures are found in patients with fistulas and in carriers of indwelling catheters. Most infections of the urinary tract are caused by Gram-negative enterobacteria. *Escherichia coli* is found in 70–95 % of ambulatory patients with a urinary tract infection. *Proteus mirabilis*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, and *Serratia marcescens* are detected

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to a much lesser extent. Another 5–20% of urinary tract infections in ambulatory patients are caused by coagulase-negative staphylococci and 1–2% by *Enterococcus* (both are Gram-positive bacteria). Fungi (*Candida albicans*), as well as *Pseudomonas aeruginosa*, are frequently found in diabetics and immunosuppressed persons.

Microscopic Analysis of the Urinary Sediment

Microscopic analysis of the centrifuged urinary sediment provides important indications about disease processes in the kidney and the genitourinary tract. The analysis of the sediment is, therefore, particularly useful for the diagnosis of infections of the urogenital tract, glomerulonephritides, and tubulointerstitial nephropathies.

It is recommended that the sediment is analysed by phase contrast microscopy at magnifications of 100× and 400×. With polarized light, double refractive elements such as uric acid crystals, lipid droplets or oval fat bodies (Maltese crosses) can be identified.

The following elements are examined in the urinary sediment:

- erythrocytes and their morphology, leukocytes, and epithelial cells
- erythrocyte (hemoglobin) casts
- leukocyte, epithelial, and mixed cell casts
- flat, broad, and granular casts
- bacteria, trichomonads, pathognomonic crystals (cystine), and squamous cells as indication for a vaginal contamination of the urine sample.

The normal urinary sediment contains only a small number of erythrocytes (< 5/visual field) and a small number of leukocytes (< 5/visual field; magnification 400x).

A few squamous cells and some hyaline casts, as well as spermatozoa, can also occur in a normal urinary sediment. Increased numbers of erythrocytes and leukocytes are already identified with the test strip. It is therefore important to compare the result of the test strip with the sediment findings. If the hemoglobin test is positive, but no erythrocytes found in the urine, a myoglobinuria must be considered. However, it is possible that the erythrocytes might also have been lysed.

Erythrocytes

When increased numbers of erythrocytes occur in the urine, a *microhematuria* or even a *macrohematuria* is present. *Eumorphic* erythrocytes originate mostly in the lower urinary tract and are passed into the urine by tumors, stones, or infections (Fig. 29.**5a**). *Dysmorphic* erythrocytes indicate a glomerular origin, and the percentage of dysmorphic erythrocytes should be > 70% with glomerular hematuria. However, the specificity of this finding is not very high. *Acanthocytes* are a special type of dysmorphic erythrocytes with bubblelike extrusions. If acanthocytes constitute > 5% of the total erythrocytes in the urine, this is highly suspicious of a glomerulonephritis (Fig. 29.**5b**). If one or several *erythrocyte casts* are found in the sediment together with dysmorphic erythrocytes, the diagnosis of a glomerular disease (mostly a glomerulonephritis) is confirmed (Fig. 29.**5c**). Tab. 29.**6** summarizes the criteria that differentiate between glomerular and nonglomerular hematuria.

Table 29.**6** Distinction between glomerular and nonglomerular hematuria

	Glomerular hematuria	Extraglomerular cause of bleeding
Dysmorphic erythrocytes	> 70%	< 70%
Acanthocytes	> 5%	< 5%
Erythrocyte casts	+	–
Proteinuria	+	–

Leukocytes

An increased number of leukocytes in the urine can indicate a urinary tract infection (Fig. 29.**6a**). In an established infection the leukocytes often cumulate in clusters. In addition, bacteria are found and the nitrite and leukocyte esterase tests are positive in the dipstick test. The additional presence of squamous cells is suggestive of a vaginal contamination (Fig. 29.**6b**). If *leukocyte casts* are found in the sediment as well, this indicates that the infection is localized in the kidneys (pyelonephritis; Fig. 29.**6c**). An increased excretion of eosinophilic leukocytes is predominantly observed in drug-induced acute interstitial nephritis.

A *sterile leukocyturia* (negative bacterial growth on conventional immersion culture media) can indicate an infection by atypical pathogens, e. g., *Chlamydia* or mycobacteria (urogenital tuberculosis). A sterile leukocyturia is also observed in tubulo-interstitial diseases (acute and chronic interstitial nephritis, analgesic nephropathy).

Epithelial Cells

Various epithelial cells can be found in the urinary sediment. They can originate from tubuli, the renal pelvis, the ureters, the bladder, the urethra, or the vagina. We differentiate between *squamous cells* (large and polygonal, with pycnotic nucleus, deriving from the genital

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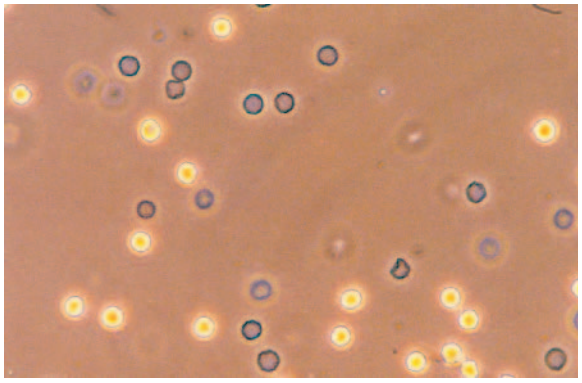

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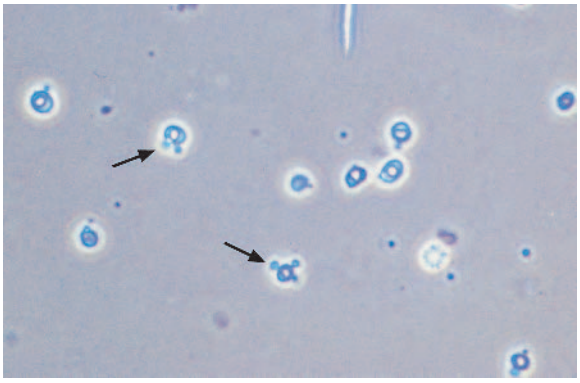

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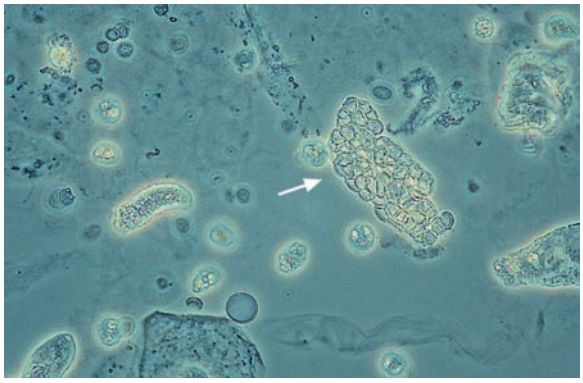

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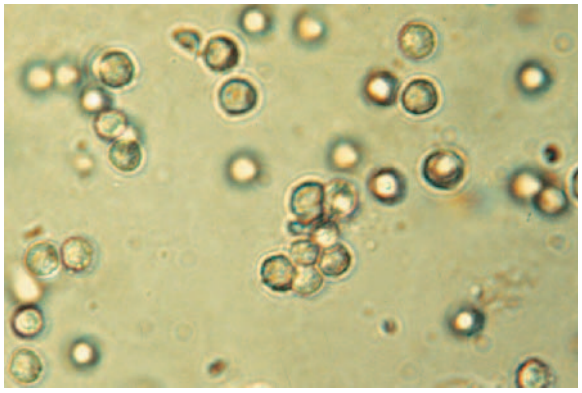
Fig. 29.**5** Typical urinary sediment findings in hematuria.
a Eumorphic erythrocytes
b Acanthocytes, a characteristic form of dysmorphic erythrocytes with ear-shaped extrusions (Mickey Mouse forms) (arrows).
c Red cell cast (arrow).



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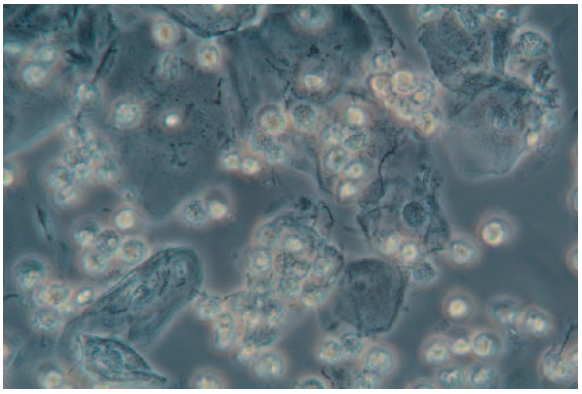

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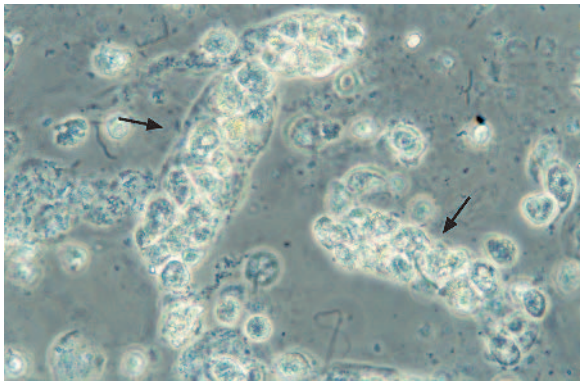

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Fig. 29.**6** Typical urinary sediment findings in leukocyturia.
a Several leukocytes, partly in clusters.
b Urinary sediment with contamination from the genital area, squamous cells, and leukocytes.
c Typical leukocyte casts (arrows).

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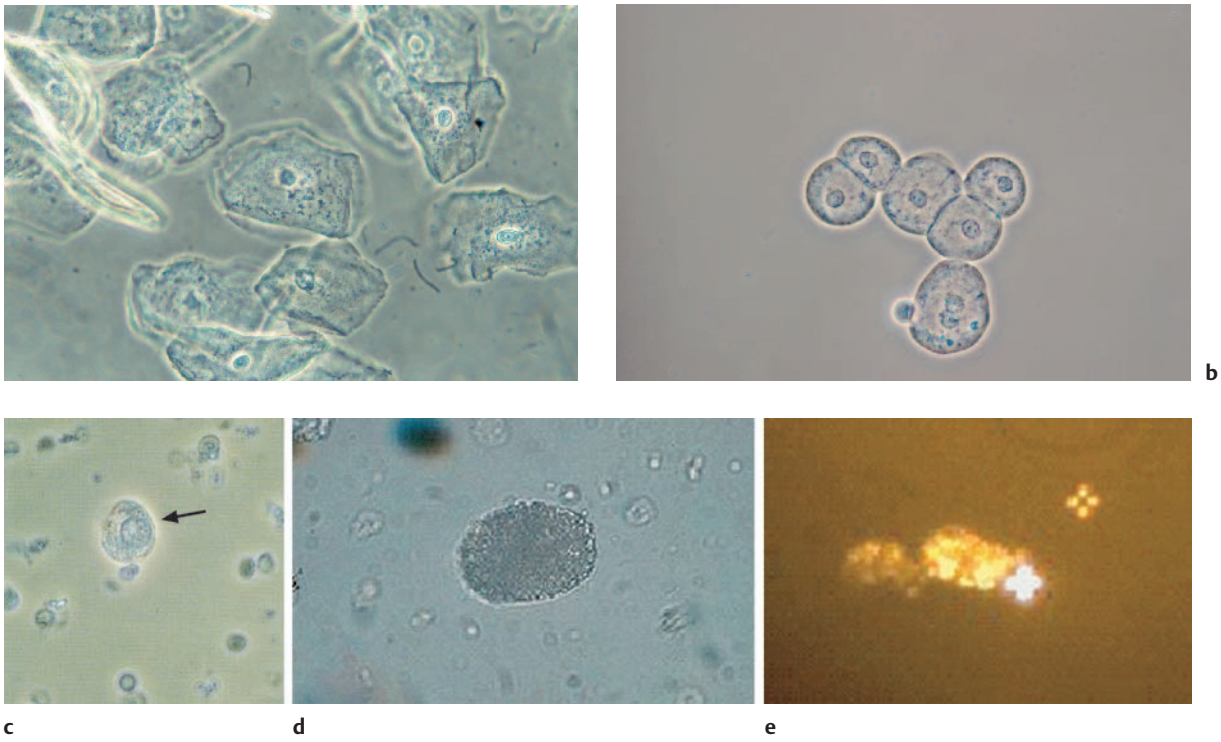

Fig. 29.**7** Various epithelial cells
a Large polygonal squamous cells with pycnotic nucleus, partly in clusters.
b Round epithelial cells with small nucleus, stemming from the transitional epithelium of the lower urinary tract.
c Rarely occurring tubular cell with large nucleus (arrow).
d Fatty granular cell (oval fat body) in nephrotic syndrome.
e Typical Maltese crosses in lipiduria.

region; Fig. 29.**7a**), *transitional epithelial cells* (round epithelial cells with small nucleus, coming from the urothelium; Fig. 29.**7b**), and *renal or tubular epithelial cells* (small round epithelial cells with larger nucleus, coming from the nephrons; Fig. 29.**7c**). Tubular epithelial cells can display a fatty degeneration with cholesterol droplets in the cytoplasm (so-called oval fat bodies or fatty granular cells; Fig. 29.**7d**), in which, under polarized light, the typical *Maltese crosses* can be observed (Fig. 29.**7e**).

Casts

Cell casts are derived from the tubular lumina. A number of types of casts can be identified in the urinary sediment. Their significance depends on their structure and cell content. The hyaline matrix consists almost completely of Tamm–Horsfall mucoprotein, which is produced in the ascending limb of the loop of Henle. This protein gelates easily to *hyaline casts* in the acidic urine and at high salt concentrations in the distal tubule and in the collecting duct (Fig. 29.**8a**). The occurrence of hyaline casts is, in particular, observed at a low diuresis rate. *Granulated casts* (Fig. 29.**8b**) have superpositions from cell detritus, fat, or aggregated serum proteins. Acellular hyaline and granulated casts can also be found in normal urine. Cell casts are characterized by cell deposits in the hyaline matrix and practically always indicate a disease of the renal parenchyma. The detection of *erythrocyte casts* confirms the presence of a glomerulonephritis. *Leukocyte casts* are found in pyelonephritis and interstitial nephritis. Epithelial casts (Fig. 29.**8c**) indicate tubular damage. Waxy casts (Fig. 29.**8d**) and broad casts indicate advanced chronic renal failure.

Crystals

Various crystals can occur in the normal urinary sediment. Often, the crystals do not have a pathologic significance. Crystals are formed only rarely in the kidneys. In most patients they arise from precipitation in the urine sample as a consequence of cooling down and changes of the pH value. For a precise identification of urinary crystals it is necessary to know the pH of the urine. Acidic urine contains mostly oxalate crystals, uric acid crystals, and amorphous urates. Amorphous phosphates, triple phosphate crystals, and calcium phosphates precipitate predominantly in alkaline urine.

The most common crystals are *oxalate crystals* (envelopes; Fig. 29.**9a**) and they are also found in healthy persons, particularly after consumption of high doses of vitamin C. They are frequently found in connection with recurrent calcium oxalate nephrolithiasis, in the rare

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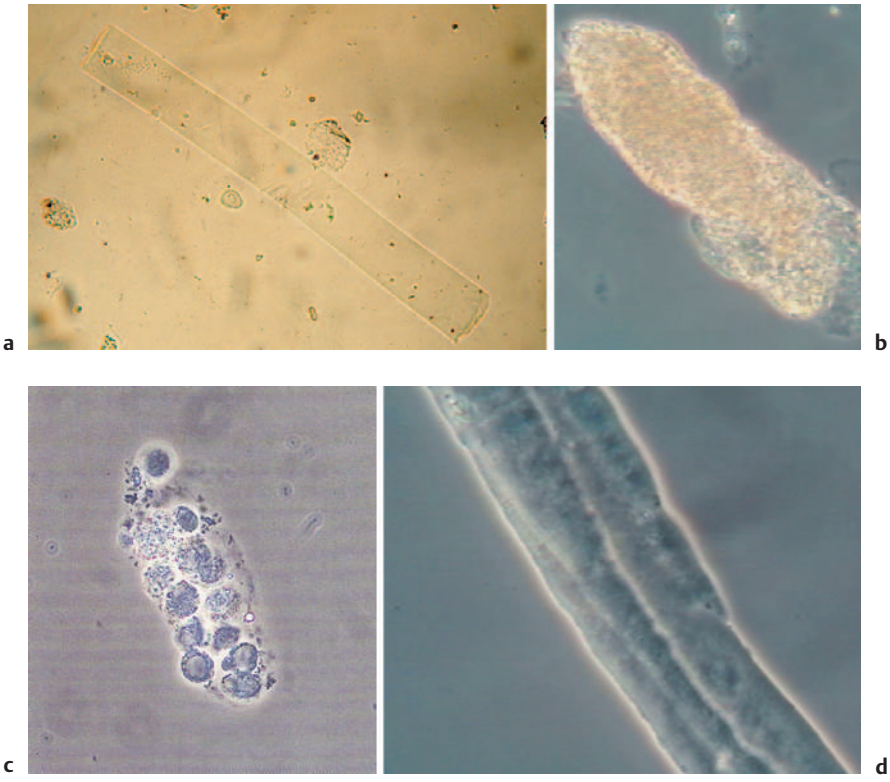

Fig. 29.**8** Various urinary casts
a Hyaline cast
b Fine granular cast
c Epithelial cell cast
d Broad, notched waxy cast.

clinical disease of oxalosis, and in acute renal failure due to ethylene glycol intoxication. *Uric acid crystals* (Fig. 29.**9b**), as well as *amorphous urates*, can be found in larger quantities in urine in uric acid nephropathy and in tumor lysis syndrome. Very rare, but pathognomonic for the clinical picture of cystinuria, is the presence of typical hexagonal-shaped *cystine crystals* (Fig. 29.**9c**). *Triple phosphates* (coffin lids; Fig. 29.**9d**) are observed in chronic inflammation of the kidney and the urinary tract. They may suggest the presence of urolithiasis. The rare *leucine crystals* (spherical, brown–yellow in color; Fig. 29.**9e**) and tyrosine crystals (needle-shaped, appearing in bunches or rosettes) are mostly found together in severe diseases of the liver.

Various *drugs* can precipitate as urinary crystals and can, in rare cases, even cause crystal-induced acute renal failure. Sulfonamides, e. g., sulfadiazine, or drugs used for HIV treatment, e. g., indinavir, can produce a variety of crystal forms in the urine (Fig. 29.**9f**).

Finally, a large number of artifacts can be found in the urine, including dust, fibers, and hairs. Starch granules from latex gloves also have a characteristic morphology.

Practical Value of Urinary Sediment Findings

The analysis of the urinary sediment can lead to a precise diagnosis of numerous diseases (e. g., pyelonephritis, glomerulonephritis, cystinuria). Furthermore, serial examination of the urinary sediment may allow early recognition, e. g., of the transition of a prerenal kidney failure into acute tubular necrosis (occurrence of numerous granular and epithelial cell casts), or a renal vein thrombosis can be suspected in a severe nephrotic syndrome when an additional microhematuria or red cell cylindruria is detected.

Constellations of Findings. Often it is not an individual abnormal parameter in the urinalysis (test strip examination and microscopic analysis of the sediment) that leads to a specific diagnosis, but it is the total constellation of urinary findings that allows a clinical diagnosis. Some typical constellations are summarized in Tab. 29.**7**.

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Table 29.**7** Typical urinary sediment patterns

Urinary tract infection	– positive nitrite test – abundant leukocytes, partly in clumps – few erythrocytes – bacteria – leukocyte casts in case of pyelonephritis
Microhematuria	– low amount of protein – abundant hemoglobin – eumorphic or partly dysmorphic erythrocytes – no leukocytes
Nephrotic syndrome	– massive proteinuria – few or no erythrocytes and leukocytes – hyaline casts, waxy casts – lipid droplets, oval fat bodies and fatty casts – Maltese crosses
Nephritic syndrome	– protein ++ to +++ – hemoglobin abundant – dysmorphic erythrocytes, acanthocytes and erythrocyte casts
Acute tubular necrosis (ATN)	– slight renal glucosuria – no protein – no erythrocytes and leukocytes – abundant granular casts, epithelial casts, pigmented casts
Acute tubulointerstitial nephritis (TIN)	– slight proteinuria – leukocyturia, leukocyte casts – erythrocyturia – eosinophiluria

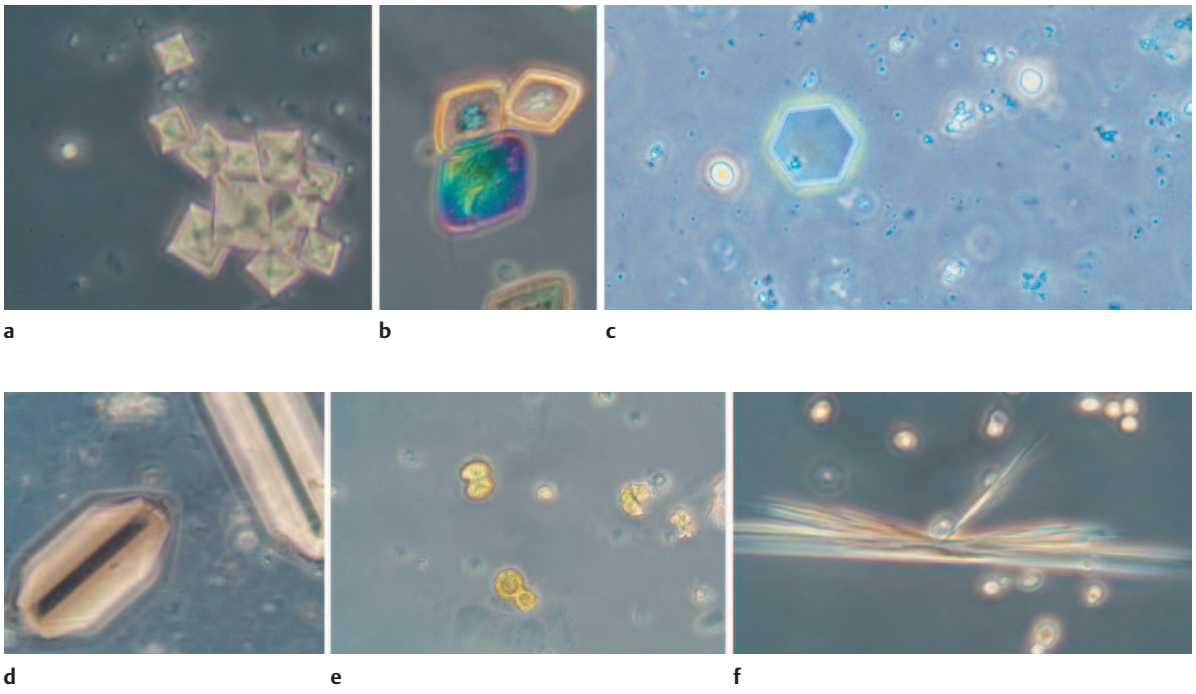

Fig. 29.**9** Various urinary crystals
a Typical oxalate crystals (envelope form).
b Rhomboid uric acid crystals, appearing colorful under polarized light.
c Characteristic hexagonal cystine crystals.
d Triple phosphate crystals
e Leucine crystals
f Indinavir crystals in a patient with antiretroviral therapy.

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29.3 Differential Diagnosis of Reduced Glomerular Filtration Rate

The kidneys can be impaired in their function as isolated organs, or they can be involved in diseases of other individual organs, as well as in systemic diseases. In addition, primary renal diseases can have immediate effects on the function of other organs, sometimes with complex clinical pictures. The spectrum of nephropathies ranges from acute life-threatening conditions to chronic diseases that can be diagnosed at an advanced stage only.

An early recognition of renal disease, which often starts with discrete symptoms like hypertension, edema, proteinuria, and hematuria, is of utmost importance. This allows a timely diagnosis, ideally prior to a significant reduction of the renal function. An early and correct diagnosis is important for planning the therapy and has an impact on the prognosis.

Acute Renal Failure (ARF)

Definition. Acute renal failure (ARF) is a clinical syndrome that is characterized by a rapid decrease (occurring within hours to weeks) of the GFR, along with an increase in creatinine and BUN and disturbances of the water, electrolyte, and acid–base balance. Often ARF is asymptomatic and is only diagnosed by laboratory analyses. An oliguria (decrease of the urine output to < 400 mL/day) is not obligate, but is present in about 50 % of patients. ARF is often reversible, but is associated with a significant morbidity and mortality, which is mostly due to the severity of the primary disease and the complications.

Classification. Although ARF occurs in conjunction with various diseases, it is classified into three categories for diagnostic and management purposes (Fig. 29.**10**):

- prerenal, by renal hypoperfusion
- intrarenal (intrinsic, renal parenchymal), by processes located within the kidney
- postrenal, by obstruction.

In prerenal and intrarenal ARF, a further distinction is made between *oliguric* ARF (with a worse prognosis) and *nonoliguric* ARF. Due to obstruction of urine flow, ARF can also be linked with decreased diuresis and therefore with oliguria or anuria. In cases of subtotal obstruction, however, a normal urine quantity or even polyuria can be observed.

On the basis of the above classification of ARF (Fig. 29.**10**), Tab. 29.**8** lists the most important clinical pictures.

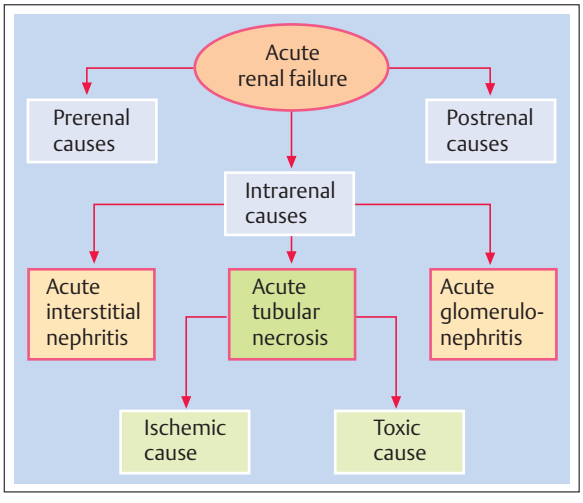

Fig. 29.**10** Classification of acute renal failure into the principal categories prerenal, intrarenal and postrenal acute renal failure, and further differentiation of the intrarenal kidney failure.

Prerenal Kidney Failure

Prerenal kidney failure by renal hypoperfusion, the most frequent type of ARF, has to be considered in the following cases:

- occurrence of one of the diseases mentioned in Tab. 29.**8**
- evidence of the following urinary findings:
  - normal urinary sediment (no hematuria or proteinuria)
  - high urine osmolality and low urine sodium (< 10 mmol/L), as well as low fractional sodium excretion ($FE_{Na+} < 1\,\%$) with simultaneous oliguria.

In prerenal kidney failure the integrity of the renal parenchyma is maintained. This type of ARF is reversible, provided that the basic cause is treated in time. Otherwise, prerenal kidney insufficiency can turn into an acute tubular necrosis (see below).

Causes. The most important causes are vomiting, diarrhea, insufficient fluid uptake, fever, and administration of diuretics. Further causes are congestive heart failure, disturbances of liver function, or septic shock. Rarely, bilateral renal artery stenoses are observed, whereby, these are often also assigned to the intrarenal ARF.

Diagnostic difficulties occasionally arise when patients with prerenal kidney failure show clinical signs of hyperhydration, although the effective circulating blood volume (intravascular space) is reduced. This constellation is predominantly observed in patients with cardiac insufficiency and liver cirrhosis (DD: hepa-

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Table 29.**8** Most important causes of acute renal failure

Prerenal diseases
- intravascular volume depletion
  - insufficient fluid intake
  - gastrointestinal bleeding and fluid loss (vomiting/diarrhea)
  - renal losses (diuretics, diabetes insipidus, osmotic diuresis)
  - skin/mucosal losses (burns, hyperthermia) or third spacing (pancreatitis, Crush syndrome)
- low cardiac output
  - severe congestive heart failure
  - pulmonary embolism
- systemic vasodilatation
  - sepsis
  - anaphylaxis
  - antihypertensive drugs
  - hepatorenal syndrome
- altered autoregulation of renal blood flow and GFR
  - ACE inhibitors/angiotensin II receptor antagonists in case of renal artery stenoses or stenoses of the intrarenal arteries
  - NSAIDs and renal hypoperfusion

Intrarenal diseases
- glomerular diseases
  - acute glomerulonephritis (e. g., poststreptococcal glomerulonephritis)
  - rapidly progressive glomerulonephritis (RPGN) with extracapillary proliferation (formation of crescents)
- vascular diseases
  - vasculitides, e. g., Wegener granulomatosis, microscopic polyangiitis
  - cholesterol embolism (spontaneous, after catheter intervention, or precipitated by anticoagulants)
  - hemolytic–uremic syndrome
  - malignant hypertension, scleroderma
  - renal artery stenosis or occlusion, renal vein thrombosis
- tubulo-interstitial diseases
  - acute tubular necrosis (ATN), ischemic (bleeding, hypotension) or toxic (NSAIDs, aminoglycosides, radiocontrast agents, cytostatic drugs, e. g., cisplatin, rhabdomyolysis)
  - acute tubulo-interstitial nephritis (antibiotics, NSAIDs, and other drugs)
  - acute bilateral pyelonephritis
- intratubular obstruction
  - uric acid crystals (chemotherapy-induced cell lysis: tumor lysis syndrome), calcium oxalate or light chains (multiple myeloma: cast nephropathy)

Postrenal kidney failure
- prostatic enlargement (hyperplasia, carcinoma)
- malignant tumor in lower pelvic region, lymphomas
- urolithiasis (bilateral or in functionally single kidney)
- bladder dysfunction (neurogenic bladder, drugs)
- retroperitoneal fibrosis (Ormond disease)

torenal syndrome) and is made worse by the administration of diuretics.

Postrenal Kidney Failure by Obstruction

Causes. Postrenal kidney failure is caused by complete or partial bilateral obstruction, or unilateral obstruction of diuresis, when the nonobstructed kidney itself shows preexisting nephropathy.

Prostate diseases or tumors in the lesser pelvis are the most frequent causes of postrenal kidney failure. In rare cases a neurogenic bladder disorder or retroperitoneal fibrosis (Ormond disease) can cause bilateral hydronephrosis. The diagnosis is obtained by sonographic evidence of urinary retention with pyelocaliectasis.

Intrarenal Kidney Failure

Causes. Tubular necrosis is the most important intrarenal cause of acute kidney failure. Primary damage of the glomeruli (glomerulonephritis), tubular interstitium (tubulointerstitial nephritis), and blood vessels (vasculitis, administration of ACE inhibitors in patients with stenoses of the intrarenal arteries/arterioles), as well as collagenoses, can lead to acute kidney failure (see Tab. 29.**8**).

The clinical picture of acute tubular necrosis is discussed here in more detail. Glomerulonephritides and tubulointerstitial nephritides will be dealt with elsewhere in this chapter.

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Fig. 29.**11** Clinical symptoms of cholesterol embolism following coronary angiography.
a Livedo reticularis
b Necroses in the region of the toes; development of advanced renal failure within three weeks following catheter intervention.

Acute Tubular Necrosis (ATN)

Acute tubular necrosis (ATN) represents the most frequent cause of intrarenal ARF (> 75 % of all cases). The following are the two main causes of ATN:

- renal ischemia
- effect of exogenous or endogenous toxins.

Ischemia. Acute ischemic tubular necrosis is generally a consequence of arterial hypotension. Clinically, these are periods of low blood pressure to actual shock states, mostly in connection with cardiac failure (reanimation), hemorrhages, intravascular fluid loss, sepsis, or circulatory instabilities during surgical procedures.

The probability for ATN increases with more severe and prolonged arterial hypotensive phases. Open cardiac surgery and patients with jaundice are at particularly high risk for the development of ATN.

Exogenous Toxins. Toxic ATN frequently occurs in conjunction with sepsis and after administration of nephrotoxic antibiotics (in particular, aminoglycosides, amphotericin B). Furthermore, cytostatic agents (e. g., cisplatin), NSAIDs (e. g., diclofenac), and radiographic contrast agents can lead to ATN, and patients with reduced kidney function, diabetics with nephropathy, and patients with multiple myeloma are particularly exposed to high risks.

In ARF after invasive angiographic catheterization the two differential diagnoses are contrast agent toxicity and atheroembolic renal disease (cholesterol embolism). Delayed occurrence of ARF after days, or less frequently after weeks to months, with a progressive creatinine increase, eosinophilia, and increased lactate dehydrogenase (LDH), livedo reticularis of the skin (Fig. 29.**11a**), digital necroses (Fig. 29.**11b**), as well as ophthalmoscopically visible emboli in the retina vessels, suggest the presence of cholesterol embolisms and militates against contrast-induced renal failure (Tab. 29.**9**).

Rare causes of nephrotoxic ARF are intoxications by solvents (carbon tetrachloride, glycols) and heavy metals.

Endogenous Toxins. *Rhabdomyolysis* and *severe hemolysis* can also lead to acute renal insufficiency. Increase of the muscle enzymes (creatine kinase, aldolase) and evidence of myoglobinuria indicate rhabdomyolysis, whereas hemolytic serum, decrease of the hemoglobin value, and a marked increase of LDH in the serum suggest hemolysis.

Table 29.**9** Differential diagnosis of acute renal failure after angiography

	Radiocontrast toxicity	Cholesterol emboli
Pathogenesis	Vasoconstriction and direct tubular toxicity	Occlusion of renal arterioles by microemboli, consecutive inflammatory reaction
Occurrence	Approximately one to three days after application of radiocontrast agents	Approximately five days to four weeks (rarely months) after catheter interventions (angiography)
Accompanying symptoms	None (very rarely allergic exanthema)	Livedo reticularis, digital necroses, emboli in retinal vessels
Specific laboratory signs	None	Eosinophilia, increased LDH, often decreased complement levels (C3, C4)
Course	Excellent restitution	Rarely complete remission, mostly persistent or progressive renal failure

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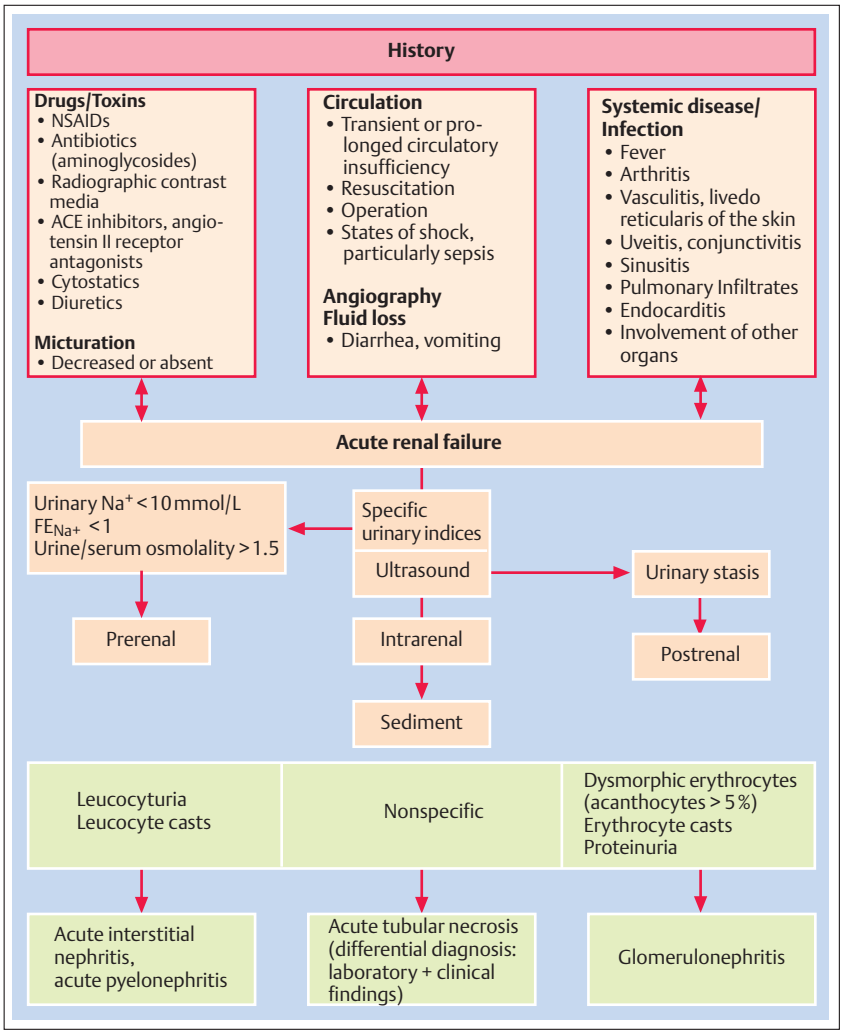

Fig. 29.**12** Schematic representation of the differential diagnosis in acute renal failure.

Diagnostic Procedure and Differential Diagnosis of ARF

The various forms of ARF mentioned in Tab. 29.**8** can, in most cases, be differentiated as follows:

- history and clinical signs
- physical examination
- urinalysis: microscopy/dipstick tests of urine, biochemical findings
- blood analyses (Tab. 29.**10**)
- radiologic examinations
- renal biopsy.

History and Clinical Examination. Approximately 50 % of all patients with ARF are *surgery patients*, in whom acute renal failure occurs in conjunction with perioperative hypotension, hemorrhage, or sepsis (aminoglycosides). Other frequent causes of ARF are the administration of *nephrotoxic drugs* (nephrotoxic antibiotics like aminoglycosides, cytostatic agents, NSAIDs), or previous administration of contrast agents, especially in patients with preexisting renal insufficiency (e. g., diabetic nephropathy). *Systemic diseases*, e. g., vasculitis, can lead to a rapid decrease of the GFR within days to weeks.

The symptoms to be determined are listed in Fig. 29.**12**: the presence of fever, arthralgia (with/without arthritis), muscular pain, purpura, livedo reticularis, uveitis/conjunctivitis, sinusitis, pulmonary infiltrates, or weight loss have to be followed by immunologic testing (ANCA, ANA, anti-GBM antibodies, cryoglobulins, etc). It has to be considered, however, that systemic diseases may have an asymptomatic course and can be confined to the kidneys only.

Physical Examination. Signs of reduced effective circulating arterial blood volume or of extracellular volume deficit are reduced filling of the deep cervical veins, arterial hypotension, and reduced skin turgor. Signs of hyperhydration due to reduced excretory function of the kidneys are congestion of the deep cervical veins,

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Table 29.**10** Main laboratory investigations for acute renal failure (ARF)

Parameter	Cause/Differential Diagnosis
Urine	
Hematuria, erythrocyte casts, proteinuria	Glomerulonephritis
Sodium, osmolality	Prerenal ARF versus ATN (see Tab. 29.**11**)
Blood	
Creatinine ↑	GFR ↓ (creatinine rises above normal values often only when GFR is decreased by ≥50 %)
BUN ↑	GFR ↓, dehydration, protein catabolism, gastrointestinal bleeding
Na^+, K^+, Cl^-, pH/bicarbonate/P_{CO_2}	Electrolyte imbalance, metabolic acidosis/alkalosis
Complete blood count	Leukocytosis (infection), anemia (hemolysis), thrombocytopenia (hemolytic–uremic syndrome, sepsis)
Uric acid ↑	Dehydration, cell lysis (chemotherapy)
Calcium ↑	Multiple myeloma (total protein also ↑) or other malignancy, excessive vitamin D ingestion, thiazide diuretics
Creatine kinase ↑	Rhabdomyolysis
LDH ↑	Cholesterol emboli, hemolysis
Lipase ↑, amylase ↑	Pancreatitis
Protein electrophoresis	Monoclonal gammopathy
Blood culture	Infection (sepsis, endocarditis, etc.)
Autoantibodies (ANA, anti-DNA, ANCA, anti-GBM), cryoglobulins, antistreptolysin O titer	SLE, vasculitis, Goodpasture syndrome, cryoglobulinemia, poststreptococcal GN

Table 29.**11** Indices for distinction between prerenal acute renal failure (ARF) and acute tubular necrosis (ATN)

	Urine Na^+ (mmol/L)	Fractional Na^+ excretion in % (FE_{Na+})*	Urine osmolality (mOsm/kg)	Urine:plasma osmolality ratio
Prerenal ARF	< 10	< 1	> 500	> 1.5
ATN	> 20	> 2	< 250	< 1.1

* $FE_{Na+} = \frac{[U_{Na+}] \times [P_{creatinine}]}{[P_{Na+}] \times [U_{creatinine}]} \times 100$

arterial hypertension, and edema (ankle edema, pulmonary edema). Further signs of systemic diseases are the aforementioned changes of skin and joints. The abdominal examination must include a search for urinary retention by means of palpation and percussion.

Urinalysis. The urinalysis comprises the analysis of the urine sediment by means of test strips and/or microscopy, as well as various biochemical parameters.

Inflammatory diseases of the glomeruli with rapid decrease of the GFR (e. g., postinfectious glomerulonephritis, RPGN with crescent formation) show a glomerular (deformed erythrocytes in the phase contrast microscope) microscopic hematuria and pathognomonic red cell casts in the *urinary sediment*. Leukocyturia, often with leukocyte casts, is diagnostically important in acute tubulointerstitial nephritis and pyelonephritis. In addition, bacteria are usually observed in pyelonephritis. In practice, the urine sediment generally does not yield much information in the case of acute tubular necrosis, yet granular casts and tubular cells can be observed.

The *biochemical analysis* of the urine comprises the determination of osmolality, sodium, and fractional sodium excretion, particularly in oliguric ARF. This allows a differentiation between prerenal kidney failure and ATN (Tab. 29.**11**). As a reaction to the reduced intravascular fluid volume, the tubular reabsorption of sodium and water is generally increased in prerenal kidney failure. Therefore, concentrated urine with low sodium content is excreted. In ATN, however, the tubular functions are impaired; the urine is not or barely concentrated, and contains a high amount of sodium. Hence, in prerenal insufficiency the concentrated urine shows an osmolality of > 350–400 mOsm/kg. In ATN with impaired tubular concentration ability the osmolality of urine corresponds approximately to the osmolality of plasma or serum (isosthenuria). Furthermore, in particular in oliguria, a fractional sodium excretion (FE_{Na+}) > 2 % indicates acute tubular necrosis, while an excretion < 1 % indicates prerenal kidney failure (Tab. 29.**11**).

Blood Analyses. The most important blood analyses are summarized in Tab. 29.**10**. With unclear ARF, the exclusion of a systemic disease is mandatory.

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Radiologic Examinations. A postrenal cause of ARF can be detected or excluded in the majority of cases by *sonography* of the kidneys and the lower urinary tract. In addition, the determination of kidney size yields information on whether there exists (concurrently) a chronic kidney insufficiency with reduced kidney size. Furthermore, perfusion disorders, e. g., occlusions or stenoses of the renal arteries, can be identified. MRI or CT can be used as an alternative or complement to sonography.

Renal Biopsy. Histologic analysis of the kidneys is only occasionally performed in ARF. A renal biopsy is indicated after exclusion of a prerenal or postrenal cause, if the renal parenchymal etiology remains unclear, or in particular, if there is a suspicion of an inflammatory systemic disease such as ANCA-positive vasculitis, Goodpasture syndrome, or systemic lupus erythematosus. Biopsy is also indicated in acute interstitial nephritis.

Chronic Renal Failure (CRF)

Definition. Chronic renal failure (CRF) or insufficiency results from a long-lasting, mostly irreversible, reduction of the glomerular, tubular, and endocrine functions of the kidneys. CRF is associated with impairments of:

- excretion of metabolic products
- excretion of acid, electrolytes, and water
- production/secretion of hormones, e. g., erythropoietin, active vitamin D_3 (1,25-$[OH]_2$ vitamin D_3).

Staging. The degree of severity of chronic renal diseases, including CRF, can be classified into five stages according to the Guidelines of the Kidney/Dialysis Outcome Quality Initiative (K/DOQI), as shown in Tab. 29.**12**. The management of patients with CRF is currently of great interest in clinical nephrology.

Consequences. A *reduced GFR* manifests with decreased endogenous creatinine clearance and increased serum creatinine. Further consequences of GFR reduction are increases in BUN, inorganic phosphate, uric acid, and magnesium in the serum. Retention of sodium and water leads to edema and to hypertension.

The *reduction of tubular function* becomes apparent as a reduced excretion of acids (H^+ ions) and potassium (metabolic acidosis and potentially life-threatening hyperkalemia), and often in a reduced ability to concentrate the urine.

A reduction in the endocrine kidney functions is also responsible for the development of renal anemia (lack of erythropoietin) and of renal osteodystrophy (disturbed vitamin D metabolism).

Causes. Acquired and congenital nephropathies can be responsible for CRF (Tab. 29.**13**; Fig. 29.**13**). In the Western world, the main kidney diseases leading to advanced kidney failure are:

- diabetic nephropathy
- arterial hypertension with nephroangiosclerosis, renal artery stenoses
- glomerulonephritides
- tubulointerstitial nephritides
- hereditary nephropathies, in particular autosomal dominant polycystic kidney disease (ADPKD).

In particular, *diabetic nephropathy* is increasing in the Western world. Only rarely do clinical history, examination, and laboratory findings allow an accurate diagnosis (Tab. 29.**13**). For therapeutic and prognostic reasons, however, an early and precise diagnosis (often by means of a kidney biopsy) should be attempted whenever possible. With regard to future renal transplantation, it is highly important to know whether there is nephropathy that might recur in the transplant and impair its function (e. g., focal segmental glomerulosclerosis, FSGS).

Table 29.**12** Stages of chronic renal diseases (1–5) including CRF (2–5) according to K/DOQI guidelines

Stage	Renal disease	GFR mL/min/1.73 m²	Clinical presentation
1	Nephropathy with normal GFR	≥ 90	Hematuria, proteinuria, hypertension secondary to nephropathy
2	Mild renal failure	60–89	See above
3	Moderate renal failure	30–59	Secondary hyperparathyroidism
4	Severe renal failure	15–29	Renal anemia
5	Advanced or end-stage renal failure; renal replacement therapy has to be considered	< 15	Progressive Na^+/water retention, metabolic acidosis, lack of appetite, nausea/vomiting, hyperkalemia, encephalopathy

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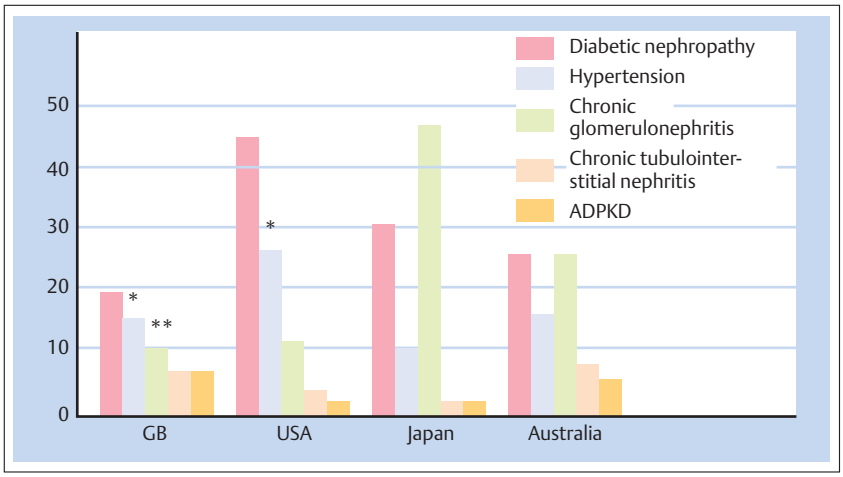

Fig. 29.**13** Most frequent causes of advanced or end-stage renal failure (in %): *including renal artery stenoses; **only verified glomerulonephritides. Remaining, nonrecorded causes: various diseases or cause unknown (Sources: USRDS 2003, Annual data report; ANZDATA Registry Report 2003; The UK Renal Registry Report 2003; Iseki et al. 2002).

Table 29.**13** Identifying the cause of chronic renal failure by medical history, clinical features, and investigations

	Medical history	Clinical features	Investigations
Primary glomerulopathies	Often nonrevealing	Hypertension, edema	– renal ultrasound: parenchymal alterations – urine: erythrocyte casts, microhematuria (dysmorphic erythrocytes), proteinuria (> 3 g/day = proof of glomerular injury)
Systemic diseases with secondary glomerulopathies			
Diabetes mellitus type 1	Diabetes mellitus for many years	Hypertension, edema, retinopathy, neuropathy	– renal ultrasound: relatively well preserved renal size in relation to distinctly reduced GFR – urine: proteinuria (microalbuminuria)
ADPKD	Often positive family history	Bilaterally enlarged kidneys (often palpable)	– renal ultrasound: detection of cysts and enlarged kidneys – extrarenal findings
Nephroangiosclerosis	Longstanding hypertension	Fundus hypertonicus	– left ventricular hypertrophy (ECG/echocardiography
Obstructive nephropathy	Voiding problems, nocturia, pollakisuria	Enlarged prostate, palpable carcinoma, overflow bladder	– renal ultrasound: detection of hindered urine outflow
Alport syndrome	Familial clustering of renal failure, typically with hearing loss	Inner ear hearing loss, ocular defects (e. g., lenticonus)	– audiometry – ophthalmoscopy
Chronic tubulo-interstitial nephritis	Longstanding analgesic abuse	Analgesic abuse syndrome, gastrointestinal problems (ulcerations)	– urinary concentrating capacity ↓ – (partial) renal tubular acidosis – papillary necrosis
Multiple myeloma	Bone pain, infections	Spontaneous fractures	– erythrocyte sedimentation rate (ESR) ↑ – paraproteins in blood/urine, hypercalcemia, anemia – typical bone marrow findings (plasmocytes ↑)

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Clinical Characteristics of Chronic Renal Failure (CRF)

General Symptoms

There are no specific symptoms of CRF. In cases of slightly or moderately reduced renal function the patients are often asymptomatic or complain about unspecific symptoms, e. g., exercise intolerance and fatigue. Renal insufficiency is frequently diagnosed by chance, in connection with a pathologic urinary finding (proteinuria or microhematuria), hypertension, or in the context of investigating another disease.

In advanced CRF, symptoms like inappetence, pruritus, gastrointestinal and neuromuscular disturbances occur, and also bone pain is described when renal osteopathy is left untreated (Fig. 29.**14**). Numerous additional symptoms can occur as a consequence of the primary disease leading to renal failure, e. g., joint pain in systemic lupus erythematosus.

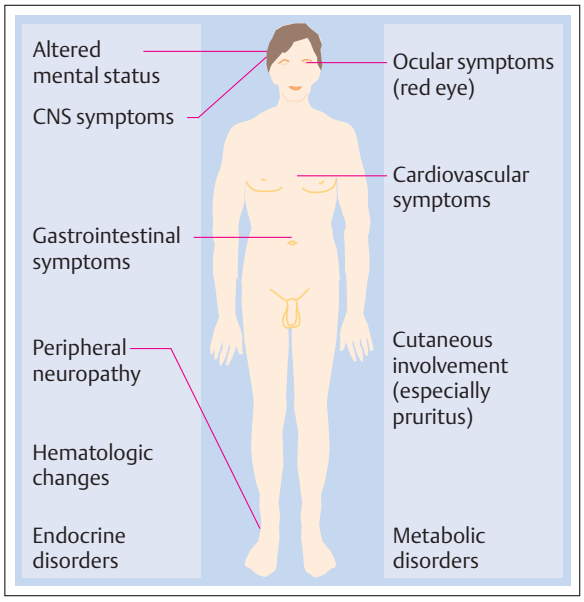

Fig. 29.**14** Organ involvement in chronic renal failure with uremia.

Hematologic Changes

Anemia. Virtually all patients with CRF and a decrease of the creatinine clearance to ≤35 mL/min develop *normochromic normocytic anemia*. However, a commencing anemia can be identified earlier by a GFR of < 50–60 mL/min. In ADPKD the anemia is often less distinct, while diabetics, or patients with tubulointerstitial nephritis, tend to develop an anemia earlier. Clinical symptoms of anemia are fatigue, vertigo, and dyspnea. Preexisting angina pectoris in patients with coronary heart disease is frequently exacerbated.

The causes for anemia in CRF are manifold:

- reduced renal synthesis of erythropoietin (primary cause)
- blood losses due to bleeding tendency (see below) and due to frequent blood drawings
- simultaneous iron deficiency in about one-quarter up to one-third of patients
- Further contributing causes: hemolysis, osteitis fibrosa in hyperparathyroidism.

Anemia contributes to cardiac dysfunction insofar as the consecutively increased cardiac output favors left ventricular hypertrophy. The anemia can be kept under control by subcutaneous administration of erythropoietin (treatment goal: Hb around 11–13 g/dL).

Bleeding Tendency. Another hematologic manifestation of CRF is the bleeding tendency (hemorrhagic diathesis) as a consequence of altered thrombocytic function. This can lead to occult gastrointestinal blood loss. In addition, heavier menstrual bleeding, epistaxis, and bleeding from wounds can occur in patients with CRF.

Cardiovascular Manifestations

The most important cardiovascular complications of CRF are: coronary artery disease (favored by an increased calcium phosphate product), uremic/hypertensive cardiomyopathy, renal hypertension (fluid retention), and uremic pericarditis. In addition, dyslipidemia occurring early in the course of CRF represents an important cardiovascular risk factor.

Hypertension. The majority of CRF patients are hypertensive, often due to fluid retention. Appropriate blood pressure stabilization with values ≤130/80 mmHg, or even ≤125/75 mmHg, in patients with proteinuria > 1 g/day slows the progression of CRF and has a protective effect on the cardiovascular system. Renal hypertension is discussed in more detail in Chapter 23.

Uremic Pericarditis. The occurrence of thoracic pain may indicate the presence of uremic pericarditis. Further diagnostic criteria are a pericardial friction rub and echocardiographic evidence of an accompanying pericardial effusion. An enlargement of the cardiac silhouette in the chest radiograph is only seen with massive pericardial effusion. Also, the ST-segment elevation in the ECG, which is typical of pericarditis, is often lacking. In the majority of patients the pericarditis is asymptomatic and can only be diagnosed during heart auscultation or with echocardiography.

The identification of uremic pericarditis is important, because it represents an absolute indication for dialysis.

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Neurologic and Muscular Changes

Among the typical neurologic manifestations of severe CRF are:
- uremic encephalopathy
- peripheral polyneuropathy
- autonomous neuropathy.

Uremic Encephalopathy. Apathy, lack of concentration, myoclonus, and sleeplessness are frequent early symptoms of uremic encephalopathy. Without treatment, convulsions and coma may develop. With the availability of dialysis these two serious symptoms are currently rarely seen.

Disturbances of the Peripheral Nervous System. In the peripheral nervous system, a distally accentuated mixed sensorimotoric polyneuropathy can occur. Uremic polyneuropathy is a complication of advanced CRF (GFR usually < 10 mL/min), which often first occurs at the dialysis stage. Sensory symptoms, e. g., burning or stabbing dysesthesia, are most commonly observed. Motor deficits, e. g., foot drop, are rarely seen.

Some patients display the so-called burning feet and restless legs syndrome. Among these symptoms are paresthesia and distinct plantar touch sensitivity (burning feet), occurring predominantly at night, with disturbing stabbing sensations in the region of the lower extremities, relieved by movement of the legs. The patient is often forced to get up and walk around (restless legs). In the differential diagnosis the following diseases must be considered: diabetes mellitus, panarteriitis nodosa, amyloidosis (e. g., carpal tunnel syndrome through compression of the median nerve in connection with β_2-microglobulin deposition), or multiple myeloma.

Autonomous Neuropathy. The clinical consequences of autonomous neuropathy are diverse, including attenuated cardiovascular reflexes during hemodialysis with subsequent hypotension associated with fluid withdrawal. In addition, sexual dysfunction can occur in men.

Uremic Myopathy. Uremic myopathy comprises functional and also, in part, structural muscle disorders as a consequence of uremia. Myopathy only occurs with severe renal insufficiency, predominantly in the dialysis stage. It is manifested by muscle weakness, muscle loss, rapid fatigue, and exercise intolerance. The exact pathogenesis still remains unclear. Uremic myopathy can be exacerbated by a simultaneously developing polyneuropathy and therapeutically correctable factors, e. g., hyperkalemia and hypokalemia or, in rare cases, by phosphate depletion due to overdose of phosphate binders.

Dermatologic Manifestations

The possible effects of CRF on the skin are frequently a great strain on uremic patients. The most frequently encountered problems include:
- diffuse brownish pigmentation (uremic color)
- pruritus
- ecchymoses through increased bleeding tendency
- bullous changes (pseudoporphyria or, rarely, side effect of drugs), predominantly in patients receiving hemodialysis.

Generalized pruritus, which occurs particularly during dialysis, can be very distressing and immensely impede quality of life. Causally, histamine release, possibly in connection with a deposition of calcium phosphate in the skin, is postulated. Parathyroidectomy, as a result of concomitant hyperparathyroidism, can lead to alleviation. Furthermore, dry skin with ichthyosis and lichenification can contribute to pruritus.

Renal Osteodystrophy

The osseous changes that occur in conjunction with CRF are summarized as renal osteodystrophy (osteopathy). Renal osteodystrophy is subdivided as follows:
- *parathyroid osteitis fibrosa cystica:* high-turnover osteopathy due to hyperparathyroidism with increased activity of osteoblasts and osteoclasts
- *osteomalacia:* low-turnover osteopathy with increased demineralized osteoid (mineralization defect), mostly due to lack of active vitamin D
- *adynamic or aplastic bone disease:* reduced bone turnover, mostly due to excessive treatment with vitamin D products or due to aluminum deposition
- *mixed renal osteodystrophy*
- *amyloidosis due to dialysis:* deposition of β_2-microglobulin.

Osteitis fibrosa cystica and adynamic bone disease are the most frequently found bone diseases in dialysis patients. The origin of the individual entities differs (Fig. 29.**15**).

Osteitis Fibrosa Cystica and Secondary Hyperparathyroidism. A decreasing GFR leads to phosphate retention because of reduced phosphate filtration. The consequent increase in parathyroid hormone (PTH) in the context of secondary hyperparathyroidism (when GFR decreases to around 30 mL/min) is adequate and keeps phosphate within the normal range by inhibition of proximal tubular phosphate reabsorption. If the GFR drops to < 20 mL/min, however, hyperphosphatemia develops and secondary hyperparathyroidism becomes maladaptive.

In addition to the direct effect of hyperphosphatemia on the stimulation of PTH, there are additional factors that promote hyperparathyroidism, in particular hypocalcemia due to a decrease in calcitriol (1,25-$[OH]_2$ vi-

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tamin D) with reduced enteral calcium resorption and reduced calcium efflux from the bone. Ultimately, a diffuse or nodular hyperplasia of the parathyroid gland develops. In addition, because of the hyperphosphatemia, a reduction in the synthesis of the calcium-sensing receptors of this gland occurs. Furthermore, an increased alkaline phosphatase level as a sign of increased osteoblast activity can be found in the serum.

Osteomalacia. Osteomalacia is characterized by reduced bone turnover with a decrease of osteoclasts and osteoblasts, as well as an increase in unmineralized bone (osteoid). The main cause is aluminum intoxication by phosphate binders, which contain aluminum. These aluminum-containing phosphate binders were previously in common use. An additional factor might be calcitriol deficiency.

Adynamic Bone Disease. Bone turnover is strongly reduced but, in contrast to osteomalacia, no increased osteoid formation is observed. The precise cause of this osteopathy is unclear. Proposed causes are excessive suppression of PTH by vitamin D products, aluminum deposition, and circulating uremic toxins.

Clinical Features. Effective prevention of renal osteodystrophy, in particular osteitis fibrosa cystica, is now possible, and the clinical symptoms are therefore encountered less frequently. Nonspecific bone pain in the region of the back, hips, and legs, which increases under physical strain, is most commonly encountered.

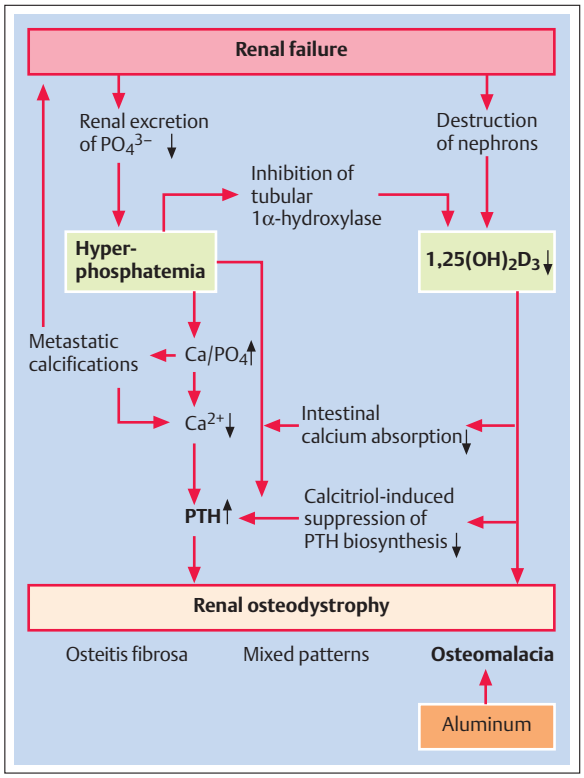

Fig. 29.**15** Pathogenic mechanisms of renal osteodystrophy, particularly with regard to the development of secondary hyperparathyroidism and osteomalacia.

Gastrointestinal Symptoms

Numerous gastrointestinal disorders can be caused by advanced renal insufficiency:

- uremic foetor
- nausea, vomiting, heartburn
- tendency to constipation with ensuing diverticulosis/diverticulitis
- gastrointestinal hemorrhages
- rarely, clinical picture of acute abdomen.

In particular, nausea, inappetence, and vomiting occur during the predialytic stage of renal insufficiency and improve after the start of dialysis treatment.

> With timely dialysis therapy, the aforementioned gastrointestinal symptoms occur only in exceptional cases.

Gastrointestinal hemorrhage can also be caused by angiodysplasia in the stomach, small bowel, or colon.

Acute Abdomen. In addition to pathologies, e. g., appendicitis, cholecystitis, pancreatitis, ileus, and ulcus, the following diseases have to be considered within the symptom complex of acute abdomen:

- diverticulitis and colon perforation (risk factor: chronic constipation)
- familial Mediterranean fever with recurrent abdominal pain and renal insufficiency due to secondary amyloidosis
- systemic lupus erythematosus with serositis
- (retroperitoneal) hemorrhages due to cystic rupture in ADPKD
- mesenteric ischemia or infarction.

Malnutrition

Malnutrition is a frequent problem in renal insufficiency and contributes particularly to the high mortality rate found in dialysis patients. Causes are inappetence, acidosis (protein catabolism), and insulin resistance. Symptoms and signs are weight loss, decrease of muscle mass, and low albumin level in the serum. This can even cause a drop in serum creatinine levels, which is frequently misinterpreted as improvement of the renal function.

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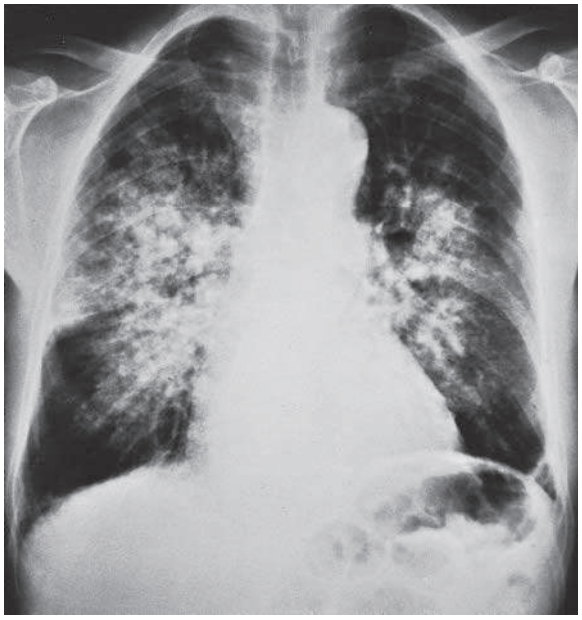

Fig. 29.**16** "Fluid lung" with bihilar, butterfly-like pulmonary congestion.

Disturbances of the Water, Electrolyte, and Acid–Base Balance

Sodium and Water. A sodium and water balance is maintained in most patients with a GFR of > 10 mL/min. This is possible because the kidneys are able to excrete a variable part of the filtered sodium and water via tubular resorption. The adaptation range of the kidneys with regard to fluid output, however, is severely limited due to a reduced dilution and concentration ability in established renal insufficiency. With increasing deterioration of renal function the urine osmolality fluctuates around 300 mOsm/L, i. e., it corresponds approximately to the plasma osmolality. Excessive supply of free water can therefore lead to dilutional hyponatremia, while a reduced supply can cause hypernatremia.

A decrease in the extracellular volume with reduction of the renal perfusion can induce a further drop of the GFR. Equally critical is an excessive salt and water supply with the risk of hyperhydration, which is manifested by rising weight, until eventually peripheral edema or a pulmonary edema occur (Fig. 29.**16**). Subjective cardinal symptoms are (nocturnal) cough and, especially, dyspnea.

Table 29.**14** Frequent causes of hyperkalemia in cases of renal failure

Excessive potassium ingestion
– unsuitable diet (including intake of salt replacements)
– parenteral nutrition
Decrease in distal tubular potassium secretion
– GFR ↓ (in particular in cases of oliguria)
– hyporeninemic hypoaldosteronism (in particular in cases of diabetic nephropathy)
– type IV renal tubular acidosis
– potassium sparing diuretics (spironolactone), NSAIDs, ACE inhibitors, angiotensin II receptor antagonists
Alterations in potassium distribution (intracellular/extracellular)
– metabolic or respiratory acidosis
– β-blockers
– insulin deficiency
Cellular potassium release
– rhabdomyolysis
– tumor lysis syndrome (cell lysis under chemotherapy)

Hyperkalemia. Hyperkalemia is seen only in the presence of a severe CRF with a GFR ≤10 mL/min. In rare cases, e. g., in hyporeninemic hypoaldosteronism or generally in renal tubular acidosis type IV, hyperkalemia can occur at an earlier stage, at a GFR of around < 30 mL/min. Hyperkalemia can have numerous causes, which are summarized in Tab. 29.**14**, and can often be distinguished by history and by laboratory analyses.

A hyperkalemia that is disproportional to the degree of renal insufficiency is encountered in patients with hyporeninemic hypoaldosteronism (in particular in diabetes mellitus), hypercatabolism, or acidosis.

Clinically severe hyperkalemia (mostly > 7 mmol/L) can initially be manifested by weakness of the skeletal muscles and ECG changes (acute and high T waves in the beginning) with arrhythmia.

Metastatic Calcifications. Organ injuries due to metastatic calcifications occur in connection with hyperphosphatemia and mostly normal or high calcium, with a high probability at a calcium phosphate product of > 5.7 $mmol^2/L^2$. Calcium phosphate deposits develop vascularly and periarticularly (Fig. 29.**17**), with arthritic symptoms, and viscerally (skeletal muscle, myocardium, lungs, cornea, conjunctiva, skin).

Metabolic Acidosis. With increasing renal insufficiency the tubular production of ammonium (NH_4^+) ions is limited, such that the renal excretion for H^+ ions becomes insufficient. In addition, a bicarbonate loss occurs, particularly in tubulointerstitial nephropathies. Therefore, a metabolic renal tubular acidosis develops, which can become manifest through a reduced pH value and low bicarbonate levels.

The clinical complaints are mostly minor with dyspnea as the cardinal symptom. However, acidosis intensifies hyperkalemia, inhibits protein anabolism, and promotes the release of calcium from the bone, where H^+ ions are buffered.

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Fig. 29.**17** Metastatic calcifications
a Tumor of approximately 4 × 4 cm in the region of the lateral tibial plateau.
b The radiograph shows a distinct calcification of the tumor (metastatic calcification) in a patient with severely altered calcium/phosphate balance.
c Conjunctivitis induced by calcium phosphate deposits in a patient with end-stage renal failure and increased calcium phosphate product.

Infections

After cardiovascular causes, infections represent the second most frequent cause of death in patients with advanced CRF. Etiologically predominant are frequent vascular punctures, insertions of central venous catheters for dialysis, and an impairment of the immune system. Uremia represents a state of chronic immune suppression with defects in the cellular and humoral immune system.

Malignancies

Compared to individuals with healthy kidneys, CRF patients suffer more frequently from malignant diseases, probably because of immunologic reasons (see above). Especially in dialysis patients, a higher incidence of a number of malignancies has been described in various investigations, e. g., carcinomas of the kidneys, urinary bladder, and thyroid gland.

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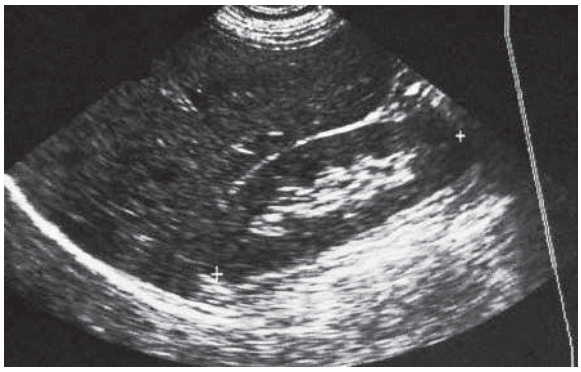

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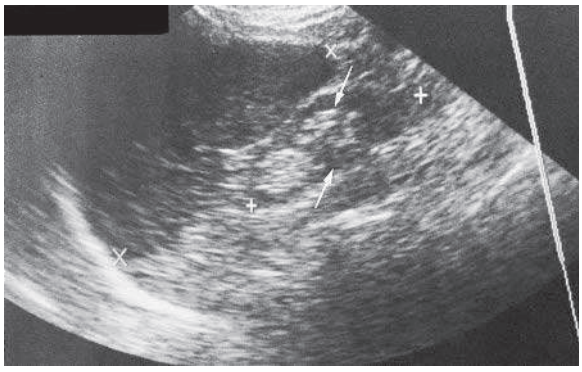

b

Fig. 29.**18** Determination of kidney size by means of ultrasound.
a Normal-sized kidney (11.2 cm) with normal-sized parenchymal border.
b Small kidney (7.7 cm) with narrowed parenchymal border (arrows) in chronic renal insufficiency due to chronic glomerulonephritis.

Particular attention needs to be paid to patients with acquired cystic kidney disease. This disease includes macroscopic renal cysts and is a consequence of CRF of any etiology with a prevalence of about 100% after 10 years of dialysis treatment. Malignant transformation is the most feared complication and is responsible for approximately 80% of kidney tumors in uremic patients.

Diagnostic and Differential Diagnostic Considerations in Renal Insufficiency

At the center of diagnosis of renal diseases is the following principle:

> All diagnostic and therapeutic steps must aim at searching for, and whenever possible treating, a reversible cause of renal insufficiency, respectively a treatable primary disease (e. g., inflammatory systemic disease, infection, malignant tumor, or drug side effect).

In this context, it is important to distinguish between ARF and CRF as the cause of the reduced renal function.

Distinction Between Acute and Chronic Nephropathy. This distinction can often be made by the history, laboratory, and radiologic examinations mentioned in Tab. 29.**15**.

In particular, the history, sonographic evidence of small kidneys (Fig. 29.**18**), radiologic signs of secondary hyperparathyroidism (radiographs of the hands and the acromioclavicular joints), laboratory signs for the presence of renal osteopathy (increased alkaline phosphatase), and, with restriction, a normocytic normochromic anemia are all suggestive of a chronic renal disease. Further clarification can be obtained by kidney biopsy.
In addition, it has to be considered that an ARF can be superimposed on a CRF. This is a frequent occurrence in the course of disease in CRF patients (e. g., contrast agent administration in diabetic nephropathy). Table 29.**16** shows the most important treatable diseases that can deteriorate an already existing reduced kidney function. Furthermore, this table contains diagnostic measures for exclusion of the aforementioned diseases.

Table 29.**15** Differentiation between acute and chronic renal failure

Parameter	Acute renal failure	Chronic renal failure
Creatinine in serum/plasma	Distinct rise in creatinine within days (up to a few weeks)	Constant and slow rising creatinine over months to years
Renal ultrasound	Normal-sized kidneys	Reduced kidney size with small echogenic parenchyma (exception: ADPKD, sometimes diabetes mellitus)
Anemia	Lack of anemia suggests ARF	Renal anemia (normochromic normocytic)
Renal osteodystrophy (hyperparathyroidism)	Lack of signs for renal osteopathy	Periosteal erosions in hands and acromioclavicular joints (radiograph), increased alkaline phosphatase in blood

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Table 29.**16** Potentially reversible causes of reduced GFR in CRF

Causes	Diagnostic investigations
Prerenal (decreased renal perfusion)	
– congestive heart failure/pericardial effusion	Clinical signs, echocardiography
– volume deficit (e. g., diuretics, diarrhea, vomiting)	Clinical signs, drug history
– renovascular diseases (bilateral renal artery stenoses, aortic aneurysm, embolism)	Clinical history and signs, renal ultrasound, CT/MRI, angiography
Intrarenal	
– nephrotoxic agents	Drug history, clinical signs of acute interstitial nephritis (e. g., drug rash)
– antibiotics (aminoglycosides)	
– NSAIDs	
– radiocontrast agents	
– systemic diseases	Clinical signs and immunologic findings, renal biopsy
– with glomerular injury (SLE, Wegener disease, ANCA-positive vasculitis with rapidly progressive glomerulonephritis, sarcoidosis)	
– with malignant hypertension (e. g., progressive systemic sclerosis = scleroderma)	
– infections (e. g., endocarditis) with immune-complex nephritis, viral diseases	Clinical history, blood cultures, auscultation, echocardiography, serology
– infiltrative diseases (lymphomas, sarcoidosis)	Renal biopsy
– hypercalcemia with polyuria and/or nephrocalcinosis	Search for cause (e. g., myeloma, hyperparathyroidism, thiazides, vitamin D)
– analgesic nephropathy	Clinical history, papillary necroses
Postrenal	
– nephro-urolithiasis	Renal ultrasound, CT, retrograde urography
– papillary necroses (e. g., analgesic nephropathy, diabetic nephropathy)	abdominal radiograph, renal ultrasound, CT
– retroperitoneal fibrosis	ESR ↑, CT, MRI
– prostate hypertrophy/carcinoma	PSA, ultrasound, CT, MRI
– gynecological tumors	Clinical examination, ultrasound, CT, MRI

29.4 Differential Diagnosis of Nephrologic Syndromes

Nephrologic diseases are caused by a multitude of damaging mechanisms. These can directly affect the glomeruli and cause so-called glomerulopathies or glomerulonephritides. However, the damaging effect can also develop in the tubulointerstitial space and cause diseases like acute or chronic tubulointerstitial nephritis (TIN). Arterial and venous changes in the renal vessels, resulting in perfusion disorders, can cause a number of renal functional disorders. Furthermore, pathologies of the lower urinary tract can develop and lead to nephrologic–urologic diseases with specific symptomatology.

Glomerular Syndromes and Glomerulopathies

Definition. Glomerulopathies are inflammatory or noninflammatory diseases of the glomeruli and are associated to a variable extent with hematuria, proteinuria, hypertension, and a decrease in the GFR.

Classification. A classification of glomerulopathies can be made according to etiologic, pathogenic, histopathologic, and clinical criteria. Glomerulopathies can occur as:

- *Idiopathic primary glomerulopathy* without obvious cause and without involvement of other organ systems.
- *Secondary glomerulopathy*. Here, disease of the glomeruli occurs within a variety of systemic diseases and vasculitides, in infections, drug exposition, and tumor diseases.

In both types of glomerulopathy damage to the glomeruli can take place via immunologic or nonimmunologic mechanisms.

Immunologic Factors. The majority of glomerulopathies are caused by immunologic processes, whereby, in particular, deposition of *antigen–antibody complexes* in the glomerular capillaries or their mesangium is significant.

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Table 29.**17** Clinical glomerulopathy syndromes

Acute nephritic syndrome	– hematuria with dysmorphic erythrocytes (acanthocytes), erythrocyte casts, proteinuria – acute renal failure, hypertension, edema
Nephrotic syndrome	– marked proteinuria > 3.5 g/24 h, lipiduria – edema, hypoalbuminemia, hyperlipidemia, tendency for thrombosis and infections
Rapidly progressive glomerulonephritis (RPGN)	– hematuria, proteinuria – renal failure with > 50 % functional loss within weeks to months, hypertension
Asymptomatic urinary findings	– isolated hematuria and/or proteinuria
Chronic glomerulonephritis	– nonspecific urinary findings

Much less frequently the capillaries are destroyed by antibodies against elements of the GBM (rapidly progressing glomerulonephritis, Goodpasture syndrome) or by cellular immune reactions. Through various mediator systems, these immunologic processes lead to the pathologic–anatomic basic patterns of glomerular lesions (exudation, intracapillary, and extracapillary proliferation, thickening of the basement membranes, necrosis, and sclerosis). These glomerular changes cause the clinical and laboratory findings found with glomerulopathies.

Nonimmunologic Factors. Glomerulopathies of nonimmunologic origin are found in diabetes mellitus (Kimmelstiel–Wilson lesion of the glomeruli), AL amyloidosis, hemolytic–uremic syndrome, hereditary nephritis (Alport syndrome), and Fabry disease (hereditary β-galactosidase deficiency).

The glomerular lesion causes an increased permeability of the glomerular capillaries and leads to pathologic urine findings with hematuria, proteinuria, and cylindruria. The loss of nephrons due to proliferation, necrosis, or fibrosis leads, in addition, to the development of renal hypertension and progressive renal insufficiency.

Clinical Syndromes. Based on the predominant clinical and laboratory findings, and on the course of disease, five different clinical syndromes, partly occurring simultaneously, can be defined. These can be observed in primary and secondary glomerulopathies (Tab. 29.**17**):

- acute nephritic syndrome
- nephrotic syndrome
- rapidly progressive glomerulonephritis (RPGN)
- asymptomatic hematuria/proteinuria
- chronic glomerulonephritis.

The most important differential diagnostic principle in case of evidence of one of these five clinical syndromes is the exclusion of a secondary glomerulopathy in connection with systemic diseases, infections, or malignancies.

Acute Nephritic Syndrome

Clinical Features. Acute nephritic syndrome is characterized by:

- sudden onset of disease, frequently after preceding infections
- presence of a nephritic sediment (microhematuria or macrohematuria, dysmorphic erythrocytes, and red cell casts) and of variable proteinuria
- decreased GFR
- sodium and water retention with volume expansion and hypertension
- edema and oliguria.

Fluid retention occurs due to the reduced GFR and can, in addition to the edema, cause dyspnea/orthopnea due to pulmonary congestion, as well as severe hypertension. The kidneys can swell transiently and present with percussion dolence and flank pains. Due to nephronal hematuria, the urine can appear dark red or dark brown. The proteinuria is not severe and only rarely in the nephrotic range.

Acute renal failure can occasionally have a serious course and lead to a temporary need for dialysis. However, all symptoms of the disease are not always present, i. e., the complete clinical picture of acute nephritic syndrome. In focal or segmental limitation of the glomerulopathies sometimes only a glomerular hematuria is found.

Causes. The causes of acute nephritic syndrome are summarized in Tab. 29.**18**. These include:

- infections
- autoimmune diseases and vasculitides.
- primary idiopathic glomerulonephritides.

The spectrum of *postinfectious glomerulonephritides* has significantly changed in the last few decades. Classical poststreptococcal glomerulonephritis is now only rarely observed in Western countries, while, conversely, glomerulonephritides associated with *Staphylococcus and Gram-negative bacterial infections* are more frequent and can sometimes have a severe course. In contrast to classical poststreptococcal glomerulonephritis, these postinfectious glomerulonephritides occur especially in older patients with impaired immunocompetence, and in alcoholics, diabetics, and drug addicts. The location of infection can be quite variable and is not merely confined to the oropharynx and the skin (lung, endocardium, multiple localizations of the infection). The prognosis has become worse in recent years.

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The criteria for an unfavorable prognosis include age > 50 years, occurrence of purpura, and endocarditis as original disease.

Poststreptococcal Glomerulonephritis as Paradigmatic Example of Acute Nephritic Syndrome

Poststreptococcal glomerulonephritis is more frequently observed in children than in adults, although it can occur at any age. It is also more frequent in men than in women. It is an acutely occurring and mostly spontaneously abating immune-complex nephritis, which occurs after a symptom-free interval of six to 30 days following an infection with β-hemolytic Group A streptococci. Etiogenic diseases are pharyngitis and impetigo, less frequently otitis media, and infected skin ulcerations.

Laboratory Findings. Laboratory analyses show a proteinuria of (mostly) < 3.5 g/24 h, and a nephritic sediment. Retention parameters (creatinine and BUN) are frequently elevated. Complement values CH_{50} and C3, and to a lesser extent C4, are reduced. Cryoglobulins and circulating immune complexes can also be found. Increasing antistreptolysin O (ASLO) as well as anti-Dnase B antibody titers are typical, but are not always present.

Histology. Histologically, a diffuse proliferative glomerulonephritis with infiltration of neutrophils and monocytes in the glomeruli is found in the renal biopsy in poststreptococcal glomerulonephritis (Fig. 29.**19a**). Granular deposits of IgG and C3 can be identified by immunofluorescence staining (Fig. 29.**19b**). In the electron microscopic examination, electron dense subepithelial cluster-shaped deposits (so-called "humps") are detected, which are a typical sign of poststreptococcal glomerulonephritis (Fig. 29.**19c**).

Differential Diagnosis. When poststreptococcal glomerulonephritis is suspected, all glomerulonephritides associated with an acute nephritic syndrome have to be considered in the differential diagnosis. Often, fever and the involvement of other organ systems indicate the presence of a systemic disease or of a systemic vasculitis. In addition, fever, in combination with a nephritic syndrome, is found in numerous other infections. A frequently overlooked cause of nephritic syndrome is bacterial endocarditis. In particular, in the presence of suspicious cardiac auscultation findings, repeated blood cultures are required.

Table 29.**18** Most important causes of acute nephritic syndrome

Parainfectious and postinfectious causes
- acute poststreptococcal glomerulonephritis (after pharyngeal or skin infection with β-hemolytic Group A streptococci)
- glomerulonephritis in the context of other acute pharyngeal or skin infections
- glomerulonephritis in the context of acute and subacute bacterial endocarditis
- glomerulonephritis in the context of visceral abscesses
- glomerulonephritis in cases of infected ventriculo-atrial shunt (shunt nephritis)
- immune-complex nephritis in the context of other bacterial, viral (hepatitis B and C), or parasitic infections

Autoimmune causes
- systemic vasculitides (Henoch–Schönlein purpura)
- systemic lupus erythematosus
- cryoglobulinemia

Primary idiopathic glomerulonephritides
- IgA nephropathy and other mesangial proliferative glomerulonephritides
- membranoproliferative glomerulonephritis

Membranoproliferative Glomerulonephritides

Membranoproliferative glomerulonephritides are a rare cause of nephritic syndrome. Clinically, they manifest with severe proteinuria and a nephritic urinary sediment. This disease is associated with severe glomerular inflammation and can manifest as a nephritic or (due to severe proteinuria) a nephrotic syndrome with edema. These glomerulonephritides with intermittent exacerbations can occur primarily, but are also observed secondarily with systemic immune complex diseases e. g., lupus nephritis or cryoglobulinemia. The latter is frequently seen in infections with *Hepatitis C virus*. Complement consumption can typically be documented (reduced C3 and C4).

Henoch–Schönlein Purpura

This disease is characterized by the acute occurrence of a palpable purpura (Fig. 29.**20**), arthralgia and arthritides, abdominal pain, intestinal hemorrhages, and renal disease, the latter manifesting with a nephritic urinary sediment. In the renal biopsy an immune complex nephritis with IgA and complement deposition is typically identified. The disease occurs frequently in children, but is also observed in adulthood. After an acute phase it remits spontaneously within weeks to months, although chronic courses, particularly in adults, are described. The diagnosis can be verified with a skin biopsy, which shows a leukocytoclastic vasculitis with IgA deposits.

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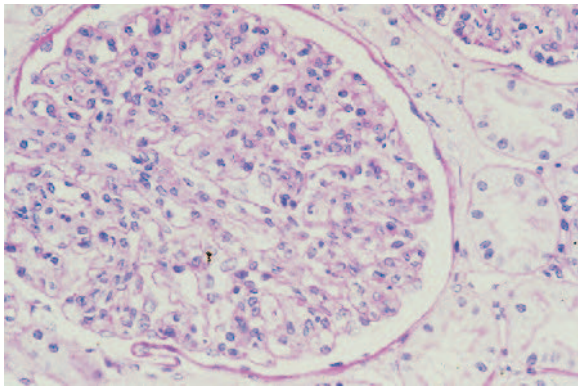

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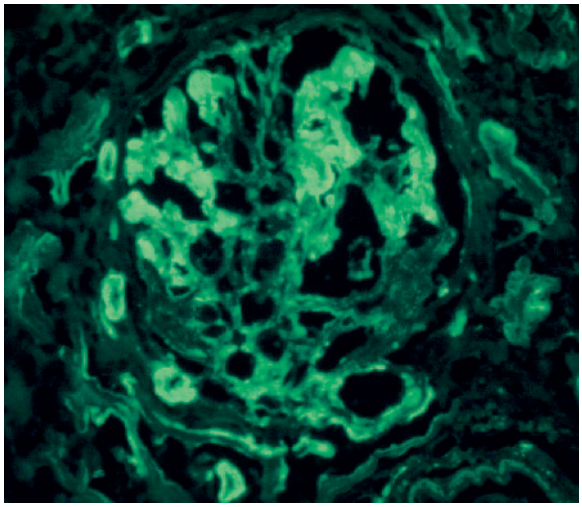

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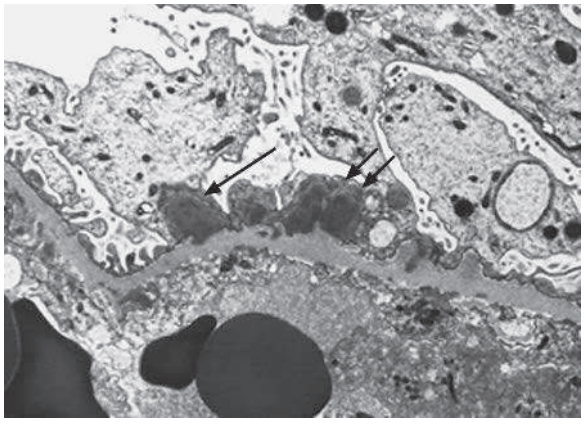

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Fig. 29.**19** Renal biopsy findings in poststreptococcal glomerulonephritis.
a Light microscopic finding with exudative glomerulonephritis.
b Immunofluorescence staining with immune complex depositions (IgG).
c Electron microscopic finding showing the typical subepithelial electron dense deposits (humps).

Fig. 29.**20** Palpable purpura in Henoch–Schönlein vasculitis.

Nephrotic Syndrome

Clinical Features. Nephrotic syndrome is defined by *massive proteinuria*, *hypoalbuminemia*, and *edema*. The cause of nephrotic syndrome is an increased permeability of the glomerular capillaries for plasma proteins with consecutive albuminuria. In clinical routine, nephrotic syndrome is indicated by protein excretion > 3.5 g/24 h. In addition, severe proteinuria, hypoalbuminemia, hyperlipidemia, as well as lipiduria, are also observed with nephrotic syndrome. A proteinuria of this extent can remain asymptomatic for a long time. Only when the protein loss by the kidneys exceeds the compensatory increase of protein synthesis by the liver can the clinical consequences of the proteinuria develop. Among these are:

- edema (malleolar and crural edema, lid edema, ascites)
- hyperlipoproteinemia and consecutive diseases
- tendency to thromboses and thromboembolic complications
- loss of immunoglobulins in the urine with tendency to infections
- prerenal azotemia, sensitivity to diuretics, rarely acute kidney failure.

Edema develops due to reduced oncotic pressure in the plasma, whereby fluid from the vascular compartment permeates into the interstitium. The resulting reduction of the intravascular volume stimulates the renin–angiotensin–aldosterone system, as well as the sympathetic nervous system, and leads to the release of antidiuretic hormone (ADH). This results in increased salt and water retention by the kidney, which further promotes the development of edema. Edema in nephrotic patients not only collects in dependent areas, e. g., the malleolar and crural regions, but is also

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found in the periorbital region (Fig. 29.**21**) and in the hands. These latter parts of the body are usually not edematous in patients where the edema is associated with heart or liver failure.

It is important to distinguish edema occurring with nephrotic syndrome from edema occurring in acute nephritic syndrome.

Tab. 29.**19** shows additional clinical and laboratory findings that enable a differential diagnosis between these two types of edema.

Hyperlipidemia in nephrotic syndrome develops due to increased hepatic lipoprotein synthesis and is characterized by increased cholesterol (VLDL, LDL) and also by increased triglycerides. Hyperlipidemia accompanies lipiduria, which manifests as free fatty granules in the urinary sediment or as so-called fatty granular cells in degenerated tubular cells. In polarized light these fatty droplets appear as so-called Maltese crosses. A long-standing hyperlipidemia in the nephrotic syndrome represents a risk for atherosclerosis.

In severe nephrotic syndrome various other plasma proteins in addition to albumin are lost. The loss of *immunoglobulins* and certain *complement proteins* (factors B and D) predisposes nephrotic patients to bacterial infections, in particular to pneumococcal pneumonia and peritonitis.

The renal loss of 25(OH) vitamin D-binding globulin implies a *vitamin D deficiency* with tendency to hypocalcemia, osteomalacia, secondary hyperparathyroidism, and renal osteodystrophy. The renal loss of transferrin can lead to microcytic anemia, which responds poorly to ferrotherapy.

Moreover, there is a state of *hypercoagulability* in severe nephrotic syndrome, which can lead to thrombosis of the renal vein or even of the inferior vena cava. In conjunction with these thromboses in nephrotic syndrome, the occurrence of pulmonary embolism is also frequently observed. The state of hypercoagulability is either explained by the renal loss of antithrombin III with its anticoagulatory effect, or by the relative increase of other coagulation factors, e. g., fibrinogen, factor V, VII, VIII, and X. *Renal vein thrombosis* caused by a state of hypercoagulability manifests clinically with unilateral flank pain, asymmetric leg edema, varicocele on the left (the left testicular vein drains into the left renal vein), pulmonary embolism, macrohematuria, and reduced GFR.

A decrease of the GFR is possible (*prerenal azotemia*) due to a reduction of the plasma volume. In exceptional cases *ARF* can occur in nephrotic syndrome, which can be explained by hypoperfusion due to *hypovolemia* and through development of intrarenal edema in severe hypoalbuminemia. Hypovolemia in nephrotic syndrome can, in rare cases, lead to hypotension and shock and also explains the sensitivity to diuretics of some patients.

Fig. 29.**21** Periorbital edema in nephrotic syndrome.

Table 29.**19** Differential diagnosis of edema in nephrotic and acute nephritic syndrome

	Acute nephritic syndrome	Nephrotic syndrome
Edema	+ to ++	++ to +++
Hypertension	Frequent	Seldom
Proteinuria	Moderate	Marked
Urinary sediment	Active (hematuria, dysmorphic erythrocytes, erythrocyte casts)	Depending on lesion unremarkable or slight microhematuria
Renal function	Decreased	Normal or decreased
Serum albumin	Normal or slightly reduced	Markedly reduced
Serum cholesterol	Normal	Increased

Causes. Table 29.**20** lists the most frequent causes of nephrotic syndrome. Again a distinction can be made between primary and secondary glomerulopathies.

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Table 29.**20** Causes of nephrotic syndrome

Primary glomerulopathies (primary nephrotic syndrome)
- minimal-change glomerulonephritis (lipoid nephrosis, nil disease)
- focal and segmental glomerulosclerosis
- membranous glomerulonephritis
- membranoproliferative glomerulonephritis
- hereditary forms: congenital nephrotic syndrome of the Finnish type (CNF)

Secondary glomerulopathies (secondary nephrotic syndrome)
- infections
  - bacterial: poststreptococcal glomerulonephritis, infectious endocarditis, congenital and secondary syphilis, infections of ventriculo-atrial shunt in case of hydrocephalus, leprosy
  - viral: hepatitis B and C, mononucleosis, *Cytomegalovirus*, smallpox, HIV infection
  - protozoa: malaria (in particular quartan malaria), toxoplasmosis
  - parasites: schistosomiasis, filariasis, trypanosomiasis, echinoccocal infection
- drugs: gold, penicillamine, NSAIDs, mercury, captopril, lithium
- systemic diseases: lupus erythematosus, Sharp syndrome (mixed connective tissue disease [MCTD]), rheumatoid arthritis, dermatomyositis, Schönlein–Henoch purpura, primary and secondary amyloidosis, cryoglobulinemia, sarcoidosis, dermatitis herpetiformis
- metabolic diseases: diabetes mellitus type 1 and type 2, familial Mediterranean fever (amyloidosis)
- malignant tumors: Hodgkin disease, non-Hodgkin lymphoma, chronic lymphocytic leukemia, plasma cell dyscrasia (AL amyloidosis, light-chain deposition disease), carcinoma in lung, stomach, colon, breasts, and kidneys
- allergic reactions: insect stings, serum sickness, allergy to pollen
- genetic diseases: Alport syndrome, Fabry disease, nail–patella syndrome, sickle cell disease
- other: preeclampsia, vesico-ureteral reflux, IgA nephropathy, chronic transplant failure

Minimal-Change Glomerulonephritis

Minimal-change glomerulonephritis is the most frequent cause of nephrotic syndrome in childhood. However, the disease can also occur in adults. The disease is characterized by a heavy proteinuria, which is mostly "selective," i. e., it shows predominantly as albuminuria in the urine *protein electrophoresis*.

Renal function is usually normal, although in extremely severe courses acute renal failure can develop. In the kidney biopsy, light microscopy shows unremarkable glomeruli ("minimal change"), the immunofluorescence staining is negative, and under electron microscopy a fusion of the epithelial cell foot processes, but no deposition of immune complexes can be identified.

Spontaneous remissions are quite frequent. The disease responds well to steroid treatment. In adults the course is more serious and the response to therapy is not as good. In these patients it is important to exclude secondary causes e. g., lymphoproliferative diseases. Further causes of minimal-change glomerulonephritis are the administration of nonsteroidal antirheumatic agents or allergies.

Focal Segmental Glomerulosclerosis (FSGS)

Focal segmental glomerulosclerosis (FSGS) can occur as primary glomerulopathy or secondarily in connection with HIV disease, heroin abuse, associated with lymphomas, or, less frequently, in severe obesity. The histologic signs of FSGS are also observed in the advanced stage of many glomerulonephritides or as a consequence of glomerular overload (hyperfiltration).

Patients with FSGS show a distinct nephrotic syndrome. Urine sediment is usually hypocellular, although it can also show microhematuria. FSGS patients are hypertensive and develop a progressive renal insufficiency over several years. Within 10 years about 50% of patients with primary FSGS develop end-stage renal disease. Patients with a more rapid progression are also described. The response to immunosuppression is unfavorable; in many cases a steroid resistance is observed.

Membranous Glomerulonephritis

Membranous glomerulonephritis is found in 30–50% of all biopsies from adults with nephrotic syndrome. It can occur primarily (idiopathically) or is observed secondarily in connection with lupus nephritis, infections (hepatitis B), medications, e. g., gold and D-penicillamine, or associated with tumors. Clinically this disease manifests with edema and proteinuria. Hypertension is found in 25–40% of patients. Urine sediment is often hypocellular, but can present a microhematuria with dysmorphic erythrocytes. The disease can remit spontaneously, but more often persists and CRF can develop over several years.

Histopathologically, a widening of the capillary loops in the glomeruli is found in the kidney biopsy, which is caused by immune-complex deposits in the GBM (Fig. 29.**22**). In immunofluorescence staining IgG and C3 are identified. The complement values in the serum are always normal in membranous glomerulonephritis, although this is an immune-complex disease.

Diabetic Nephropathy

The diabetic nephropathy occurring in diabetes mellitus is a frequent cause of the nephrotic syndrome and of end-stage renal disease in adults. About 30–45% of patients with type 1 diabetes mellitus develop pro-

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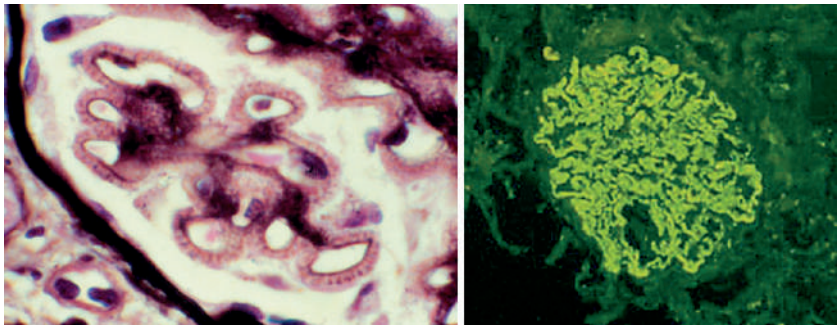

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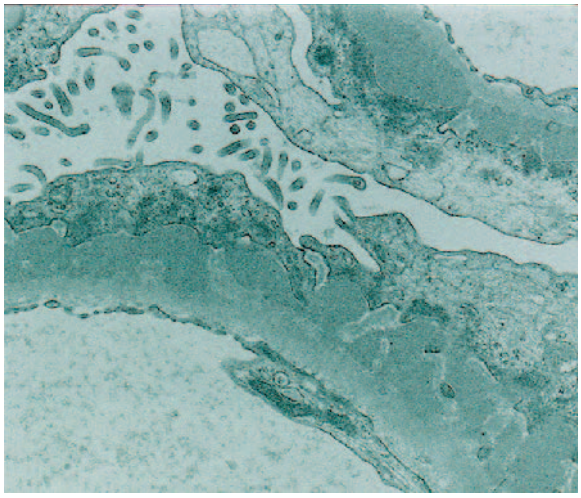

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Fig. 29.**22** Renal biopsy findings in membranous glomerulonephritis.
a Light microscopic finding with thickening of the basement membrane and distinct spikes corresponding to immune-complex deposits.
b Immunofluorescence staining with immune-complex deposits (IgG) in the basement membrane.
c Electron microscopic finding showing typical electron dense deposits in the basement membrane.

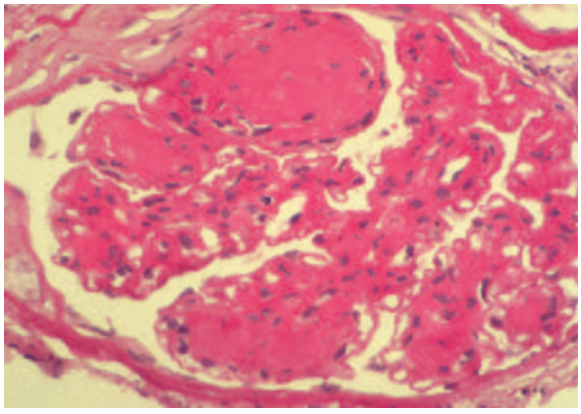

Fig. 29.**23** Diabetic nephropathy (nodular glomerulosclerosis, Kimmelstiel–Wilson type).

teinuria after 10–30 years of disease, and renal insufficiency some years later. In patients with type 2 diabetes mellitus, nephropathy is also frequently observed after many years of insufficiently managed diabetes and hypertension. The damage to the glomeruli occurs through nonimmunological mechanisms and is characterized histopathologically by nodular glomerulosclerosis (Kimmelstiel–Wilson) (Fig. 29.**23**).

Course. Although the first pathologic–anatomic changes of the kidneys become visible one to three years after the onset of diabetes, a distinct proteinuria with nephrotic syndrome can only be expected after approximately 10–20 years of disease (Tab. 29.**21**). This can be preceded by microalbuminuria (albumin excretion of 30–300 mg/day), evidence of which predicts the later occurrence of nephropathy and, on a prognostic level, must be taken seriously. After the onset of a constant proteinuria, slowly progressive decrease of the GFR and development of end-stage renal failure follows. Timely administration of angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists can significantly slow the progression of renal failure. Hence, at this time the occurrence of end-stage renal failure can be deferred to later periods of life.

Diagnosis. The diagnosis of diabetic nephropathy in patients with type 1 and type 2 diabetes mellitus with proteinuria, hypertension, nephrotic syndrome, and progressive decrease of the GFR after 10–30 years of disease can be established without further diagnostic measures. The simultaneous evidence of diabetic retinopathy supports the diagnosis. However, in type 2 diabetics with bioptically identified *diabetic nephropathy*, fundus changes can be less distinct or even be absent. A nephropathy with a cause other than the diabetes mellitus should be considered when:

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Table 29.**21** Stages of diabetic nephropathy

Stage	Designation	Time elapsed	GFR	Blood pressure	Albuminuria
I	Hyperfiltration	At the time of diagnosis	↑	Type 1 mostly ⇔ Type 2 often ↑	None
II	Latency	0–5 years	⇔	⇔ to ↑	None
III	Microalbuminuria	5–10 years	⇔ to ↓	⇔ to ↑	30–300 mg/24 h
IV	Macroalbuminuria	10–15 years	↓	↑ to ↑ ↑	> 300 mg/24 h
V	Renal failure	15–30 years	↓ ↓ to ↓ ↓ ↓	↑ to ↑ ↑	Proteinuria often in the nephrotic range

Table 29.**22** Classification of immunologically mediated RPGN

ANCA vasculitis
- c-ANCA: Wegener disease
- p-ANCA: microscopic polyangiitis
- rare: Churg–Strauss syndrome, panarteritis nodosa

Anti-GBM nephritis
- renal-limited form
- pulmonary–renal syndrome (Goodpasture syndrome)
- anti-GBM nephritis occurring after transplantation in patients with Alport syndrome

Immune-complex glomerulonephritis
- infectious and postinfectious glomerulonephritides
- autoimmune diseases (lupus nephritis, cryoglobulinemia, Henoch–Schönlein purpura)
- primary glomerulonephritides (IgA nephritis, membrano-proliferative glomerulonephritis)

Idiopathic pauci-immune RPGN

- ➤ proteinuria appears less than 10 years or more than 30 years after the onset of type 1 diabetes
- ➤ other secondary complications of diabetes are absent
- ➤ asymmetrical kidney size is present
- ➤ GFR decreases rapidly and creatinine levels rise rapidly after beginning of treatment with ACE inhibitors, particularly in type 2 diabetes patients (suspicion of renal artery stenosis).

Rapidly Progressive Glomerulonephritis (RPGN)

Rapidly progressive glomerulonephritis (RPGN) is characterized by a range of symptoms from a subacute decrease in the GFR until dialysis becomes necessary within weeks to months. The disease can be confined to the kidneys or affect other systems, e. g., in the form of a pulmonary–renal syndrome.

In the context of a RPGN, a rapid decrease in the GFR or a progressive increase in creatinine is a medical emergency and requires immediate further clarification.

Clinical Features. The cardinal symptoms of RPGN include:
- ➤ nephritic urinary sediment with glomerular hematuria, red cell casts, and variable proteinuria (usually < 3.5 g/day)
- ➤ rapid decrease of GFR with occurrence of progressive renal insufficiency occurring within weeks
- ➤ sonographically normal-sized kidneys
- ➤ under light microscopy: lesion of the extracapillary proliferation with crescent formation
- ➤ under immunofluorescence microscopy: variable findings, indicating the possibility of heterogeneous pathogenesis
- ➤ clinical (arthralgia, purpura, pulmonary symptoms) and immunologic (ANCA, anti-GBM antibodies, ANA) findings frequently indicating an underlying vasculitis or autoimmune disease
- ➤ low tendency to spontaneous remission.

Patients with RPGN often present with nonspecific symptoms, e. g., reduced general condition, weight loss, and fever. Since the cause of the RPGN is mostly a vasculitis or an autoimmune disease, various other systems, in addition to the kidney, can be involved. These include skin, joints, upper respiratory tract, lung, other visceral organs, as well as the peripheral and central nervous system. Clinically, the extrarenal symptom complex manifests with arthralgia, eye symptoms (iritis, uveitis, scleritis), rhinitis and sinusitis, neuritis multiplex, and palpable purpura. If pulmonary infiltration or hemoptysis occur in the context of the RPGN, the prognostically significant differential diagnosis between pulmonary–renal syndrome in ANCA positive vasculitis and Goodpasture syndrome must be considered.

Causes. The causes of RPGN are manifold. A broad differential diagnosis must be established. Immunologic diagnostic tests need to be performed urgently, along with

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optical immunofluorescence testing (kidney biopsy) to narrow down the differential diagnosis presented in Tabs. 29.**22**, 29.**23**.

RPGN includes *microscopic polyangiitis* (p-ANCA positive), *Wegener disease* (c-ANCA positive), *anti-GBM nephritis*, as well as further idiopathic types with or without immune-complex deposition in the glomeruli. With every clinical suspicion of RPGN (active sediment, rapid decrease of GFR) a renal biopsy should be performed when there is no contraindication, in addition to the immunologic tests. Histopathologically, RPGN is characterized by an extracapillary proliferative glomerulonephritis with crescent formation. In immunofluorescence staining of the kidney usually no immune complexes are identified (so-called pauci-immune glomerulonephritides). In anti-GBM nephritis linear deposits of antibodies along the GBM can be identified.

Table 29.**23** Extended differential diagnosis of RPGN

Disease	Characteristics
Hemolytic–uremic syndrome	– hemolytic anemia with detection of fragmentocytes – elevated LDH and bilirubin – thrombocytopenia – subacute renal failure
Scleroderma renal crisis	– in the context of scleroderma
Cholesterol emboli	– triggered by vascular catheter interventions or in the context of anticoagulant use in patients with severe atheromatosis

Wegener Disease

Wegener disease (Wegener granulomatosis) represents a necrotizing vasculitis of medium-sized and small vessels. The disease occurs mostly between the 50th and 70th years of life and is found slightly more frequently in men than in women. There can be an isolated involvement of the kidneys, but in most cases the ear, nose, and throat (ENT) region and the lungs are affected as well. The disease can manifest in other organs, including joints (arthralgia and arthritides), muscles (myalgia, myositis), eyes (conjunctivitis, episcleritis, uveitis), skin (palpable purpura and ulcerations), nervous system (mononeuritis multiplex), and heart (pericarditis and myocarditis, arrhythmia).

Course. At the start, nonspecific complaints can predominate. The disease is often initiated by an infection of the upper respiratory tract. General symptoms such as fatigue, inappetence, slight fever, and joint and muscle pains, take a protracted course and the symptoms of the upper respiratory tract persist. Chronic sinusitis, rhinitis, otitis media, as well as destructive changes of the nasal septum with formation of a saddle nose are typical signs of a granulomatous affection of the ENT region. An atypical pulmonary infiltration, which is visible on the radiograph, can simulate an infection and delay the timely diagnosis of Wegener granulomatosis. Chronic bronchitic complaints, as well as pulmonary hemorrhages with hemoptysis, can persist over weeks. Only during the further course does the renal symptomatology with development of RPGN become evident.

Laboratory Findings. In addition to the nonspecific increase of inflammatory parameters (ESR, C-reactive protein (CRP), serologic tests usually reveal c-ANCA in Wegener disease (Fig. 29.**24a**) (antibodies against proteinase 3). The complement values (C3, C4) are normal. Renal involvement can initially be mild, but can rapidly progress with increase of the retention parameters in the serum. The urine sediment shows proteinuria that is usually in the nonnephrotic range, as well as nephritic sediment. To confirm the diagnosis a renal biopsy or a biopsy from other affected tissues should be performed. In addition to the extracapillary proliferative glomerulonephritis, granulomatous lesions are often found in the kidneys.

Microscopic Polyangiitis

Microscopic polyangiitis (polyarteritis) is a pauci-immune (i. e., occurring without immune-complex formation and complement consumption) vasculitis of small vessels (capillaries, arterioles, venules). It frequently manifests in isolation in the kidneys with proteinuria, nephritic urinary sediment, and RPGN. Involvement of the pulmonary capillaries is frequent (approximately 50% of cases) and manifests with pulmonary hemorrhages. However, there is no granulomatous involvement of the upper and lower respiratory tracts. More than 70% of patients with microscopic polyangiitis show p-ANCA (Fig. 29.**24b**).

Churg–Strauss Syndrome

Churg–Strauss syndrome, which is similar to Wegener granulomatosis, is characterized by additional asthmatic complaints, pulmonary infiltration with eosinophilia, and increased IgE. Renal involvement is less frequent in Churg–Strauss syndrome than in Wegener disease. p-ANCA are found in approximately 60% of cases, c-ANCA in only 10%; in 30%, the ANCA results are negative.

Panarteritis Nodosa (PAN)

Polyarteritis (panarteritis) nodosa (PAN) is a systemic necrotizing arteritis of the visceral vessels. This disease is very rare and can be associated with hepatitis B. Besides the renal vessels, further visceral vessels can be in-

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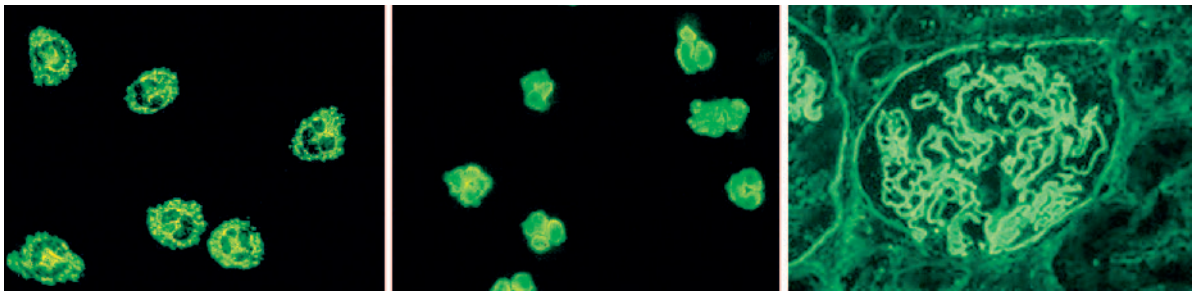
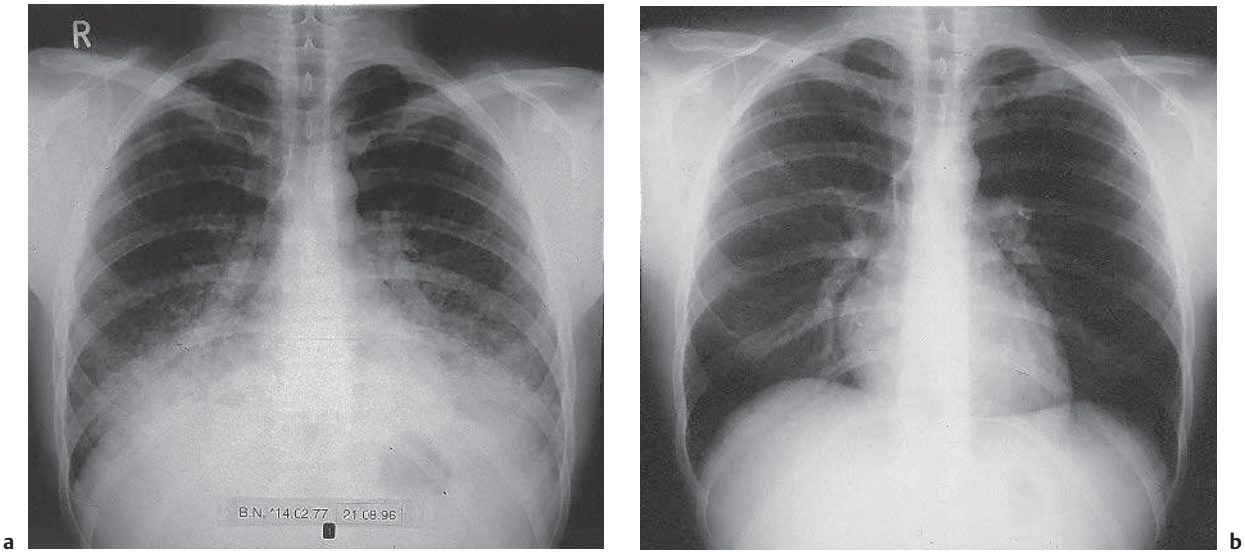


a b c

Fig. 29.**24** Indirect immunofluorescence staining with the serum from patients with RPGN.
a Positive cytoplasmic staining of neutrophils (c-ANCA).
b Positive perinuclear staining of neutrophils (p-ANCA).
c Positive anti-GBM antibody staining in a renal biopsy of a patient with Goodpasture syndrome.



a b

Fig. 29.**25** Pulmonary infiltrates in a 19-year-old patient with Goodpasture syndrome.
a Before therapy
b After therapy

volved in PAN. In contrast to microscopic polyangiitis, PAN does not cause RPGN or pulmonary hemorrhages. The nodular inflammation of the middle-sized vessels leads to the development of pseudoaneurysms in the kidneys and other visceral organs (bowel). These pseudoaneurysms can rupture spontaneously and lead to infarctions and severe hemorrhages (hematuria, flank pains, intestinal hemorrhage). PAN patients often show renovascular hypertension.

Goodpasture Syndrome

Goodpasture syndrome is an autoimmune disease with production of antibodies against an antigen (anti-GBM antibody) localized in the glomerular basement membrane. The C-terminal end of the α_3 chain of type IV collagen has been identified as the antigen. This rare disease predominantly afflicts men between the 20th and 40th years of life and is characterized by:

- development of RPGN with progressive creatinine increase and active urine sediment
- occurrence of pulmonary hemorrhage with hemoptysis and radiologic evidence of rapidly changing infiltrations (Fig. 29.**25**)
- evidence of circulating anti-GBM antibodies
- light-microscopic evidence of an extracapillary proliferative glomerulonephritis with crescent formation (less frequently focal or segmental proliferative glomerulonephritis) and in immunofluorescence microscopy, evidence of linear IgG deposits along the glomerular basement membranes (see Fig. 29.**24c**)
- low tendency to spontaneous remission with occurrence of renal insufficiency and the need for dialysis in $>80\%$ of patients within one year, in the absence of a timely start of aggressive therapy.

Clinically, the lung is often affected, manifesting with hemoptysis (alveolar hemorrhage) and rapidly changing infiltrations (Fig. 29.**25**). Hemoptysis can precede the

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development of glomerulonephritis. The presence of Goodpasture syndrome should be considered in every patient with acute glomerulonephritis (active sediment), ARF with rapid creatinine increase, and pulmonary hemorrhage.

Differential Diagnosis. The combination of symptoms, which is summarized by the term pulmonary–renal syndrome, suggests in particular an ANCA-positive vasculitis (Wegener granulomatosis or microscopic polyangiitis) in the differential diagnosis. The identification of ANCA and anti-GBM antibodies must take place without delay. In addition, a renal biopsy must be performed, since, with the occurrence of RPGN and pulmonary hemorrhages, the findings obtained by immunofluorescence microscopy allow a differential diagnosis between vasculitis and Goodpasture syndrome.

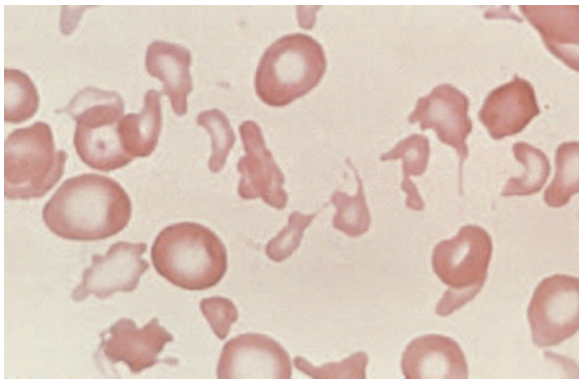

Fig. 29.**26** Fragmentocytes in hemolytic–uremic syndrome.

Differential Diagnosis of RPGN and Exclusion of Other Diseases with Rapid GFR Decrease

In addition to the aforementioned diseases, there are further diseases that must be differentiated from RPGN. Laboratory analyses, e. g., ANCA, anti-GBM antibodies, antibodies against DNA, cryoglobulins, markers of a streptococcal infection, hepatitis serology, and complement factors, are helpful in the differential diagnosis of RPGN. The performance of a kidney biopsy is helpful in the presence of atypical RPGN.

Cholesterol Embolism. These can usually be differentiated from RPGN by the medical history and clinically. They occur predominantly in men > 60 years, in whom preexisting hypertension and arteriosclerosis are known. The clinical picture is characterized by a progressive deterioration of the renal function developing usually one to three weeks after catheter examinations of the aorta, cardiovascular surgery, or induction of anticoagulation. Clinically, there are analogies to the clinical picture of systemic vasculitis with evidence of livedo reticularis (marble skin; see Fig. 29.**11a**) and microemboli in the region of the toes (see Fig. 29.**11b**). Immunologic findings (ANCA), however, are negative, though complement factors may be reduced in patients with cholesterol emboli, and the occurrence of eosinophilia is also possible.

Scleroderma. Progressive systemic sclerosis is a heterogeneous disease of unclear etiology, which is characterized by uncontrolled connective tissue proliferation in the skin and the visceral organs. In addition, the small vessels are thickened and stenosed. Renal involvement can be mild (slight proteinuria, slight creatinine increase), but can decompensate in the sense of a scleroderma renal crisis, leading rapidly to a progressive renal insufficiency with need for dialysis, and to hypertensive decompensation.

Hemolytic–Uremic Syndrome (Thrombotic Microangiopathy). This clinical picture can be differentiated because of negative immunologic findings, the presence of distinct hemolysis with evidence for fragmentocytes (Fig. 29.**26**) in the blood smear, and accompanying thrombopenia.

Asymptomatic Urinary Abnormalities

Frequent manifestations of glomerulopathies include *proteinuria* and/or *hematuria* in otherwise asymptomatic patients. These findings are usually detected coincidentally in urine analyses with dipsticks. Less frequently, patients are seen in consultation because of a self-diagnosed recurrent macrohematuria.
Possible constellations are:

- ➤ an isolated proteinuria with a normal urine sediment
- ➤ glomerular hematuria with or without proteinuria.

Tab. 29.**24** summarizes the most important differential diagnoses of these asymptomatic urine findings.

Table 29.**24** Differential diagnosis of asymptomatic proteinuria or microhematuria

Proteinuria	Microhematuria
– Transient proteinuria in case of fever or physical exercise – Orthostatic proteinuria – Chronic glomerulonephritis	– IgA nephropathy – Alport syndrome – Thin basement membrane disease – Nail–patella syndrome – Hypercalciuria/hyperuricosuria

Isolated Proteinuria. An isolated, mild proteinuria (< 2 g/24 h) with normal urinary sediment and without the presence of accompanying edema and hypertension should be confirmed by repeated measurement and

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should also be quantified. A mild proteinuria can be classified depending on the body position into:

- *transient or intermittent proteinuria:* harmless finding, evidence of proteinuria mostly with fever or following physical activity
- *orthostatic proteinuria:* dependent on the body position and with marked decrease of protein excretion in the morning urine after nocturnal bed rest
- *persisting proteinuria:* not dependent on body position.

The three forms of proteinuria can occur with or without structural changes of the glomerular capillaries. Due to the favorable long-term prognosis, a morphologic differentiation by means of kidney biopsy is usually unnecessary.

Glomerular Hematuria with or without Proteinuria. In case of microhematuria or macrohematuria the following are considered as reliable signs for the presence of glomerular hematuria:

- evidence of red cell casts in the sediment
- detection of $>70\%$ dysmorphic red cells or $>5\%$ acanthocytes in the urine sediment by phase contrast microscopy
- concomitant proteinuria of >2 g/day.

Differential Diagnosis of Nonglomerular Bleeding. When none of the aforementioned concomitant phenomena (in the presence of hematuria) can be confirmed, the search for nonglomerular renal and extrarenal bleeding sources is mandatory. The required diagnostic tests are dependent on the *age of the patient*. In all patients in whom clinical history, physical examination, and evaluation of the urinary sediment provide no reliable indication for a bleeding source in the region of the lower urinary tract, *sonography* is recommended for the exclusion of tumors, cysts, and stones.

In *young patients* (<35 years) tumors of the urinary tract are rare. Therefore, in patients <35 years of age, exclusion of a *metabolic cause* of the hematuria (hypercalciuria, hyperuricosuria) is necessary. If in first degree relatives microhematuria is also identified, the presence of thin basement membrane nephropathy or Alport syndrome is possible. The indication for further examinations such as an intravenous urogram (medullary sponge kidneys) or a renal biopsy (most frequent diagnosis is IgA nephropathy) should be considered conservatively.

> In patients >35 years of age, the examinations serve initially for the exclusion of a tumor in the lower urinary tract, particularly in at-risk patients (abuse of analgesics, nicotine).

If a tumor can be excluded with the aforementioned examinations, further investigation for the exclusion of a metabolic cause of hematuria is recommended as in younger patients.

Differential Diagnosis of Glomerular Hematuria. The diagnosis of a glomerular hematuria opens a broad differential diagnosis, since practically all glomerular diseases can manifest initially solely with hematuria. In particular the following should be mentioned:

- *proliferative* diseases of the glomeruli
- *nonproliferative* diseases of the glomeruli
- *familial diseases* with glomerular hematuria.

IgA Nephropathy

A frequent cause of glomerular hematuria is IgA nephropathy (Berger disease). This disease occurs predominantly in men between the 20th and 30th years of life. A microhematuria is often diagnosed upon routine examination, or patients consult a physician because of recurrent macrohematuria occurring typically two to three days after a nonspecific infection of the upper respiratory tract.

Evidence of IgA. In approximately 50% of patients with IgA nephropathy, increased IgA levels are measurable in the serum. However, this finding is not pathognomonic for this disease, since increased IgA is also observed in chronic alcoholics and in patients with systemic lupus erythematosus and Henoch–Schönlein disease. This statement is equally true for extrarenal IgA depositions in the skin. Some patients with IgA nephropathy develop in the course of their disease chronic renal insufficiency, renal hypertension, or, less frequently, a nephrotic syndrome. Confirmation of the diagnosis is only possible by renal biopsy. Histopathologically, a mesangioproliferative glomerulonephritis is found with evidence for IgA in the mesangium by immunofluorescence microscopy (Fig. 29.**27**).

Differential Diagnosis. On the basis of the typical time course the differential diagnosis versus acute poststreptococcal glomerulonephritis is simple. In IgA nephritis hematuria occurs two to three days after infections of the upper respiratory tract, in poststreptococcal glomerulonephritis the interval between streptococcal infection and renal symptoms is between six and 28 days. The clinical signs (edema, hypertension) and laboratory findings (increased antistreptolysin titer, reduction of complement factors), which are additionally observed in acute poststreptococcal glomerulonephritis, further facilitate the differentiation from IgA nephritis.

Congenital Diseases with Hematuria

Alport Syndrome. Hereditary nephritis (Alport syndrome) is a genetic progressive nephropathy, which is frequently associated with deafness of the inner ear and other extrarenal symptoms (Tab. 29.**25**). The disease is predominantly inherited via the X chromosome and manifests with structural changes of the GBM due to disturbed formation of type IV collagen. A severe course

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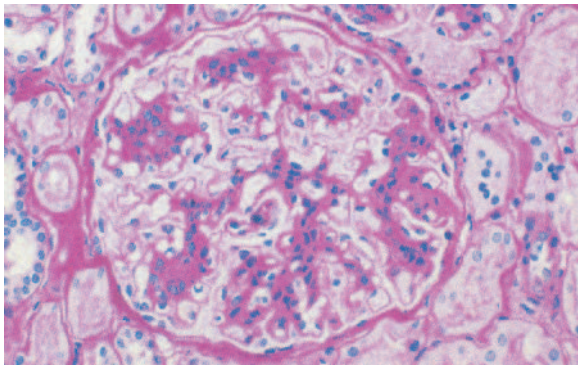

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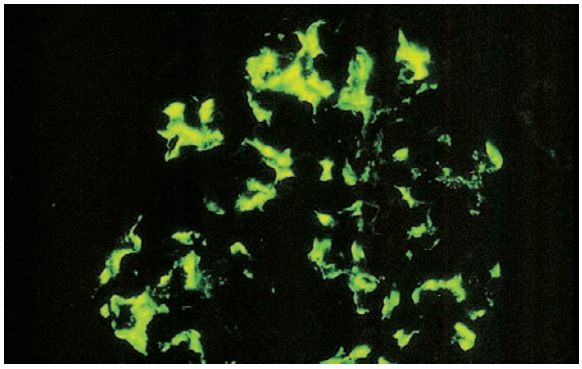

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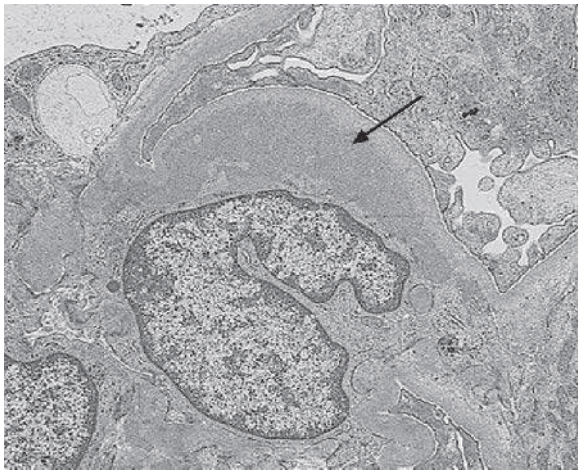

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Fig. 29.**27** Renal biopsy findings in IgA nephropathy.
a Light microscopic finding with increased matrix and cell proliferation.
b Immunofluorescence staining for mesangial IgA.
c Mesangial deposition of electron dense material (arrow).

with development of nephrotic syndrome and/or progressive renal failure is more frequently observed in men than in women. The diagnosis of hereditary nephritis is based on:

- a positive family history (nephropathy, deafness particularly in male family members)
- the combined occurrence of a nephropathy together with the extrarenal symptoms mentioned in Tab. 29.**25**
- audiometry, which is able to detect high-frequency deafness that is clinically not apparent
- the renal biopsy with typical lamellar splitting of the GBMs visible by electron microscopy and the evidence of lipid-containing foam cells in the interstitium.

Thin Basement Membrane Nephropathy. Patients in whom a persisting familial hematuria (benign familial hematuria) occurs can have thin basement membrane nephropathy. Characteristic of this benign disease are:

- presence of glomerular hematuria in patients with normal renal function and only mild proteinuria (< 1.5 g/day)
- occasional flank pain
- familial occurrence of the disease.

Table 29.**25** Clinical manifestations of hereditary nephritis (Alport syndrome)

Renal symptoms
– microhematuria and macrohematuria
– proteinuria/nephrotic syndrome
– slowly progressive renal failure
Extrarenal manifestations
– ears: labyrinthine hearing loss, in particular in the high frequency range
– eyes: cataracts, myopia induced by lenticonus and keratoconus

Similar to Alport syndrome, a narrowing of the GBM is found as a cause of the hematuria. It is possible that this disease represents a variant form of Alport syndrome, though with a more favorable prognosis.

Nail–Patella Syndrome. Nail–patella syndrome is a congenital disease with changes in bones, nails, and kidneys. Clinically dysplastic or hypoplastic nails are found on the fingers and toes, and a missing or diminished patella, and further osseous dysplasias (iliac horns), as well as renal changes (histologically nonspecific glomerulosclerosis and mesangial hypercellularity) are ob-

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served. The involvement of the kidneys is manifested in the form of mild proteinuria and hematuria, which is usually first detected in adolescence. The occurrence of a nephrotic syndrome is rare (in approximately 10% of patients), as is the development of end-stage renal failure.

Chronic Glomerulonephritis

Clinical Features. Chronic glomerulonephritis is a possible consequence of all primary and secondary glomerulonephropathies. The term indicates a persistence of the described clinical syndromes. A frequent final stage of chronic glomerulonephritis is the development of end-stage renal insufficiency.

In some patients, one of the aforementioned clinical syndromes has been known for years and the glomerular lesion has possibly been identified by a renal biopsy. In numerous patients, however, the clinical history is silent. The disease is diagnosed incidentally, e.g., in the context of an employment or insurance examination or check-up, when an unusual urine finding (hematuria, proteinuria) is noted. In a few patients, the practitioner is only consulted because of increasing anemia, hypertension, or other uremic symptoms, when an advanced stage of renal failure has already been reached. Any acute glomerulonephritis, which occurred previously, is mentioned only exceptionally in the clinical history.

Prognosis. When a creatinine increase is already measurable at the time of diagnosis in sonographically small kidneys, the prognosis is unfavorable. End-stage renal failure must be expected within months or years. Occasionally, however, patients with compensated renal insufficiency are observed during longer periods of time with lacking or low tendency to progression.

Diagnostic Procedures. During the early stage of chronic glomerulonephritis the diagnostic measures listed in the aforementioned "clinical syndromes" serve, in the first place, to exclude a basic disease that is accessible to therapy (systemic lupus erythematosus, infection, drug exposition). In the final stage of chronic glomerulonephritis with ultrasonographic evidence for small kidneys, further diagnostic testing with a renal biopsy becomes unnecessary, since therapy is limited to symptomatic measures and a histologic classification of the nephropathy is no longer possible.

Tubulointerstitial Nephritides (TIN)

Numerous noxious substances and diseases can lead to a predominant damage of the tubules and the renal interstitium. In contrast to most glomerulopathies, the causes of a tubulointerstitial nephritis (TIN) can usually be determined by medical history or clinically. The most significant causes of TIN are listed in Tab. 29.**26**.

Table 29.**26** Causes of tubulointerstitial nephropathies

Drugs
– analgesics (chronic interstitial nephritis)
– acute allergic interstitial nephritis
Infections
– protozoa (toxoplasmosis)
– bacteria (diphtheria, streptococci, brucellosis)
– *Rickettsia*
– viruses (in particular *Cytomegalovirus*, Epstein–Barr virus, *Hantavirus*)
Electrolyte disorders
– hypercalcemic nephropathy
– hypokalemic nephropathy
– uric acid nephropathy
Other rare causes
– acute interstitial nephritis with uveitis (TINU syndrome)
– sickle cell anemia
– radiation nephritis
– Balkan nephropathy
– Chinese herb nephropathy
– sarcoidosis
– Sjögren syndrome
– systemic lupus erythematosus

Classification. Based on the time course, a classification of the interstitial nephropathy into *acute* interstitial nephritis and *chronic* interstitial nephritis is possible. Moreover, TIN can occur as a *primary* disease or *secondarily* in conjunction with systemic diseases, e. g., in sarcoidosis. In the course of many glomerular diseases associated with a severe glomerular inflammation, a secondary TIN occurs as a so-called interstitial accompanying nephritis e. g., in lupus nephritis or IgA nephritis. The extent of this accompanying nephritis influences the prognosis of many glomerulopathies and essentially defines the progression of renal failure.

Diagnosis. Diagnosis of an interstitial nephritis is obtained from evidence of a *toxic substance* or an *underlying disease* as mentioned in Tab. 29.**26**. Clues for TIN are also provided by partially *disturbed tubular functions* like reduced excretion of H^+ ions with hyperchloremic metabolic acidosis or reduced potassium secretion in the distal tubule with hyperkalemia and a reduced concentration ability (urine osmolality usually < 400 mOsm/L) with polyuria and nocturia. In addition, there are typical *urinary findings* that are characterized by mild proteinuria and, in particular, by leukocyturia in the urinary sediment (Tab. 29.**27**).

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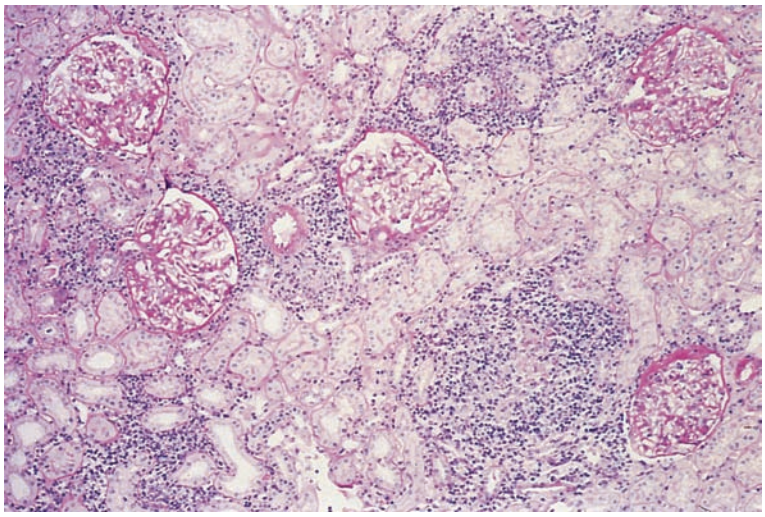

Fig. 29.**28** Mononuclear infiltration of the interstitium in drug-induced acute interstitial nephritis.

Acute Tubulointerstitial Nephritis

Causes. Acute TIN is induced by drugs in the sense of an allergic reaction, or develops in the context of infections. It is not always possible to identify the cause of a primary TIN. TIN caused by drugs occurs as a *dose-independent* hypersensitivity reaction and is frequently coupled with extrarenal manifestations. It has to be distinguished from a *dose-dependent* toxic lesion of the renal interstitium, e. g., by aminoglycoside antibiotics or amphotericin B.

Dose-Independent Hypersensitivity Reaction. Table 29.**28** indicates the most relevant drugs, which, independent of dose, can lead to an interstitial nephritis via a protracted hypersensitivity reaction. The clinical picture is characterized by:

- the occurrence of oliguric (60%) or nonoliguric (40%) acute renal failure following drug exposition
- clinical and laboratory indications for a hypersensitivity reaction (fever, rash, arthralgias eosinophilia, increased IgE, eosinophiluria)
- sonographically enlarged kidneys with inhomogeneous, condensed parenchymal structure
- partial loss of tubular functions
- in many patients, improvement of renal function after discontinuation of the inducing drug.

Diagnosis. The diagnosis is simple when drug exposition, acute renal failure, and symptoms of a systemic allergic reaction like fever, maculopapular rash, arthralgias, and eosinophilia coincide (Tab. 29.**29**). When eosinophils are found in the urine, an acute interstitial nephritis must be considered, particularly with the simultaneous occurrence of extrarenal manifestations. Tubular proteinuria < 1.5 g/day, hematuria, leukocyturia, and eosinophils in the urine support the diagnosis. If in doubt, a renal biopsy should be performed, which typically shows a mononuclear tubulointerstitial infiltration with evidence of eosinophils (Fig. 29.**28**).

Table 29.**27** Urinary findings in interstitial nephritis

Urinary sediment	Few cells, rare erythrocytes, leukocyturia, leukocyte casts, epithelial cell casts, eosinophiluria
Proteinuria	> 1.5 g/day
Urine electrophoresis	Excretion of low molecular weight proteins, e. g., β_2-microglobulin
Glucose	Glucosuria

Table 29.**28** Drugs known to cause acute interstitial nephritis

Antibiotics
– penicillin derivatives (in particular methicillin, but also ampicillin, oxacillin, nafcillin)
– cephalosporin
– rifampicin
– cotrimoxazol and other sulfonamides
– ciprofloxacin and other gyrase inhibitors
Diuretics
– thiazides
– furosemide, bumetanide, torasemide
Nonsteroidal anti-inflammatory drugs
Other drugs
– allopurinol
– cimetidin, very rarely other H_2 blockers
– anticoagulants
– ticlopidine
– mesalazine

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Table 29.**29** Clinical, laboratory, and morphological findings in drug-induced acute interstitial nephritis

Clinical findings
– history of drug exposure
– symptoms of hypersensitivity: rash, fever, arthralgias
– oliguric or nonoliguric acute renal failure
Laboratory data
– blood: rise in creatinine, eosinophilia
– urine: hematuria, leukocyturia, leukocyte casts, eosinophiluria, proteinuria (< 1.5 g/24 h)
Ultrasound examination
– evidence of normal-sized or enlarged kidneys with increased echogenicity and enlargement of the parenchymal rim
Pathology
– interstitial infiltrates, consisting of lymphocytes/plasma cells and eosinophils (see Fig. 29.**27**)
– interstitial edema
– in general, negative immunofluorescence staining
– normal glomeruli

Table 29.**30** Analgesic abuse syndrome

Nephropathy
– pathologic–anatomic findings
– chronic interstitial nephritis
– papillary necroses, possibly with obstructive uropathy
– clinical manifestations
– slowly progressive renal failure
– urinary tract infection and urosepsis
– renal tubular acidosis
– renal sodium loss
– renal hypertension
Urothelial carcinoma
Gastrointestinal symptoms
– ulcerations and erosions with complications (gastrointestinal bleeding, perforations)
Anemia
– renal anemia in case of renal failure
– gastrointestinal blood loss with iron deficiency
– hemolysis
– formation of methemoglobin and sulfhemoglobin
Psychological and psychiatric manifestations
– headaches and other chronic pain symptomatology without obvious cause
– depression
Typical skin color

Course. Acute renal failure occurs within days to weeks after taking the medication. There is no dose dependency. However, the course may not always be typical. Therefore, in each patient with acute renal failure of unclear etiology, the possibility of an acute interstitial nephritis should be included in the differential diagnosis, in particular after taking one of the drugs listed in Tab. 29.**28**.

TINU syndrome. Acute tubulointerstitial nephritis and *uveitis* syndrome (TINU syndrome) is predominantly observed in young girls and is characterized by:
- general symptoms of inflammation
- anterior bilateral uveitis
- acute TIN with tubular proteinuria, leukocyturia, glucosuria, aminoaciduria, and GFR decrease.

Histologically, a TIN with interstitial mononuclear infiltration is found in the kidneys. The reduced renal function is restored spontaneously or with steroid therapy within weeks to months.

Chronic Interstitial Nephritis

Chronic interstitial nephritides comprise essentially:
- analgesic nephropathy
- chronic bacterial pyelonephritis
- Balkan nephritis
- radiation nephritis.

Analgesic Nephropathy

Analgesic nephropathy is a chronic interstitial nephritis that is complicated by *papillary necroses* (Fig. 29.**29a**) and *urothelial carcinomas* (Fig. 29.**29b**) and occurs due to excessive and long-lasting intake of analgesic compounds. These originally contained phenacetin, which has been now replaced by the less nephrotoxic compound paracetamol, in combination with acetylsalicylic acid and caffeine or codeine. Disease usually develops following the ingestion of several kilograms of these compounds over five to 10 years or longer. The long-term ingestion of NSAIDs can also lead to chronic renal insufficiency.

Analgesic Abuse Syndrome. The ingestion of these substances in large quantities does not only lead to renal changes. Simultaneous changes in the gastrointestinal tract, a distinct anemia, and a psychiatric illness have led to the term of analgesic abuse syndrome in these patients (Tab. 29.**30**).

Renal Symptoms. Renal symptoms, e. g., colics, which are caused by the passage of papillae, and dysuria from a complicating urinary tract infection frequently occur late in the course of analgesic nephropathy. Most patients consult the physician with symptoms of progressive renal insufficiency.

Among the renal symptoms and objective findings are:
- *colics* with or without dysuria due to passing papillae, possibly in conjunction with obstruction of the lower urinary tract
- recurrent *dysuria* due to urinary tract infections
- *sterile leukocyturia* (early symptom)
- minor *tubular proteinuria*

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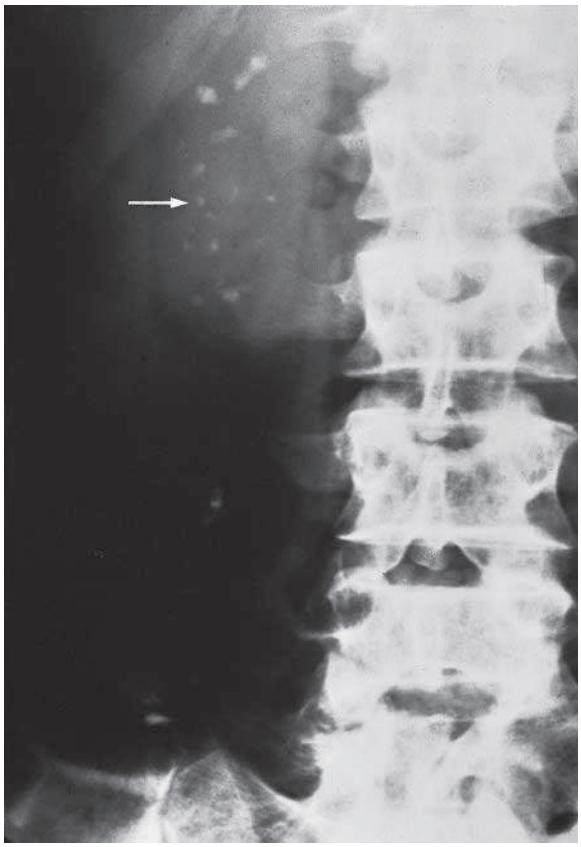

a

b

Fig. 29.**29** Analgesic abuse syndrome
a Multiple calcified papillary necroses in interstitial nephritis after long-standing analgesic abuse.
b Right-sided renal pelvic carcinoma in analgesic nephropathy.

- progressive *decrease of GFR* in advanced interstitial nephritis
- symptoms of *progressive renal insufficiency*.

Extrarenal Symptoms. Prior to the occurrence of renal symptoms, symptoms originating from other organ systems may indicate possible analgesic abuse. The symptoms listed in Tab. 29.**30** pertain to the analgesic abuse syndrome. Seventy to eighty percent of patients are middle-aged women, who frequently look older than their age, and may have an altered mental status. They complain multiple pains of differing localization, in particular, about *headaches* and *gastrointestinal symptoms*. The latter are caused by the acetylsalicylic acid portion contained in analgesic compounds, which leads to erosions or ulcerations in stomach or duodenum. Chronic, occult, or manifest hemorrhages from the gastrointestinal tract explain the distinct anemia frequently present in analgesic abuse. The long-term ingestion of salicylates increases the *bleeding tendency* through inhibition of the thrombocytic aggregation. Thus, it can be considered a rule that the presence of a distinct *anemia* with only moderate creatinine increase should lead to the search for an analgesic abuse.

Tumors of the Urinary Tract. Patients with analgesic abuse frequently develop urothelial tumors of the lower urinary tract (renal pelvis, ureter, urinary bladder; see Fig. 29.**29b**). Approximately 10% of these patients are expected to develop tumors of the urinary tract, whereby from an absolute point of view, bladder carcinoma represents the most frequent tumor.

> Every microhematuria of nonglomerular origin (no evidence of red cell casts or dysmorphic erythrocytes in the sediment) and each macrohematuria without simultaneous papillary necrosis should lead to the exclusion of a tumor.

Urine cytology frequently leads to the diagnosis. Depending on the renal function, sonography of the renal pelvis, CT scan cystoscopy, and retrograde imaging of the lower urinary tract complete the localization tests.

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Chronic Pyelonephritis

Indications for the diagnosis of chronic bacterial pyelonephritis are obtained by:

- typical *radiologic findings* with deformations of the calix and destructive changes of the renal parenchyma
- evidence of *chronic bacteriuria*
- clinical and laboratory indications for the presence of tubulointerstitial disease.

In most patients with chronic bacterial pyelonephritis there is an underlying renal disease, which leads secondarily to bacterial colonization. In particular, *reflux nephropathy* or *obstructive uropathies* with urinary flow disorders in the region of the lower urinary tract, or an analgesic abuse must be mentioned. However, it is often difficult to determine whether the secondary bacterial colonization of the renal interstitium or the underlying disease is responsible for the symptoms of chronic pyelonephritis. It is certainly correct to use the term chronic bacterial pyelonephritis as a symptom diagnosis and to search for predisposing factors.

Radiation Nephritis

Radiation of the kidneys (> 2000–2500 rad = 20–25 Gy) leads to glomerular, tubular, and vascular changes, which after six months to 10 years result in the development of radiation nephritis with distinct interstitial fibrosis. Asymptomatic proteinuria, renal hypertension, or progressive decrease of the renal function are symptoms of radiation nephritis, which can occur *acutely* six to 12 months following radiation or as chronic radiation nephritis after several years, associated with a progressive decline in renal function.

Previously, radiation nephritis has occasionally been observed after radiation therapy of retroperitoneal lymphomas, metastatic testicular tumors, Wilms tumors of the kidneys, and ovarian tumors. As a result of the relative increasing application of chemotherapeutic measures and better delimitation of regions receiving radiation, radiation nephritis is rarely seen.

Balkan Nephritis

This chronic interstitial nephritis occurs endemically in Bulgaria, Romania, and other Balkan regions along the course of the Danube and its tributaries, and leads to renal failure between the 30th and 60th years of life. The etiology of this disease is unclear. Clinically, a slowly progressive renal insufficiency is predominant; the frequent occurrence of urothelial carcinomas shows similarities to analgesic nephropathy.

Urinary Tract Syndromes

Diseases of the lower urinary tract can manifest through specific symptoms and clinical findings. A frequent complication in diseases of the lower urinary tract is infections with their own symptom complex (fever, chills, flank pain, dysuria, pyuria). Schematically, the symptomatology of the *upper urinary tract* (pyelocaliceal system, ureter) can be distinguished from that of the lower urinary tract.

The *acute* unilateral or bilateral obstruction of the upper urinary tract results in a symptom complex of colics, oligoanuria, and renal insufficiency (the latter two only when bilateral pathology is present). *Chronically* developing obstructions do not cause pain. However, there is often hyperkalemia and nephrogenic diabetes insipidus due to disturbed tubular function. Bilateral obstruction leads to chronic progressive renal failure.

The symptomatology of the lower urinary tract is often characterized by altered micturition. The micturition can be disturbed due to obstruction or neurologic problems.

Infections of the Urinary Tract

Cystitis, Vaginitis, Urethritis, and Prostatitis. Infections of the bladder present clinically with the triad *dysuria*, *frequent micturition*, and urgency. Suprapubic cystalgia and hematuria can also occur. This symptom complex is predominantly found in infections, less frequently also in cases of bladder calculi and bladder tumors. Cystitis can occur in isolation or in combination with pyelonephritis or possibly prostatitis. Cystitides occur predominantly in young and sexually active women (so-called honeymoon cystitis). Acute cystitis must be distinguished from vaginitis, which manifests with pruritus, dyspareunia, vaginal discharge, and dysuria. Urethritis is mainly caused by a gonococcus (*Neisseria gonorrhoeae*) and by *Chlamydia*. It manifests clinically with painful urethral discharge and dysuria. Prostatitis can occur acutely and often also chronically. It is characterized by pelvic pain, tenesmus, and dysuria.

Infections of the urinary tract are considered *uncomplicated* when they are caused by common microorganisms (usually *Escherichia coli*) and occur in otherwise healthy, nonpregnant women. Infections of the urinary tract are considered *complicated* when uncommon

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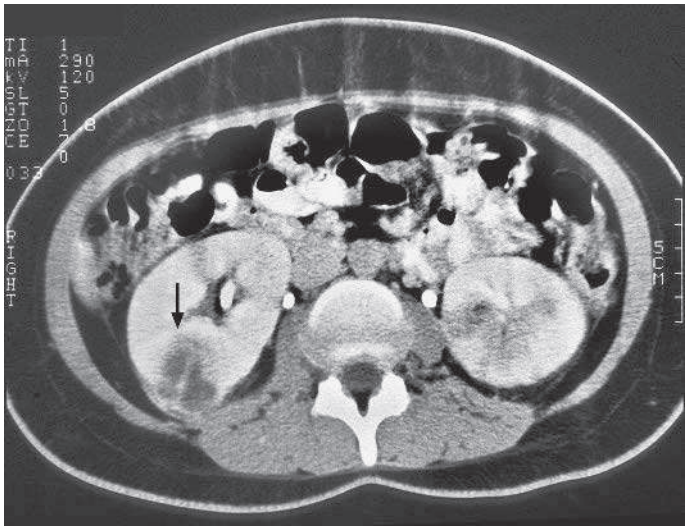

Fig. 29.**30** Right-sided renal abscess (CT with contrast media).

microorganisms are cultivated (*Pseudomonas*, *Candida*, drug-resistant Gram-negative bacteria), when cystitis occurs during pregnancy, when a pyelonephritis develops, and in the presence of a structural abnormality of the urinary tract or the kidneys.

Pyelonephritis. Among the clinical symptoms of acute pyelonephritis are high fever and chills, a strong feeling of illness, nausea, vomiting, and pain in the respective kidney. *Uncomplicated* acute pyelonephritis, which occurs predominantly in women, must be distinguished from *complicated* acute pyelonephritis, which is usually associated with an underlying structural or functional disorder in the urogenital tract or a weakness of the host defense system.

Uncomplicated pyelonephritis in women is usually preceded by dysuric complaints arising from a harmless urinary tract infection, until suddenly fever, chills, flank pain, and a strong feeling of illness occur. Inducing pathogens are predominantly *E. coli* with evidence of $> 10^5$ bacteria/mL (immersion culture media), although in approximately 30% of the female patients $< 10^5$ microorganisms/mL are found. As a rule, pyuria and systemic signs of infection like leukocytosis, ESR acceleration, and increase in the C-reactive protein (CRP) can be identified.

Complicated Infections of the Urinary Tract. These are more frequently found in men than in women. Possible causes are:

- obstruction of the lower urinary tract by kidney stones or tumors
- indwelling bladder or ureteric catheters
- metabolic disorders and reduced immunocompetence (diabetes mellitus, renal insufficiency, kidney transplantation)
- functional disorders like neurogenic urinary bladder and vesico-ureteral reflux.

In elderly men, the cause of an obstruction is often due to *prostatic disease*, which is further clarified by determining residual urine in the bladder with sonography, palpatory findings, determination of the prostate specific antigen, and, in cases of tumor suspicion, by means of transrectal sonography and punch biopsy.

Infected renal cysts, as well as *intrarenal* (Fig. 29.**30**) and *perirenal abscesses* clinically manifest in a similar way to acute pyelonephritis, whereby the infection symptomatology shows a protracted course. In all three diseases, bacteriuria and leukocyturia can be missing, so that evidence of pathogens is sometimes only obtained through blood cultures. Intrarenal abscesses usually develop due to a hematogenic bacterial dissemination and are mainly caused by staphylococci.

Xanthogranulomatous Pyelonephritis. Xanthogranulomatous pyelonephritis represents a bacterial *granulomatous destruction* of kidney with tissue colliquation and extension to the kidney capsule and the neighboring tissue. Predominantly affected are middle-aged women who complain of flank and back pain and of recurrent infections of the urinary tract. At the time of examination weakness, weight loss, and general symptoms of inflammation are prevalent. Only 50% of patients complain of symptoms of lower urinary tract infection or display pathologic urinary findings.

The etiology of this disease is usually a *complete* or *partial obstruction* of the urinary flow by a stone or tumor. A changed immunologic defense mechanism or an atypical virulence of the pathogens is taken as explanation for the clinical course and the granulomatous tissue reaction. The clinical and histologic differentiation from tuberculosis can be extremely difficult.

Malacoplakia and Megalocytic Interstitial Nephritis. Malacoplakia and megalocytic interstitial nephritis are differentiated from xanthogranulomatous pyelonephritis mainly by means of histopathologic criteria.

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Fig. 29.**31** Intravenous pyelogram in right-sided renal tuberculosis; obstruction of the upper calyx group with cavity formation.

Malacoplakia is an uncommon inflammatory reaction to an infection in the pyelocaliceal system (mostly by *E. coli*). The disease is histologically diagnosed by the presence of Michaelis–Gutmann bodies.

Genitourinary Tuberculosis. In genitourinary tuberculosis, mycobacteria can disseminate hematogenously to the kidneys during primary manifestation of pulmonary tuberculosis. Usually, granulomas in the renal cortex heal spontaneously. However, they can invade the tubular system early or after a longer latency of 20–30 years and then lead to a caseating inflammation. Dissemination occurs along the lower urinary tract, and the prostate, seminal glands, and epididymis can be also affected.

Clinically, *symptoms of an infection of the lower urinary tract* with dysuria, pyuria, and/or hematuria predominate. The urine is sterile in conventional analyses with immersion culture media, the tuberculin test is usually positive. A leukocyturia without bacteriuria is designated as sterile leukocyturia and needs to be further investigated.

The *diagnosis* of genitourinary tuberculosis is confirmed by specific urine cultures. Usually three to six morning urines are analyzed, since the incidence of positive findings is only around 40 % due to the intermittent excretion of mycobacteria. Recently, the indirect evidence of pathogens by polymerase chain reaction is used in the diagnosis of tuberculosis. In addition, the intravenous urogram (Fig. 29.**31**), which shows cavitary papillary lesions, strictures, constrictions of calices and the lower urinary tract, as well as scar formations and intrarenal calcifications, is of important diagnostic value.

Obstruction of the Urinary Tract

Hydronephrosis

Hydronephrosis develops as a consequence of chronic obstruction of the urinary tract and, when unilateral, usually occurs supravesically. When a hydronephrotic kidney is infected, this often leads to pyonephrosis, which is accompanied by high fever, chills, and severe pain. The most important and age-dependent causes of unilateral hydronephrosis are:

- in *children*, congenital malformations at the junction between renal pelvis and ureter, or between ureter and bladder
- urolithiasis in *young adults*
- in *elderly patients*, carcinoma of the prostate with obstruction of the ureteric opening, other pelvic tumors (e. g., colonic carcinomas or tumors of the retroperitoneum), nephrolithiasis, and retroperitoneal fibrosis (the latter usually causing bilateral hydronephrosis).

Unilateral Hydronephrosis. Unilateral hydronephrosis occurs due to:

- *Obstruction of the ureteric lumen:* passing stones, coagula, or renal papilla leads to an acute obstruction of the ureter. In the presence of strictures or lumen-narrowing neoplasms (urothelial carcinomas) hydronephrosis develops protractedly.
- *External compression on the ureter:* vascular lesions, e. g., aortic aneurysm and aberrant vessels, pelvic tumors, inflammatory or malignant gastrointestinal diseases, and inflammatory or malignant processes of the retroperitoneum must be considered in the differential diagnosis.

Bilateral hydronephrosis occurs predominantly with:

- retroperitoneal fibrosis (Ormond disease)
- neurogenic bladder
- medications that disturb the bladder function
- deep-lying pelvic tumors
- diseases of the prostate
- strictures of the urethra.

Clinical Features and Diagnosis. When unilateral hydronephrosis develops rapidly, pain is the predominant symptom. It is localized in the renal bed in cases of obstruction of the upper ureter, whereas in cases of obstruction of the lower ureter it radiates to the genital re-

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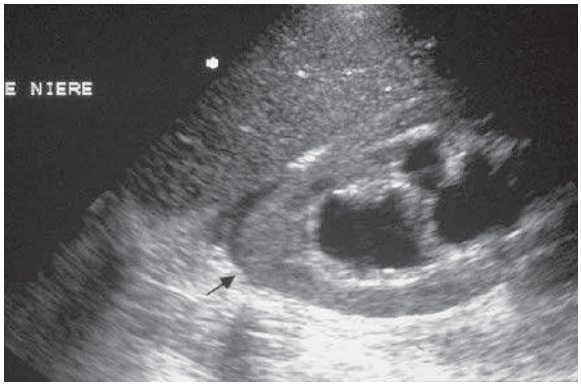

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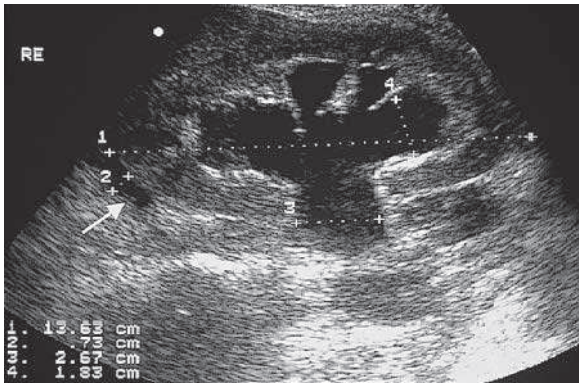

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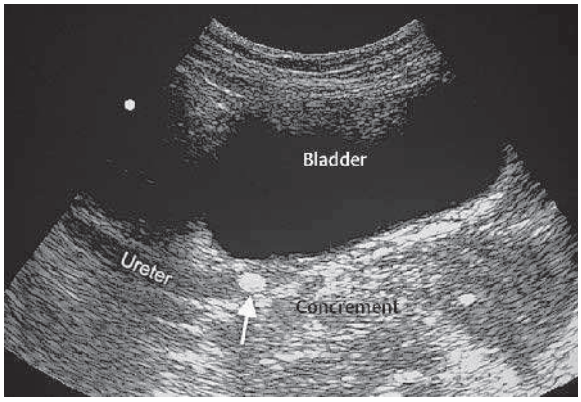

c

Fig. 29.**32** Sonographic findings in a patient with acute right-sided renal colic.
a, **b** Evidence of acute urinary tract obstruction on the right side with rupture of the fornix (fluid rim of 7–10 mm) (arrows).
c The cause is a concrement of approximately 8 × 5 mm located prevesically, approximately 5–8 mm in front of the ostium (arrow).

gion. The diagnosis is typically made with ultrasonography (Fig. 29.**32**). In search of the cause, abdominal radiography and a CT scan are also performed. With these three examinations the cause of an obstruction of the urinary tract is diagnosed in 90 % of patients. In addition, evidence of an intraluminal etiology of a hydronephrosis is obtained by intravenous urography.

Nephrolithiasis and Nephrocalcinosis

Nephrolithiasis. Renal calculi are often asymptomatic and are incidentally detected by sonographic or radiologic examination of the abdomen. A renal colic occurs when stones leave their anchorage and reach the ureters. A renal colic starts suddenly and grows within 15–30 minutes to a steadily increasing and unbearable pain, which is accompanied by nausea and vomiting. This pain, which is first localized to the region of the renal bed, radiates caudally with the passage of the stone through the ureter and leads, shortly before the passage of the concrement into the bladder, to tenesmus and occasionally to violent pain in scrotum and testis, glans of penis, or labia. When the stone reaches the ureterovesical junction, dysuria and urge can occur. Upon entry of the stone into the bladder, the renal colic disappears spontaneously. A stone passage always causes microhematuria; occasionally the occurrence of macrohematuria is also observed.

In differential diagnosis it must be considered that a renal colic can be caused not only by stone passage, but also by the passage of blood clots (e. g., in case of renal tumors or after renal biopsy), detritus (e. g., renal tuberculosis), or papillary necroses.

Nephrocalcinosis. In contrast to nephrolithiasis, with stone formation in the hollow systems of the kidneys and the lower urinary tract, the presence of *intrarenal calcifications* is designated as nephrocalcinosis (Fig. 29.**33**). The precipitation of calcium salts occurs typically bilaterally in distal tubular segments or in the renal parenchyma. It is generally asymptomatic and therefore often detected incidentally or in conjunction with a stone passage. The detection of nephrocalcinosis requires the differential diagnosis between:
- primary hyperparathyroidism
- distal renal tubular acidosis (RTA)
- medullary sponge kidneys (Fig. 29.**34**)
- analgesic nephropathy.

Stone Composition and Etiology. In the presence of *recurrent nephrolithiasis*, a clarification of the etiology of

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Fig. 29.**33** Typical nephrocalcinosis in a patient with renal tubular acidosis in conjunction with Sjögren syndrome; plain abdominal radiograph. The grape-shaped calcifications are predominantly located in the medullary parts of the kidney.

the stones is essential. The differential diagnosis is based on the analysis of stones already passed, or the probable nature of not yet passed concrements (radiographic density, accompanying crystalluria, accompanying infection of the urinary tract, etc).

According to their composition, a distinction is made between:

- *calcium stones* containing predominantly oxalate and phosphate: 75%
- *struvite stones* in urinary tract infections (secondary phosphate stones): 10–15%
- *uric acid stones:* 10–15%
- *cystine stones:* < 1%.

Among these, *calcium nephrolithiasis* is the most frequent, and the urine pH value determines formation of either calcium oxalate or calcium phosphate stones. Since the majority of patients excrete acidic urine, calcium oxalate stones prevail. In patients with recurrent calcium phosphate stones, the causes of the alkaline urine should be investigated (infection with urealytic bacteria, hyperparathyroidism, renal tubular acidosis, acetazolamide). Risk factors for the development of calcium nephrolithiasis are hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria.

Uric acid calculi are predominantly formed due to excretion of acidic urine, low urine volume, and evidence of hyperuricosuria. Hyperuricosuria is usually caused dietetically by high protein supply, but may also be observed in some patients with gout and with endogenous overproduction of uric acid.

Fig. 29.**34** Intravenous urogram in a patient with medullary sponge kidneys. Small cavities, which are filled with contrast agent, and calcifications are particularly visible on the left side in the region of the papillary tips.

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Struvite stones are predominantly observed in women. Typically coral calculi form in the context of infections with urease-producing bacteria (Fig. 29.**35**). In particular, *Proteus*, *Klebsiella*, *Citrobacter*, *Pseudomonas*, and, less frequently, *Escherichia* are able to produce urease, which splits urea into ammonia and thus causes an increase of the urine pH value to > 7.

Cystine stones develop in patients with the autosomal recessive hereditary disease cystinuria. The diagnosis is based on evidence of cystine crystals in the concentrated morning urine (see Fig. 29.**9c**), kidney stone analysis, and evidence of increased renal excretion of cystine, arginine, ornithine, and lysine.

Fig. 29.**35** Coral calculus in the left renal pelvis in a patient with stenosis of the pyelo-ureteral junction; plain abdominal radiograph.

Differential Diagnosis of Pathologic Sonography Findings

Cystic Renal Diseases

Solitary or Simple Renal Cysts. Various renal diseases manifest with cyst formation in one or both kidneys. Tab. 29.**31** summarizes the different forms of cysts.

Table 29.**31** Cystic kidney diseases

Solitary renal cyst
Formation of cysts in chronic renal failure
Polycystic renal diseases – autosomal dominant forms – in the context of von Hippel–Lindau syndrome – associated with tuberous sclerosis – sporadic forms – autosomal recessive forms
Nephronophthisis complex – juvenile nephronophthisis – medullary cystic kidney disease
Medullary sponge kidney

Solitary or Simple Renal Cysts. Renal cysts are frequently diagnosed as incidental findings with renal ultrasonography. Simple renal cysts are often solitary or only present in small numbers and are found unilaterally or bilaterally. In contrast to cysts that occur in patients with polycystic renal diseases, they usually do not lead to an enlargement of the kidneys and do not impair excretory function. Only in rare cases do solitary renal cysts become so large that they are palpable or lead to local complications.

Sonographic monitoring has demonstrated that *secondary cyst formation* in the shrunken kidneys, an acquired cystic transformation of the kidneys, is frequently observed in patients with CRF or in patients undergoing dialysis. The extent of cyst formation correlates with the duration of the renal insufficiency. After many years of dialysis, multiple cyst formation is found in about 90 % of patients. The sonographic finding (small kidneys with cysts) allows differentiation from cystic kidney diseases.

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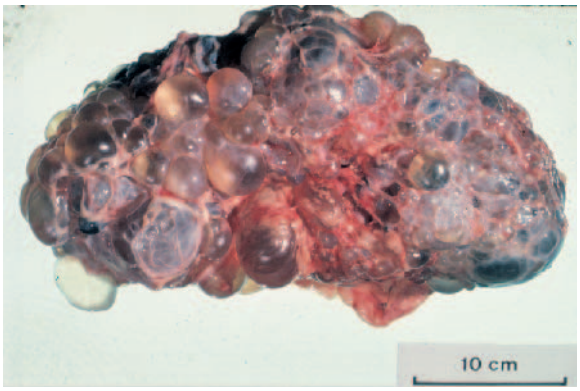

Fig. 29.**36** Autosomal dominant polycystic kidney (nephrectomy specimen).

Polycystic Kidney Diseases

A distinct cyst formation with enlargement of both kidneys and progressive functional deterioration indicates the presence of hereditary cystic renal disease. The *autosomal dominant* inherited type manifests between the 20th and 50th years of life. The *autosomal recessive* type is already manifest at birth or in childhood. *Nephronophthisis* has to be distinguished from these two types of polycystic kidney disease. This latter disease usually leads to end-stage renal failure in adolescence.

Autosomal Dominant Polycystic Kidney Disease (ADPKD) leads to distinct cyst formation in both kidneys (Fig. 29.**36**). This disease is caused by mutations in the genes *PKD1* and *PKD2*. The gene products of mutated *PKD1* and *PKD2*, polycystin-1 and -2, lead to a malfunction in the kidneys which results in cyst formation in adult life. Characteristic is the positive family history of cystic kidneys with occurrence of end-stage renal failure in one parent or grandparent, in siblings (50%), or in uncles and aunts.

Expansion of the cysts in the renal parenchyma usually leads to a *distinct enlargement* of the kidneys, which are often palpable and might be misinterpreted as a tumor. Additional symptoms arise via local complications of the disease, namely:

- recurrent flank pain
- hematuria and cyst hemorrhage
- recurrent cyst infection and infection of the urinary tract
- renal hypertension
- progressive renal failure.

Pain and/or hematuria usually prompts imaging with sonography or CT (Fig. 29.**37**), which together with the positive family history leads to the diagnosis.

ADPKD is characterized by a series of *extrarenal manifestations*. Thus, cysts are found in other organs, e. g., *liver*, *spleen*, and *pancreas* (Fig. 29.**37**). Aneurysms of the cerebral arteries develop in 4–10% of patients, representing the most life-threatening concomitant disease of polycystic kidney disease because of the increased risk of subarachnoid hemorrhage. Also, the frequent occurrence of cardiac valve dysfunctions, e. g., mitral valve prolapse and aortic insufficiency has been described in patients with polycystic kidney disease. Finally, there is an increased occurrence of colonic diverticulosis and umbilical and inguinal hernias in patients with polycystic kidney disease.

Autosomal Recessive Polycystic Kidney Disease (ARPKD). This autosomal recessive disease is characterized by cyst formation in utero and usually leads to congenital or early childhood end-stage renal failure. Relative to age, the kidneys are increased in size in utero and in early childhood. If the child survives and if regular dialysis treatment can be performed, the kidneys will become rather small. In addition, the disease is accompanied by congenital liver fibrosis. Mutations in the *PKDH1* gene are responsible for the disease.

Juvenile Nephronophthisis Complex. In this disease congenital cyst formation is found in the region of the corticomedullary junction and the cortical medulla, with interstitial fibrosis and secondary glomerulosclerosis. Two variant forms with different inheritance mode and age of manifestation are described:

- *Juvenile nephronopthhisis* is an autosomal recessive disease, which leads to renal failure in childhood and adolescence. Extrarenal manifestations are observed, in particular in the eyes (retinitis pigmentosa, tapetoretinal degeneration, coloboma).
- The autosomal dominant *medullary cystic renal disease* manifests in adulthood with progressive renal failure without involvement of extrarenal organs.

Sonographically, the kidneys are small; cysts are often not identified due to their small size. The diagnosis is mostly based on the positive family history and the typical clinical course in the absence of other causes for progressive renal insufficiency.

Renal Tumors

In addition to the cystic diseases, various benign or malignant renal neoplasms can be detected by ultrasonography. Among the malignant tumors are renal cell carcinomas (adenocarcinomas; formerly called “hypernephromas”), nephroblastomas (Wilms tumor, occurring predominantly in the age group up to six years old), and urothelial carcinomas. In addition, metastases of other primary tumors are also possible. Angiomyolipomas (Fig. 29.**38**) and oncocytomas are benign renal tumors.

Renal Cell Carcinoma. These can present with hematuria and/or with flank pain and are rarely palpable in clinical

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Fig. 29.**37** Computed tomography scan of the abdomen in a patient with autosomal dominant polycystic kidneys; multiple cysts in kidneys and liver.

Fig. 29.**38** Evidence of a benign renal tumor, using ultrasound; angiomyolipoma on the cranial pole of the right kidney.

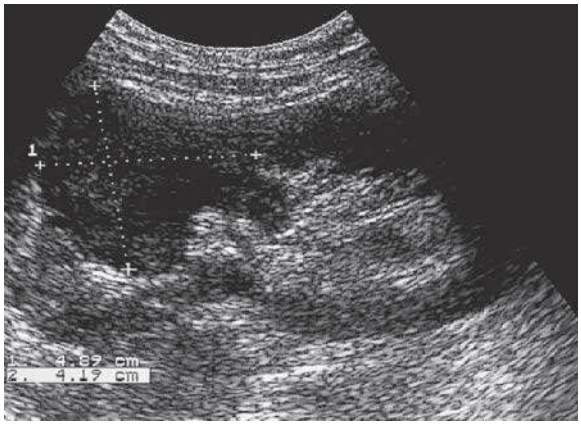

Fig. 29.**39** Sonographic finding of a renal cell carcinoma in the middle/upper third of the right kidney; maximal size 4.1 × 4.8 cm. The tumor, which appears almost anechoic and inhomogeneous, is polycyclic, irregular, and with indistinct demarcation.

examination. Tumor diagnosis is often made in the context of:

- the investigation of a nonglomerular microhematuria or macrohematuria, or of unclear abdominal complaints
- a sonography of the abdomen (Fig. 29.**39**) for other indications
- the search for a primary tumor in the presence of identified metastases (e. g., CT scan of the abdomen, Fig. 29.**40**).

In some patients, renal cell carcinoma occurs bilaterally. Renal cell carcinomas can be associated with *paraneoplastic syndromes*. Among these are:

- erythrocytosis (ectopic production of erythropoietin by the tumor)
- hypercalcemia due to production of PTH-related peptides
- liver function disorders with reduced prothrombin time, increased alkaline phosphatase, and reduced serum albumin (*Stauffer syndrome*).

The differentiation between cystic tumor and solitary cyst can sometimes be difficult.

> The presence of a tumor should always be considered when sonographically inhomogeneous structures, echoes within cysts, and calcifications are identified.

If in doubt, differentiation between a cyst and a tumor can be achieved by CT scan with contrast agent application or by MRI.

Phakomatoses. Solid neoplasms in the kidney can also occur in phakomatoses, particularly in *von Hippel–Lindau disease* and in *tuberous sclerosis*.

Renal cell carcinomas occur frequently in the autosomal dominant von Hippel–Lindau disease (VHL). The

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Fig. 29.**40** CT imaging of a renal cell carcinoma; hypervascularized tumor on the lateral circumference of the middle third of the right kidney; arterial perfusion phase after intravenous contrast agent bolus injection.

disease is characterized by retinal angiomas, hemangioblastomas of the cerebellum and the spinal cord, pheochromocytoma, as well as angiomatous or cystic lesions in the kidneys, liver, pancreas, lungs, skin, and epididymis. In 75 % of patients with VHL renal cell carcinomas occur bilaterally.

Tuberous sclerosis is a progressive neurologic and dermatologic disease. Many patients have cysts in the kidneys. Angiomyolipomas of the kidney are frequently found in this disease and can bleed when they are very large (> 4 cm). The occurrence of renal cell carcinomas is frequent in tuberous sclerosis.

Urothelial Carcinomas. Urothelial carcinomas develop in the urinary tract, i. e., in the renal pelvis, ureters, and bladder. They occur predominantly in patients with analgesic nephropathy and in patients with a history of nicotine use. Typically the tumors develop after 15–20 years of analgesic abuse and present with microhematuria or macrohematuria. In patients with known analgesic nephropathy these symptoms should lead to the performance of a sonography, an intravenous urogram of the lower urinary tract, and urine cytology. If necessary, a more extensive diagnostic approach, which includes cystoscopy and retrograde pyelography, is warranted.

Nephroblastomas. These tumors occur predominantly during the first years of life and are rare in adulthood. Due to their remarkable size the abdominal palpation finding in affected children is often particularly striking, whereas hematuria, pain, and fever are less impressive.

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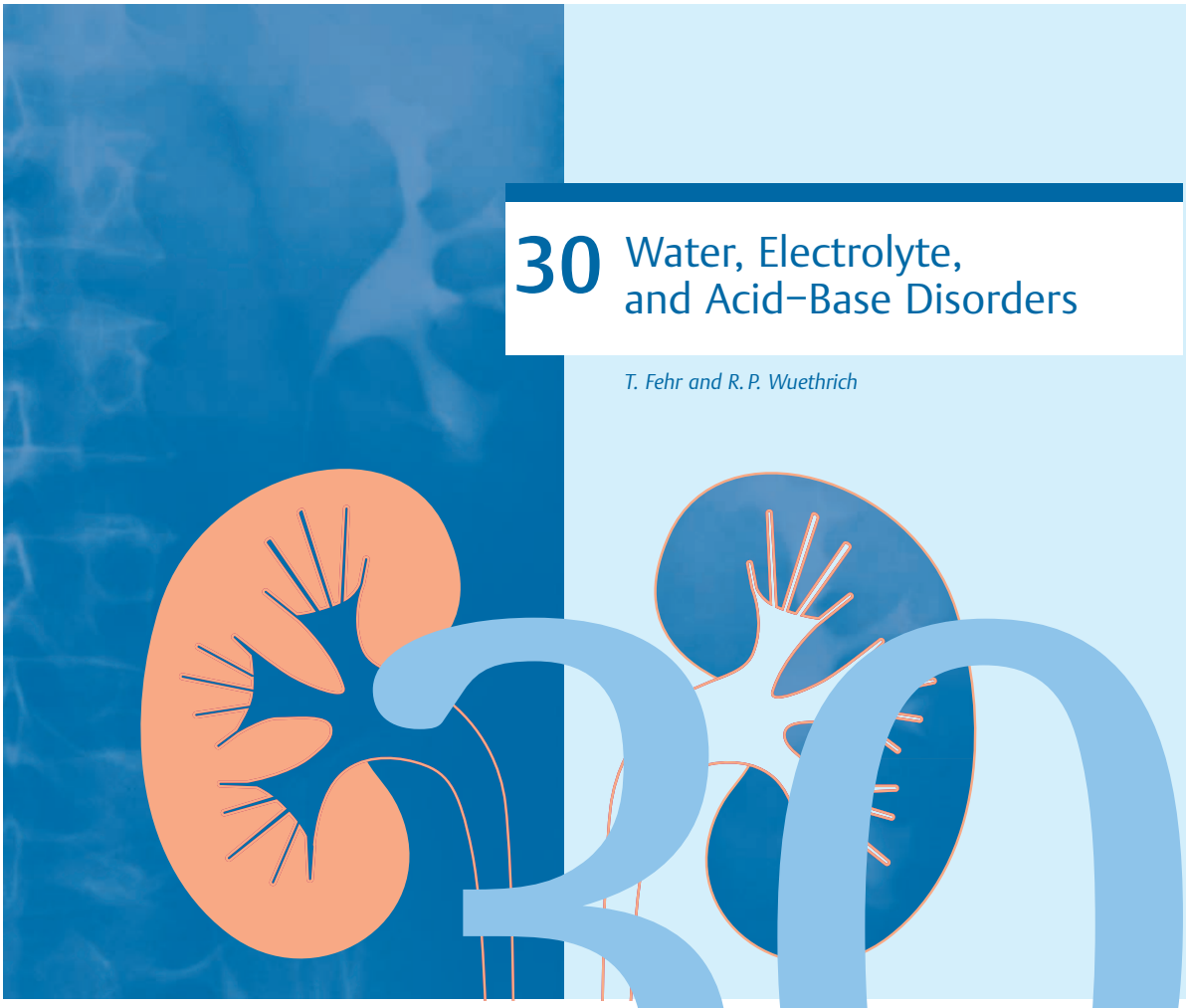
30 Water, Electrolyte, and Acid–Base Disorders

T. Fehr and R. P. Wuethrich



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30.1 Disorders of Sodium and Water Homeostasis

Physiologic Principles

Disorders of sodium and water homeostasis result in changes of volume status, serum osmolality, and serum sodium concentration. Basic knowledge of physiologic principles is fundamental for understanding these disorders. Some of these principles are briefly described below.

Fluid Compartments

General Pathogenesis of Electrolyte Disorders. The human body consists of different fluid compartments, and each of them has a characteristic electrolyte profile (Tab. 30.**1**). Electrolyte disorders, which are usually measured in the serum, can occur by three different mechanisms (Fig. 30.**1**): by a *net change in intake*, by a *shift between different compartments*, and by a *net change in excretion*.

The kidney is the main organ responsible for excretion of electrolytes. Therefore, the differential diagnosis usually distinguishes between renal and extrarenal disorders of electrolyte excretion/loss. The renal excretion of a substance X can be estimated by determination of the fractional excretion (FE) in spot urine. The fractional excretion is defined as the amount of a substance X excreted via urine divided by the total amount of glomerular filtration of X. In this chapter the concentration of a substance X in the plasma/serum or in the urine is described as P_X or U_X, respectively. The fractional excretion of X can then be calculated as follows:

$$FE_X = \frac{(U_X \times P_{Creatinine})}{(P_X \times U_{Creatinine})}$$

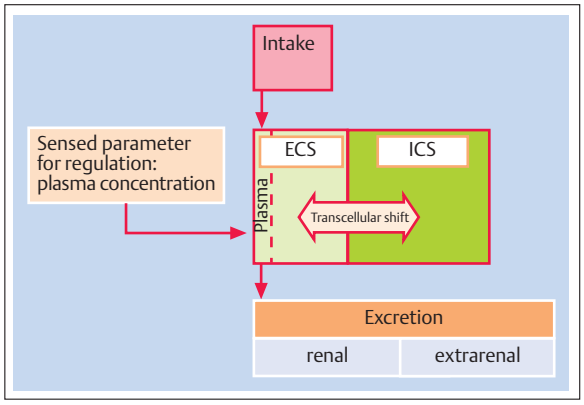

Fig. 30.**1** Fundamental pathogenesis of electrolyte disorders. Electrolyte disorders principally arise in three different ways: by altered intake, by internal shifts (mainly between intracellular space [ICS] and extracellular space [ECS]), and by altered excretion.

Size of Fluid Compartments. On average, the human body consists of 60% water and 40% solid substances. Based on a body weight of 70 kg, the total body water is distributed as follows (Fig. 30.**2**):

- *intracellular volume (ICV)*: 40% (28 L)
  - blood cells: 3% (2 L)
- *extracellular volume (ECV)*: 20% (14 L)
  - intravascular compartment (plasma): 5% (3.5 L)
  - interstitial compartment: 15% (10.5 L).

The *blood volume* consists of the combined volume of blood cells and plasma. It represents about 8% of body weight.

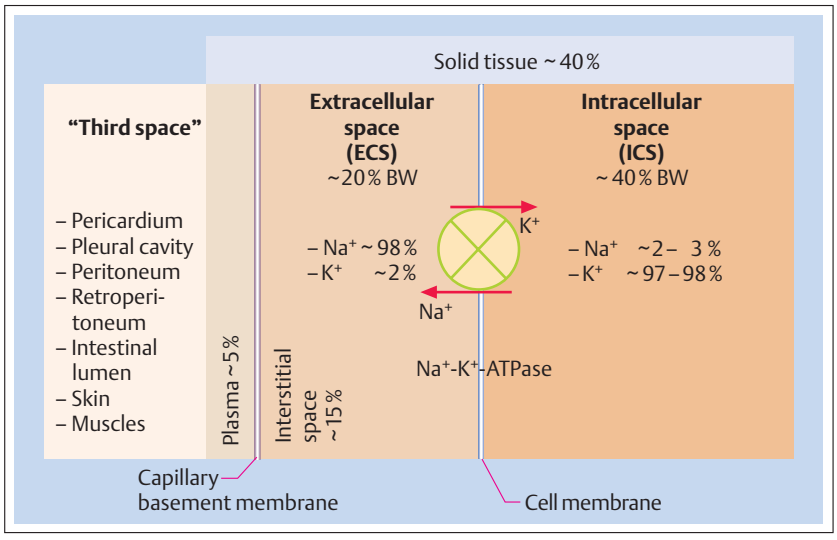

Fig. 30.**2** Distribution of water and cations in the adult body; water in percent of body weight (BW), cations in percent of total body stores.

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Table 30.**1** Electrolyte profiles in various fluid compartments (in mEq/L)

Ions	Plasma	Interstitial fluid	Intracellular fluid
Cations			
Sodium	142	145	12
Potassium	4.3	4.4	140
Calcium (ionized)	2.5	2.4	4
Magnesium (ionized)	1.1	1.1	34
Anions			
Chloride	104	117	4
Bicarbonate	24	27	12
Phosphate	2.0	2.3	40
Proteins	14	0	50
Others	5.9	6.2	84

In particular clinical situations sequestration of large volumes of fluid is observed in serous cavities (pleural, pericardial, peritoneal space) or in traumatized tissue (muscle, retroperitoneal space). This is described as a *transcellular third space*. Under physiologic conditions, this volume is negligible, but it can consist of several liters of fluid in certain disease states, and therefore, considerably influence volume homeostasis.

Each fluid compartment has a characteristic electrolyte profile, which is summarized in Tab. 30.**1**. Under physiologic conditions, the sum of osmotic and oncotic pressure is identical in all the compartments, which allows stable volume homeostasis. However, it is important to understand that the regulation of volume and osmolality are fundamentally different and independent of each other. Each of these is regulated by different hormone systems.

Principles of Osmoregulation

Intracellular and extracellular spaces are separated by the cell membrane, which is permeable to water and urea, but impermeable to electrolytes and proteins. The osmotic pressure within a compartment can be determined by the total concentration of all soluble constituents and is described as serum *osmolality*. In the steady state it is identical in all the compartments and highly correlated with the serum sodium concentration. The osmolality (Osm) is tightly regulated (285–290 mOsm/L) and can be approximately calculated by the following formula:

$$P_{Osm} = (2 \times P_{Na}) + P_{Glucose} + P_{urea}$$

If there is a considerable difference between calculated and effectively measured osmolality, this is referred to as an *osmotic gap*. Substances which are not included in the formula above (e. g., alcohol, glycol, and certain drugs) may be responsible for this difference (see Metabolic Acidosis, below).

Feedback Loop of Osmoregulation. The feedback loop of osmoregulation is shown in Fig. 30.**3**. Osmolality is sensed in specialized cells of the hypothalamus (afferent part of the loop). Regulation of osmolality then occurs via a change in water intake and water excretion in the kidney. Two effector mechanisms are mainly responsible (efferent part of the loop):

- Hyperosmolality *stimulates thirst* and leads to increased water intake.
- Hyperosmolality induces the *secretion of vasopressin* (antidiuretic hormone [ADH]) in the hypothalamus. Vasopressin activates the vasopressin receptor type 2 (V_2 receptor), which reduces renal water excretion. In contrast, hypoosmolality suppresses vasopressin secretion, which leads to activation of water channels (aquaporins) in the collecting duct and increased water excretion.

The daily urine output can be regulated between 0.5 and 15–20 L, which allows stable serum osmolality, independent of water intake. Variability of serum osmolality remains within ± 2 %.

Principles of Volume Regulation

Feedback Loop of Volume Regulation. The maintenance of the extracellular volume (ECV) to allow for stable circulation and adequate perfusion of vital organs is one of the most fundamental principles of water homeostasis. The feedback loop of volume regulation is depicted in Fig. 30.**4**. Since the ECV cannot be measured directly, it is determined indirectly by *arterial baroreceptors*, which are located in the carotid sinus, aortic arch, and left ventricle (afferent part of the loop). These receptors

Fig. 30.**4** Scheme of the feedback loop of volume regulation. ▷ ANP = atrial natriuretic peptide.

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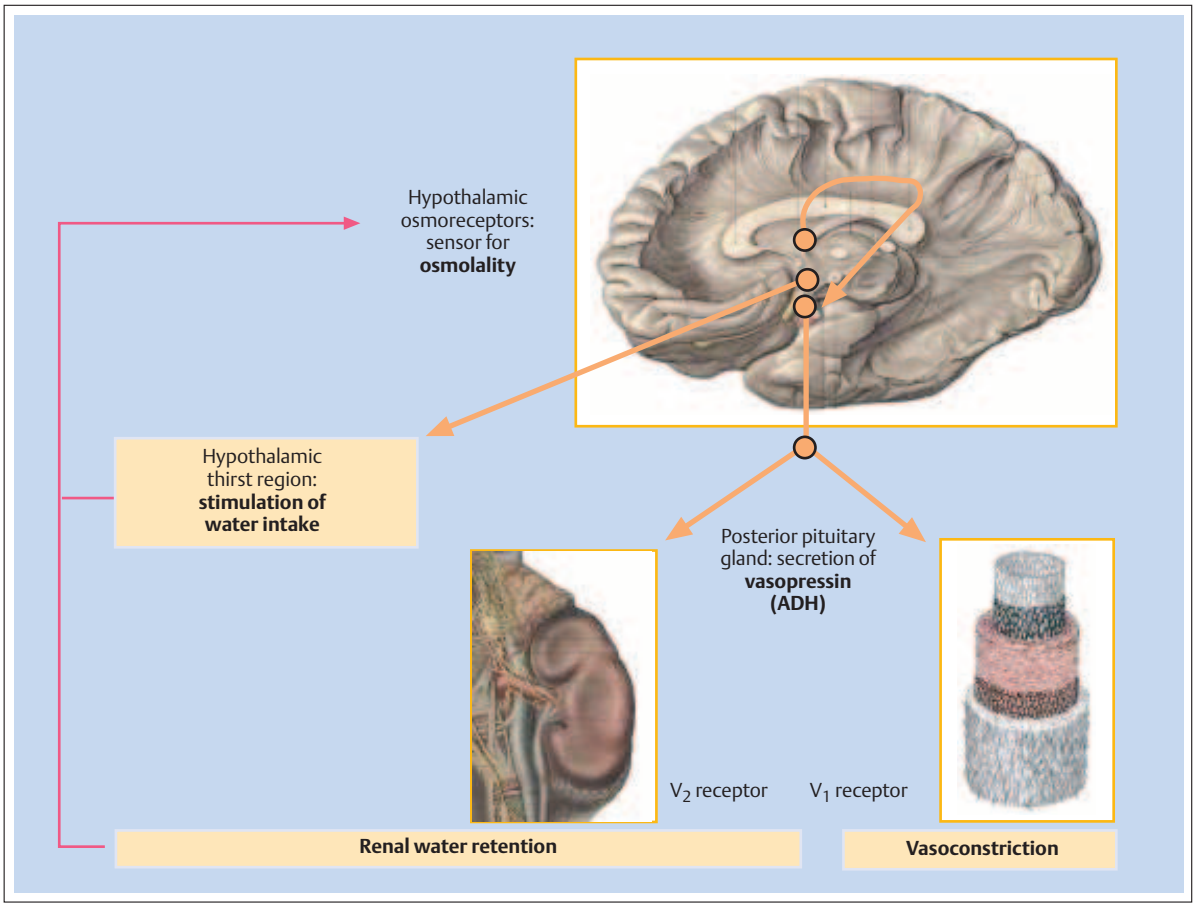
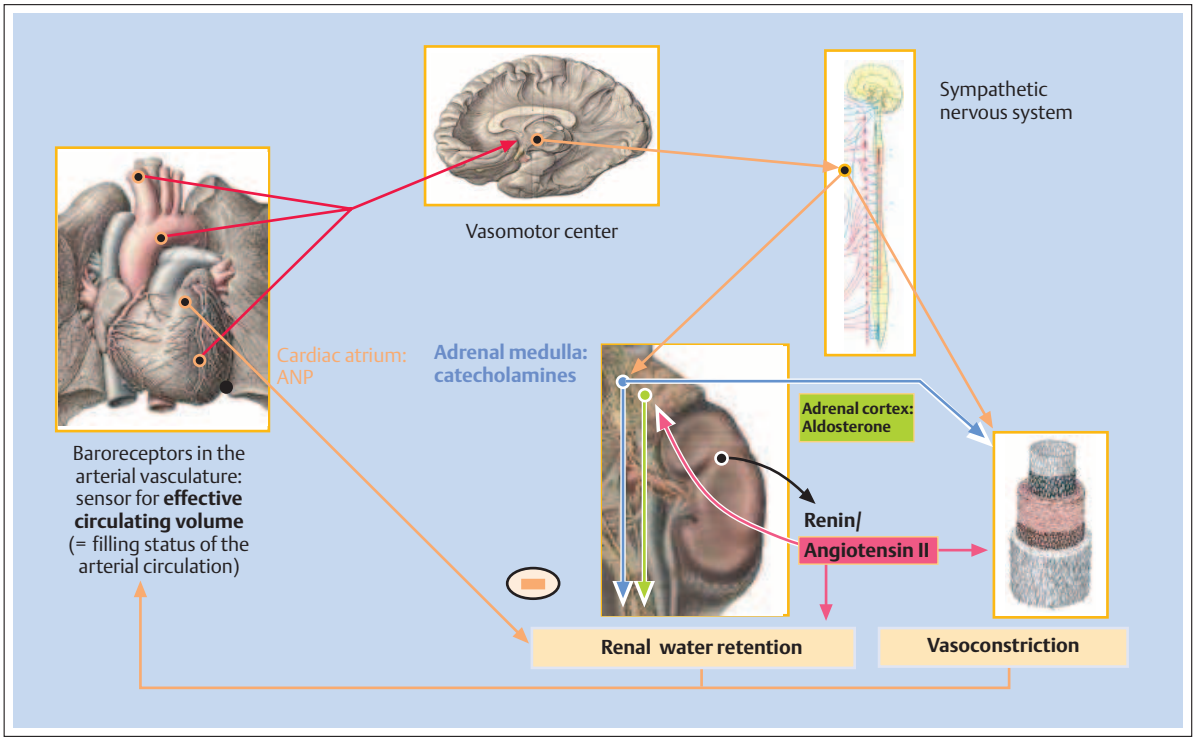


Fig. 30.**3** Scheme of the feedback loop of osmoregulation. V_1/V_2 receptor: vasopressin receptor type 1 (on blood vessels) and 2 (on collecting duct cells).



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measure the *effective circulating volume*, therefore the filling status of the arterial circulation, which is determined by ECV and vascular tonus. Under physiologic conditions ECV and the effective circulating volume are highly correlated, but in certain pathophysiologic situations they can be highly discrepant (e.g., edematous disorders with an increase of ECV, but a decrease in the effective circulating volume).

The ECV is determined by the *total body sodium*, which is mainly located in the ECV. An increase of total body sodium leads to volume expansion, whereas a decrease leads to volume contraction. Therefore, volume regulation occurs mainly by variation of renal sodium excretion (efferent part of the feedback loop). The following hormone systems regulate renal sodium excretion:

- ➤ Hypovolemia activates baroreceptors, which stimulate the *sympathetic nervous system*, which leads directly and indirectly to secretion of catecholamines and consecutive increase of vascular tone. In addition, catecholamines increase sodium reabsorption in the proximal tubule.
- ➤ Hypovolemia leads to renal hypoperfusion, which triggers *renin* secretion in the juxtaglomerular apparatus of the kidney. Renin stimulates the synthesis of bioactive angiotensin II and ultimately aldosterone. *Angiotensin II* is a potent vasoconstrictor and also stimulates sodium reabsorption in the proximal tubule. In contrast, *aldosterone* leads to sodium reabsorption and potassium secretion in the collecting duct.
- ➤ Hypervolemia induces secretion of *atrial natriuretic peptide* (ANP) in the heart. ANP leads to renal sodium excretion by increasing glomerular filtration and inhibition of sodium reabsorption in the proximal tubule.

Overview of Volume and Osmoregulation

The fundamental principles of volume and osmoregulation are summarized in Tab. 30.**2** and can be described as follows:

- **The kidney regulates the ECV via renal sodium excretion.** The clinical parameter is the urine sodium concentration U_{Na}. Volume contraction leads to sodium retention. Volume expansion leads to increased natriuresis.
- **The kidney regulates serum osmolality via renal water excretion.** The clinical parameter is the serum sodium concentration P_{Na}. Hyperosmolality leads to renal water retention. Hypoosmolality leads to increased renal water excretion.

Therefore, disorders of sodium and water homeostasis can be classified as follows:

- extracellular volume contraction (with primarily normal serum sodium concentration)
- extracellular volume expansion (with primarily normal serum sodium concentration)
- hyponatremia
- hypernatremia.

Table 30.**2** Overview of volume and osmoregulation

	Volume regulation	Osmoregulation
What is measured? (input)	– effective circulating volume	– plasma osmolality
Sensor (afferent part of the loop)	– arterial baroreceptors (left ventricle, aortic arch, carotid sinus)	– hypothalamic osmoreceptors
What is regulated? (output)	– renal sodium excretion	– renal water excretion – water intake
Effector (efferent part of the loop)	– proximal sodium reabsorption via catecholamines and angiotensin II – sodium reabsorption in the collecting duct via aldosterone	– water retention in the collecting duct via vasopressin – water intake via stimulation of thirst

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Disorders of Volume Homeostasis (Extracellular Volume Contraction and Expansion)

Definition, Diagnosis, and Clinical Features

Increase or Decrease of Total Body Sodium and Water to the Same Extent. Disorders of volume homeostasis lead to expansion or contraction of the ECV, which manifests in the typical cardiopulmonary symptoms of hypovolemia or fluid overload. These disorders are particularly frequent in clinical routine, and therefore the clinical evaluation of the volume status of a patient is of utmost importance for differential diagnosis. Chest radiograph and certain laboratory parameters can give some additional guidance. These symptoms and signs are summarized in Tab. 30.**3**.

Clinical Features. *Volume contraction* manifests with orthostatic hypotension, tachycardia, collapse of central veins, dry skin and mucosal surfaces, oliguria, and disorientation. In contrast, *volume expansion* leads to hypertension, increased body weight, peripheral edema, dyspnea, and crackles over the base of the lungs.

Diagnosis. In the case of volume expansion an increased heart size, pulmonary congestion, and pleural effusions can be seen in the *chest radiograph*. In intensive care units measurement of the central venous pressure allows reliable assessment of volume status.

Laboratory parameters can be helpful in the case of volume contraction. An increase of hematocrit or serum albumin level is not very reliable by itself, but can be used for follow-up investigations under therapy. Since volume contraction leads to renal sodium retention, a decrease in urine sodium level is a reliable parameter for a volume deficit. In spot urine, U_{Na} is usually < 20 mmol/L and $U_{Osm} > 600$ mOsm/L. The *fractional excretion of sodium, FE_{Na}*, allows differentiation between prerenal and parenchymal acute renal failure in the oliguric patient and is below 1 % in the case of volume depletion. FE_{Na} is calculated as follows:

$$FE_{Na} = \frac{(U_{Na} \times P_{Creatinine})}{(P_{Na} \times U_{Creatinine})}$$

Table 30.**3** Signs of extracellular volume contraction or expansion

	Volume contraction	Volume expansion
Clinical signs		
cardiopulmonary system	– orthostatic hypotension (> 15–20 mmHg systolic) – orthostatic increase in heart rate (> 15–20 beats/min) – collapsed central veins (at 45° back inclination) – shock in case of severe volume depletion	– hypertension – distended central veins, positive hepatojugular reflux – pulmonary congestion on auscultation
skin and mucosal surfaces	– reduced skin turgor – dry mucosal surfaces	– peripheral edema – increased body weight
Chest radiograph		
heart	– small heart silhouette	– heart silhouette ↑
lungs and pleura		– diffuse pulmonary vasculature, peribronchial cuffing, lung edema – pleural effusion
Laboratory parameters		
blood	– hematocrit ↑ – serum albumin ↑	– hematocrit ↓ – serum albumin ↓
urine	– $U_{Na} < 20$ mmol/L – fractional sodium excretion $FE_{Na} < 1$ %	
Hemodynamics		
pressures	– central venous pressure ↓ – pulmonary–capillary wedge pressure ↓ – mean arterial pressure ↓	– central venous pressure ↑ – pulmonary–capillary wedge pressure ↑ – mean arterial pressure ↑
cardiac output	– cardiac output ↓	– heart failure: cardiac output ↓ – others: cardiac output ↑
peripheral resistance	– peripheral resistance ↑	– peripheral resistance ↓

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Table 30.**4** Differential diagnosis of volume depletion

Extrarenal causes (U_{Na} < 20 mmol/L)	Renal causes (U_{Na} > 20 mmol/L)

– Insufficient salt and water intake
– Fluid sequestration in the third space
  – crush injury, rhabdomyolysis
  – internal bleeding
  – pancreatitis, peritonitis, ileus, sepsis
– Gastrointestinal loss
  – vomiting, nasogastric tube
  – diarrhea, fistulas
  – bleeding
– Skin loss
  – intense sweating
  – burns
– External bleeding
	– Osmotic diuresis
	  – severe hyperglycemia
	– Drugs
	  – chronic diuretic abuse
	– Renal salt wasting
	  – tubulointerstitial nephropathies
	  – postobstructive diuresis
	  – renal tubular acidosis
	  – congenital salt-wasting disorders (Bartter syndrome etc.)
	– Mineralocorticoid deficiency (see Tab. 30.**12**)

Table 30.**5** Differential diagnosis of volume expansion

ECV ↑, effective circulating volume ↑	ECV ↑, effective circulating volume ↓

– Primary renal disease
  – acute glomerulonephritis
  – acute and chronic renal failure
– Mineralocorticoid excess (see Tab. 30.**11**)
	– Edematous disorders with secondary hyperaldosteronism
	  – heart failure
	  – nephrotic syndrome
	  – liver cirrhosis
	  – severe hypoalbuminemia (nutritive)

Extracellular Volume Contraction (with Primarily Normal Serum Sodium)

Volume contraction with consecutive decrease in the effective circulating volume occurs with combined net loss of sodium and water. Three basic mechanisms can be responsible and are not mutually exclusive:

- *insufficient intake* of sodium and water
- fluid shift with *sequestration* in the third space
- increased renal or extrarenal *loss*.

Renal loss occurs in the context of primary renal diseases with tubulointerstitial damage, but also indirectly as a consequence of osmotic diuresis and in all forms of mineralocorticoid deficiencies (see Disorders of Potassium Homeostasis, p. 907). The differential diagnosis of volume depletion is summarized in Tab. 30.**4**.

Extracellular Volume Expansion (with Primarily Normal Serum Sodium)

If the net intake of sodium and water overcomes excretion, the ECV expands. ECV expansion over 2–4 L leads to peripheral edema. Based on pathophysiology, two fundamentally different situations can be distinguished (Tab. 30.**5**):

- *concomitant increase* of ECV and the effective circulating volume as a consequence of increased sodium and water intake and/or reduced renal excretion
- increase of ECV associated with *reduced* effective circulating volume in the context of classical edematous disorders (heart failure, liver cirrhosis, nephrotic syndrome).

Volume expansion, as a consequence of *increased intake*, occurs in the context of infusion therapy, but usually only in situations where *excretion is also reduced*. This is mainly the case in patients with acute or chronic renal failure. The renin–angiotensin–aldosterone system is suppressed in these patients, and they are hypertensive due to an increase in the effective circulating volume. The same is the case in patients with primary mineralocorticoid excess (e. g., Conn syndrome). These diseases are usually associated with disorders in potassium homeostasis (see below).

In the case of *classical edematous disorders* a primary underfilling of the arterial circulation is observed. In the case of heart failure this is a consequence of reduced cardiac output, whereas in patients with nephrotic syndrome it is due to hypoproteinemia and consecutive fluid shifts into the interstitial space. In the case of liver cirrhosis, the reduced effective circulating volume occurs as a consequence of splanchnic vasodilatation and ascites. All of these patients have an activated renin–angiotensin–aldosterone system (*secondary hyperaldosteronism*), and they manifest with hypotension due to a reduction of the effective circulating volume. Renal hypoperfusion and hyperaldosteronism lead to renal sodium and water retention, and therefore, edema formation. Concomitant hyponatremia is often observed, because the reduction of the effective circulating volume leads to nonosmotic stimulation of vasopressin secretion. This is particularly dangerous in the context of therapy with thiazide diuretics (see below).

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Disorders of Water Homeostasis and Osmoregulation (Hyponatremia and Hypernatremia)

Definition, Diagnosis, and Clinical Features

Increase or decrease of the serum sodium concentration represents disorders in water homeostasis and osmoregulation. *Hyponatremia* (P_{Na} < 135 mmol/L; severe: < 125 mmol/L) occurs due to an excess of water, and *hypernatremia* (P_{Na} > 145 mmol/L; severe: > 155 mmol/L) due to a water deficit, always in relation to the concomitant total body sodium. Both disorders can be associated with a net increase or decrease of total body water. For differential diagnosis, it is therefore of critical importance to also assess the volume status of such patients (see above).

Diagnosis. Until recently, the serum sodium concentration was measured by means of flame photometry of total plasma samples (therefore including plasma lipids and proteins). As a consequence, massive hyperlipidemia (e. g., with triglycerides) or hyperproteinemia (e. g., with paraproteins) led to artificially low sodium concentrations due to expansion of total plasma volume (so-called *pseudohyponatremia*). The serum osmolality is normal in these cases. With the introduction in laboratories of ion-selective electrodes, for determining ion concentrations, this discrepancy has disappeared.

The accumulation of *osmotically active, nonpermeable substances* in the extracellular space leads to a net shift of water from the intracellular to the extracellular space as an attempt to correct hyperosmolality. The serum sodium concentration decreases; so-called *translocation hyponatremia.* In these patients serum osmolality is increased. The most important clinical example is severe hyperglycemia. Finally, it is important to notice that the accumulation of *osmotically active, permeable substances* does not alter the serum sodium concentrations, since these substances distribute equally between the intracellular and the extracellular space, but the serum osmolality is increased. The most important clinical example is the accumulation of urea in the context of azotemia. Tab. 30.**6** shows an overview of these particular situations and underlines the importance of measuring serum osmolality in patients with unclear hyponatremia.

Clinical Features. Disorders of serum osmolality and serum sodium lead to a volume shift between the intracellular and the extracellular space. As a consequence, cellular swelling occurs with hyponatremia and cellular shrinking with hypernatremia. Because the brain is located in a fixed volume, it is primarily affected by shifts in cellular volume due to disorders in serum sodium concentration or quick therapeutic correction measures. *Neurologic and psychiatric symptoms and signs* are therefore very typical in both situations, e. g., headache, nausea and vomiting, confusion, delirium, lethargy, and eventually coma. Hyponatremia is also associated with muscle weakness, whereas hypernatremia results rather in spasticity and hyperreflexia.

> Acute brain edema is observed with acute hyponatremia and also with a too rapid correction of severe hypernatremia, and can result in the death of the patient.

Hyponatremia (P_{Na} < 135 mmol/L)

Hyponatremia indicates water excess in the extracellular space. For differential diagnosis the volume status has to be considered at the same time. Three different clinical situations can be distinguished as follows (Tab. 30.**7**):

- *hypovolemic hyponatremia:* deficiency in total body water and sodium with an excess loss of salt compared to water

Table 30.**6** Osmotically active substances, serum sodium, and serum osmolality

	Group 1	Group 2	Group 3
Serum osmolality	normal	increased	increased
Serum sodium	decreased	decreased	normal
Examples	– lipids (hypertriglyceridemia) – proteins (paraproteinemia)	– glucose – mannitol – glycine – maltose (with intravenous immunoglobulin)	– urea (azotemia) – alcohols (methanol, ethanol, isopropanol) – glycols (ethylene glycol)
Classification	isotonic hyponatremia, "pseudohyponatremia"*	hypertonic hyponatremia, "translocational hyponatremia"	hyperosmolality with normal serum sodium

* Observed with older methods of sodium measurement such as flame photometry; is not currently a problem with ion-selective electrodes.

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Table 30.**7** Differential diagnosis of hypotonic hyponatremia

Hypovolemic hyponatremia	Euvolemic hyponatremia	Hypervolemic hyponatremia
Third space – crush injury, rhabdomyolysis – pancreatitis, peritonitis, ileus, sepsis **Extrarenal loss** – *skin*: severe burns – *gastrointestinal tract:* vomiting with metabolic alkalosis, diarrhea **Renal loss** – *osmotic diuresis*: glucosuria, ketonuria, bicarbonaturia – *diuretics*: mainly thiazides! – *renal salt wasting*: interstitial nephropathies, cystic kidney diseases, proximal renal tubular acidosis, congenital tubular disorders – cerebral salt wasting – mineralocorticoid deficit (see Tab. 30.**12**)	**Excessive water intake** – primary psychogenic polydipsia **Syndrome of inappropriate ADH secretion (SIADH)** – *CNS diseases*: tumors, inflammatory conditions (meningitis, encephalitis, abscess), brain trauma, ischemic or hemorrhagic stroke, Guillain–Barré syndrome, acute psychosis – *malignancies*: lung and pancreas carcinoma, lymphomas – *pulmonary diseases*: inflammatory conditions (pneumonia, abscess, tuberculosis, aspergillosis), asthma, cystic fibrosis, respiratory insufficiency – *drugs*: ADH analogues (desmopressin DDAVP, oxytocin), chlorpropamide, vincristin, cyclophosphamide, carbamazepin, tricyclic antidepressive and antipsychotic drugs, NSAIDs – postoperative state, other stress and/or painful situations **Endocrine diseases** – glucocorticoid deficit – hypothyroidism **Reset osmostat** – pregnancy – chronic malnutrition	**Edematous diseases with secondary hyperaldosteronism** – cardiac failure – nephrotic syndrome – liver cirrhosis **Acute and chronic renal failure**

- *euvolemic hyponatremia:* moderate excess in total body water without edema formation and clinically normal volume status
- *hypervolemic hyponatremia:* excess of total body water and sodium with retention of more water than salt.

It is important for the understanding of hypovolemic hyponatremia, as well as hypervolemic hyponatremia (in the context of edematous disorders with secondary hyperaldosteronism), to know that a decrease in the effective circulating volume leads to *nonosmotic* stimulation of vasopressin secretion. This is an expression of the body's priority for volume regulation over osmoregulation. In these cases, the main therapeutic principle is correction of the volume status or the effective circulating volume (e. g., treatment of low cardiac output), whereas euvolemic hyponatremia is mainly treated by water restriction.

Hypovolemic Hyponatremia

Causes. Either renal or extrarenal losses of sodium and water can be responsible for this disorder. For differential diagnosis U_{Na} is a good parameter to measure:

- U_{Na} < 20 mmol/L suggests extrarenal losses via gastrointestinal tract, via skin with severe burns, or into a third space with sepsis, pancreatitis, or peritonitis.
- U_{Na} > 20 mmol/L suggests renal sodium and water loss. Main causes are either secondary due to osmotic diuresis, mineralocorticoid deficiency (see below), or diuretics. Alternatively, this condition can occur in the context of primary renal diseases (interstitial nephritis, polycystic kidney disease, or nephropathy in the contest of analgesic abuse).

Diuretics. In clinical settings, hypovolemic hyponatremia is most often observed following the use of diuretics. It mainly occurs when the dosage of these drugs is not adjusted with reduced water and salt intake or when increased losses occur in the context of acute diseases (e. g., diarrhea). Risk is highest with the use of thiazide diuretics. *Thiazide diuretics* block sodium transport in the distal tubule. As for all other diuretics, urinary dilution is compromised due to sodium loss. However, the interstitial concentration gradient is unchanged, since it is built up in the loop of Henle. In contrast, loop diuretics block sodium transport directly in the loop of Henle and therefore interfere with urinary dilution and concentration by inhibiting the establishment of an interstitial concentra-

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tion gradient. If hypovolemia results in nonosmotic vasopressin stimulation, water retention is much more efficient in the context of thiazide medication than with loop diuretics, which can result in severe hyponatremia in very short time!

Euvolemic Hyponatremia

Causes. The most frequent cause of this disorder is the so-called syndrome of inappropriate anti-diuretic hormone (ADH) secretion (SIADH, Schwartz–Bartter syndrome). The differential diagnosis includes diseases of the central nervous system, pulmonary diseases, malignancies, and drugs, which stimulate ADH secretion or mimic the effect of ADH. The common denominator in all these situations is impaired water excretion due to enhanced vasopressin activity. The typical laboratory signs are:

- hyponatremia
- low serum osmolality
- impaired urinary dilution ($U_{Osm} > 300$ mOsm/L)
- hypouricemia.

Low serum uric acid is a sensitive parameter for the distinction of SIADH and subclinical volume depletion (e. g., in the context of diuretics or a renal or cerebral salt-wasting syndrome). The latter is associated with hyperuricemia.

It is important to recall that any *postoperative state* is associated with inappropriate ADH secretion. Therefore, volume repletion with glucose or hypotonic salt infusion immediately after an operation bears a high risk of acute severe hyponatremia. Young women after gynecologic or obstetric operations represent a patient group with a particularly high risk!

Differential Diagnosis. For diagnosis of SIADH, certain *endocrine disorders* should be excluded, particularly hypocortisolism and hypothyroidism. The pathogenesis of hyponatremia in these diseases is unclear. Another condition with identical laboratory results constellation to SIADH is called *reset osmostat*. These patients have stable mild hyponatremia in the range of 125–130 mmol/L. Typical causes are pregnancy (via human chorion gonadotropin secreted in the placenta) and chronic malnutrition.

Diagnostic Approach to Hyponatremia

The differential diagnosis in patients with hyponatremia is depicted in Fig. 30.**5**. The most important parameters are the serum osmolality, assessment of volume status, urinary osmolality, and urinary sodium concentration.

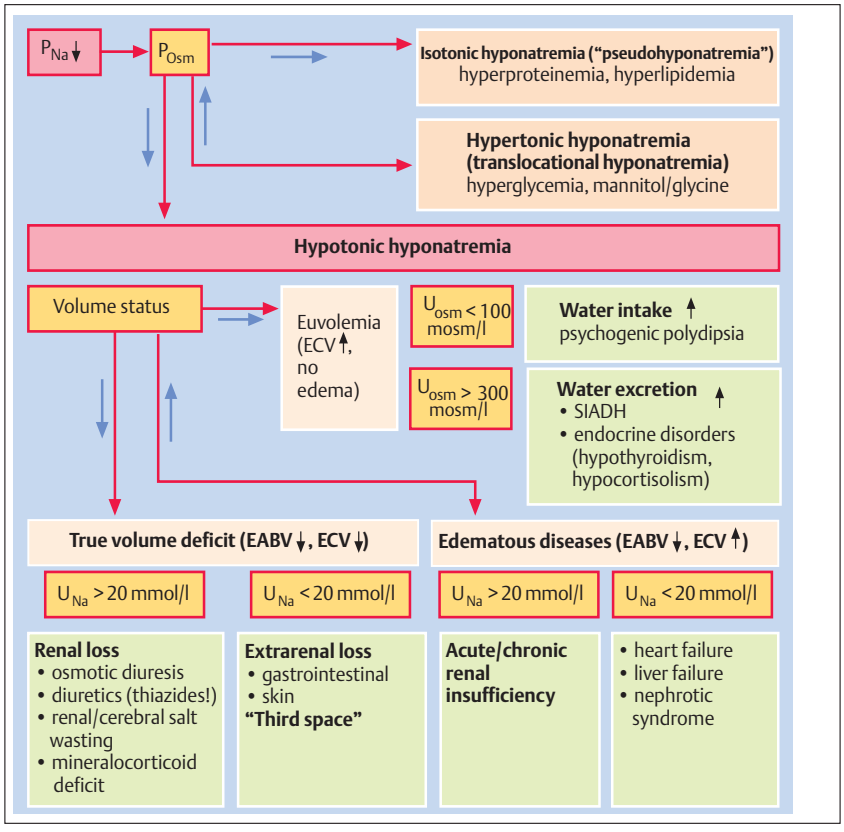

Fig. 30.**5** Diagnostic approach to hyponatremia. ECV = extracellular volume, EABV = effective arterial blood volume.

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Table 30.**8** Differential diagnosis of hypernatremia

Hypovolemic hypernatremia	Euvolemic hypernatremia	Hypervolemic hypernatremia
Extrarenal losses – *skin*: intense sweating, severe burns – *gastrointestinal loss*: diarrhea, fistulas and tubes **Renal losses** – *osmotic diuresis*: severe hyperglycemia with diabetes mellitus, osmotic and loop diuretics – *renal salt wasting*: interstitial and cystic nephropathies, polyuria after obstruction or acute renal failure	**Reduced water intake** – patients with no access to water (children, severely ill and elderly patients) – disturbed thirst sensation (hypothalamic organic lesion) **Extrarenal losses** – *lungs*: hyperventilation with metabolic acidosis, fever and mechanical ventilation – *skin*: intense sweating **Renal losses with central diabetes insipidus** – *congenital/genetic*: *dominant:* vasopressin gene mutation *recessive*: Wolfram syndrome (DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy, deafness) – *acquired*: CNS diseases (trauma, tumor, inflammatory and granulomatous diseases, aneurysm, Guillain–Barré syndrome) **Renal losses with nephrogenic diabetes insipidus** – *congenital/genetic*: *X-linked:* vasopressin V_2 receptor gene mutation *recessive:* aquaporin 2 gene mutation – *acquired*: interstitial nephropathies (analgesics, cystic kidney diseases, obstruction, myeloma kidney, sarcoidosis), chronic renal insufficiency, electrolyte disorders (hypokalemia, hypercalcemia), drugs (lithium, tetracyclines, amphotericin) **Renal losses with gestational diabetes insipidus (placenta-derived vasopressinase secretion)**	**Increased salt intake** – hypertonic infusions (e. g., $NaHCO_3$) – hypertonic dialysis – NaCl tablets **Endocrine diseases** – primary hyperaldosteronism – hypercortisolism

SIADH should be distinguished from *primary polydipsia*. Water intake > 15–20 L per day exceeds the renal capacity for water excretion and will lead to hyponatremia. This condition is easily distinguished from SIADH by measurement of the urinary osmolality, which is below < 100 mOsm/L in the case of polydipsia, but > 300 mOsm/L in the case of SIADH.

Hypervolemic Hyponatremia

This condition is usually associated with *edematous disorders* e. g., heart failure, nephrotic syndrome, and liver cirrhosis. The pathogenesis includes secondary hypoaldosteronism and nonosmotic stimulation of vasopressin secretion, as a consequence of reduced effective circulatory volume, and results in low U_{Na}. The differential diagnosis is usually easy in the clinical context of a given patient.

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Hypernatremia (P_{Na} > 145 mmol/L)

Hypernatremia indicates water deficit in the extracellular space in relation to the total body sodium and is always associated with hyperosmolality. Similar to hyponatremia, we can distinguish three different conditions based on the volume status of the patient. The differential diagnosis is summarized in Tab. 30.**8**:

- *hypovolemic hypernatremia:* deficiency in total body water and sodium with an excess loss of water compared to sodium
- *euvolemic hypernatremia:* moderate excess in total body sodium without edema formation and clinically normal volume status
- *hypervolemic hypernatremia:* excess of total body water and sodium with retention of more salt than water.

Hypernatremia is a rare disorder, since the thirst mechanism is a very efficient compensation of water loss through skin, gastrointestinal tract, and respiration. Therefore, mainly patients with impaired access to free water intake (e. g., small children, elderly, severely ill patients) and patients with hypothalamic lesions affecting the thirst mechanism are affected.

Hypovolemic Hypernatremia

Either *renal or extrarenal causes* can lead to this disorder, which is characterized by an excess of water loss compared to salt loss. Extrarenal losses occur via the gastrointestinal tract (diarrhea, vomiting, fistulas) or the skin (sweating, burns) and are associated with U_{Na} < 20 mmol/L. Renal losses are observed in the context of ketoacidosis or hyperosmotic diabetic coma, but also with primary renal diseases (e. g., postobstructive renal disease or the polyuric phase of acute renal failure).

Euvolemic Hypernatremia

If only water is lost with stable total body sodium, the volume status remains stable. Water shifts occur from the intracellular to the extracellular space in order to maintain ECV and the effective circulatory volume. In the differential diagnosis a differentiation is made between inadequate water intake and renal and/or extrarenal water losses.

Causes. As described above, *inadequate intake* is only seen in patients with impaired access to free water ("too small, too old, too sick") and in patients with hypothalamic lesions affecting the thirst mechanism. Extrarenal water losses occur via the *lungs* and the *skin* (hyperventilation with metabolic acidosis, fever, sweating), whereas renal losses are caused by various forms of *diabetes insipidus*. These two situations can be distinguished by measurement of U_{Osm}. In the case of extrarenal losses urine is concentrated, with U_{Osm} > 800 mOsm/L, whereas in the case of diabetes insipidus urine is diluted, with U_{Osm} < 300 mOsm/L.

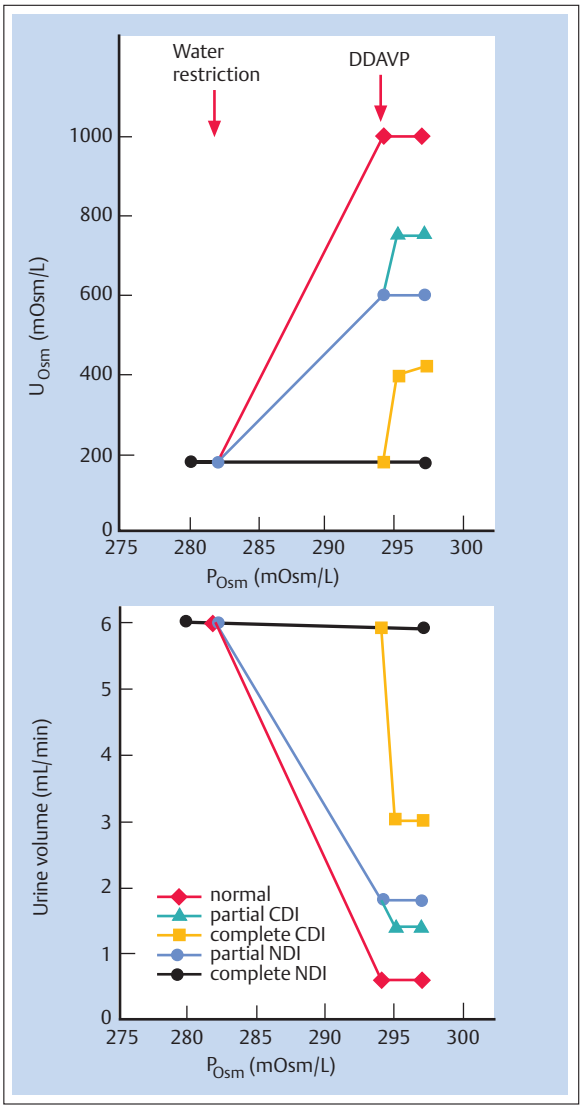

Fig. 30.**6** Scheme for interpretation of a thirst test. The thirst test is used for differential diagnosis between central (CDI) and nephrogenic (NDI) diabetes insipidus. The change of urine osmolality and urine volume is shown after a period with water restriction and subsequent application of a synthetic analogue of vasopressin (DDAVP).

Diabetes Insipidus. Diabetes insipidus is caused by a lack of vasopressin activity and results in polyuria and polydipsia. We can distinguish between *central diabetes insipidus* (CDI) with a lack of *ADH secretion* and *nephrogenic diabetes insipidus* (NDI) with a lack of *ADH effect* at the target organ. The former occurs as a congenital form (e. g., mutation in the vasopressin gene) or acquired in the context of central nervous system diseases. It can be corrected with exogenous application of vasopressin (e. g., the synthetic desmopressin, DDAVP). In contrast,

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NDI does not respond to desmopressin. It also occurs as a congenital disease (mutations in the genes for the vasopressin receptor or the water channel). Acquired forms of NDI are observed with various chronic renal diseases (e. g., interstitial and cystic nephropathies), in the context of electrolyte disorders, e. g., hypokalemia and hypercalcemia, and it can also be caused by certain drugs (e. g., lithium). A particular form of diabetes insipidus is described during *pregnancy*, when placental secretion of an enzyme, called vasopressinase, can lead to accelerated degradation of vasopressin.

The differential diagnosis between central and nephrogenic diabetes insipidus can be made by experimental increase in serum osmolality by water restriction and subsequent application of 5 IU vasopressin ("thirst test").

Typical results of such a test are shown in Fig. 30.**6**.

Hypervolemic Hypernatremia

This disorder is mostly caused by *iatrogenic infusion* of hypertonic salt solutions. This can occur by excess of $NaHCO_3$ in the context of metabolic acidosis or cardiopulmonary reanimation, but also with hypertonic dialysis.

Endocrine disorders, e. g., hyperaldosteronism or hypercortisolism, should also be considered.

Diagnostic Approach to Hypernatremia

The differential diagnosis in patients with hypernatremia is depicted in Fig. 30.**7**. The most important parameters are assessment of the volume status, urine osmolality, and urine sodium concentration.

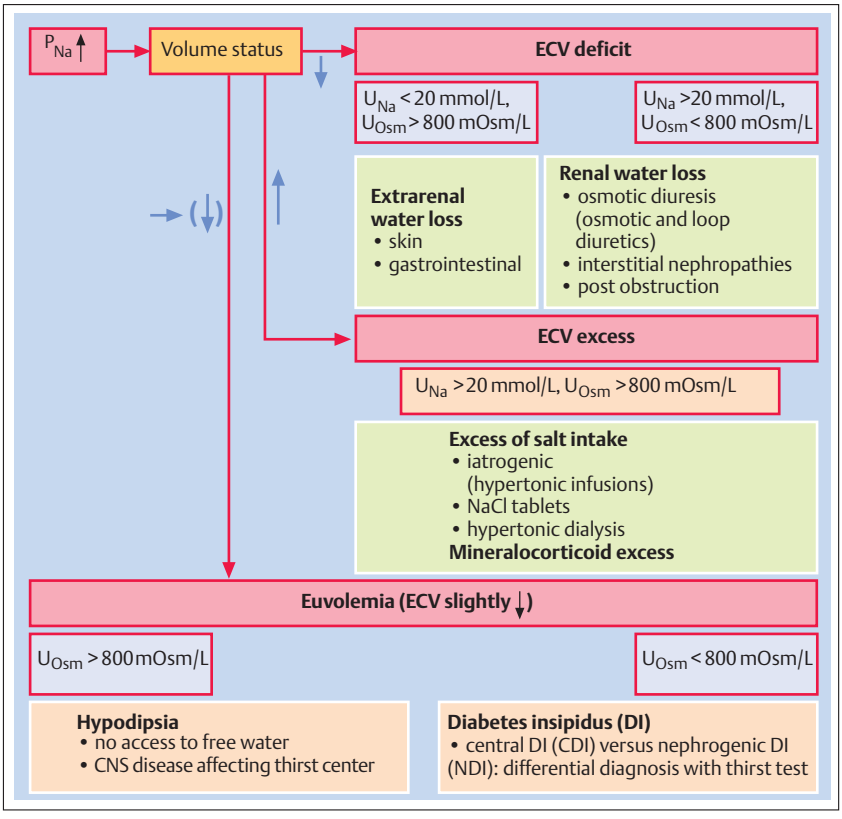

Fig. 30.**7** Diagnostic approach to hypernatremia.

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30.2 Disorders of Potassium Homeostasis

Physiologic Principles

Potassium Distribution and Internal Potassium Balance

As mentioned earlier, potassium is the *main cation in the intracellular space*, where 98 % of total body potassium is stored (see Fig. 30.**2**; Tab. 30.**1**). Potassium, therefore, mainly determines intracellular osmolality. Because of the gradient over the cellular membrane, potassium, together with calcium and magnesium, also considerably influences neuromuscular excitability and the electrochemical gradient for many transport processes in the kidney and the gastrointestinal tract.

Transcellular Potassium Shifts. The serum potassium concentration is regulated in a narrow concentration range (3.5–5.0 mmol/L). Short-term alteration of serum potassium concentration is corrected by potassium shifts between the intracellular and the extracellular space. However, under pathologic conditions such shifts can also cause alterations of serum potassium concentration. The following parameters influence transcellular potassium shifts and therefore the internal potassium balance:

- *Acid–base homeostasis:* with acidosis, hydrogen ions enter the intracellular space along the pH gradient, and, for maintenance of electroneutrality potassium is released to the extracellular space. With alkalosis the contrary happens. Therefore, in most (although not all!) cases acidosis is associated with hyperkalemia, and alkalosis with hypokalemia.
- *Hormones:* insulin and catecholamines both lead to potassium shifts into the intracellular space, the former via sodium–hydrogen exchange, and the latter by activation of Na–K ATPase via β-adrenergic receptors. Both effects are explored therapeutically for treatment of hyperkalemia.
- *Osmolality:* an osmolality increase in the extracellular space leads to a shift of water and potassium into the extracellular space. As a general rule, an osmolality increase of 10 mOsm/L leads to a potassium increase of 0.6 mmol/L.

Potassium Excretion and External Potassium Balance

Apart from transcellular shift, disorders of potassium balance can occur due to changes in *potassium intake and/or potassium excretion*. Both influence the external potassium balance. Potassium excretion is particularly efficient and occurs via the kidney (90 %) and intestines (10 %). Therefore hyperkalemia due to increased intake usually only arises when potassium excretion is decreased, e. g., with renal insufficiency. Conversely, hypokalemia is only observed if the potassium-sparing mechanism of the kidneys is inhibited, e. g., by use of diuretics.

Potassium Regulation in the Kidney. As a general principle, disorders of potassium balance (severe disturbances of internal balance excluded) are always associated with a *disturbance of potassium regulation in the kidney*. Potassium excretion in the kidney depends on two parameters: *mineralocorticoid activity* and *distal sodium delivery*. Only if both parameters are altered in the same direction can disorders in potassium balance occur. This principle is shown schematically in Fig. 30.**8**. Hormones with mineralocorticoid activity (mainly aldosterone) have two main effects in the collecting duct: stimulation of Na–K ATPase and stimulation of the luminal sodium channel. The net effect is increased sodium reabsorption combined with increased potassium excretion. An increased distal sodium delivery to the collecting duct also leads to increased sodium reabsorption and, for maintenance of electroneutrality, to increased potassium loss.

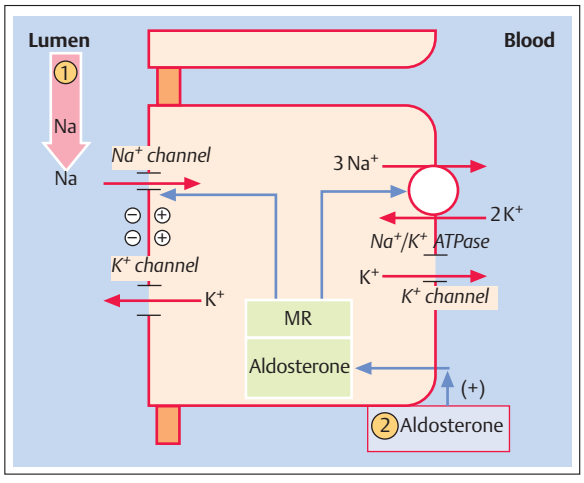

Fig. 30.**8** Mechanisms of potassium excretion in the collecting duct. A disorder of renal potassium excretion can occur via two principle mechanisms: (1) via a change in distal sodium delivery, or (2) via a change in mineralocorticoid activity. MR = mineralocorticoid receptor.

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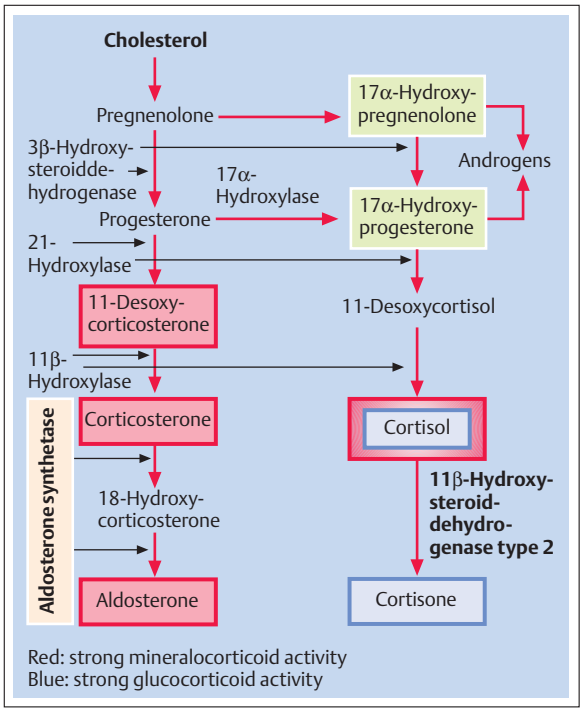

Fig. 30.**9** Scheme of steroid biosynthesis. The different steps in aldosterone and cortisone synthesis are shown with the respective enzymes.

Potassium homeostasis is linked to volume regulation via sodium excretion and mineralocorticoid activity.

The basic pathogenetic determinants of disorders of potassium excretion are summarized in Tab. 30.**9** and are discussed systematically in the following paragraphs.

Acid–base disorders not only lead to transcellular potassium shifts, but also modulate mechanisms of renal potassium excretion. As a general rule, alkalosis promotes, and acidosis inhibits, potassium excretion in the distal nephron.

Steroid Biosynthesis

Aldosterone. The main hormone with mineralocorticoid activity is aldosterone, which is synthesized in the *adrenal cortex*. Aldosterone secretion is stimulated via the renin–angiotensin–aldosterone system in the context of renal hypoperfusion, but also directly by hyperkalemia. Apart from aldosterone, other steroid hormones also have mineralocorticoid activity. To understand potassium disorders, we therefore have to review the pathways of steroid biosynthesis. The respective steps and responsible enzymes are shown in Fig. 30.**9**.

11-Desoxycorticosterone. The most important hormone with mineralocorticoid activity, apart from aldosterone, is 11-desoxycorticosterone. Cortisol also binds to the mineralocorticoid receptor with similar affinity as aldosterone. However, this is normally prevented by an enzyme called 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which immediately transforms cortisol into cortisone. Cortisone has only glucocorticoid activity, but does not bind to the mineralocorticoid receptor. Congenital and acquired disorders with decreased 11β-HSD2 activity, therefore, lead to mineralocorticoid excess.

Table 30.**9** Determinants of renal potassium excretion

Clinical situation			Determinant		Potassium homeostasis	
Pathophysiology (primary disorder)	Volume	Example	Distal sodium delivery	Mineralocorticoid activity	Renal potassium excretion	Serum potassium
ECV deficit	↓ ↓	Bleeding	↓	↑	→	→
ECV excess	↑ ↑	NaCl infusion	↑	↓	→	→
Mineralocorticoid deficit	↓	Addison disease	↓	↓ ↓	↓	↑
Mineralocorticoid excess	↑	Conn disease	↑	↑ ↑	↑	↓
Decreased distal sodium delivery	↑	Renal failure	↓ ↓	↓	↓	↑
Increased distal sodium delivery	↓	Diuretics	↑ ↑	↑	↑	↓

Double arrows indicate the primary disorder.

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Hypokalemia and Hyperkalemia

Definition, Diagnosis, and Clinical Features

Hypokalemia is defined as a decrease in serum potassium concentration < 3.5 mmol/L (severe: < 2.5 mmol/L), *hyperkalemia* as an increase > 5.0 mmol/L (severe: > 6 mmol/L). Internal and external disorders of potassium balance cannot be distinguished by measurement of serum potassium concentration and have to be analyzed as described below.

Diagnosis. When analyzing potassium disorders the potential of an artifact in serum potassium measurement should always be considered. Whereas the measurement of potassium concentration with ion-selective electrodes is very reliable, preanalytical conditions can have a major influence on the results. *Pseudohyperkalemia* occurs when cytolysis occurs in-vitro. This is observed with very high cell numbers (thrombocytosis, chronic myelogenous leukemia), with in-vitro hemolysis (long transport times), and with difficult blood draws. Conversely, *pseudohypokalemia* can occur via transcellular shift into cells after intravenous insulin application shortly before a blood draw, but also with high cell numbers and long transport times at room temperature.

Renal potassium excretion can be estimated by the measurement of urinary potassium concentration (U_K). However, it is important to recall that urinary potassium excretion is also influenced by renal sodium and water excretion. Therefore, a change in urinary potassium concentration is more difficult to interpret in the context of such concomitant disorders.

Clinical Features. Because of the mentioned functions of potassium as the main intracellular cation, symptoms of potassium disorders are mainly characterized by alteration in *neuromuscular excitability*. In general, hypokalemia leads to an increase in the membrane potential and therefore to reduced excitability, whereas hyperkalemia leads to a decreased membrane potential and increased excitability. The symptoms and signs for both disorders are summarized in Tab. 30.**10**. The typical ECG alterations with hypokalemia and hyperkalemia are depicted in Fig. 30.**10**.

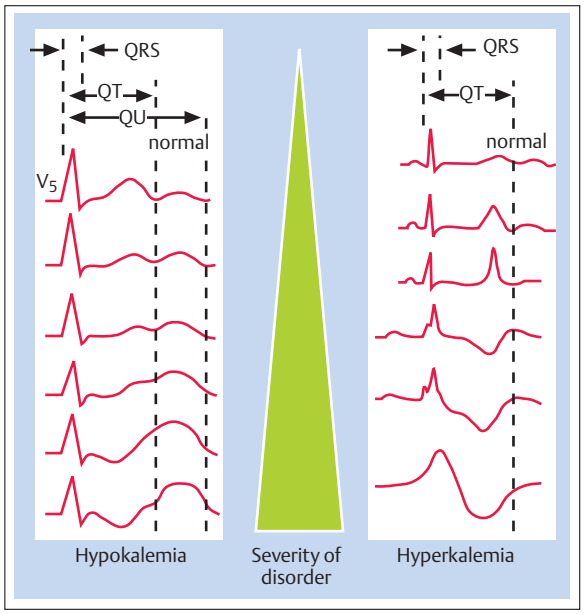

Fig. 30.**10** Typical ECG changes with potassium disorders, depending on the degree of severity. The appearance of a U wave is a hallmark for hypokalemia, whereas QRS widening and QT prolongation are seen with hyperkalemia.

Table 30.**10** Symptoms and signs of potassium disorders

	Hypokalemia	Hyperkalemia
General symptoms	– fatigue – nausea, vomiting	– fatigue – nausea, vomiting
Skeletal muscles	– muscle weakness – reduced muscle tone → paralysis due to hyperpolarization block – rhabdomyolysis (only in severe cases)	– rapid exhaustion – increased excitability → paralysis due to depolarization block
Smooth muscles	– constipation, ileus – disturbed bladder function	– ileus
Cardiac muscle	– increased sensitivity to digoxin – arrhythmias (until asystole) – ECG: flattened T wave, U wave	– reduced sensitivity to digoxin – arrhythmias (until ventricular fibrillation) – ECG: increased T wave, QRS widening, atrioventricular or intraventricular block
Other disorders	– metabolic alkalosis – nephrogenic diabetes insipidus – glucose intolerance	– metabolic acidosis

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Table 30.**11** Differential diagnosis of hypokalemia

Hypokalemia due to reduced potassium intake

- malnutrition: kwashiorkor, anorexia/bulimia, chronic alcoholism, etc.
- malabsorption: celiac sprue, Crohn disease, etc.

Note: in most cases reduced intake only plays a role if there are concomitant renal or extrarenal potassium losses!

Hypokalemia due to transcellular shifts (disorders of internal potassium balance)

Increased cell proliferation

- rapidly proliferating tumors (lymphomas, leukemias, small-cell lung cancer)
- vitamin B_{12} therapy of severe pernicious anemia
- refeeding syndrome (therapy of severe malnutrition)

Potassium shift from ECS to ICS

- metabolic alkalosis
- insulin
- catecholamines (endogenous source: stress, delirium tremens; exogenous source: β-adrenergic stimulators, therapy of shock)
- hyperthyroidism
- other drugs (theophylline, chloroquine, verapamil)
- *genetic disease*: familial periodic hypokalemic paralysis (trigger: exercise, carbohydrate-rich meals)

Hypokalemia due to extrarenal losses

Gastrointestinal loss

- diarrhea, fistulas
- laxatives, ion exchanger

Skin

- intense sweating

Hypokalemia due to renal losses

Increased distal sodium delivery (associated with hypotension)

Acquired diseases

- diuretics (= most frequent cause!): all classes of diuretics except potassium-sparing drugs
- bicarbonaturia: metabolic alkalosis, proximal renal tubular acidosis
- other anions in urine: penicillin, ketones
- magnesium deficiency (usually due to drug therapy with diuretics, aminoglycoside antibiotics, cisplatin, amphotericin B or foscarnet)

Genetic diseases

- Bartter syndrome (with hypercalciuria and mild hypomagnesemia; various subtypes/mutations)
- Gitelman syndrome (with hypocalciuria and moderate to severe hypomagnesemia)

Mineralocorticoid excess associated with hypertension

Acquired diseases

- hyperreninemic hyperaldosteronism:
  - renal artery stenosis
  - renin-producing tumor
- hyporeninemic hyperaldosteronism:
  - aldosterone-secreting adrenal adenoma (Conn disease)
  - bilateral adrenal hyperplasia
- "pseudohyperaldosteronism":
  - hypercortisolism (pituitary, adrenal, ectopic)
  - acquired 11β-HSD2 deficiency (licorice, carbenoxolon)
  - desoxycorticosterone-secreting tumor
  - therapeutic use of mineralocorticoid or glucocorticoid drugs

Genetic diseases

- hyporeninemic hyperaldosteronism: glucocorticoid remediable aldosteronism (GRA) (fusion of the aldosterone synthase gene with the promoter region of 11β-hydroxylase)
- "pseudohyperaldosteronism":
  - Liddle syndrome (activating mutation of the distal sodium channel ENaC)
  - activating mutation of the mineralocorticoid receptor (S810L)
  - congenital 11β-HSD2 deficiency (apparent mineralocorticoid excess, AME)
  - aldosterone deficiency with accumulation of desoxycorticosterone (11β-/17α-hydroxylase deficiency)

Hypokalemia ($P_K < 3.5$ mmol/L)

An overview on causes of hypokalemia is presented in Tab. 30.**11**.

Hypokalemia Due to Reduced Potassium Intake

This type of hypokalemia occurs with all variations of *malnutrition and/or malabsorption*. Examples are kwashiorkor, anorexia/bulimia, chronic alcoholism, and generalized malabsorption in the context of celiac sprue, or Crohn disease, etc. However, the potassium-sparing mechanism of the kidney is very efficient. Therefore, hypokalemia usually only occurs with *concomitant renal potassium loss*, e. g., with the additional use of diuretics.

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Hypokalemia Due to Transcellular Shifts (Disorders of Internal Balance)

Two main pathogenetic situations can be distinguished:

- *Massively enhanced cell proliferation that uses up all available potassium:* examples are rapidly growing lymphomas or acute leukemias. The same mechanism plays a role in the treatment of severe forms of pernicious anemia and of severe malnutrition. The latter situation was termed "refeeding syndrome" and was first described in World War II in patients leaving concentration camps, but it was later also observed in severely ill patients with severe malnutrition after a long stay in intensive care units.
- *Potassium shift from the extracellular to the intracellular space with constant cell proliferation:* this mechanism occurs with insulin therapy (especially in the context of diabetic coma), alkalosis, endogenous and exogenous catecholamines, hyperthyroidism, and with certain drugs (e. g., theophylline). The same mechanism plays a role in a rare genetic disease called *familial periodic hypokalemic paralysis*. Various mutations in sodium, calcium, and potassium channels were described as a potential cause of this syndrome. The common denominator is the occurrence of hypokalemia with paralytic symptoms in association with adrenergic stimuli (e. g., physical exercise) and with insulin secretion (after carbohydrate-rich meals).

Hypokalemia Due to Enhanced Potassium Loss

Under physiologic conditions only 10 % of potassium excretion occurs via extrarenal routes, mainly the gastrointestinal tract. *Diarrhea* of various origins (infectious, malabsorption, etc.) can lead to massively enhanced extrarenal potassium loss and subsequent hypokalemia. In rarer cases, certain drugs can also be responsible (abuse of laxatives, overdose of potassium-binding ion exchangers). In order to distinguish renal and extrarenal potassium loss, urinary potassium concentration should be measured.

> Renal potassium loss is by far the most common cause of hypokalemia.

As mentioned above, only two parameters influence renal potassium excretion: distal sodium delivery and overall mineralocorticoid activity. Hence, in the context of hypokalemia with renal potassium loss, we can distinguish between disorders with enhanced distal sodium delivery (ECV contraction and hypotension) and disorders with primary mineralocorticoid excess (ECV expansion and hypertension).

Hypokalemia with Normal or Reduced Blood Pressure (Enhanced Distal Sodium Delivery). Distal sodium delivery is enhanced with *diuretic therapy* (all classes of diuretics except potassium-sparing drugs). It occurs most often with the use of loop and thiazide diuretics. Distal sodium delivery also increases with the presence of high anion concentrations in the urine that use sodium as the cation for excretion. Examples are *bicarbonate* in the context of metabolic alkalosis and proximal renal tubular acidosis and also therapy with *high-dose penicillin*. Finally, *magnesium deficiency* blocks sodium reabsorption in the loop of Henle and therefore leads to enhanced distal sodium delivery and concomitant potassium loss.

A variety of genetic disorders of sodium transport lead to enhanced distal sodium delivery and potassium loss. The genetic defect in various types of *Bartter syndrome* is located in the loop of Henle and is comparable to chronic treatment with loop diuretics. The disorder is usually severe and manifests in early childhood. In contrast, the defect in *Gitelman syndrome* is located in the distal tubule and is comparable to chronic thiazide treatment. Hypomagnesemia is usually a prominent feature of this disorder, which is less severe and often diagnosed only in adulthood.

Hypokalemia with Hypertension (Mineralocorticoid Excess). *Hyperaldosteronism* leads to ECV expansion, hypertension, and hypokalemia. This includes acquired forms of hyperreninemic hyperaldosteronism in the context of renal artery stenosis as well as hyporeninemic hyperaldosteronism with an aldosterone-producing adenoma of the adrenal cortex (Conn syndrome) or with bilateral diffuse hyperplasia of the adrenal cortex.

A rare, but interesting, disease should be considered in the differential diagnosis of hyporeninemic hyperaldosteronism. The disorder is called glucocorticoid-suppressible hyperaldosteronism. Pathogenetically, a new fusion gene appears, which is comprised of aldosterone synthase linked to the promoter region of 11β-hydroxylase (11β-HSD2) (see Fig. 30.**9**). This promoter is under the control of ACTH. Therefore, ACTH stimulates aldosterone instead of cortisol production. Since aldosterone does not allow for negative feedback on ACTH production, this disease leads to mineralocorticoid excess, which can be treated by exogenous application of dexamethasone.

A variety of diseases are associated with mineralocorticoid excess, but with low aldosterone levels (sometimes called "*pseudohyperaldosteronism*"). Acquired forms occur with hypercortisolism (central or adrenal Cushing syndrome) and acquired 11β-HSD2 deficiency with licorice consumption. *Genetic forms* are activating mutations in the distal sodium channel (Liddle syndrome) or in the mineralocorticoid receptor as well as the inborn 11β-HSD2 deficiency (also-called "apparent mineralocorticoid excess," AME).

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Diagnostic Approach to Hypokalemia

The differential diagnosis in a patient with hypokalemia is depicted in Fig. 30.**11**. The most important parameters are urinary sodium excretion and blood pressure. In situations with increased distal sodium delivery, urinary chloride concentration may be useful for further distinction. In the context of mineralocorticoid excess, measurement of renin and aldosterone are helpful.

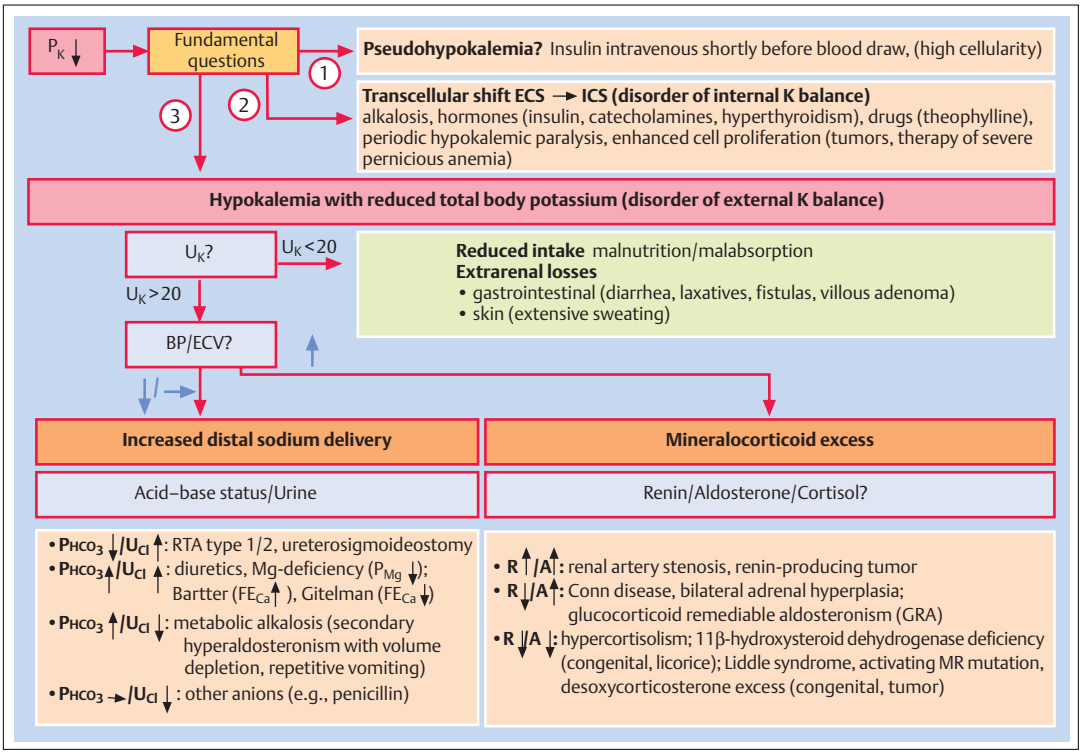

Fig. 30.**11** Diagnostic approach to hypokalemia. BP = Blood pressure, R = Renin, A = Aldosterone.

Hyperkalemia (P_K > 5.0 mmol/L)

An overview of the causes of hyperkalemia is shown in Tab. 30.**12**.

Hyperkalemia Due to Excessive Potassium Intake

Excessive potassium intake occurs via *food* or *drugs*. Food rich in potassium includes chocolate and various types of fruits (bananas, grapes, oranges, dried fruit). Overdose of therapeutically administered potassium chloride or potassium citrate can lead to hyperkalemia as well as infusion of blood and certain drugs (e. g., high-dose penicillin).

As with hypokalemia, it is also true for hyperkalemia that changes in intake only lead to relevant potassium disorders when *renal potassium excretion* is impaired at the same time, i. e., preexistent chronic renal insufficiency.

Hyperkalemia Due to Transcellular Shifts (Disorders of Internal Balance)

Analogous to hypokalemia, two main pathogenetic mechanisms can be distinguished:

- *Massive cytolysis:* classic examples are massive hemolysis, rhabdomyolysis including malignant hypothermia, and tumor lysis syndrome associated with chemotherapy of acute leukemias or rapidly growing lymphomas. In these situations combined electrolyte disorders including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia are typically found.
- *A potassium shift from the intracellular to the extracellular space* occurs with metabolic and respiratory acidosis, insulin deficiency, drugs (β-blockers, digoxin, depolarizing muscle relaxing agents [e. g., succinylcholine]). A rare genetic disorder, *familial periodic hyperkalemic paralysis*, is caused by a mutation in a sodium channel and leads to exercise-induced hyperkalemia with paralytic symptoms.

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Table 30.**12** Differential diagnosis of hyperkalemia

Hyperkalemia due to increased potassium intake

- potassium-rich food (fruits, dried fruits, dark chocolate, various salts for food seasoning)
- oral therapy with potassium chloride or potassium citrate
- potassium-rich infusions (high-dose penicillin, blood transfusions)

Note: in most cases increased intake only plays a role with concomitant disorders of potassium excretion!

Hyperkalemia due to transcellular shifts (disorders of internal potassium balance)

Increased cell death
- massive hemolysis
- rhabdomyolysis
- malignant hyperthermia
- tumor lysis syndrome

Potassium shifts from ICS to ECS
- metabolic acidosis
- insulin deficiency
- drugs: beta-blockers, digoxin, succinylcholine
- *genetic disorder*: familial periodic hyperkalemic paralysis (trigger: exercise)

Hyperkalemia due to reduced renal excretion

Reduced distal sodium delivery (with hypertension)

Acquired diseases
- acute and chronic renal insufficiency (= most frequent cause!)
  - intrinsic renal disease
  - postrenal causes

Genetic disease
- pseudohypoaldosteronism type 2 = Gordon syndrome (activating mutation of the protein kinase WNK in the distal nephron with increased sodium reabsorption = functionally "inverted Gitelman syndrome")

Mineralocorticoid deficiency

Acquired diseases
- hyperreninemic hypoaldosteronism:
  - adrenocorticoid insufficiency with combined mineralocorticoid and glucocorticoid deficiency = Addison disease (autoimmune, tuberculosis)
  - selective drug-induced mineralocorticoid deficit (ACE inhibitor, angiotensin-receptor blockers, heparin!)
- hyporeninemic hypoaldosteronism (often combined with renal tubular acidosis type 4 and mild renal insufficiency):
  - diabetic nephropathy
  - tubulointerstitial diseases
  - drugs: NSAIDs
- aldosterone resistance:
  - damage to collecting ducts due to interstitial nephropathies, sickle cell anemia, amyloidosis, obstructive nephropathy etc.
  - drugs: potassium-sparing diuretics (Na channel blockers: amiloride, triamteren; mineralocorticoid receptor blocker: spironolacton), digoxin (Na–K ATPase blocker)

Genetic diseases
- hyperreninemic hypoaldosteronism:
  - combined mineralocorticoid and glucocorticoid deficiency with various subtypes of the adrenogenital syndrome associated with bilateral adrenal hyperplasia (3β-hydroxysteroid dehydrogenase/21-hydroxylase/11β-hydroxylase deficiency)
  - selective aldosterone deficiency (aldosterone synthase deficiency)
- pseudohypoaldosteronism (aldosterone resistance):
  - pseudohypoaldosteronism type 1A (dominant; inactivating mutation of the mineralocorticoid receptor)
  - pseudohypoaldosteronism type 1B (recessive; inactivating mutation of the distal sodium channel ENaC = functionally "inverted Liddle syndrome")

Hyperkalemia Due to Reduced Potassium Excretion

Since 90% of potassium is excreted by the kidneys, hyperkalemia due to reduced potassium excretion is always of renal origin. As mentioned above, two parameters, distal sodium delivery and mineralocorticoid activity, determine renal potassium excretion. Therefore, hyperkalemia disorders with reduced distal sodium delivery can be distinguished from disorders with primary mineralocorticoid deficit.

Hyperkalemia Due to Disorders with Reduced Distal Sodium Delivery. The classical examples for this condition are all forms of *intrarenal* and *postrenal acute and chronic renal insufficiency*. The loss of nephrons leads to a reduced glomerular filtration rate and subsequently to a reduction of natriuresis with sodium and water retention and hypertension. The concomitant metabolic acidosis of renal failure exacerbates the hyperkalemia. In contrast, volume depletion in the context of prerenal renal failure does not lead to hyperkalemia, since potassium excretion is enhanced by secondary hyperaldosteronism (Tab. 30.**9**).

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Gordon syndrome (pseudohypoaldosteronism type 2) is a congenital disease with reduced distal sodium delivery. The activating mutation of a protein kinase in the distal tubule leads to increased sodium reabsorption in this nephron segment, a situation functionally comparable to an "inverse Gitelman syndrome."

Hyperkalemia Due to Mineralocorticoid Deficiency. Pathogenetically, disorders of aldosterone deficiency can be distinguished from disorders with aldosterone resistance.

Total destruction of the adrenal cortex leads to a condition with *hyperreninemic hypoaldosteronism*. It results in combined mineralocorticoid and glucocorticoid deficiency (Addison disease) including hyperkalemic acidosis, hypotension, and hyponatremia. Certain drugs lead to a selective blockade of the aldosterone axis (e. g., ACE inhibitors, angiotensin receptor blockers, heparin). In contrast, *hyporeninemic hypoaldosteronism* is classically observed in the context of diabetic and interstitial nephropathies or treatment with nonsteroidal antirheumatic drugs. The typical constellation is the combination of hyperkalemia with renal tubular acidosis type 4, hypertension, and slightly impaired renal function. Pathogenetically, a damage of the juxtaglomerular apparatus is postulated.

Genetic variants of hypoaldosteronism occur with different forms of adrenogenital syndrome as well as with isolated aldosterone synthase deficiency (see Fig. 30.**9**; Tab. 30.**12**).

Disorders with mineralocorticoid resistance but high levels of aldosterone should be differentiated from true hypoaldosteronism. Acquired mineralocorticoid resistance occurs in the context of various nephropathies with damage to the collecting ducts (e. g., tubulointerstitial nephropathies, sickle cell disease, amyloidosis, obstructive nephropathy). Certain drugs, e. g., potassium-sparing diuretics (amiloride), mineralocorticoid-receptor blockers (spironolactone), and digoxin, interfere with potassium excretion in distal nephron. Finally, genetic disorders with mineralocorticoid resistance are known as *pseudohypoaldosteronism type 1A* (inactivating mutation of the mineralocorticoid receptor) and *type 1B* (inactivating mutation of the distal sodium channel).

Diagnostic Approach to Hyperkalemia

The differential diagnosis in patients with hyperkalemia is depicted in Fig. 30.**12**. The most important parameters are renal function, aldosterone levels, and blood pressure. In special situations, renin measurement can be helpful.

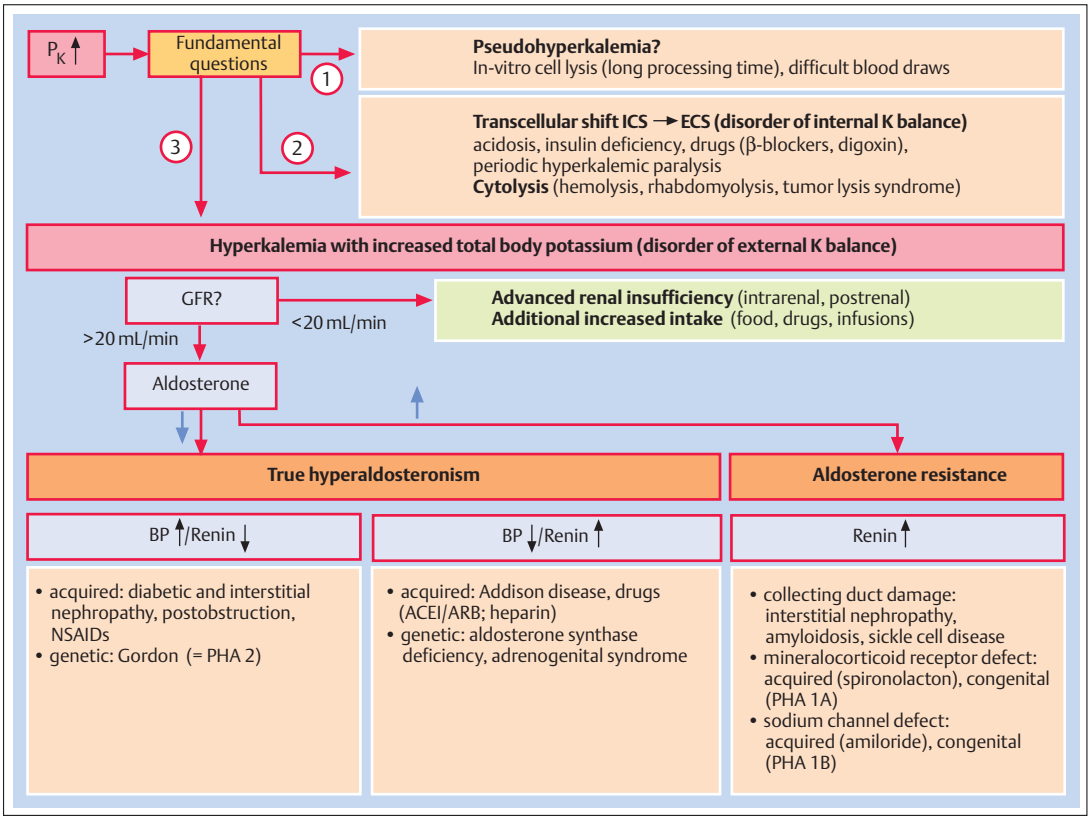

Fig. 30.**12** Diagnostic approach to hyperkalemia. GFR = Glomerular filtration rate, BP = Blood pressure, PHA = pseudohypoaldosteronism.

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30.3 Disorders of Acid–Base Homeostasis

Physiologic Principles

Basics of Acid–Base Metabolism

The acid concentration in a given fluid is determined by the concentration of free hydrogen ions (H^+) and is indicated as pH, which can be calculated as follows:

$$pH = -\log [H^+]$$

The pH is dependent on the relative concentration of acids (= H^+ donors) and bases (= H^+ acceptors) in this fluid. The chemical equilibrium can be described as follows:

$$[HA] \longleftrightarrow [H^+] + [A^-]$$

(HA = acid, A^- = base)

The strength of a given acid is characterized by its specific pK_a value, which has the following relation to pH:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Under physiologic conditions, acids and bases accumulate in the body, either by food intake or as metabolites. In total, acid accumulation exceeds base production. Therefore, without any specific mechanisms for H^+ excretion, the body would slowly acidify. Table 30.**13** gives specific information on quantitative accumulation of acids. The main component is *carbonic acid* that is transformed to water and carbon dioxide, which then can be excreted by respiration (see below).

As a general rule, the net accumulation of acids that are excreted by the kidneys is about 1 mmol H^+/kg body weight or 60–100 mmol/day.

Levels of Acid–Base Regulation

Stability of pH is essential for many vital functions. Especially, the function of most enzymes is dependent on stable pH. The physiologic pH lies between 7.35–7.40, which corresponds to a proton concentration of 40–45 nmol/L. pH values under 6.8 (corresponds to $[H^+] > 160$ nmol/L) or over 7.8 (corresponds to $[H^+] < 16$ nmol/L) are usually not compatible with life.

The human body maintains three "*lines of defense*" against excessive accumulation of acids or bases, which are summarized in Tab. 30.**14**. Some of them only allow for temporary regulation (buffer systems), whereas others allow definitive correction (true excretion of acid or base).

Intracellular and Extracellular Buffer Systems. As a first line of defense, intracellular and extracellular buffer systems can mitigate the impact of acid or base accumu-

Table 30.**13** Normal acid–base balance

Acid	Acid production (mmol/day)	Primary excretion
Volatile acids		
– H_2CO_3	15 000–20 000	pulmonary
– lactate (metabolized to CO_2)	750–1500	pulmonary
Fixed acids		
– sulfuric acid – phosphoric acid – hydrochloric acid – organic acids	60–100	renal

Table 30.**14** Physiologic compensatory responses to acid–base disorders

Level	Mechanism	Buffer system	Buffer or excretion capacity	Time to response
1	**Buffer systems** – intracellular – extracellular	proteins including hemoglobin, organic phosphates bicarbonate system	~ 1000 mmol total	minutes to hours
2	**Respiratory compensation** – ventilation	bicarbonate system	> 20 000 mmol/day	6–12 hours
3	**Renal compensation** – bicarbonate reabsorption – acid excretion	bicarbonate system ammonia, phosphate, other titrable acids	30–350 mmol/day	2–5 days

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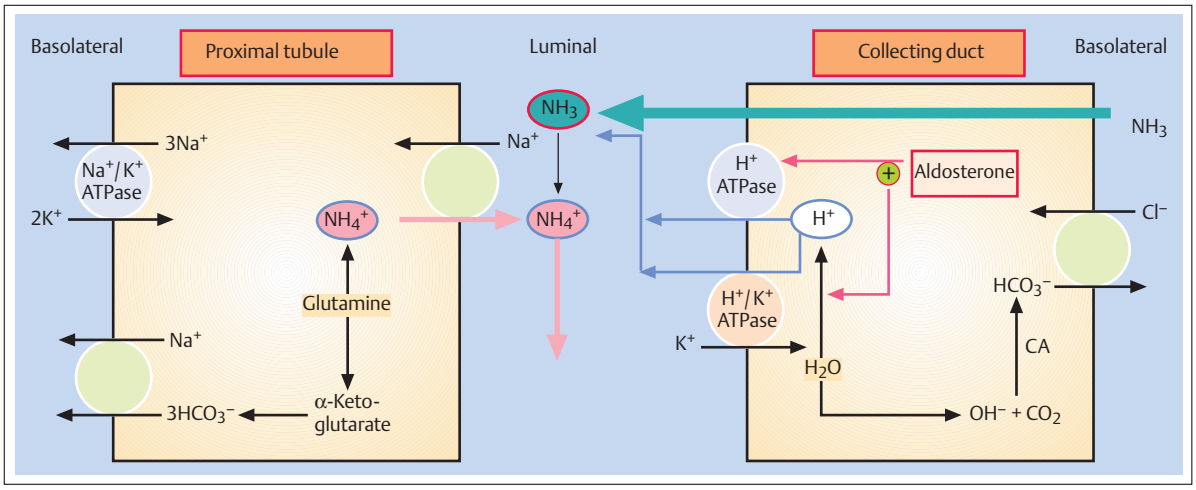

Fig. 30.**13** Mechanisms of renal ammonium excretion. The relevant channels and pumps are shown for the proximal tubule on the left and for the collecting duct on the right side. In the proximal tubule, ammonium is transported and directly excreted, whereas in the collecting duct, ammonia (NH_3) crosses the epithelium by diffusion and then forms ammonium (NH_4^+) ions on the luminal side. CA = carboanhydrase.

lation on pH changes. Buffer systems are effective within minutes to hours. The most important buffer systems and their buffering capacity are mentioned below:

- *ECS:* bicarbonate 40% (see Respiratory Compensation, below)
- *ICS:* proteins including hemoglobin 35% (mainly the basic amino acid histidine), and organic phosphates 25%.

The total body buffering capacity is about 1000 mmol H^+ and therefore, clearly below the daily acid accumulation (see Tab. 30.**13**). This underlines the important significance of efficient mechanisms for acid excretion.

Respiratory Compensation. The second line of defense is the respiratory compensation. It also relies on the bicarbonate buffering system and is effective within six to 12 hours. The bicarbonate buffer system is an open system, which allows exhalation and therefore definite excretion of CO_2 via the lungs. As shown in Tab. 30.**13**, most endogenously produced acid is excreted by this system. The relation between CO_2 and pH can be described by the Henderson–Hasselbalch equation:

$$pH = pK_a\,(H_2CO_3) + \log\frac{[HCO_3^-]}{[H_2CO_3]} = 6.1 + \log\frac{[HCO_3^-]}{0.03 \times P_{CO_2}}$$

It is, however, important to recognize that respiratory compensation is only possible for primary metabolic disorders and that it allows only the excretion of volatile, but not fixed acids (see Tab. 30.**13**).

Renal Compensation. The third line of defense is represented by renal compensation of acid–base disorders. It is fully effective only after two to five days. In contrast to respiratory compensation, metabolic as well as respiratory acid–base disorders are compensated, and also fixed acids can be excreted by renal compensation. The kidney uses various mechanisms to accomplish this task:

- tubular reabsorption of bicarbonate
- tubular excretion of acid via titration of ammonia and titrable acid (TA; mainly phosphate) in the urine.

The *net urinary acid excretion* (NAE) can be described as follows (normal values are given in brackets):

NAE (80 mmol) = NH_4^+ (40 mmol) + TA (40 mmol) – HCO_3^- (0 mmol)

This formula shows that the bicarbonate system does not contribute to net acid excretion in the kidney, but it only allows regeneration of filtrated bicarbonate. However, in the case of proximal renal tubular acidosis, renal bicarbonate loss is the pathogenetic principle of acidosis.

Regulation of Renal Acid Excretion

Since urinary titrable acid (mainly phosphate) has a pK_a value of 6.8 and cannot be regulated in quantity, the capacity for acid excretion is saturated with a urinary pH of 6.0 and limited to 40 mmol/day.

Ammoniogenesis. Ammoniogenesis is the main mechanism of regulation of acid excretion in the kidney. It can be varied between 30–300 mmol/day. Fig. 30.**13** shows the mechanisms of ammoniogenesis, which differ between the proximal tubule (left side) and the collecting duct (right side). In the proximal tubule ammonia combines with H^+ to form ammonium intracellularly,

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whereas in the collecting duct ammonia freely diffuses to the luminal side, where it combines with H^+ that is actively secreted via a H^+ ATPase and H^+/K^+ ATPase. Three main parameters influence ammoniogenesis:

- *decrease of extracellular pH:* stimulates proximal and distal mechanisms
- *aldosterone:* stimulates distal H^+ ATPase and H^+/K^+ ATPase activity
- *decrease of plasma potassium concentration:* stimulates the H^+/K^+ ATPase activity (ΔP_K of +0.6 mmol/L → ΔpH of –0.1).

Acidosis and Alkalosis

Definition, Diagnosis, and Clinical Features

Acidosis means net acid accumulation with a decrease of pH < 7.35. In contrast, *alkalosis* occurs with net accumulation of base (or net loss of acid) with an increase of pH > 7.40.

Based on pathogenesis, acid–base disorders can be classified as follows:

- *simple disorders:*
  - respiratory disorders with primary change in P_{CO_2}: respiratory acidosis/alkalosis
  - metabolic disorders with primary change in $[HCO_3^-]$: metabolic acidosis/alkalosis
- *complex disorders:*
  - combination of a metabolic and a respiratory disorder
  - combination of two metabolic disorders
  - triple acid–base disorders (two metabolic and one respiratory or three metabolic disorders).

Arterial Blood Gas Analysis. Diagnosis of acid–base disorders is performed with arterial blood gas analysis. It is important to recall that with this method *pH is measured in the extracellular space*. Intracellular pH values are normally lower (7.1 instead of 7.4) and probably physiologically more important. However, since there is a largely linear correlation between intracellular and extracellular pH, arterial blood gas analysis is sufficient for clinical purposes.

Simple Acid–Base Disorders. These can be diagnosed when:

- P_{CO_2} and $[HCO_3^-]$ change in the same direction
- the compensation is in the expected range

Tab. 30.**15** shows the pattern for the four principle acid–base disorders. Double arrows indicate the primary change. As mentioned above, respiratory compensation of metabolic disorders occurs within a few hours, whereas the renal compensation of respiratory disorders requires a few days. Therefore, the analysis of compensation in the case of respiratory disorders has to distinguish between acute and chronic conditions. The analysis of compensation can be performed by various means:

- by using empiric formulas, which are summarized in Tab. 30.**15**
- by using acid–base nomograms as depicted in Fig. 30.**14**
- in the case of metabolic disorders with $[HCO_3^-]$ between 10–40 mmol/L, a simple general rule can be applied as follows:

$$[HCO_3^-] + 15 = P_{CO_2} = \text{pH (digits after decimal point)}$$

Example: A metabolic acidosis with $[HCO_3^-]$ = 15 mmol/L has adequate respiratory compensation, when P_{CO_2} is around 30 mmHg and the pH is 7.30.

Complex Acid–Base Disorders. If the compensation of a primary acid–base disorder is not in the expected range, we have to search for a complex disorder. Tab. 30.**16**

Table 30.**15** Simple acid–base disorders and their compensation

Disorder		pH	P_{CO_2}	$[HCO_3^-]$	Expected compensation	Maximal compensation
Respiratory acidosis	acute	↓	↑ ↑	(↑)	$\Delta [HCO_3^-] = 0.1 \times \Delta p_{CO_2}$	30 mmol/L
	chronic	↓	↑ ↑	↑	$\Delta [HCO_3^-] = 0.35 \times \Delta p_{CO_2}$	45 mmol/L
Respiratory alkalosis	acute	↑	↓ ↓	(↓)	$\Delta [HCO_3^-] = 0.2 \times \Delta p_{CO_2}$	18 mmol/L
	chronic	↑	↓ ↓	↓	$\Delta [HCO_3^-] = 0.4 \times \Delta p_{CO_2}$	15 mmol/L
Metabolic acidosis		↓	↓	↓ ↓	$\Delta p_{CO_2} = 1.2 \times \Delta [HCO_3^-]$	10 mmHg
Metabolic alkalosis		↑	↑	↑ ↑	$\Delta p_{CO_2} = 0.6 \times \Delta [HCO_3^-]$	65 mmHg

Double arrow indicates the primary disorder.

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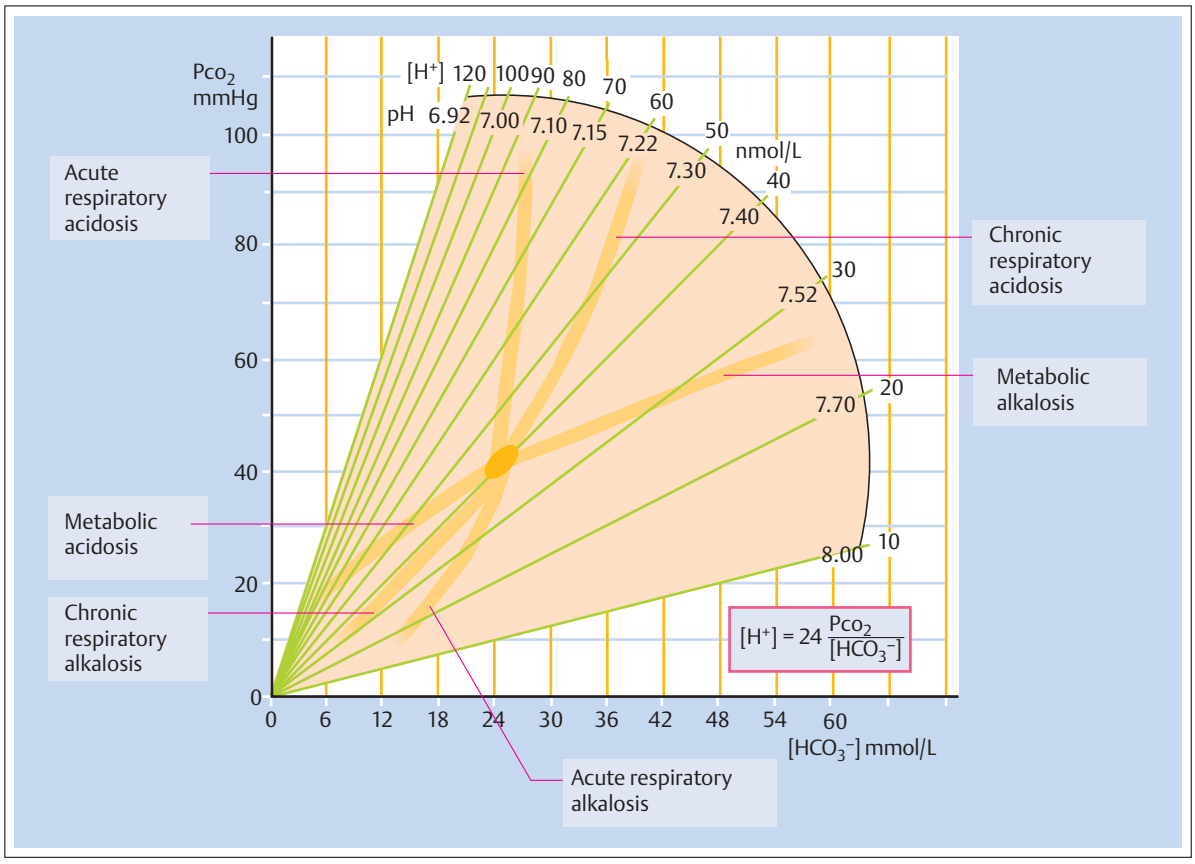

Fig. 30.**14** Nomogram for evaluation of acid–base disorders. The Henderson–Hasselbalch equation is the basis of this nomogram. If the intersection of P_{CO_2} and HCO_3^- lies within the darker shaded areas in the diagram, then the patient most likely suffers from a simple acid–base disorder as indicated. However, if the intersection remains outside the shaded areas, a mixed or complex disorder is most likely. The diagram has to be interpreted in the context of the history and relevant clinical information of the patient.

Table 30.**16** Representative examples for complex acid–base disorders

Disorder type	Clinical situation	pH	P_{CO_2}	$[HCO_3^-]$	P_{Na}	P_K	P_{Cl}	Anion gap
Metabolic and respiratory alkalosis	heart failure and diuretics	7.60	40	38	131	3.6	77	16
Metabolic alkalosis and respiratory acidosis	COPD and diuretics	7.44	55	36	135	3.8	84	15
Metabolic acidosis and respiratory alkalosis	salicylate intoxication	7.56	15	13	140	3.5	106	21
Metabolic acidosis and respiratory acidosis	liver failure and respiratory insufficiency	7.18	44	16	133	5.7	100	17
Metabolic acidosis and metabolic alkalosis	alcoholism with repetitive vomiting and lactate acidosis	7.36	31	17	132	4.0	89	26
Mixed normochloremic and hyperchloremic metabolic acidosis	diabetic ketoacidosis	7.12	16	5	137	3.6	114	18

Examples modified from Androgue and Madias 1998.

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shows typical examples with the respective findings in arterial blood gas analysis.

For closer analysis of acid–base disorders and their etiology, *secondary laboratory parameters* are often necessary. These include electrolyte measurements in serum and urine and based on these the calculation of anion gaps in serum and urine (SAG, UAG). An overview is given in Tab. 30.**17**. The use of these parameters for differential diagnosis is explained in the following paragraphs.

Clinical Features. The clinical symptoms and signs of acid–base disorders depend on the cause and the associated electrolyte disorders. Tab. 30.**18** gives symptoms and signs of the four basic disorders, which are independent of the etiology.

Table 30.**17** Parameters for analysis of acid–base disorders

Primary parameters	**Calculation**
– pH	
– P_{CO_2}	
– $[HCO_3^-]$	
– respiratory compensation of metabolic disorders	$[HCO_3^-] + 15 = P_{CO_2}$ = pH (digits after decimal point!)
Secondary parameters	**Calculation**
– serum electrolytes (Na, K, Cl, Ca)	
– urine electrolytes (Na, K, Cl)	
– serum anion gap (SAG)	$[Na^+] - ([Cl^-] + [HCO_3^-])$
– urine anion gap (UAG)	$[Na^+] + [K^+] - [Cl^-]$

Table 30.**18** Symptoms and signs of acid–base disorders

Metabolic disorders

Metabolic acidosis

pulmonary
- respiratory compensation (Kussmaul breathing)

cardiovascular
- reduced catecholamine effects (negative inotropy, vasoplegia)
- ventricular arrhythmias (due to associated potassium disorders!)

neurologic
- lethargy, coma

bone (chronic metabolic acidosis)
- demineralization (osteoporosis, osteomalacia, osteitis fibrosa with hyperparathyroidism)
- growth retardation
- nephrocalcinosis/nephrolithiasis

Metabolic alkalosis

pulmonary
- respiratory compensation (hypoventilation)

cardiovascular
- symptoms of hypovolemia (hypotension, weakness)
- ventricular arrhythmias (due to associated potassium disorders!)

neurologic (similar to hypocalcemia)
- paresthesias, muscle cramps, tetany
- confusion, sopor

Respiratory disorders

Respiratory acidosis

cardiovascular
- peripheral vasodilatation: warm red skin
- hypertension
- arrhythmias
- severe: myocardial depression

neurologic
- anxiousness, restlessness
- headache (increased intracerebral pressure)
- confusion, coma (CO_2 intoxication)

renal/metabolic
- salt and water retention (the sympathetic nervous system and the renin–angiotensin–aldosterone system as well as vasopressin secretion are all activated)
- severe: vasoconstriction, hypoperfusion

Respiratory alkalosis

cardiovascular
- chest pain (coronary spasms: Prinzmetal angina, esophageal spasms)
- arrhythmias (hypokalemia)

neurologic ($P_{CO_2} < 20$)
- paresthesias, muscle cramps (hypocalcemia)
- vertigo, anxiousness, confusion, hallucinations, loss of consciousness

metabolic (transcellular shifts)
- hypokalemia
- hypophosphatemia
- hypocalcemia

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Metabolic Acidosis

Pathogenesis and Use of the Serum Anion Gap (SAG)

A metabolic acidosis is defined as a decrease of pH < 7.35 with low serum bicarbonate and subsequent decrease of P_{CO_2} due to respiratory compensation (Kussmaul breathing; see Tab. 30.**15**). Two main pathophysiologic situations lead to metabolic acidosis:

- net intake (extrarenal: endogenous/exogenous) and/or retention of acid (renal)
- net loss of bicarbonate (extrarenal or renal).

Tab. 30.**19** shows the differential diagnosis of metabolic acidosis classified according to the underlying pathogenetic mechanism.

Serum Anion Gap. For the differential diagnosis of metabolic acidosis the serum anion gap (SAG) is a very helpful tool (see Tab. 30.**17**). In Fig. 30.**15** the definition of the SAG is shown schematically with the use of ionograms: the SAG is defined as the difference between nonmeasured anions and cations in serum. Its normal value is 12 ± 2 mmol/L (ionogram A). In the case of a metabolic acidosis with bicarbonate loss, the SAG does not change. However, for electroneutrality reasons the kidney retains chloride, which leads to a *hyperchloremic metabolic acidosis with normal SAG* (ionogram B). In contrast, intake or retention of fixed acids leads in most cases (except HCl) to an increase of nonmeasured anions, e. g., lactate, citrate, ketones, etc. Serum bicarbonate decreases in an equimolar range, which leads to a *normochloremic metabolic acidosis with increased SAG* (ionogram C). If the increase of SAG is smaller than the decrease in serum bicarbonate, the diagnosis of a *combined normochloremic and hyperchloremic acidosis* (ionogram D) can be made. When analyzing the SAG, it is important to notice that the SAG changes with the serum protein concentration, since part of the nonmeasured anions are represented by proteins.

> As a general rule, a decrease of the serum albumin concentration by 10 g/L leads to a decrease of SAG by 2.5 mmol/L.

Normochloremic Metabolic Acidosis (with Increased SAG)

All acidoses of this group occur by endogenous acid accumulation or by exogenous acid intake. We have to search for the nonmeasured anion leading to an enhanced SAG. The most common clinical causes are the following:

- *Diabetic ketoacidosis*: the hallmark of this disorder is the accumulation of ketoacids that are generated from free fatty acids under the influence of glucagon in the absence of insulin. The most important ketones are *acetoacetic acid* and *β-hydroxybutyric acid*. They can be measured in the urine using standard test stripes. However, the following two problems may arise:
  - Standard test stripes only measure acetoacetic acid. Since in severe forms of ketoacidosis mainly β-hydroxybutyric acid is generated, the test results can be paradoxically negative.
  - Ketonuria leads to volume depletion. As a consequence, the test results will be positive in the early phase of ketoacidosis, when the kidney func-

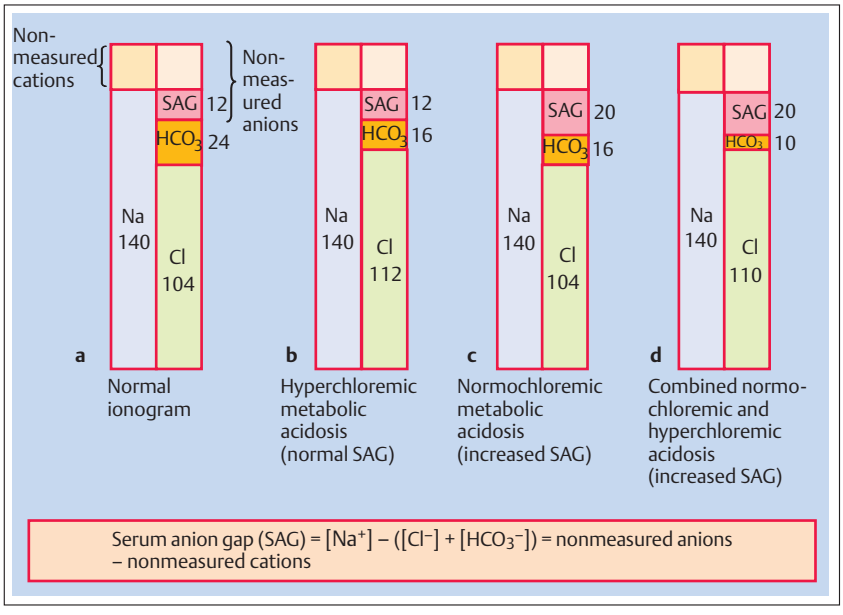

Fig. 30.**15** Definition of the serum anion gap (SAG) shown with ionograms. Cations are represented on the left and anions on the right side.

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Table 30.**19** Differential diagnosis of metabolic acidosis

Metabolic acidosis due to increased acid load	Metabolic acidosis due to bicarbonate loss

Increased acid load, endogenous sources*
– *ketoacidosis*
  – diabetic
  – fasting
– *lactic acidosis*
  – L-lactic acidosis type A (with hypoxemia): shock, respiratory insufficiency, severe anemia, CO intoxication, pheochromocytoma
  – L-lactic acidosis type B (without hypoxemia): liver failure, mitochondrial toxins (cyanide poisoning), drugs (biguanides!), tumors, hypermetabolism (extreme exercise, grand mal epilepsy), several congenital errors of metabolism (e. g., glycogen storage diseases)
  – D-lactic acidosis: bacterial overgrowth in the colon
	Extrarenal bicarbonate loss
	– diarrhea
	– external drainage of bile and pancreatic fluid
	– ureterosigmoidostomy

Increased acid load, exogenous sources*
– hyperalimentation with amino acid solutions
– *intoxications*
  – salicylate
  – alcohols, glycols	

Reduced renal acid excretion – renal failure* – hypokalemic distal RTA type 1 – hyperkalemic RTA type 4 with hyporeninemic hypoaldosteronism	**Renal bicarbonate loss** – hypokalemic proximal RTA type 2 – generalized proximal tubular syndrome = Fanconi syndrome

* Diseases with normochloremic metabolic acidosis with increased serum anion gap; all the others are hyperchloremic acidoses with normal anion gap. RTA = renal tubular acidosis.

tion is still maintained, and later under therapy with fluid resuscitation. However, in the severe forms of ketoacidosis with concomitant prerenal failure, the ketonuria decreases and may wrongly suggest an amelioration of the metabolic situation.

➤ *Fasting ketoacidosis*: milder forms of ketoacidosis due to increased fat metabolism occur with chronic malnutrition due to starving or alcoholism. Acetoacetic acid is the main ketone generated in these situations.

➤ *Lactic acidosis*: in the situation of tissue hypoxia, glucose and alanine are metabolized via anaerobic glycolysis. The end product of this pathway is L-lactate, which leads to an increased anion gap. We can distinguish the following variants of lactic acidosis:
- All situations with tissue hypoxia (respiratory failure, shock, carbon monoxide intoxication, etc.) may lead to *lactic acidosis type A*.
- *Lactic acidosis type B* occurs without tissue hypoxia. Common causes are cyanide intoxication, biguanide medication, liver failure, etc.
- A particular variant is a lactic acidosis caused by the stereoisomer *D-lactate*, which can be produced in the gut by an altered gut flora. This isomer is not measured with standard techniques to determine lactate concentration, but can be determined upon special request.

➤ *Exogenous acid intake:* metabolic acidosis due to exogenous acid intake occurs in the context of hyperalimentation with amino acid solutions, but also with various intoxications. The most common intoxications are *salicylates* and *alcohol/glycol*. In the latter case formic acid, as the end product of alcohol/glycol metabolism, represents the unmeasured anion leading to the increased SAG. These intoxications are also associated with an increased serum osmolal gap. In addition, typical calcium oxalate crystals can be found in the urine with ethylene glycol intoxication.

➤ *Reduced acid excretion:* The kidney is the only organ to excrete fixed acids. Therefore, *chronic renal failure* usually leads to metabolic acidosis due to retention of sulphuric, phosphoric, and organic acids, which increases the SAG.

Hyperchloremic Metabolic Acidosis (with Normal SAG)

➤ *Renal causes:* if a hyperchloremic metabolic acidosis occurs due to a problem in the kidney, it is called renal tubular acidosis (RTA). We can distinguish three major forms:
- Bicarbonate loss in the proximal tubule leads to *type 2 or proximal renal tubular acidosis*. Urinary bicarbonate loss leads to increased natriuresis with increased distal sodium delivery. This leads to concomitant volume depletion and hypokalemia (see above).

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- In contrast, acid secretion in the distal nephron is impaired in the case of *type 1 or distal renal tubular acidosis*. This variant is often associated with polyuria (renal diabetes insipidus) and nephrolithiasis/nephrocalcinosis due to concomitant calcium loss.
- Patients with hyporeninemic hypoaldosteronism in the context of a diabetic or interstitial nephropathy often present with hyperkalemic hyperchloremic metabolic acidosis, known as *type 4 or hyperkalemic renal tubular acidosis*. The pathology seems to lie in the juxtaglomerular apparatus.

➤ *Extrarenal causes:* mineralocorticoids stimulate renal acid secretion. Therefore, all situations with mineralocorticoid deficit can lead to a hyperchloremic metabolic acidosis, which is typically associated with hyperkalemia (see Hyperkalemia, above, Tab. 30.**12**).

In contrast, bicarbonate loss is the main pathogenetic mechanism leading to hyperchloremic metabolic acidosis with gastrointestinal causes, e. g., diarrhea, fistulas, ureterosigmoidostomy.

For the differential diagnosis between renal tubular acidosis and extrarenal causes of hyperchloremic metabolic acidosis the urinary anion gap (UAG) is a helpful tool (see Tab. 30.**17**). The UAG measures the capacity of the distal nephron to excrete acid. Its normal value is around +30–50 mmol/L. In the case of metabolic acidosis with a functioning renal compensation, the UAG should become negative (due to enhanced ammonium secretion). However, if the UAG stays positive, it indicates tubular dysfunction and suggests renal tubular acidosis.

Diagnostic Approach to Metabolic Acidosis

The differential diagnosis in patients with metabolic acidosis is depicted in Fig. 30.**16**. For further diagnosis, an arterial blood gas analysis, as well as measurement of electrolytes in serum and urine is necessary in order to calculate SAG and UAG. The differential diagnosis of hyperchloremic metabolic acidoses is further detailed in Tab. 30.**20**.

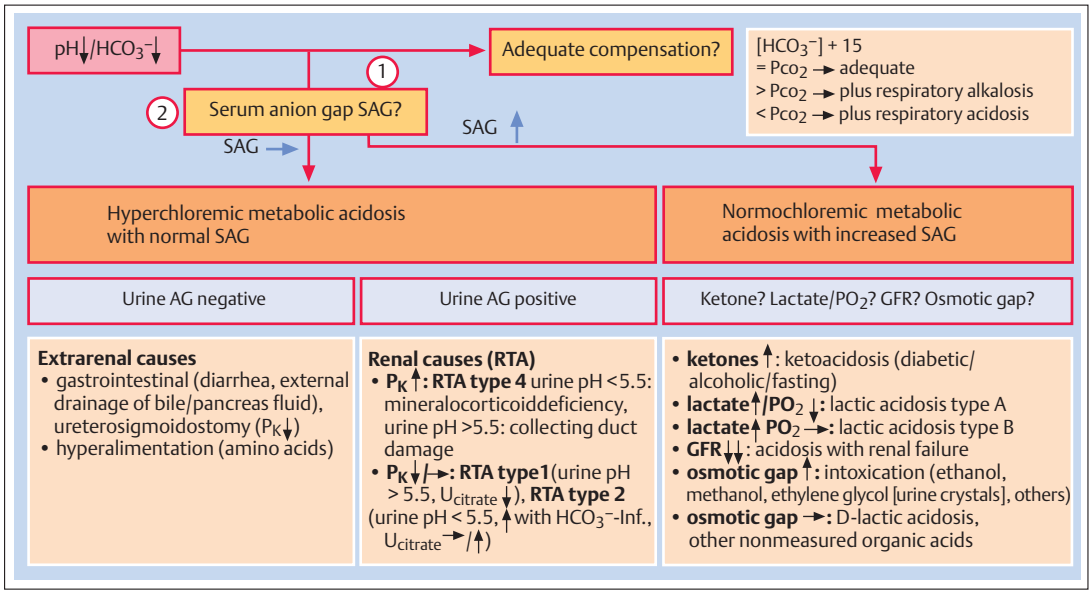

Fig. 30.**16** Diagnostic approach to metabolic acidosis.

Metabolic Alkalosis

Pathogenesis and Importance of the Urine Chloride Concentration

A metabolic alkalosis is defined as an increase of pH > 7.40 in arterial blood gas analysis with a primary increase in serum bicarbonate and secondary increase in P_{CO_2} due to respiratory compensation (hypoventilation; see Tab. 30.**15**). Two main pathophysiologic situations lead to metabolic alkalosis:

➤ net intake of bicarbonate
➤ net loss of acid (extrarenal or renal).

Tab. 30.**21** shows the differential diagnosis of metabolic alkaloses classified according to their pathogenesis. Bicarbonate excretion in the kidney is very efficient. Therefore, a metabolic alkalosis can only persist when at least one of the following maintenance factors is

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Table 30.**20** Differential diagnosis of hyperchloremic metabolic acidoses

Disorder	RTA type 1	RTA type 2	RTA type 4	Extrarenal
Pathogenesis	Reduced distal acidification	proximal tubular HCO_3^- loss	Mineralocorticoid deficiency	extrarenal HCO_3^- loss
P_K	↓	↓	↑	↓
TTKG	↑	↑	↓	↓
$P_{HCO_3^-}$	< 10–12	14–20	> 15	> 15
Urine pH	> 5.5	< 5.5 without therapy > 5.5 with therapy	variable	5.5
$FE_{HCO_3^-}$	< 3 % (adults) 5–10 % (children)	> 15 % with therapy	10–15 %	< 5 %
HCO_3^- dose for therapy (mmol/kg/d)	1–2 (adults) 4–10 (children)	10–15	1–3	0.5 × BW (kg) × $\Delta[HCO_3^-]$
SAG	→	→	→	→
UAG	positive	positive	strongly positive	negative
$U_{Citrate}$	↓	↑	↓	→
Causes	– *congenital form* with hypercalciuria, nephrolithiasis and nephrocalcinosis – *acquired disorders* with: nephrocalcinosis (primary hyperparathyroidism, medullary sponge kidney), hypergammaglobulinemia (Sjögren, cryoglobulinemia), drugs (amphotericin B, analgesics), tubulointerstitial nephropathies, sickle cell disease	**Isolated form** – *congenital:* carboanhydrase deficiency – *acquired:* acetazolamide **As part of Fanconi syndrome** – *congenital* – *acquired:* with dysproteinemia including multiple myeloma, cystinosis, Wilson disease, drugs (ifosfamide), tubulointerstitial nephropathies	– all diseases with mineralocorticoid deficit (see Tab. 30.**12**) – *most frequent causes:* hyporeninemic hypoaldosteronism with diabetic and interstitial nephropathy	– diarrhea – external drainage of bile and pancreatic fluid – ureterosigmoidostomy

RTA = renal tubular acidosis
TTKG = transtubular potassium gradient = $(P_{Osm}/U_{Osm}) \times (U_{Creatinine}/P_{Creatinine})$
SAG = serum anion gap, UAG = urine anion gap
$FE_{HCO_3^-}$ = fractional excretion of bicarbonate
BW = body weight

present: *volume depletion, hypokalemia, or hyperaldosteronism.*

Urine Chloride Concentration, U_{Cl}. For the differential diagnosis of metabolic alkaloses the urinary chloride concentration is a very helpful tool. Chloride depletion is a major pathogenetic mechanism for metabolic alkalosis, since the excretion of bicarbonate requires the reabsorption of another anion, namely chloride. If the U_{Cl} is < 20 mmol/L, chloride depletion, often combined with volume depletion, is a very likely diagnosis, and therefore correction of alkalosis requires volume and NaCl repletion. We call this situation a *chloride-sensitive metabolic alkalosis* as opposed to the *chloride-resistant form*, when U_{Cl} is > 20 mmol/L.

Chloride-Sensitive Metabolic Alkaloses

A source of chloride loss, renal or extrarenal, has to be searched for.

- *Extrarenal loss of chloride and acid:* this occurs with the loss of gastric fluid (repetitive vomiting, especially in the context of anorexia/bulimia; *gastric alkalosis = very frequent*!) or with the loss of chloride-rich fluid from the small intestine (chloride diarrhea occurs in the context of villous adenomas or as a congenital disease; rare).
- *Renal chloride loss:* the main cause is the use of *diuretics*. Under persistent therapy U_{Cl} is > 20 mmol/L, however it drops quickly after stopping the treatment.

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Use or abuse of diuretics is the absolute most frequent cause of metabolic alkalosis, which persists due to concomitant volume and potassium depletion.

Chronic hypercapnia leads to chloride loss, since the renal compensation of respiratory acidosis saves bicarbonate and excretes chloride. Therefore, the therapy of chronic hypercapnia unmasks a so-called *posthypercapnic alkalosis*, which can be corrected with chloride repletion.

Chloride-Resistant Metabolic Alkaloses

- *Increased renal acid excretion:* all disorders with primary *mineralocorticoid excess* lead to the stimulation of distal acid excretion and therefore metabolic alkalosis. They are usually associated with volume expansion, hypertension, and hypokalemia (see Hypokalemia, above). Based on the pathogenesis they do not respond to chloride substitution.
- *Renal chloride loss:* it occurs if tubular chloride reabsorption is impaired. This is the case with *persistent abuse of diuretics*, but also with congenital disorders of chloride transporters, e. g., *Bartter* and *Gitelman syndromes*. In all these cases, the concomitant volume depletion and loss of potassium and magnesium lead to persistence of metabolic alkalosis.

Metabolic Alkalosis via Exogenous Alkali Intake

Exogenous alkali intake occurs either via bicarbonate infusion or alkali tablets (sodium bicarbonate, sodium or potassium citrate). A particular disorder is milk-alkali syndrome, which is discussed below. It is important to notice that even in the case of exogenous alkali intake a metabolic alkalosis only occurs with the presence of an additional maintenance factor, which may be either chronic renal insufficiency (with reduced capacity for bicarbonate excretion) or a volume, chloride, and/or potassium deficit (as discussed above).

Diagnostic Approach to Metabolic Alkalosis

The differential diagnosis in a patient with metabolic alkalosis is depicted in Fig. 30.**17**. The most important parameters are the medical history (drugs!), urinary chloride concentration, and blood pressure.
The differential diagnosis of hypokalemic metabolic alkalosis with hypotension in young patients includes eating disorders, e. g., anorexia and bulimia, but also the abuse of diuretics and/or laxatives. Since these problems are usually not admitted to the treating physician at the beginning, laboratory parameters, e. g., urine electrolyte concentrations can be very helpful. The typical constellation is shown in Tab. 30.**22**.

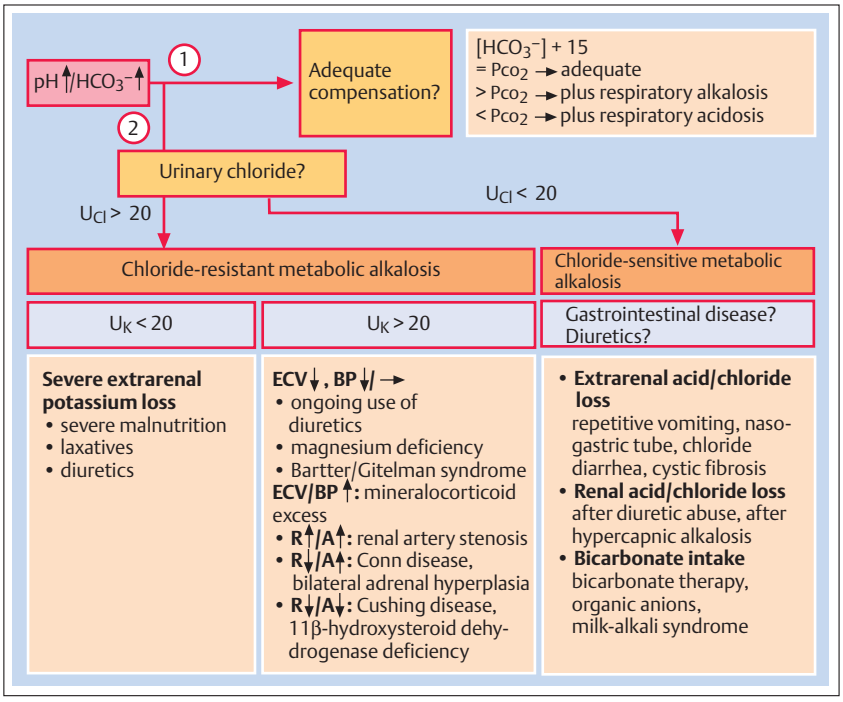

Fig. 30.**17** Diagnostic approach to metabolic alkalosis.

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Table 30.**21** Differential diagnosis of metabolic alkalosis

Metabolic alkalosis induced by acid loss	Metabolic alkalosis induced by bicarbonate excess

Extrarenal acid and/or chloride loss*
– *gastric alkalosis:* loss of stomach fluid (HCl = chloride and acid loss!)
  – repetitive vomiting (alcoholism, anorexia/bulimia)
  – drainage of stomach fluid
– *chloride diarrhea*
  – congenital
  – villous adenoma
– *chloride loss via skin*
  – cystic fibrosis
	Exogenous bicarbonate intake
	– *bicarbonate therapy of metabolic acidosis:* "overshoot alkalosis" with therapy for ketoacidosis or lactic acidosis
	– *organic anions metabolized to bicarbonate*
	  – citrate 1:3 (blood constituents, hemofiltration/hemodialysis with regional anticoagulation, potassium citrate)
	  – lactate/acetate 1:1 (Ringer lactate infusions, hemodialysis/hemofiltration)
	– *milk-alkali syndrome*
	(see Disorders of Calcium, Phosphate, and Magnesium Homeostasis, below)

Renal acid and/or chloride loss
– *mineralocorticoid excess* (see Tab. 30.**11**) with stimulation of distal acid excretion; secondary hyperaldosteronism in the context of volume depletion is an important maintenance factor of metabolic alkalosis
– *renal chloride and potassium depletion**
  – diuretics (mainly loop diuretics and thiazides)
  – congenital: Bartter/Gitelman syndrome
– *posthyperkapnic alkalosis**
after therapy for chronic respiratory acidosis
	Renal bicarbonate retention
	– not a primary disorder since bicarbonate is fully reabsorbed under physiological conditions
	– renal insufficiency with bicarbonate retention is an important maintenance factor for metabolic alkalosis

* Chloride-sensitive metabolic alkaloses; however, with Bartter/Gitelman syndrome chloride loss is often enormous and cannot be adequately compensated by therapy.

Table 30.**22** Urinary findings with hypokalemic metabolic alkalosis and volume depletion

Disorder		U_{Na}	U_K	U_{Cl}	Urine pH
Anorexia/bulimia		↑ *	↑ *	↓ ↓	alkaline
Diuretic abuse	continuing stopped	↑ ↓	↑ ↓	↑ ↓	variable normal
Laxative abuse		↓	↓	↓	normal
Bartter/Gitelman syndrome		↑	↑	↑	normal

* With severe metabolic alkalosis.

Respiratory Acidosis

Acute and Chronic Disorders

A respiratory acidosis is defined as a decrease of the arterial pH to < 7.35 with primary increase of P_{CO_2} and secondary increase of serum bicarbonate as a result of renal compensation (see Tab. 30.**15**). The following main pathophysiologic situations can lead to respiratory acidosis:

- central disorders of respiratory regulation with hypoventilation
- mechanical diseases of the chest wall (skeletal, neuromuscular)
- gas exchange disorders (ventilation and/or diffusion)
- lung perfusion disorders
- mechanic hypoventilation ("permissive hypercapnia").

Since renal compensation requires several days, we have to distinguish between acute and chronic forms of respiratory acidosis. Severe forms of acidosis occur in the context of severe acute diseases or with decompensation of a preexistent chronic disease ("acute or chronic respiratory failure"). Patients with chronic respiratory insufficiency suffer from chronic hypercapnia, and their main stimulus for respiration remains hypoxemia. Uncontrolled therapy with oxygen or sedative drugs (e. g., central analgesics, sleeping pills) leads to severe CO_2 retention, acidosis and eventually CO_2 coma.

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Table 30.**23** Differential diagnosis of acute and chronic respiratory disorders

Respiratory acidosis	
Acute	*Chronic*
Disorders of respiratory regulation (CNS)	
– sedative drugs (morphine and derivates) – O_2 therapy with chronic hypercapnia – circulatory failure	– (O)SAS = (obstructive) sleep apnea syndrome – CNS diseases (tumor)
Mechanical diseases of the chest wall (skeletal, neuromuscular)	
– Guillain–Barré syndrome – myasthenia gravis – periodic paralysis – severe hypokalemia or hypophosphatemia – serial rib fractures	– spinal diseases: amyotrophic lateral sclerosis, postpolio syndrome, multiple sclerosis, others – muscular dystrophies – kyphoskoliosis – extreme obesity, severe ascites
Disorders of gas exchange (ventilation, diffusion)	
– aspiration – laryngeal spasm, acute asthma – acute pulmonary edema, pneumonia, ARDS – pneumothorax	– tracheal stenosis – COPD/emphysema – pulmonary fibrosis
Disorders of perfusion	
– central pulmonary embolus – circulatory failure	– severe pulmonary hypertension
Controlled mechanical hypoventilation (“permissive hypercapnia”, e. g., with ARDS)	
Respiratory alkalosis	
Acute	*Chronic*
Disorders of respiratory regulation (CNS)	
– psychogenic hyperventilation – stroke, meningoencephalitis – acute pain – fever/sepsis – compensation of metabolic acidosis (ketoacidosis, liver failure, salicylate intoxication) – methylxanthines (theophylline)	– pregnancy/luteal phase of menstrual cycle (progesterone-induced) – pons tumor
Extrapulmonary causes of hypoxemia	
– acute cardiac failure with pulmonary edema – shock – severe anemia	– chronic cardiac failure – congenital heart disease with cyanosis – high altitude disease – severe anemia
Pulmonary causes of hypoxemia	
– aspiration – pneumonia – noncardiogenic pulmonary edema – pulmonary embolism	– chronic pulmonary diseases at the stage of partial respiratory insufficiency (pulmonary fibrosis, COPD etc.)
Controlled mechanical hyperventilation (e. g., therapy of increased intracranial pressure)	

Differential Diagnosis of Respiratory Acidosis

The main causes of respiratory acidosis are summarized in Tab. 30.**23**. As mentioned earlier, many diseases leading to respiratory acidosis also cause hypoxemia and lead to a metabolic acidosis through lactate generation. The combination can lead to life-threatening forms of acidosis.

With *controlled alveolar hypoventilation* in the context of therapy for “acute respiratory distress syndrome” (ARDS), hypercapnia and respiratory acidosis are intentionally tolerated (“permissive hypercapnia”), since it allows lung-protective modes of mechanical ventilation with lower airway pressures and fewer barotraumas.

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Universal Scheme for Analysis of Acid–Base Disorders

Types of Acid–Base Disorders. As mentioned earlier, a distinction is made between simple and complex acid–base disorders. The complex disorders can be further classified as mixed respiratory and metabolic or combined metabolic disorders. When they are additive, e. g., combination of two acidoses or two alkaloses, it leads to severe or even life-threatening pH changes, whereas the combination of an acidosis with an alkalosis partially neutralizes the effect of each of them. Complex triple disorders are mainly observed in critically ill patients in intensive care units.

Systematic Analysis of Acid–Base Disorders. Fig. 30.**18** depicts a systematic approach for analysis of blood gas analyses, which allows the classification of any given acid–base disorders. The following four steps are involved:

- pH: acidosis or alkalosis?
- $[HCO_3^-]$: primary respiratory or metabolic disorders?
- expected compensation (nomogram, formulas): simple or complex disorder?
- $\Delta [HCO_3^-]$, ΔSAG (serum anion gap): further differential diagnosis of complex disorders.

Tab. 30.**16** gives various examples of complex acid–base disorders, in a step-by-step-analysis. After classifying the disorders, an etiology has to be found. Tabs. 30.**19**–30.**23** provide the necessary information and criteria for this.

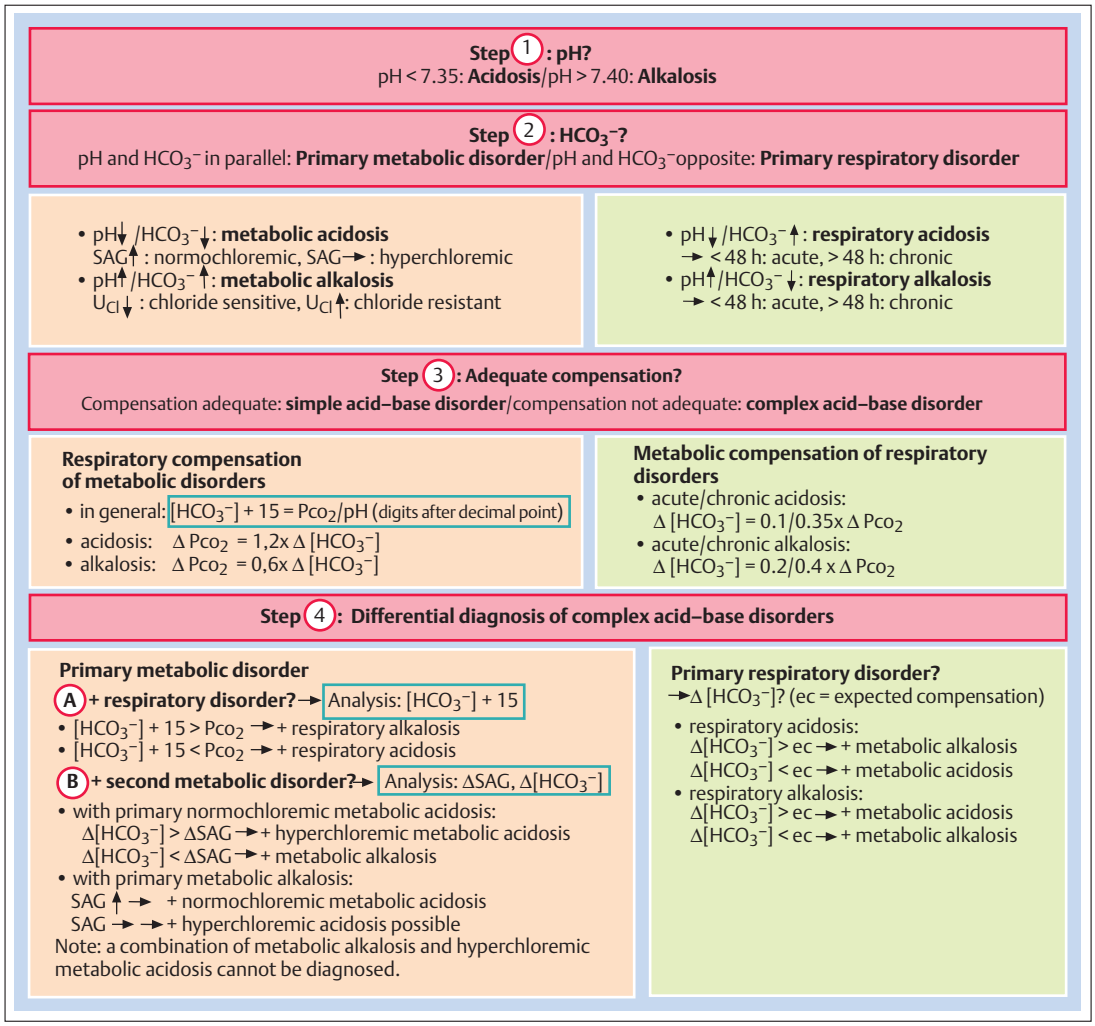

Fig. 30.**18** Systematic universal approach to acid–base disorders.

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Respiratory Alkalosis

Acute and Chronic Disorders

Respiratory alkalosis is defined as an increase of the arterial pH > 7.40 with primary decrease of P_{CO_2} and secondary decrease of serum bicarbonate due to renal compensation (see Tab. 30.**15**). The following main pathophysiologic situations can lead to respiratory alkalosis:

- central disorders of respiratory regulation with hyperventilation
- extrapulmonary causes of hypoxemia
- pulmonary causes of hypoxemia
- mechanical hyperventilation.

The main stimulators of respiration are first hypercapnia and second hypoxemia. Hypoxemia with P_aO_2 < 60 mmHg leads to alveolar hyperventilation and subsequent decrease of P_{CO_2} with respiratory alkalosis. However, hypocapnia limits the degree of hyperventilation. Since renal compensation, i. e., the adaptation to increase bicarbonate excretion, requires several days, we have to distinguish acute and chronic forms of respiratory alkalosis.

A particular form of this disorder is called *pseudo-respiratory alkalosis* and occurs in the context of severe circulatory failure. A severe decrease in cardiac output leads to tissue hypoxemia and severe venous hypercapnia. However, the arterial pH is normal or even slightly increased due to hyperventilation. Therefore, in patients with shock the measurement of central venous oxygen pressure is crucial to get an idea of tissue oxygenation.

Differential Diagnosis of Respiratory Alkalosis

The causes of respiratory alkalosis are summarized in Tab. 30.**23**. The most common cause of respiratory alkalosis is *acute psychogenic hyperventilation*. This disorder is benign and usually responds to a nonpharmaceutic calming intervention. Acute hyperventilation can, however, lead to an impressive clinical picture with tetany, paresthesia, muscle shivering, and carpopedal spasms. These symptoms occur due to cerebral hypoperfusion in the context of an acute rise of pH and due to concomitant electrolyte disorders e. g., hypocalcemia.

It is clinically important to distinguish primary hyperventilation with respiratory alkalosis from secondary hyperventilation due to metabolic acidosis (Kussmaul respiratory pattern), which is easily done with an arterial blood gas analysis (see Tab. 30.**15**).

Controlled alveolar hyperventilation can occur with mechanical ventilation in the attempt to correct metabolic acidosis or arterial hypoxemia. In addition, it is a therapeutic approach to diseases with increased intracranial pressure.

30.4 Disorders of Calcium, Phosphate, and Magnesium Homeostasis

Physiologic Principles

Particular Properties of Calcium, Phosphate, and Magnesium

In this chapter the positively charged divalent ions calcium (Ca) and magnesium (Mg), as well as the negatively charged phosphate (PO_4^{3-}) are discussed. These ions have important properties in common:

- The major part is stored in the *bones*. Therefore, an overall negative balance leads to osteoporosis or osteomalacia. The fraction actually stored in the extracellular space is 0.1 % for Ca, 1 % for PO_4^{3-}, and 2 % for Mg.
- These ions are crucially important for several important *live-supporting functions*: Ca and Mg for the excitability of membranes, Ca for activation of the coagulation, as well as the complement cascade, Mg as a cofactor for many enzymes, PO_4^{3-} for the cellular energy metabolism (adenosine triphosphate [ATP], NADP), signal transduction (inosine triphosphate [IP_3]), as well as substrate for nucleic acid synthesis. Finally, PO_4^{3-} modulates the oxygen affinity of hemoglobin by variation of the 2,3–disphosphoglycerate (2,3-DPG) concentration in erythrocytes.
- In serum these ions can occur *free*, *in complexes*, or *protein bound*, which is important for the measurement technique.
- The *regulation occurs in the kidney* prior to the collecting duct, this in contrast to water, sodium, potassium, and acids, which are all mainly regulated in the collecting duct. PO_4^{3-} is regulated mainly in the proximal tubule, Mg in the loop of Henle, and Ca in the distal tubule. Parathyroid hormone (PTH) influences all three ions, but mainly Ca and PO_4^{3-}. The main parameters influencing renal excretion of these three ions are summarized in Tab. 30.**24**. For all of these ions volume depletion leads to sodium-associated increased reabsorption, and therefore, reduced excretion. In contrast, most diuretics lead, via increased natriuresis, to a renal loss of these three ions. A main exception is represented by thiazides, which impair Ca excretion. This effect is used therapeutically in patients with hypercalciuria and stones.

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Table 30.**24** Parameters determining renal excretion of divalent ions

Ion	Tubular reabsorption ↑ /excretion ↓	Tubular reabsorption ↓ /excretion ↑
Ca	– volume depletion (via FE_{Na} ↓) – PTH ↑ – hypocalcemia (via PTH ↑) – hyperphosphatemia (via P_{Ca} ↓) – metabolic alkalosis – *drugs:* thiazides, K-sparing diuretics, lithium	– volume excess (via FE_{Na} ↑) – PTH ↓ – hypercalcemia (via PTH ↓) – hypophosphatemia (via P_{Ca} ↑) – metabolic acidosis – *drugs:* loop and proximal diuretics
PO_4^{3-}	– volume depletion (via FE_{Na} ↓) – PTH ↓ – hypercalcemia (via PTH ↓) – hypophosphatemia (via P_{Ca} ↑) – chronic metabolic alkalosis	– volume excess (via FE_{Na} ↑) – PTH ↑ – hypocalcemia (via PTH ↑) – hyperphosphatemia (via P_{Ca} ↓) – chronic metabolic acidosis – *drugs:* all diuretics (except K-sparing group)
Mg	– volume depletion (via FE_{Na} ↓) – PTH ↑ – hypocalcemia (via PTH ↑) – hyperphosphatemia (via P_{Ca} ↓) – hypomagnesemia	– volume excess (via FE_{Na} ↑) – PTH ↓ – hypercalcemia (via PTH ↓) – hypophosphatemia (via P_{Ca} ↑) – hypermagnesemia – *drugs:* all diuretics (except K-sparing group), aminoglycosides, amphothericin B, cisplatin, cyclosporin

Table 30.**25** Regulation of calcium phosphate homeostasis

Parameter	Regulation Stimulated or increased by	Inhibited or decreased by	Effect On target organs	Side effects
Serum calcium*	PTH, 1,25-$(OH)_2$ vitamin D_3	$P_{PO_4^{3-}}$ ↑	– inhibits PTH secretion – inhibits tubular Ca reabsorption	$P_{PO_4^{3-}}$ ↓
Serum phosphate	1,25-$(OH)_2$ vitamin D_3	P_{Ca} ↑ PTH	– stimulates PTH secretion – inhibits 1-hydroxylase (renal 1,25-$[OH]_2$ vitamin D_3 synthesis ↓)	P_{Ca} ↓
PTH	P_{Ca} ↓ $P_{PO_4^{3-}}$ ↑	P_{Ca} ↑ 1,25-$(OH)_2$ vitamin D_3	– stimulates 1-hydroxylase (renal 1,25-$[OH]_2$ vitamin D_3 synthesis ↑) – stimulates tubular Ca reabsorption – inhibits tubular phosphate reabsorption – stimulates Ca and PO_4^{3-} resorption from bones	P_{Ca} ↑ /$P_{PO_4^{3-}}$ ↓
1,25-$(OH)_2$-vitamin D_3*	PTH	$P_{PO_4^{3-}}$ ↑	– inhibits PTH secretion – stimulates Ca and PO_4^{3-} absorption from intestine – stimulates bone mineralization	P_{Ca} ↑ /$P_{PO_4^{3-}}$ ↑

* Calcium and active vitamin D have specific receptors: the calcium-sensing receptor (CSR) is expressed on parathyroid cells and renal tubular cells, the vitamin D receptor (VDR) only on parathyroid cells.

Regulation of Calcium and Phosphate Homeostasis

Whereas no endocrine system for regulation of Mg is known, Ca and PO_4^{3-} metabolism is regulated in a complex manner. The main parameters are *parathyroid hormone* (PTH) and the *active 1,25-$(OH)_2$ vitamin D_3*. Their target organs are the *kidney* (tubular Ca and PO_4^{3-} reabsorption), *intestine* (intestinal Ca and PO_4^{3-} absorption), and the *bones* (Ca and PO_4^{3-} release), and they regulate serum calcium and phosphate levels. For Ca a specific receptor known as the "calcium-sensing receptor" (CSR) is expressed in the cells of the parathyroid gland and in

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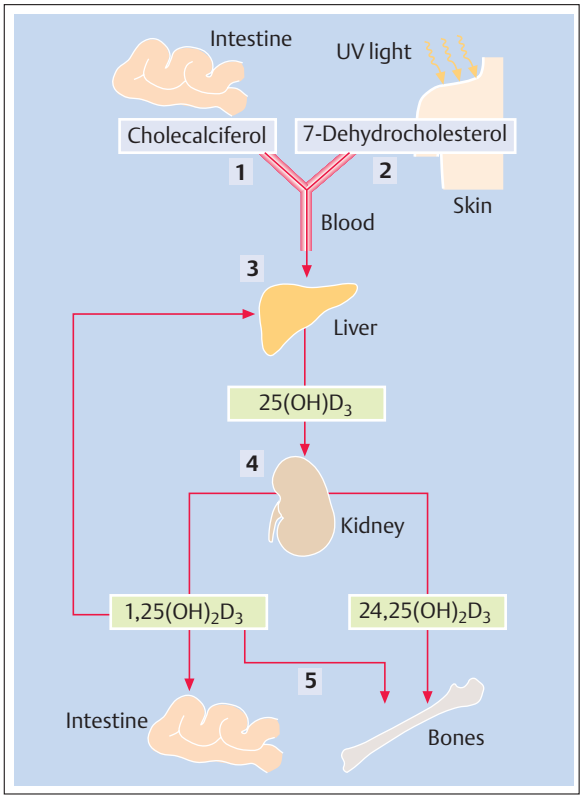

Fig. 30.**19** Scheme of vitamin D biosynthesis. (1) Intake of lipid soluble cholecalciferol (vitamin D_3) in the intestine, (2) biosynthesis of cholecalciferol from 7-dehydrocholesterol in the skin under the influence of UV radiation, (3) 25-hydroxylation in the liver → 25-OH D_3, (4) 1-hydroxylation in the kidney → 1,25-$(OH)_2D_3$ = bioactive vitamin D_3, (5) binding to bioactive vitamin D_3 to the vitamin D receptor (VDR) on the target organ.

the distal tubule in the kidney where it provides the feedback information for serum Ca regulation. All of the parameters influencing Ca and PO_4^{3-} levels are summarized in Tab. 30.**25**. Fig. 30.**19** schematically depicts the activation steps from vitamin D_3 to active 1,25-$(OH)_2$ vitamin D_3. This occurs in the skin, liver, and kidneys.

Disorders of Calcium Homeostasis

Definition, Diagnosis, and Clinical Features

The serum calcium concentration has a major impact on membrane excitability, especially in the heart, and therefore the serum Ca concentration is tightly regulated. *Hypercalcemia* is defined as an increase of serum calcium to > 2.6 mmol/L, *hypocalcemia* as a decrease to < 2.1 mmol/L.

Diagnosis. About 50% of serum calcium is protein bound. For this reason, the total serum calcium concentration can only be interpreted with knowledge of the serum albumin concentration. The concentration of ionized free biologically active serum Ca is about 1.2 mmol/L. In the context of *hypoalbuminemia*, ionized serum calcium concentration can be obtained as follows:

- direct measurement of ionized (free) Ca by blood gas analysis
- mathematical correction based on the serum albumin concentration with the following formula:

$$\Delta\,[Ca]\ (mmol/L) = 0.02 \times \Delta\,[albumin]\ (g/L)$$

Clinical Features. The clinical symptoms and signs of calcium disorders are mainly an expression of disturbed membrane excitability. A systematic overview is shown in Tab. 30.**26**. In general, hypocalcemia leads to enhanced, and hypercalcemia to reduced membrane excitability. Ca and PO_4^{3-} can form complexes in serum. When the calcium-phosphate product ($[Ca] \times [PO_4^{3-}]$) rises above 4.8 $(mmol/L)^2$ in serum, this can result in metastatic calcification of organs and tissues (nephrocalcinosis; pulmonary calcification; calciphylaxis: metastatic calcifications in vessels, tendons, joints, and fatty tissue).

Causes. Calcium disorders can arise via four different pathophysiologic mechanisms (Fig. 30.**20**):

- disorders of parathyroid function and regulation
- disorders of vitamin D metabolism and intestinal absorption
- disorders of bone metabolism
- disorders of renal calcium excretion.

The differential diagnosis of hypocalcemia is summarized in Tab. 30.**27** and that of hypercalcemia in Tab. 30.**28** and discussed further in the following paragraphs.

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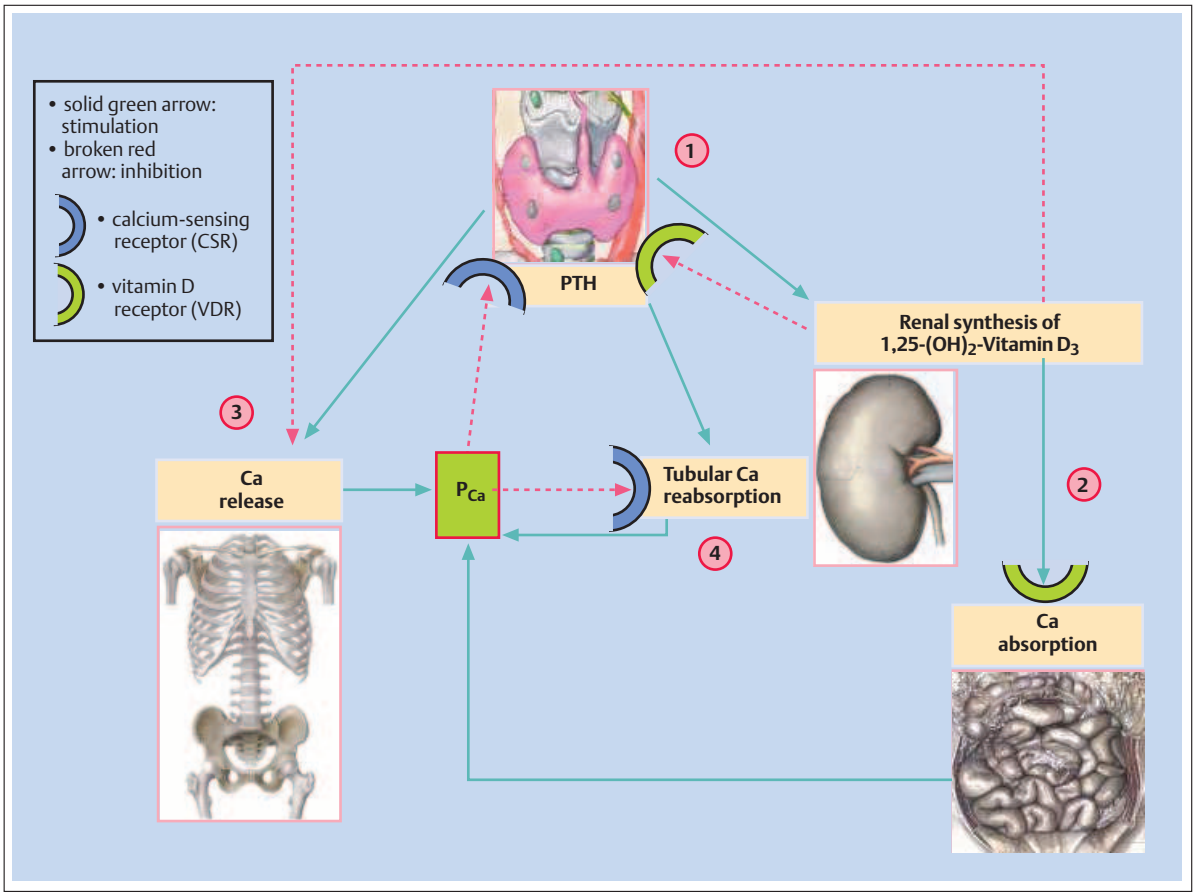

Fig. 30.**20** Fundamental pathogenesis of calcium disorders. Calcium disorders can arise by four different pathways: (1) disorders of parathyroid hormone (PTH) secretion, (2) disorders of vitamin D and intestinal Ca absorption, (3) disorders of bone metabolism, and (4) disorders of renal Ca excretion.

Table 30.**26** Symptoms and signs of calcium disorders

Hypocalcemia	Hypercalcemia
Cardiovascular – hypotension, cardiac failure (negative inotropy) – ECG: QT prolongation, tachyarrhythmias	**Cardiovascular** – hypertension, positive inotropy – ECG: QT shortening, bradycardia
Neurologic/psychiatric – fatigue, muscle weakness – paresthesias, muscle cramps (Chvostek and Trousseau sign) until tetany, laryngeal spasm – confusion, hallucinations, depression, paranoia – certain forms of hypoparathyroidism: calcification of basal ganglia	**Neurologic/psychiatric** – fatigue, muscle weakness – hyporeflexia – depression, anxiousness, confusion, somnolence, coma
	Gastrointestinal – nausea and vomiting, constipation, weight loss/anorexia – primary hyperparathyroidism: ulcus, acute pancreatitis **Renal** – polyuria (nephrocalcinosis), nephrogenic diabetes insipidus – nephrolithiasis (with hypercalciuria)
Soft tissue (with chronic hypocalcemia) – dry skin, dermatitis, brittle nails, alopecia (axilla, genital region), hypoplastic teeth – cataract	**Skeleton and soft tissues** – with increased calcium phosphate product occurrence of metastatic calcifications in eye (conjunctivitis), joints, tendons, soft tissue and arteries – itching

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Table 30.**27** Differential diagnosis of hypocalcemia

Hypoparathyroid status

True hypoparathyroidism with low PTH
- iatrogenic: thyroidectomy, parathyroidectomy, irradiation of the neck region
- metabolic causes
  - acute hyperphosphatemia (iatrogenic, acute renal failure with rhabdomyolysis or tumor lysis syndrome)
  - magnesium depletion (induces hypoparathyroidism and PTH resistance)
- autoimmune causes
  - isolated hypoparathyroidism
  - associated with other autoimmune diseases (pernicious anemia, Addison disease)
- infiltrative diseases (rare!):
  - neoplasias, granulomatous diseases, AA amyloidosis, hemochromatosis
- congenital
  - aplasia of parathyroid glands (DiGeorge); PTH gene mutation
  - familial hypercalciuric hypocalcemia (activating mutation of the Ca-sensing receptor)

Pseudohypoparathyroidism with high PTH (PTH resistance)
- type Ia (Albright osteodystrophy), Ib, Ic; II

Vitamin D deficiency

Exogenous causes
- low vitamin D intake and/or absorption (often combined with low Ca intake): malnutrition, malabsorption (mainly with steatorrhea), long-lasting cholestasis, after gastrectomy
- loss of vitamin D and its binding protein: nephrotic syndrome, exudative enteropathy

Endogenous causes
- insufficient activation of vitamin D
  - 1. activation step (skin): insufficient sunlight exposure
  - 2. activation step (25-hydroxylation in the liver): hepatopathies, antiepileptic drug (phenytoin, barbiturates)
  - 3. activation step (1-hydroxylation in the kidney): chronic renal failure, hyperphosphatemia
- vitamin D resistance (= vitamin D-dependent rickets VDDR)
  - VDDR type I: 1-hydroxylase mutation
  - VDDR type II: vitamin D receptor mutation

Reduced calcium release from bone
- benign conditions
  - "hungry bone disease": after parathyroidectomy, therapy of severe rickets/osteomalacia
  - drug overdose: bisphosphonates, calcitonin
- malignant conditions
  - extensive osteoplastic metastases, e. g., with prostate or breast carcinoma
  - calcitonin production with medullary thyroid carcinoma

Renal calcium loss
- tubular damage
  - polyuric phase of acute renal failure (after obstruction or acute tubular necrosis)
  - all causes of Fanconi syndrome (generalized proximal tubular dysfunction)
- drugs: loop diuretics
- congenital: Bartter syndrome

Miscellaneous
- calcium chelation
  - in soft tissue: acute pancreatitis (fat saponification)
  - in blood (citrate containing solutions): massive erythrocyte transfusion, cytaphreresis or plasmapheresis
  - drugs: foscarnet
- other causes: sepsis, acute respiratory alkalosis

Hypocalcemia ($P_{Ca} < 2.1$ mmol/L)

Hypoparathyroid Status

True hypoparathyroidism with low PTH values has to be distinguished from *pseudohypoparathyroidism* with PTH resistance. The latter is rare and occurs in the context of congenital disorders, e. g., Albright osteodystrophy. Also rare, but pathophysiologically very interesting, is hypoparathyroidism due to an activating mutation of the "calcium-sensing receptor" (CSR), which imitates a hypercalcemia signal and therefore leads to inhibition of PTH secretion. The disease is called *familial hypercalciuric hypocalcemia*.

The most frequent causes are disorders of the parathyroid gland itself. PTH deficiency can occur following *surgical interventions* (thyroidectomy, parathyroidectomy) or after *irradiation* of the neck area. Some *metabolic disorders* (e. g., hyperphosphatemia and hy-

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Diagnostic Approach to Hypocalcemia

The differential diagnosis in patients with hypocalcemia is depicted in Fig. 30.**21**. The most important parameters are the serum albumin (exclusion of pseudohypocalcemia) and the levels of PTH and vitamin D_3.
Important note: A hallmark of hypoparathyroidism is *hyperphosphatemia*, whereas vitamin D deficiency is characterized by hypophosphatemia. An important and frequent exception to this rule is chronic renal insufficiency, which due to the impaired phosphate excretion typically results in secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia.

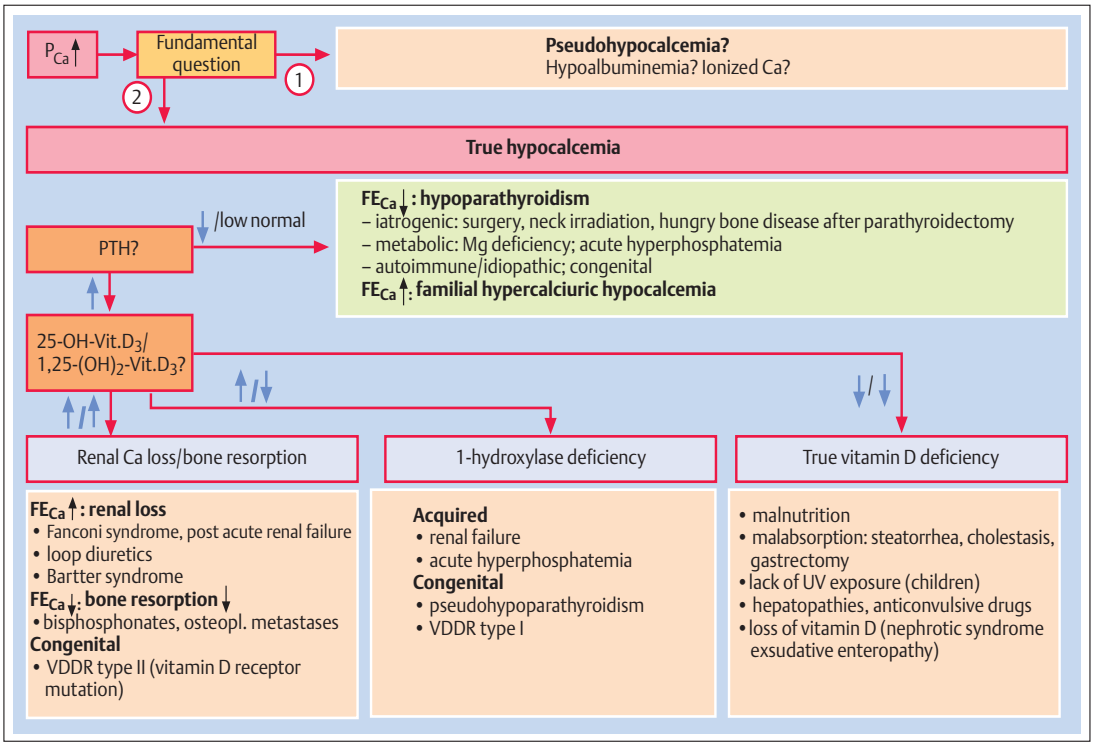

Fig. 30.**21** Diagnostic approach to hypocalcemia.

pomagnesemia) can also lead to hypoparathyroidism with hypocalcemia. *Hypomagnesemia* leads to impaired PTH secretion and PTH resistance and together with hypocalcemia to tetany. Finally, several autoimmune and infiltrative diseases can lead to destruction of the parathyroid glands (see Tab. 30.**27**).

Vitamin D Deficiency

Fig. 30.**19** depicts the different steps of 1,25-$(OH)_2$ vitamin D_3 biosynthesis. Disorders at any of these steps can lead to vitamin D deficiency. Severe *malnutrition and/or malabsorption* reduces the intake of vitamin D_3 as well as calcium, whereas a *severe nephrotic syndrome* leads to loss of vitamin D and its serum binding protein (rickets with vitamin D deficiency).

Tab. 30.**27** lists the causes of inefficient or incomplete activation of vitamin D at three different levels. Two frequent causes are *chronic renal insufficiency* and *hyperphosphatemia*. In both cases 1-hydroxylation of vitamin D_3 is impaired. Furthermore, hyperphosphatemia leads to hypocalcemia, which results in the classical constellation of *secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia.*

Rare *congenital diseases of vitamin D metabolism* are caused either by a mutation of 1-hydroxylase (vitamin D-dependent rickets, VDDR type 1) or by a mutation of the vitamin D receptor (target organ resistance, VDDR type 2).

The consequences of vitamin D deficiency are reduced intestinal absorption of Ca resulting in hypocalcemia and reduced bone mineralization with typical signs of rickets in children and osteomalacia in adults.

Calcium Sequestration in Bones and Tissues

The state in which calcium deposition in the bones is massively increased is called "*hungry bone disease.*" It occurs with vitamin D therapy of severe rickets, but also

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a

b

Fig. 30.**22** Hand radiograph in a patient with hyperparathyroidism.
a Normal hand
b Hand skeleton in a patient with primary hyperparathyroidism with subperiostal bone resorption and separation of the cortical bone layers.

after parathyroidectomy due to hyperparathyroidism, when empty calcium stores in the bones are replenished. An overdose of bisphosphonates or severe osteoplastic metastases can also lead to hypocalcemia due to deposition in the bones. Sequestration of calcium is observed in the context of acute pancreatitis (in soft tissues) and of transfusions with citrate-rich blood products (in the blood). The pathogenesis of hypocalcemia associated with sepsis and acute respiratory alkalosis (hyperventilation) is unclear.

Renal Calcium Loss

The most frequent cause of renal tubular calcium loss is *medication with loop diuretics*. In this case it is often associated with hypokalemia, hypomagnesemia, and alkalosis. However, all nephropathies with a proximal tubular damage (Fanconi syndrome) can lead to renal calcium loss. Finally, respiratory or metabolic acidosis leads to calcium loss in the kidney.

Hypercalcemia ($P_{Ca} > 2.6$ mmol/L)

Hyperparathyroid Status

Primary hyperparathyroidism due to a benign adenoma or to diffuse hyperplasia of all four glands, and autonomous (tertiary) *hyperparathyroidism* in the context of long-lasting chronic renal insufficiency are frequent causes of hypercalcemia. In contrast, *genetic disorders*, e. g., multiple endocrine neoplasia (MEN) or the inactivating mutation of the "calcium-sensing receptor," which interrupts the negative feedback of serum calcium levels on PTH secretion (so-called familial hypocalciuric hypercalcemia), are rare.

The hallmarks of hyperparathyroidism are hypercalcemia, hypophosphatemia, and nephrolithiasis. In rare cases it can cause pancreatitis, ulcus duodeni, and hypertension. Bone histology shows the typical picture of fibro-osteoclasia with subperiostal resorption zones (Fig. 30.**22**). The diagnosis is made by the measurement of serum PTH.

If hypercalcemia is observed in a patient with malignancy, but without obvious bone metastases, it is called

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humoral hypercalcemia of malignancy, which is usually caused by a paraneoplastic secretion of a PTH-related peptide (PTHrP). This peptide binds to the PTH receptor in the kidney and also leads to calcium mobilization from the skeleton. The secretion of PTH is suppressed by hypercalemia. It is important to distinguish this situation from patients with diffuse bone metastases, since humoral hypercalcemia is fully reversible with successful treatment of the primary tumor.

Vitamin D Excess

The most frequent cause of hypercalcemia is *excessive vitamin D_3 intake*. It can occur, when active 1,25-$(OH)_2$ vitamin D_3 is used for treatment of secondary hyperparathyroidism in patients with renal insufficiency. Since these patients usually suffer from concomitant hyperphosphatemia, the risk of metastatic calcifications is considerable. Other causes of vitamin D excess are the *endogenous production of 1,25-$(OH)_2$ vitamin D_3* by macrophages in the context of granulomatous diseases (especially with sarcoidosis) and by tumor cells in the context of malignant lymphomas.

Increased Bone Resorption

Long-term immobilization leads to rapid calcium release from the skeleton and leads to nephrolithiasis due to hypercalciuria if hydration is insufficient (e. g., in the context of postpoliomyelitis syndrome). However, the most frequent cause of increased bone resorption are *malignant diseases*, either by massive and diffuse osteolytic metastases (Fig. 30.**23**) or by paraneoplastic secretion of osteoclast-activating factors, e. g., tumor necrosis factor (TNF), IL-1, IL-6, transforming growth factor (TGF). The latter can be inhibited by corticosteroid therapy.

Renal Calcium Retention

Renal tubular calcium excretion is reduced in all situations with volume depletion, since tubular reabsorption of calcium is linked to sodium reabsorption. Hypercalcemia leads to polyuria thereby worsening the volume deficit ("circulus vitiosus"). Clinically important is the inhibition of renal calcium excretion by *thiazide diuretics*. It may lead to hypercalcemia, especially in the context of diuretic-induced volume depletion. On the other hand, it is used therapeutically for the treatment of nephrolithiasis with calcium-containing stones.

Other Causes

Various *endocrine disorders* can lead to hypercalcemia. In most cases, the precise pathogenesis is unknown. These diseases are mentioned in Tab. 30.**28**.

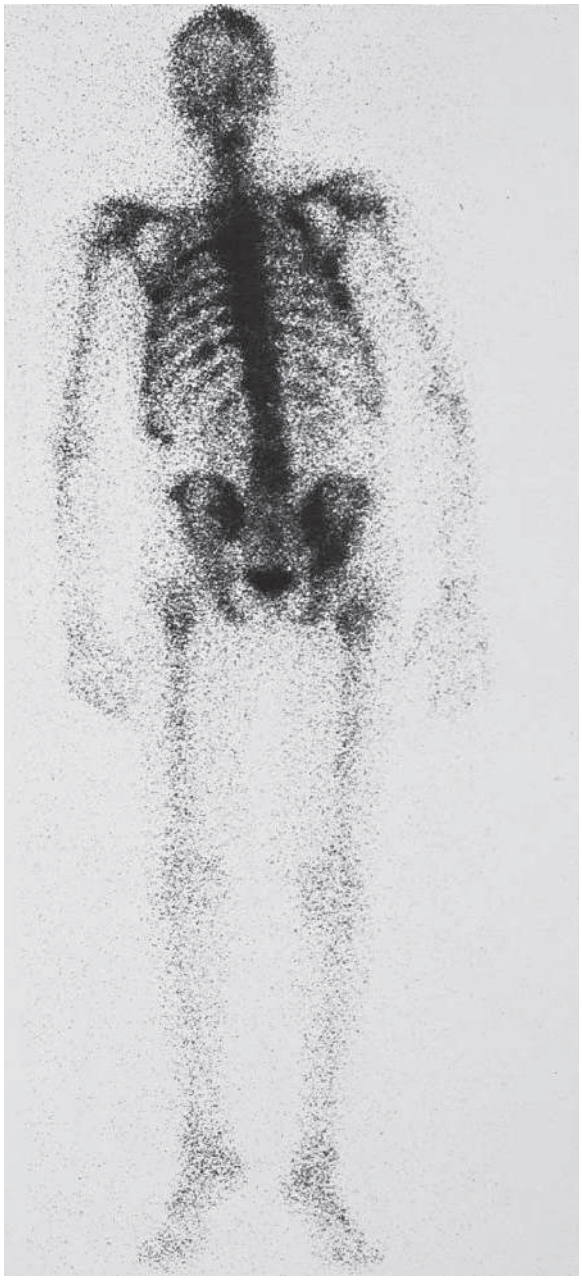

Fig. 30.**23** Nuclear bone scan with metastasizing prostate cancer. Multiple bone metastases appear in the pelvis, ribs, vertebral column, and skull.

A particular clinical manifestation of hypercalcemia is the so-called *milk-alkali syndrome*. It is caused by excessive intake of milk and calcium carbonate-containing antacids, e. g., in patients with gastroduodenal ulcer disease. The hallmarks are hypercalcemia, slight hyperphosphatemia, low PTH, and metabolic alkalosis, which lead to bicarbonaturia and consecutive volume depletion and hypokalemia due to increased distal sodium delivery. The therapy consists of volume expansion and the elimination of all calcium and alkali intake.

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Table 30.**28** Differential diagnosis of hypercalcemia

Hyperparathyroid status

True hyperparathyroidism with high PTH
- primary hyperparathyroidism
  acquired: 85 % adenoma, 10 % hyperplasia, 5 % carcinoma
  genetic: multiple endocrine neoplasia MEN
  - MEN 1 (parathyroid adenoma, pituitary tumor, gastrinoma)
  - MEN 2A (parathyroid adenoma, pheochromocytoma, medullary thyroid carcinoma)
- tertiary hyperparathyroidism (with renal failure)
- lithium induced
- familial hypocalciuric hypercalcemia (inactivating mutation of the Ca-sensing receptor)

Pseudohyperparathyroidism with low PTH
- humoral hypercalcemia of malignancy:
  paraneoplastic secretion of PTH-related peptide (PTHrP) with lung, breast, renal, and thyroid carcinoma

Vitamin D excess

Exogenous Vitamin D intake
- vitamin D overdose
- therapy of secondary hyperparathyroidism with 1,25-$(OH)_2$ vitamin D_3 in the context of chronic renal failure (often combined with calcium-containing phosphate binders)

Endogenous Vitamin D production
- granulomatous diseases (1,25-$(OH)_2$ vitamin D_3 production in macrophages)
  - sarcoidosis
  - tuberculosis, lepra, histoplasmosis, *Candida*
  - silicosis, berylliosis
- paraneoplastic 1,25-$(OH)_2$ vitamin D_3 production
  - Hodgkin disease, T-cell lymphomas
  - leiomyoblastoma

Increased calcium release from bone

Benign conditions
- long-lasting immobilization
- vitamin A intoxication

Malignant conditions
- paraneoplastic secretion of osteoclast-activating factors (OAF) such as TGF/TNF/IL-1/IL-6 with multiple myeloma and lymphomas
- extensive osteolysis with multiple osteolytic metastases (e. g., prostate carcinoma) or Paget disease

Renal calcium retention
- all conditions with volume depletion (mechanism: Na-dependent tubular reabsorption of Ca)
- thiazide diuretics
- familial hypocalciuric hypercalcemia (inactivating mutation of the Ca-sensing receptor)

Miscellaneous
- increased exogenous Ca intake
  - milk-alkali syndrome
  - iatrogenic: therapy with Ca-containing phosphate binders in the context of chronic renal insufficiency (often together with vitamin D_3)
- endocrine diseases
  hyperthyroidism, pheochromocytoma, Addison disease, acromegaly

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Diagnostic Approach to Hypercalcemia

The differential diagnosis in patients with hypercalcemia is depicted in Fig. 30.**24**. The most important parameters are the measurement of PTH and vitamin D. The most frequent causes of hypercalcemia are:

- primary hyperparathyroidism
- malignant diseases; hypercalcemia occurs through various pathways: paraneoplastic synthesis of PTHrP (humoral hypercalcemia), osteoclast-activating factors, or 1,25-$(OH)_2$ vitamin D_3; diffuse osteolytic metastases
- advanced chronic renal failure with tertiary hyperparathyroidism and/or therapy with calcium-containing phosphate binders and 1,25-$(OH)_2$ vitamin D_3.

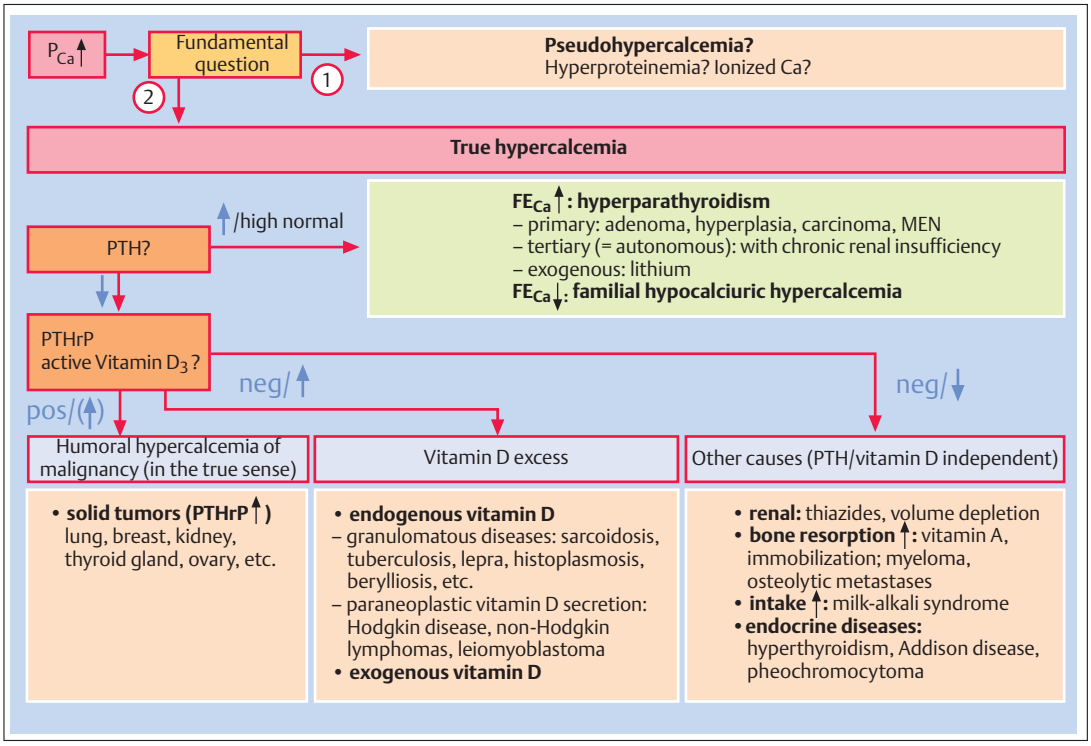

Fig. 30.**24** Diagnostic approach to hypercalcemia.

Disorders of Phosphate Homeostasis

Definition, Diagnosis, and Clinical Features

Phosphate (PO_4^{3-}) is an intracellular anion with crucial importantance for cellular energy metabolism, signal transduction, and nucleic acid synthesis. *Hyperphosphatemia* is defined as an increase in serum phosphate above 1.5 mmol/L and *hypophosphatemia* as a decrease of serum phosphate below 1.0 mmol/L.

Clinical Features. The clinical symptoms and signs of phosphate disorders are summarized in Tab. 30.**29**. *Hyperphosphatemia* mainly leads to metabolic disorders. Hypocalcemia is caused by various mechanism: inhibition of 1-hydroxylase in the kidney with reduced synthesis of active 1,25-$(OH)_2$ vitamin D_3 and direct complex formation of Ca and PO_4^{3-} in the blood plasma. The consequence is secondary hyperparathyroidism. In patients with renal insufficiency this disease is treated with phosphate binders and active 1,25-$(OH)_2$ vitamin D_3. If serum calcium rises as a consequence of treatment, the combination of hyperphosphatemia and hypercalcemia may lead to calcium phosphate deposition in various organs and tissues (calciphylaxis; see Hypercalcemia, above).

In contrast and due to the vital functions of PO_4^{3-}, *hypophosphatemia* mainly leads to disorders in tissues with high proliferation rate (e. g., bone marrow), high energy consumption (e. g., muscles, brain), and high structural PO_4^{3-} content (skeleton: hypophosphatemic rickets).

Causes. Phosphate disorders can arise via four different pathophysiologic mechanisms (Fig. 30.**25**):

➤ disorders of parathyroid function and regulation
➤ disorders of vitamin D metabolism and intestinal absorption.

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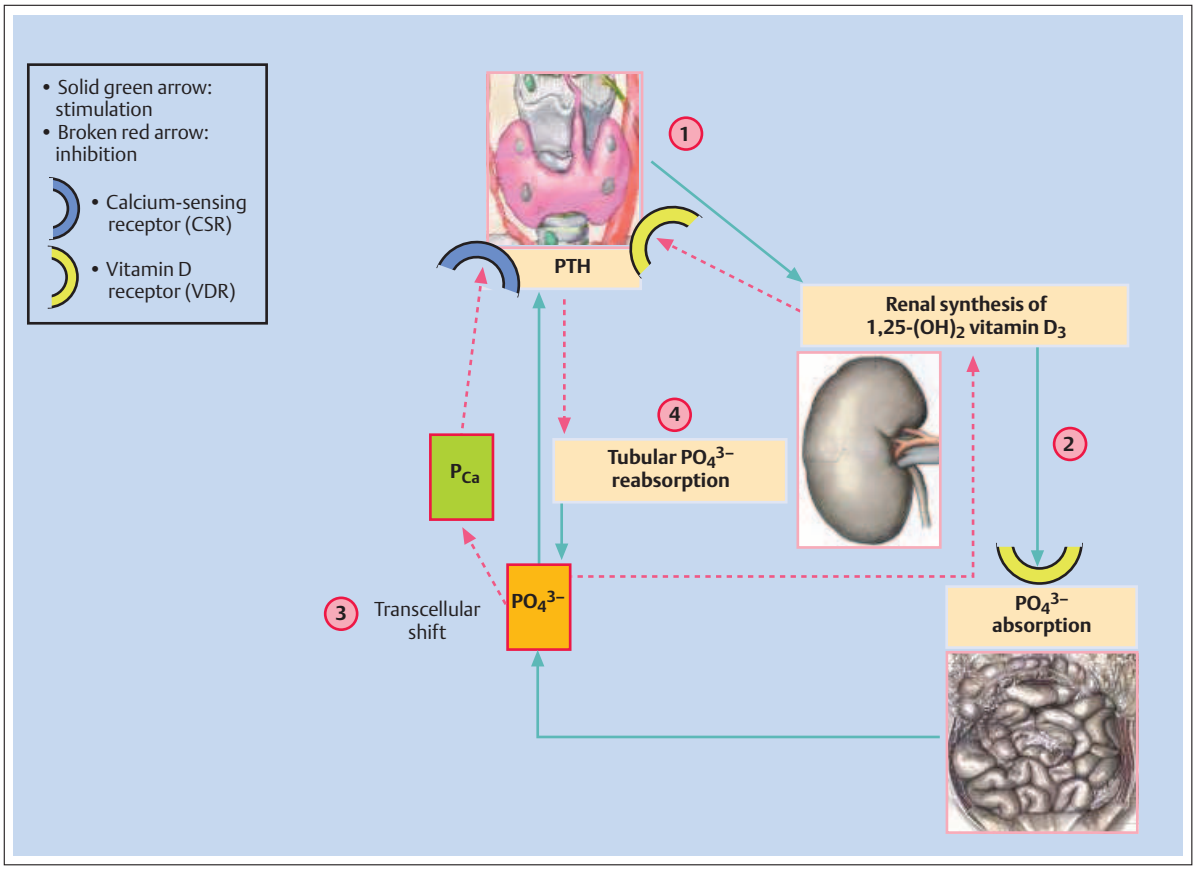

Fig. 30.**25** Fundamental pathogenesis of phosphate disorders. Phosphate disorders can arise by four different pathways: (1) disorders of parathyroid hormone (PTH) secretion, (2) disorders of vitamin D and intestinal Ca absorption, (3) transcellular shifts, and (4) disorders of renal PO_4^{3-} excretion.

Table 30.**29** Symptoms and signs of phosphate disorders

Hypophosphatemia	Hyperphosphatemia
Muscular – muscle weakness (skeletal muscles) – myocardial dysfunction **Neurologic (rare)** – paresthesias – dysarthria, ataxia, confusion, convulsion (metabolic encephalopathy)	**Neuromuscular** – (see neurologic/psychiatric symptoms of hypocalcemia Tab. 30.**26**)
Hematologic – hemolysis – leukocyte dysfunction – thrombocytopenia and platelet dysfunction	
Bone – hypophosphatemic rickets	**Soft tissue** – with concomitant hypercalcemia: metastatic calcifications of organs and soft tissues (calciphylaxis)
Metabolic – hypercalciuria – hypermagnesuria, hypomagnesemia	**Metabolic** – hypocalcemia, secondary hyperparathyroidism

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Table 30.**30** Differential diagnosis of phosphate disorders

Hypophosphatemia	Hyperphosphatemia

Hyperparathyroid status
– true hyperparathyroidism
  – primary, autonomous (tertiary)
  – congenital (multiple endocrine neoplasia MEN)
– paraneoplastic (induced by PTHrP)
	Hypoparathyroid status
	– true hypoparathyroidism
	  – iatrogenic
	  – metabolic (Mg depletion, hypercalcemia)
	  – autoimmune
	  – infiltrative
	  – congenital
	– pseudohypoparathyroidism (PTH resistance)

Reduced intestinal absorption
– absolute decreased intake
– overdose of phosphate binders/antacids
– vitamin D deficiency
  – malnutrition
  – malabsorption
  – genetic: vitamin D-dependent rickets type I/II
	Increased intestinal absorption
	– absolute increased intake (often iatrogenic):
	phosphate salts, phosphate-containing enemas
	– vitamin D excess:
	overdose of vitamin D therapy with chronic renal failure

Transcellular shifts
– rapid cell proliferation
  – leukemias/lymphomas
  – therapy of severe pernicious anemia
– refeeding syndrome
– therapy of alcoholic/diabetic ketoacidosis
– chronic respiratory alkalosis
– hormones:
insulin, catecholamines, androgens
– miscellaneous:
toxic shock syndrome, severe burns
	Transcellular shifts
	– rapid cell lysis:
	rhabdomyolysis, tumor lysis syndrome, hemolysis, catabolic states with tissue destruction (sepsis, malignant hyperthermia), mesenterial infarction
	– chronic respiratory acidosis

Renal phosphate loss
– acquired tubular disorders
(with or without Fanconi syndrome):
  – after acute tubular necrosis, obstruction or renal transplantation
  – oncogenic osteomalacia (paraneoplastic production of FGF23 = “phosphatonin”)
– congenital tubular disorders:
hypophosphatemic vitamin D-resistant rickets (phosphate diabetes): autosomal dominant, X-linked, McCune–Albright syndrome
– volume excess
– diuretics
– corticosteroids
	Renal phosphate retention
	– acute or chronic renal failure
	  – drop of glomerular filtration rate > 30 %
	  – secondary hyperparathyroidism
	– volume depletion
	– bisphosphonates
	– acromegaly, hypothyroidism

- ➤ transcellular phosphate shifts (internal phosphate balance)
- ➤ disorders of renal phosphate excretion.

The differential diagnosis for hypophosphatemia and hyperphosphatemia is summarized in Tab. 30.**30** and discussed further in the following paragraphs.

Hypophosphatemia ($P_{PO_4^{3-}} < 1$ mmol/L)

Hyperparathyroid Status

PTH stimulates renal tubular Ca reabsorption, but at the same time inhibits PO_4^{3-} reabsorption. The typical constellation for *primary hyperparathyroidism* is therefore the combination of hypercalcemia, hypophosphatemia, and hypercalciuria. Causes are the same as discussed for hypercalcemia (see Tab. 30.**28**).

Reduced Intestinal Absorption of Vitamin D and PO_4^{3-}

Intestinal absorption of vitamin D and PO_4^{3-} is reduced by net *reduced intake* (e. g., anorexia, chronic alcoholism), but also in all diseases with *malabsorption* (e. g., celiac sprue, Crohn disease). Certain *antacid drugs* complex PO_4^{3-} and lead to intestinal loss.

Active 1,25-$(OH)_2$ vitamin D_3 stimulates intestinal absorption of Ca and PO_4^{3-}. Therefore, all forms of *vitamin D deficiency* also lead to hypophosphatemia and therefore to severe disturbance of bone mineralization

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as seen in rickets and osteomalacia (see Hypocalcemia, above; Tab. 30.**27**).

Transcellular PO_4^{3-} Shifts

Acute transcellular PO_4^{3-} shifts occur in the following situations:

- *food intake after a long period of malnutrition (so-called refeeding syndrome) and parenteral hyperalimentation:* Calorie intake leads to rapid cell proliferation with rapid uptake of PO_4^{3-}, potassium, and Mg. The combination of hypophosphatemia, hypokalemia, and hypomagnesemia is therefore typical and needs aggressive substitution of all these electrolytes.
- *insulin therapy of diabetic ketoacidosis:* ketoacidosis leads to massive renal loss of PO_4^{3-} and potassium, which is usually masked by concomitant volume depletion. However, with insulin therapy and volume expansion acidosis is rapidly corrected and potassium and PO_4^{3-} are rapidly shifted to the intracellular space. Therefore, these electrolytes have to be measured frequently at the beginning of ketoacidosis therapy, and aggressive substitution is necessary to replenish the total body deficit of PO_4^{3-} and potassium.
- *respiratory alkalosis*
- *rapid cell proliferation:* in the context of malignancies (e. g., acute leukemia) and of the therapy of severe pernicious anemia.

Renal Phosphate Loss

The most frequent causes are *therapy with diuretics* and *proximal tubular disorders* in the context of acute tubular necrosis, obstructive nephropathy, and after renal transplantation. In all these situations, full recovery is normally expected, and phosphate substitution is a matter of debate.

Rare diseases with renal PO_4^{3-} loss are *hypophosphatemic vitamin D-resistant rickets* (also-called "phosphate diabetes") and *oncogenic osteomalacia*. The common pathophysiologic principle is a disorder of the phosphaturic hormone, fibroblast growth factor 23 (FGF23). In the case of hypophosphatemic rickets the metabolism of FGF23 is inhibited due to a congenital mutation in the molecule itself or in the responsible enzyme for degradation. In contrast, in oncogenic osteomalacia paraneoplastic FGF23 synthesis was found.

Diagnostic Approach to Hypophosphatemia

The differential diagnosis in patients with hypophosphatemia is depicted in Fig. 30.**26**. With the fractional PO_4^{3-} excretion, renal and extrarenal forms of hypophosphatemia can be distinguished. Measurement of PTH and vitamin D are helpful for further diagnosis.

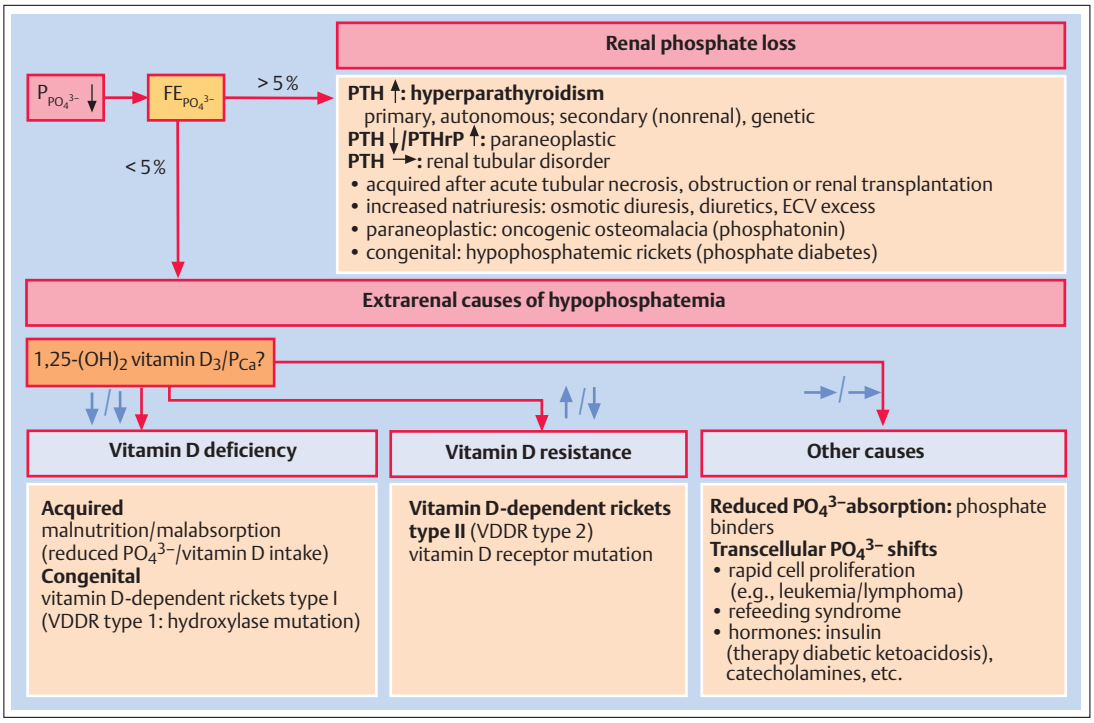

Fig. 30.**26** Diagnostic approach to hypophosphatemia.

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Hyperphosphatemia ($P_{PO_4^{3-}} > 1.5$ mmol/L)

Hypoparathyroid Status

The combination of hypocalcemia and hyperphosphatemia is typical for all situations with *hypoparathyroidism* (see Hypocalcemia, above). Hyperphosphatemia occurs due increased renal tubular PO_4^{3-} reabsorption.

Increased Intestinal Absorption of PO_4^{3-} or Vitamin D

This occurs mainly as an iatrogenic complication, when *substitution* with PO_4^{3-} and/or vitamin D is *overdosed*. However, renal PO_4^{3-} excretion is very efficient. Therefore, hyperphosphatemia usually only occurs with concomitant renal insufficiency. PO_4^{3-}-containing laxatives or enemas are dangerous in this situation!

Transcellular PO_4^{3-} Shifts

Acute transcellular shifts of PO_4^{3-} from the intracellular to the extracellular space occur in the following situations:

- *acute cytolysis:* hemolysis, rhabdomyolysis, tumor lysis syndrome, catabolic states (e. g., malignant hyperthermia), mesenteric ischemia/infarction
- *respiratory acidosis.*

Renal Phosphate Retention

This is the by far most frequent cause of hyperphosphatemia and occurs with all forms of *acute and chronic renal insufficiency*. A decrease of glomerular filtration rate below 30 mL/min leads to hyperphosphatemia. Inhibition of active vitamin D synthesis and complex formation in the plasma then leads to hypocalcemia and secondary hyperparathyroidism.

Increased PO_4^{3-} reabsorption is also observed with *hypothyroidism* and *acromegaly*, but the precise pathogenesis is unknown.

Diagnostic Approach to Hyperphosphatemia

The differential diagnosis in patients with hyperphosphatemia is depicted in Fig. 30.**27**. Measurement of renal function is the first step. PTH and vitamin D are helpful for further diagnosis.

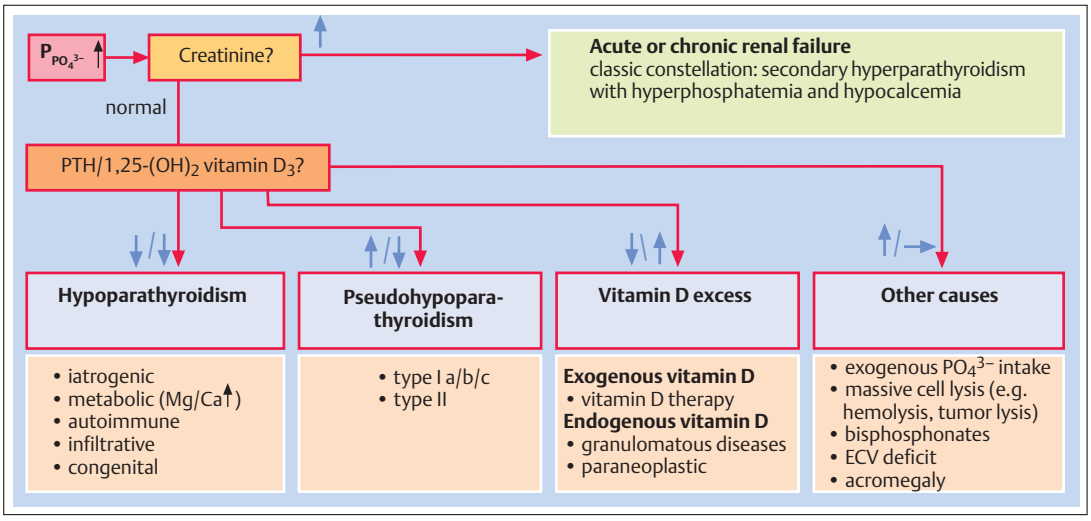

Fig. 30.**27** Diagnostic approach to hyperphosphatemia.

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Disorders of Magnesium Homeostasis

Definition, Diagnosis, and Clinical Features

Magnesium is the only ion discussed in this chapter that does not have its own hormonal system for regulation. Although PTH has some influence on magnesium excretion and magnesium also on PTH secretion, there is no strict negative feedback loop. This is rather astonishing since magnesium plays an important role in membrane excitability and also in several intracellular functions (e. g., cofactor for many enzymes involved in protein and nucleic acid synthesis). Renal magnesium excretion is stimulated by hypercalcemia, hypophosphatemia, and hypermagnesemia itself (see Tab. 30.**24**).

Hypomagnesemia is defined as a decrease of serum magnesium levels to < 0.8 mmol/L, and *hypermagnesemia*, as an increase to > 1.2 mmol/L.

Diagnosis. Similarly to calcium, a fraction of magnesium in serum is protein-bound (about 30%) and a fraction is complexed (about 15%). Alternative measurement techniques have been evaluated, e. g., measurement of intracellular magnesium levels in erythrocytes and measurement of ionized magnesium in serum, without clear advantages of either method being found. Therefore, the measurement of total magnesium in serum has remained the standard test. Similarly to calcium, a formula for correction of magnesium levels in patients with *hypoalbuminemia* has been suggested:

$$\Delta[\text{Mg}]\ (\text{mmol/L}) = 0.005 \times \Delta[\text{albumin}]\ (\text{g/L})$$

Clinical Features. The hallmarks of magnesium disorders are symptoms and signs of altered *membrane excitability* in heart and skeletal muscles and in the nervous system. They are summarized in Tab. 30.**31**. Magnesium disorders are often associated with other electrolyte disorders (e. g., potassium and calcium). Since these disorders also influence membrane excitability, the symptoms and signs can often not be clearly separated.

Causes. Magnesium disorders can be classified according to pathophysiology as suggested in Fig. 30.**1**:

- disorders of magnesium intake
- transcellular magnesium shifts
- disorders of renal and extrarenal magnesium excretion.

The differential diagnosis of each group is listed in Tab. 30.**32**.

Hypomagnesemia ($P_{Mg} < 0.7$ mmol/L)

Reduced Intake

This situation is observed with all forms of *malnutrition* e. g., kwashiorkor, anorexia, and chronic alcoholism. In addition, diseases associated with *malabsorption* (e. g., celiac sprue, Crohn disease) may lead to hypomagnesemia. Especially in patients with steatorrhea, the divalent calcium and magnesium ions are bound by nonabsorbable fatty acids and are therefore lost in the intestine.

Transcellular Magnesium Shifts

Shifts from the extracellular to the intracellular space occur, analogous to potassium and PO_4^{3-}, in the following situations:

Table 30.**31** Symptoms and signs of magnesium disorders

Hypomagnesemia	Hypermagnesemia
Cardiovascular – hypertension – QT prolongation, ST depression – ventricular arrhythmias – increased digoxin toxicity	**Cardiovascular** – hypotension, flushing – QRS widening – bradycardia, atrioventricular/intraventricular block – cardiac arrest
Neuromuscular – hyperreflexia, tremor – cramps, tetany	**Neuromuscular** – hyporeflexia – confusion, coma – hypoventilation
Metabolic – hypocalcemia (via hypoparathyroidism/PTH resistance) – hypokalemia (via inhibition of Na reabsorption in the loop of Henle → increased distal Na delivery)	

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Table 30.**32** Differential diagnosis of magnesium disorders

Hypomagnesemia	Hypermagnesemia
Reduced intake – malnutrition: kwashiorkor, anorexia, chronic alcoholism	**Increased intake** – iatrogenic – intravenous Mg (eclampsia, acute coronary heart disease) – Mg-containing laxatives (only with concomitant renal failure) – milk-alkali syndrome
Redistribution – "hungry bone disease" after parathyroidectomy due to primary or tertiary hyperparathyroidism – refeeding syndrome – therapy of alcoholic or diabetic ketoacidosis – respiratory alkalosis – miscellaneous: acute pancreatitis, acute intermittent porphyria	**Redistribution** – extensive osteolytic metastases (rare!) – endocrine disorders (mechanism unknown): Addison disease, acromegaly, hypothyroidism
Renal magnesium loss – acquired tubular disorders (with or without Fanconi syndrome) – after acute tubular necrosis, obstruction or renal transplantation – drugs: amphothericin B, cisplatin, aminoglycosides – congenital tubular disorders – Gitelman syndrome, Bartter syndrome – paracellin mutation – familial hypercalciuric hypocalcemia (activating mutation of the Ca-sensing receptor) – all situations with increased natriuresis – volume expansion – diuretics (mainly thiazides!) – osmotic diuresis (hyperglycemia, hypercalcemia, metabolic alkalosis, others)	**Renal magnesium retention** – acute and chronic renal failure (especially when associated with volume depletion) – familial hypocalciuric hypercalcemia (inactivating mutation of the Ca-sensing receptor)
Extrarenal magnesium loss – all situations with malabsorption (with chronic diarrhea and steatorrhea): celiac sprue, Crohn disease, extensive intestinal resection – intestinal fistulas – laxative abuse	**Extrarenal magnesium retention** (not existent)

- refeeding syndrome
- therapy of diabetic and alcoholic ketoacidosis
- acute respiratory alkalosis (hyperventilation).

Shifts from the extracellular space to the bones or to soft tissues occur, analogous to calcium, in the following situations:

- "hungry bone disease" (after parathyroidectomy or with vitamin D therapy of severe rickets)
- acute pancreatitis.

Extrarenal Magnesium Loss

Intestinal magnesium loss is observed with chronic diarrhea, laxative abuse, or fistulas.

Renal Magnesium Loss

Renal magnesium loss is found in the following situations:

- *proximal tubular damage* (with or without Fanconi syndrome), e. g., after acute tubular necrosis
- *congenital tubular disorders:* Gitelman syndrome (magnesium loss = important feature), Bartter syndrome (magnesium loss = less important), paracellin defect
- *all situations with increased natriuresis*, since magnesium reabsorption is linked with sodium reabsorption, e. g., osmotic diuresis (glucosuria), hypercalciuria, bicarbonaturia, therapy with diuretics.

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Diagnostic Approach to Hypomagnesemia

The differential diagnosis in patients with hypomagnesemia is depicted in Fig. 30.**28**. In general, it is important to consider hypomagnesemia, since serum magnesium levels are not routinely measured. Hypomagnesemia is often associated with other electrolyte disorders (hypokalemia, hypocalcemia) and sometimes involved in their pathogenesis. Therefore, magnesium substitution may be an important step for their correction.

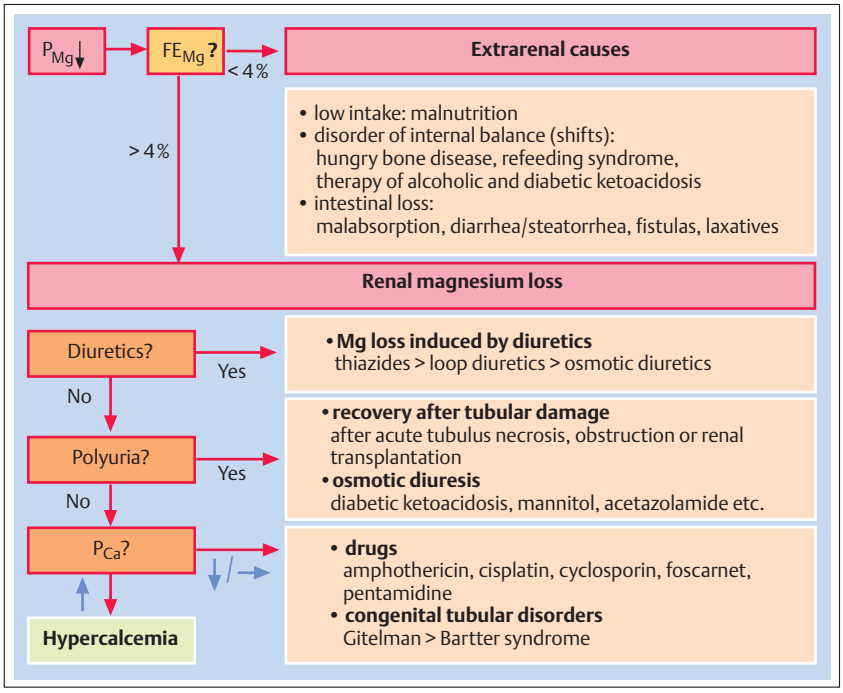

Fig. 30.**28** Diagnostic approach to hypomagnesemia.

Hypermagnesemia (P_{Mg} > 1.2 mmol/L)

Increased Intake

Hypermagnesemia is rare and occurs almost exclusively with exogenous intake. High-dose magnesium is given for therapy of eclampsia. Other exogenous sources are magnesium-containing laxatives and milk, in the context of milk-alkali syndrome. However, similar to PO_4^{3-} and potassium, renal magnesium excretion is very efficient, and therefore hypermagnesemia only occurs if renal function is impaired and/or volume depletion is present.

Transcellular Magnesium Shifts

Hypermagnesemia rarely occurs with diffuse and extensive osteolytic metastases and also in the context of various endocrine diseases, especially with adrenal insufficiency. The pathogenesis in the latter situation is unclear.

Renal Magnesium Retention

Acute and chronic renal insufficiency with concomitant magnesium intake can lead to hypermagnesemia. A rare *genetic cause* for hypermagnesemia is the familial hypocalciuric hypercalcemia with an inactivating mutation of the calcium-sensing receptor (see Hypercalcemia, above).

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Diagnostic Approach to Hypermagnesemia

The differential diagnosis in a patient with hypermagnesemia is depicted in Fig. 30.**29**. The most important parameters are the measurement of renal function, exclusion of Addison disease and the search for exogenous sources of magnesium.

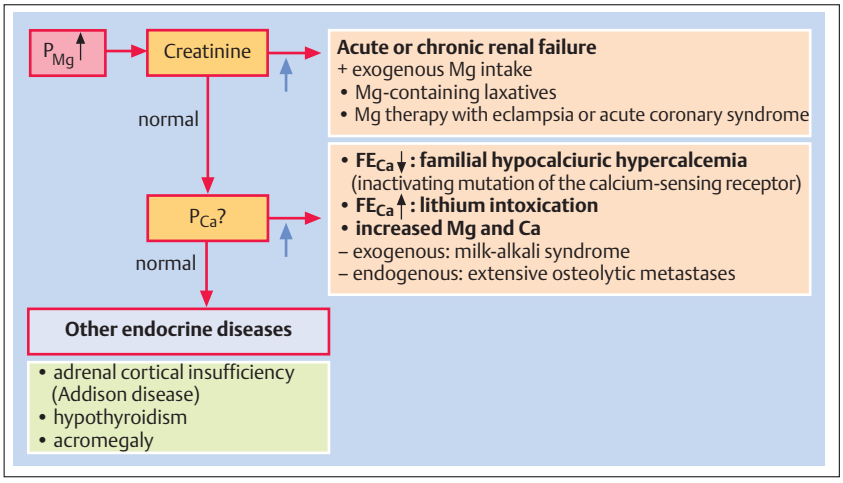

Fig. 30.**29** Diagnostic approach to hypermagnesemia.

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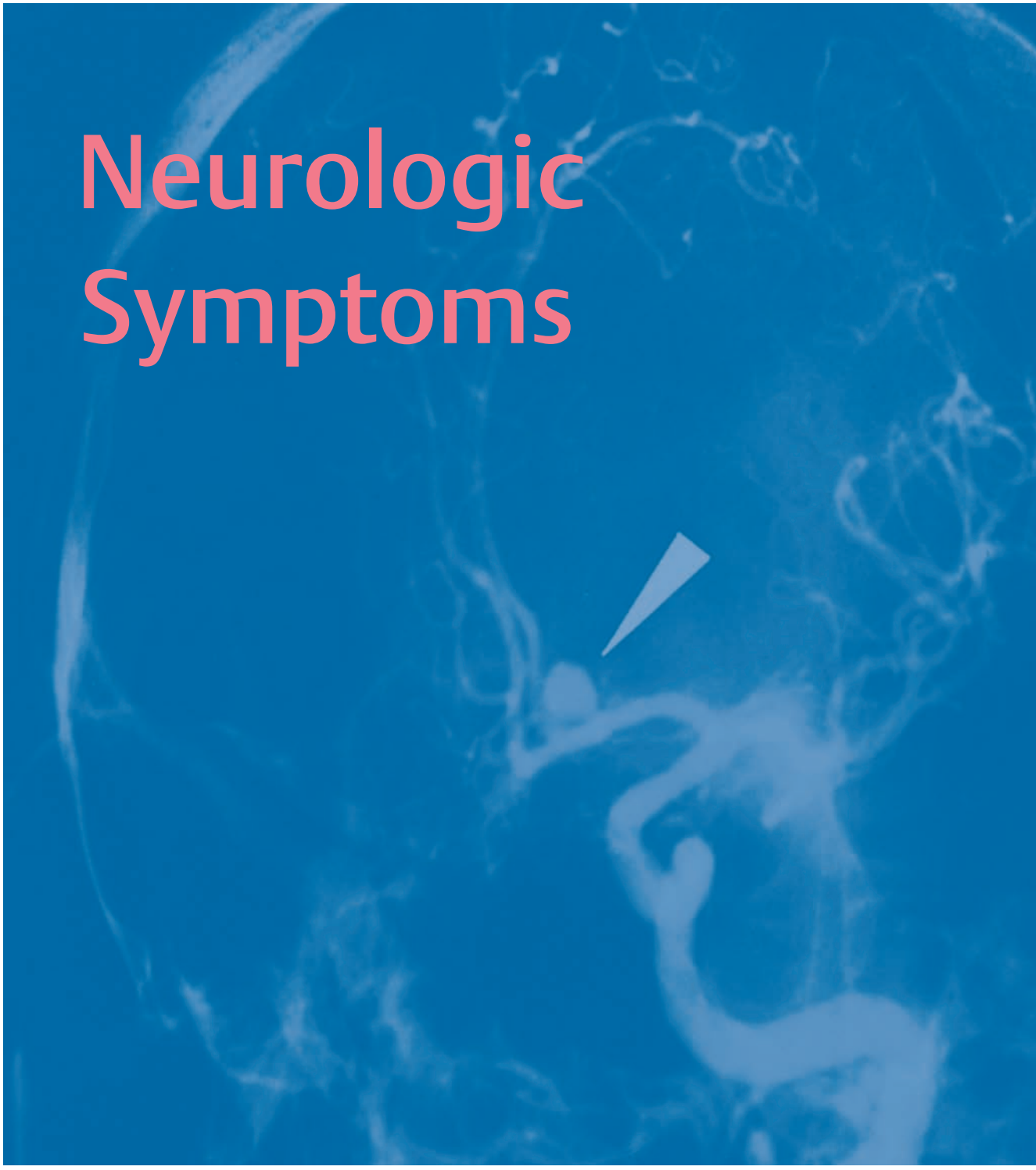
Neurologic Symptoms



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31 Vertigo and Syncopal Conditions

U. Schwarz, C. Scharf, and P. Greminger

32 Coma and Other Disturbances of Consciousness

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31 Vertigo and Syncopal Conditions

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Vertigo, Impaired Consciousness, and Syncope: An Overview

Vertigo. The term vertigo is used to denote a subjective sensation of perceived movement, in which either the subject or his surroundings seem to whirl dizzily. The disturbance can be attributed to a physiologic or pathologic failure in the processing of *afferent*, *sensory*, or *proprioceptive stimuli*, and also to the integration of this multisensory information to give an *appropriate feeling of space* (Fig. 31.**1**). Vertigo is a (multi-)sensory defecit syndrome, which can be due to a large variety of pathogenetic mechanisms and/or etiologies. However, it is expressed clinically by a range of similar disorders because of the close functional links between the involved structures, despite their wide neuroanatomic dispersal (Fig. 31.**2**), for example:

- in the predominantly cortically generated *perception of body position* and/or *body motion*: a feeling of uncontrollable intrinsic movements, such as turning, swaying, traveling in an elevator, falling
- in the predominantly cortically generated *perception of the visual surroundings*: the feeling that the world is turning independently, is slanted, or upside down; blurred vision; disordered fixation
- in the *autonomic nervous system*: nausea due to stimulation of the medullary vomiting center, sweating
- *oculomotor disturbance:* pathologic nystagmus
- *anomaly of postural reflexes:* truncal, stationary ataxia, ataxic gait.

It is important to ascertain rapidly the site of the disorder as vertigo can be due to a large number of causes that are managed very differently therapeutically and/or may require urgent intervention (e. g., *thrombosis of the basilar artery*). With a careful history and neurologic examination (especially neuro-otologic and neuro-ophthalmologic), peripheral and central vestibular lesions can generally be distinguished readily in the differential diagnosis.

Disturbances of Consciousness. Diffuse, nondirected vertigo (e. g., giddiness, light-headedness, feeling faint) is one of the most frequent symptoms preceding, or accompanying, conditions that are associated with a more or less severe *disturbance of consciousness*, including *loss of consciousness*. *Normal consciousness* cannot, and must not, be defined only on its neurophysiologic basis. However, it is generally accepted that normal consciousness requires normal neuronal excitation and glial connections for its support, which preserves its two most important aspects; *clarity of consciousness* (lucidity) and *alertness* (vigilance). This is most readily apparent in the cerebral cortex, diencephalon (particularly the thalamus and hypothalamus), and in the mesencephalic reticular formation (particularly the ascending reticular activating system [ARAS]).

Clinically, a distinction can be made between *qualitative* and *quantitative* disorders of consciousness (Tab. 31.**1**), which are due to different pathologic mechanisms and which are often present in combination (e. g., severe *encephalopathy*). Because of the very different therapeutic consequences it is urgent to rule out *intox-*

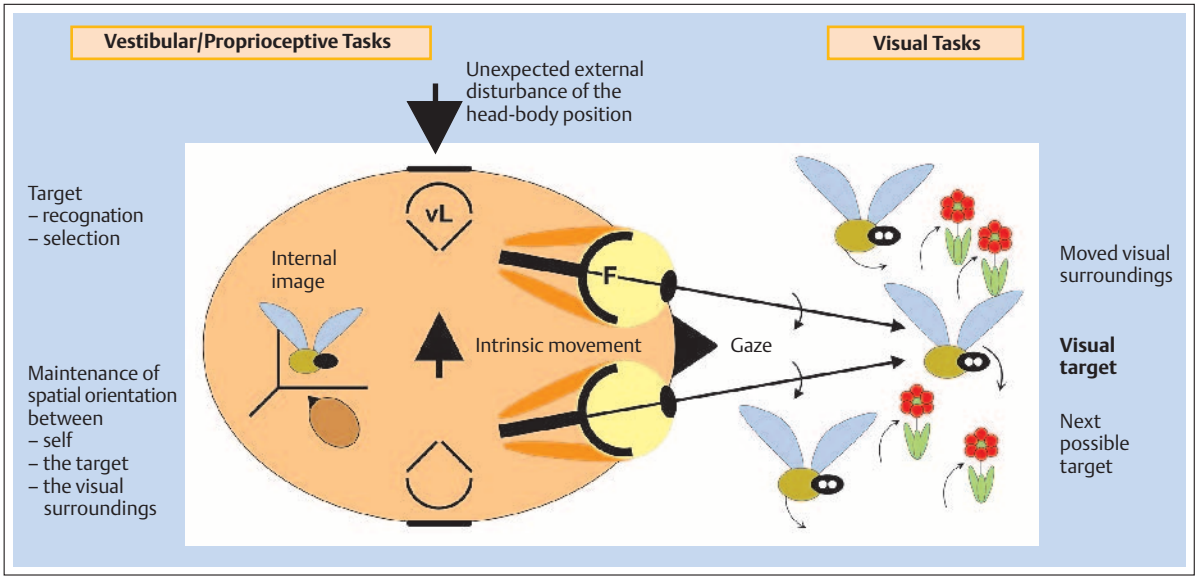

Fig. 31.**1** Importance of the oculomotor system.
The multimodal, visual, vestibular, and proprioceptive oculomotor system is used for maintaining spatial orientation and for selecting and recognizing visual targets despite varied sensory conflicts and interference. The selected target must always maintain a stable image on the fovea (F; visual axis) and a precise virtual image of the spatial relationships of all the components must be produced in the brain at any time. VL = vestibular labyrinth, F = fovea.

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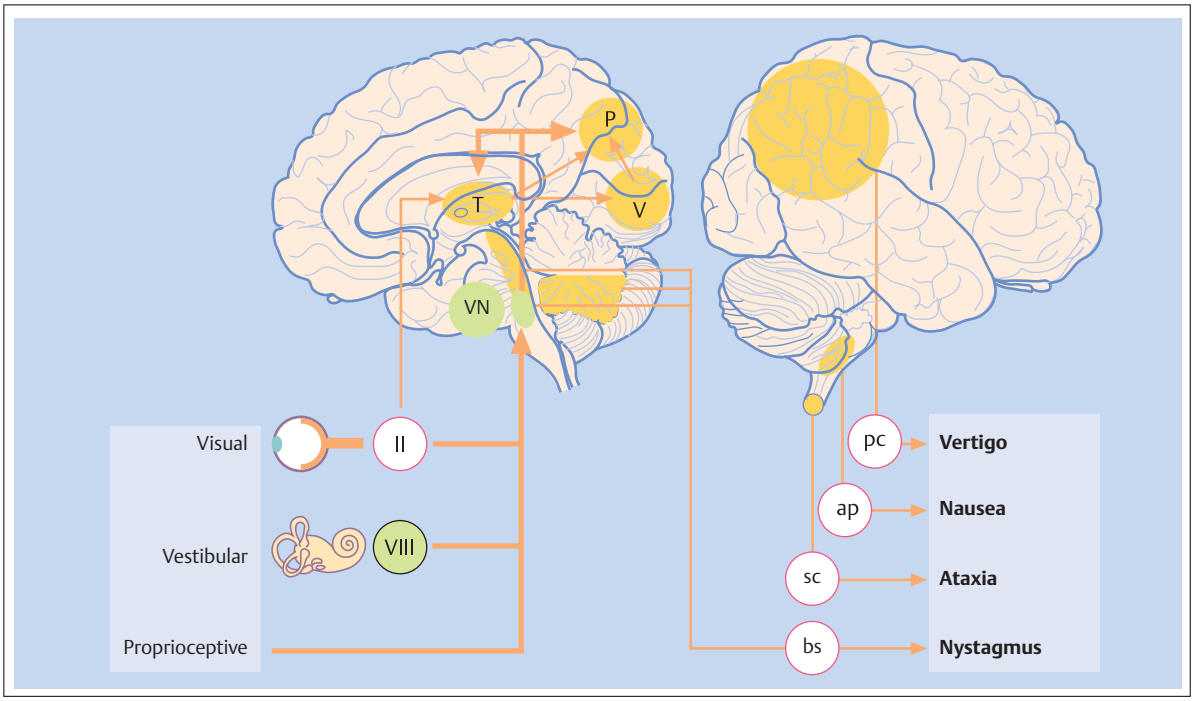

Fig. 31.**2** Cardinal disorders of vertigo.
Neuroanatomic structures involved in the development of the cardinal disorders in peripheral and central vestibular syndromes. The vestibular nucleus (VN) receives afferent signals from the visual, vestibular, and proprioceptive systems. The signals are transmitted centrally to the thalamus (T) and parietotemporal areas (P) of the cortex. The visual cortex (V) receives afferent impulses through the thalamus (T) and is also connected to the parietal cortex (P). The sites of lesions that cause typical symptoms or clinical signs are shaded. The peripheral vestibular system consists of the labyrinths, vestibulocochlear nerves (VIII), and the vestibular nuclei (VN). pc = parietal cortex, ap = area postrema, sc = spinal cord, bs = brainstem, II = optic nerve, VIII = vestibulocochlear nerve, T = thalamus, V = visual cortex, P = parietotemporal areas of the cortex.

ications (particularly those due to drugs), metabolic disorders, *neurosurgical diseases* (hydrocephalus, cerebral hemorrhage, tumors), as well as *neurologic diseases* (meningoencephalitis, cerebral ischemia) in the differential diagnosis.

Quantitative disorders of consciousness include various degrees of diminished alertness (*somnolence*, *sopor*) up to loss of consciousness, which, in the form of coma, can last for hours to years and can essentially have the same causes (see Chapter 32).

Syncope. In contrast, syncope occurs as a sudden, brief, and spontaneously reversible unconsciousness, which can be cardiac, vascular, or cerebral in origin (see Tab. 31.**10**). Syncope occurs because of a deficit in the function of the *mesencephalic reticular formation*, which in turn is an expression of a temporary disorder of the oxygen supply, cellular metabolism, or cerebral electrical activity with blocking of this activity.

Among the many causes of syncope, *cerebral seizures* (epileptic or electroencephalic) are particularly important, although overall they are rarely manifested in the form of (isolated) syncope in the strict sense. They can generally be distinguished rapidly from other causes on the basis of the family and personal history, the clinically observable temporal and spatial pattern (seizure semiology), and also further clinical and electrophysiologic (EEG) findings during, and particularly after, the seizure (which can, in principle, also occur without unconsciousness). This is a group of disorders that are extremely inhomogeneous in pathogenesis and etiology, which includes:

- accidental states (*occasional seizure*) in the course of an acute disease (encephalitis and also toxic, metabolic, and hypoxic encephalopathy)
  - usually cease after subsidence of the cause
  - occur only in certain circumstances (*fever*, *sleep deprivation*, *medications*, *alcohol*, *drugs*, including their *withdrawal*)
- defined diseases (*epilepsy*)
  - repeated (at least two) *unprovoked* cerebral seizures.

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Table 31.**1** Examples of clinical forms of impaired consciousness
Qualitative disorders involve clarity of consciousness (lucidity). Examination of orientation should not be restricted only to trivial questions about the current date, place, and reason for hospitalization. Illusionary misperceptions occur again and again, even in healthy persons. Hallucinatory misperceptions have a reality character for those affected (sometimes inducing fear) and can occur with or without insight into their unreality. Complete disintegration (e. g., as part of severe toxic [drug], metabolic, hypoxic, or septic encephalopathy) can lead to two neurologically important conditions, delirium and/or Korsakov syndrome. Psychiatric conditions are not included. Quantitative disorders affect alertness (vigilance).

Qualitative disorders	
Disorientation – time – place – person	 Test knowledge of world history also Test geographic knowledge also Test entire life history
Misjudgement – illusion – hallucination	 A real sensory stimulus (visual, auditory, olfactory, somatosensory) is misinterpreted by the corresponding primary sensory cortex Sensory delusions produced autonomically by the brain without corresponding real sensory stimuli
Disintegration – delirium – Korsakov syndrome	 – disoriented – (visual) hallucinations – psychomotor (fearful–aggressive) agitation, erethic – disoriented – memory disorder – confabulation
Quantitative disorders	
Syncope	Sudden, brief and spontaneously reversible loss of consciousness
Somnolence	Pathologic drowsiness with arousability to a normal level of consciousness
Sopor	Pathologic drowsiness without arousability to a normal level of consciousness
Coma	Condition with closed eyes without a reaction to: *internal* – cognitive – emotional – autonomic *and external* painful stimuli

The only thing this group has in common is a disorder of neuronal interaction with pathologic excitation patterns in the form of acute onset, excessive discharges (*hypersynchronization*), which can either occur focally at the start (though with subsequent *secondary generalization*) or are *primarily generalized*.

A cerebral (epileptic) seizure is a temporary disturbance that may be due to a disease but is not a disease in itself.

With epileptic seizures, rapid diagnosis and initiation of therapy without delay are of the greatest importance for those affected because of the major *social effects* (e. g., loss of driver's license, pregnancy) and should generally be conducted and followed up by specialists in neurology/epileptology.

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31.1 Medical History of the Vertigo Patient

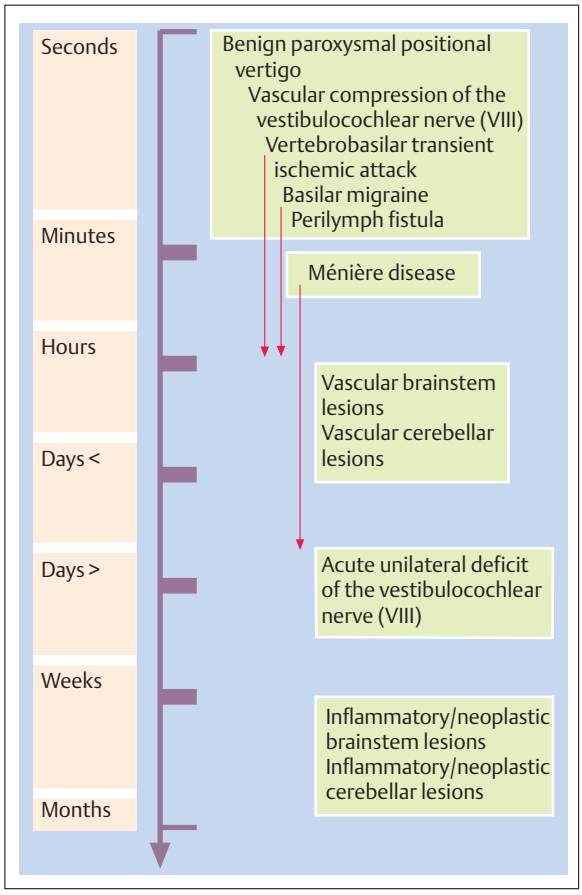

Fig. 31.**3** Duration of peripheral and central vestibular disorders (examples).

Typically, the description of the symptoms constituting "dizziness" is colorful and at times bizarre. Severe to disabling physical symptoms (e. g., vomiting and falls with an acute unilateral labyrinth deficit or a cerebral infarct in the dorsolateral medulla [Wallenberg syndrome] with deficit of central vestibular structures, as well as with palpable fear), can make it more difficult to obtain the *history*. However, it is still the most important tool in working out the differential diagnosis and must be carefully taken in every case. Particular attention should be paid to the nature, duration (Fig. 31.**3**), and *onset of the vertigo*, as this also forms the basis of further clinical classification.

Nature of Vertigo

The direction of vertigo (rotary, vertical, dizziness) is one of the more important indicators of a *peripheral vestibular disorder* (labyrinth, vestibular nerve, vestibular nucleus), but often cannot be elicited consistently and with certainty from the patient and can also sometimes change repeatedly in a short time because compensatory central vestibular mechanisms commence rapidly.

Auditory symptoms, which occur simultaneously (e. g., tinnitus, hypacusis) indicate an additional *disorder of the cochlea* (Ménière disease), cochlear nerve, or parts of the cochlear nucleus.

In contrast, vertigo due to *central vestibular disorders* is often less intense and is usually nondirectional (swaying or tilting).

With additional transient neurologic accompanying symptoms, an *epileptic seizure* or a *migraine attack* (possibly sans migraine) must be considered, especially when they occur in parietotemporo-occipital areas. In this case, the vertigo can be regarded as an aura. Accompanying symptoms may include:

- headache
- visual illusions and/or hallucinations
- motor automatisms
- complex autonomic disorders: drop in pulse rate and/or blood pressure, gastric discomfort, incontinence of urine and/or feces
- quantitative disorders of consciousness: somnolence, sopor, coma.

A very slight directional or nondirectional vertigo can be an expression of a *cerebellar disorder*; however in this case, the additional neurologic brainstem signs and symptoms, particularly oculomotor disorders, usually suggest the diagnosis.

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The widely described ocular vertigo, which often varies in severity, is found with lesions of the efferent oculomotor system with double vision. Apart from the double vision, apparent movements when looking in the direction of pull of the paralyzed muscle or nerve are also important.

In the differential diagnosis the following disorders must be considered:

- *acute* or *subacute paresis of the nerves to the ocular muscles* (see Tabs. 31.**2**, 31.**3**)
- *disorders of neuromuscular transmission* (myasthenia gravis pseudoparalytica; see Tab. 31.**4**)
- *paresis of the ocular muscles*
- disorders of the *refractive media* with incongruent retinal images (asymmetric refraction anomaly, cataract).

Immobilizing vertigo often occurs acutely when the eyes are closed (loss of visual control), with interruptions of the *sensory afferent input* at any level in the form of polyneuropathy, polyradiculo-(neuro-)pathy, and myelopathy with involvement of the posterior funiculus and dramatic unsteadiness when standing and walking, which can even lead to falls.

Duration of Vertigo

Brief Attacks of Vertigo. When vertigo occurs in the form of attacks lasting *seconds to minutes*, the following disorders should be considered:

- *benign paroxysmal positional vertigo*
- transient *cerebrovascular disorders* especially in the vertebrobasilar region (usually normal neurologic examination between episodes)
  - in the region of the inner ear or vestibular nerve: *anterior inferior cerebellar artery* (AICA)
  - in the region of the pons and cerebellum: perforating branches of the *posterior inferior cerebellar artery* (PICA)
- complex partial *cerebral seizure disorders*
- *basilar migraine*
- *vestibular migraine* (pathologic findings also rarely between episodes).

More Prolonged Vertigo. Vertigo of a decrescendo character lasting *minutes to hours* is found mainly in Ménière disease. Additional auditory symptoms (tinnitus, hypacusis) and complaints of a "feeling of pressure" in the affected ear are indicative.

Vertigo lasting *hours to days* occurs especially with central vestibular disorders in the brainstem with established cerebrovascular lesions (Wallenberg syndrome after PICA occlusion) or during an episode of multiple sclerosis. There are usually further focal neurologic deficits, which aid the diagnosis.

Vertigo of *hyperacute onset* and only resolving slowly over *days* is typically found in *acute unilateral vestibular* or *labyrinthine deficit*.

Prolonged Vertigo. Persistent vertigo, sometimes of varying severity, can occur in the course of *chronic processes* (Fig. 31.**3**) of the types described below.

- *In the peripheral vestibular system:*
  - hereditary degenerative or autoimmune-associated diseases of both labyrinths (Cogan syndrome I with recurrent episodes of vertigo, hearing loss, keratitis, often vasculitis, rarely aortic insufficiency)
  - tumors of the vestibular nerve, especially in the cerebellopontine angle (acoustic neuroma, neurofibromatosis 2).
- *As part of central vestibular lesions in the cerebellum and pons:*
  - hereditary degenerative, specifically inflammatory or immunologic diseases (multiple sclerosis)
  - ischemic and paraneoplastic diseases (breast carcinoma)
  - spinocerebellar degeneration
  - olivopontocerebellar atrophy (OPCA)
  - Arnold–Chiari malformation.
- *With involvement of the extrapyramidal system:*
  - Parkinson disease
  - corticobasal degeneration
  - progressive supranuclear paresis (PSP)
  - multisystem atrophy (MSA).
- *With dementia:*
  - chronic cerebrovascular diseases with rarefaction (leukoaraiosis) of subcortical neuronal support tissue and vascular dementia
  - (hereditary degenerative) cortical degeneration
  - Alzheimer disease, Pick disease, frontal lobe atrophy.

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Onset of Vertigo

Vertigo can occur at rest (acute unilateral partial deficit of the vestibular nerve or labyrinth), during or after head movements (benign paroxysmal positional vertigo), or only in certain contexts (phobic attack vertigo).

The oculomotor examination findings before, during, and after a provocative maneuver (posture, positioning, head shaking) are of great importance for localization.

31.2 Differential Diagnosis of Oculomotor Disorders

The stabilization of gaze in space is one of the important tasks of multisensory information processing. The ocular muscles must always be controlled in such a way that the entire visual surroundings appear as a stationary image on the retina despite the presence of intrinsic movements, and rapid precise movements can be performed that direct the fovea toward a new object. Fig. 31.**4** shows the essential elements of this regulation, which together are called the oculomotor system. With all peripheral vestibular and many central neurologic causes of vertigo, there are characteristic disorders of this regulation and the site of the lesion can usually be determined very precisely by careful examination of the oculomotor system.

Functional examination is often superior to imaging procedures, as the disorders are often located infratentorially in the pons, cerebellum, or labyrinths. Because of its immense clinical importance, a solid knowledge of

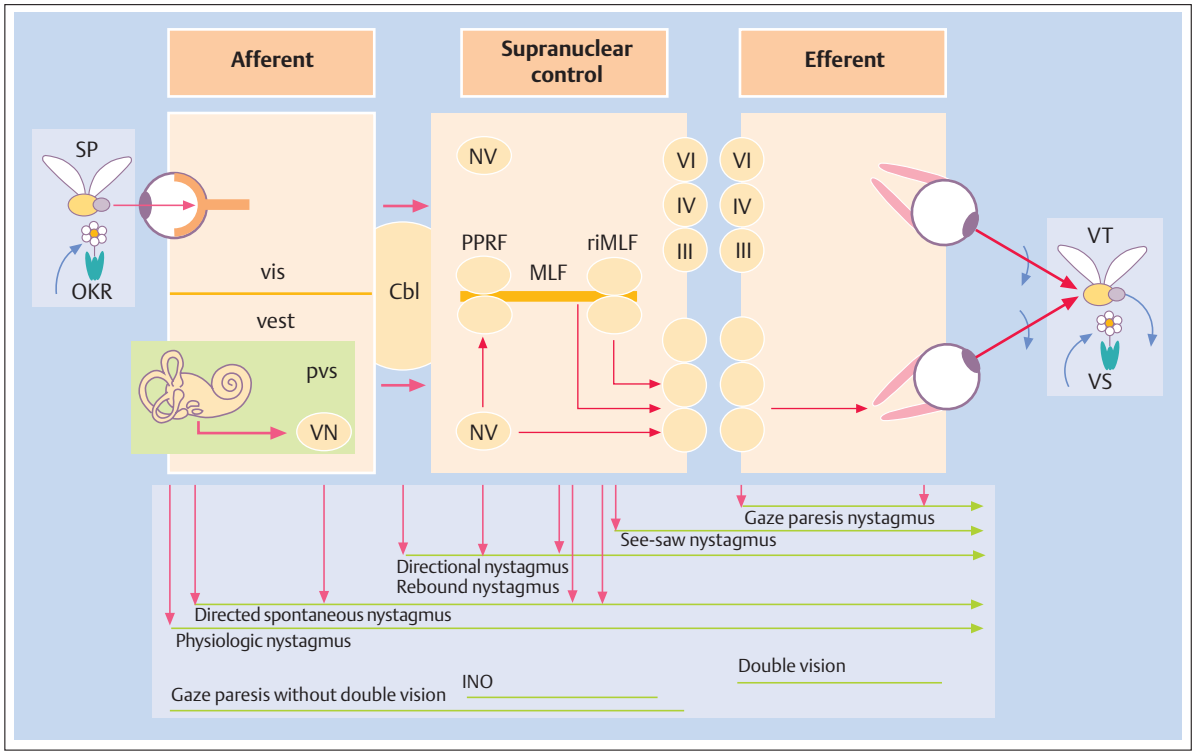

Fig. 31.**4** Synopsis of the oculomotor system.
The visual (vis) and vestibular (vest) afferent inputs are integrated in the cortex and subcortical areas and send signals to the supranuclear control, which generates a suitable eye movement pattern. This structure organizes the impulses that each ocular muscle must receive for orderly eye movements to be carried out. It is the common final motor pathway for all cortical or subcortical systems that produce eye movements, e. g., when following the visual target (VT), the visual surroundings (VS) move more in the opposite direction, which produces an optokinetic stimulus. The task of sensory integration is to decide between these two opposing visual stimuli and transmit the signals for the selected eye movement to the supranuclear control for execution. VT = visual target, VS = visual surroundings, SP = smooth pursuit, OKR = optokinetic reflex, pvs = peripheral vestibular system, Cbl = cerebellum, VN = vestibular nucleus, PPRF = paramedian pontine reticular formation, MLF = medial longitudinal fasciculus, riMLF = rostral interstitial nuclear group of the MLF, III = oculomotor nerve, IV = trochlear nerve, VI = abducens nerve, INO = internuclear ophthalmoplegia.

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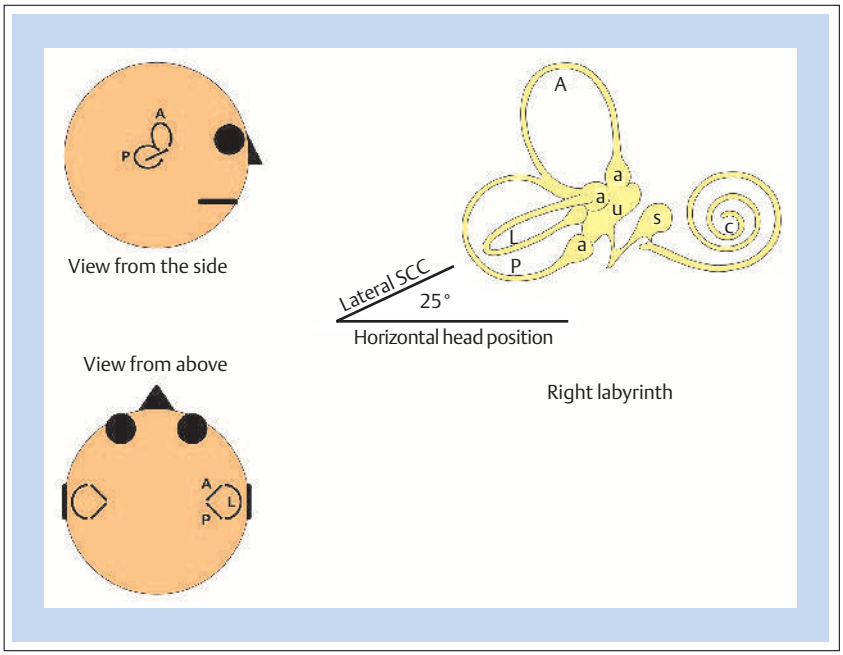

Fig. 31.**5** Anatomy of the vestibular labyrinth and cochlea. Hair cells in the ampullae of the semicircular canals react to angular acceleration, those in the utricle and saccule to linear acceleration, depending on their alignment. A = anterior semicircular canal (SCC), L = lateral SCC, P = posterior SCC, a = ampulla, c = cochlea, u = utricle, s = saccule.

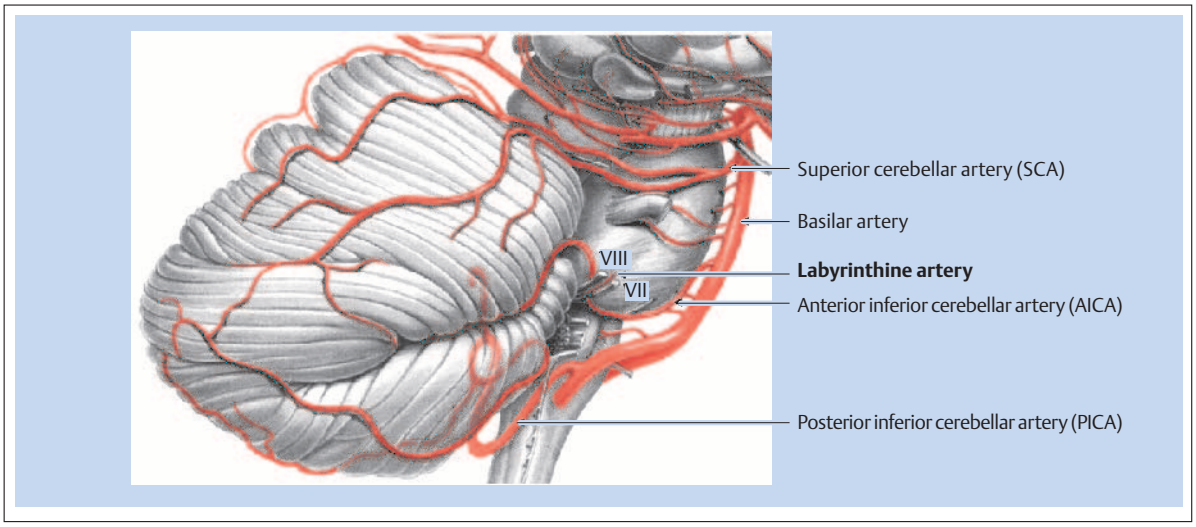

Fig. 31.**6** Main branches of the arterial blood supply of the brainstem and cerebellum.

the anatomy of the vestibular and cochlear organs (Fig. 31.**5**) and of the blood supply in this region (Figs. 31.**6**, 31.**7**) is an essential tool for recognition of the varied clinical pictures of vestibular-induced disorders. Figs. 31.**8** and 31.**9** give a synopsis of the examination sequence, which tests the efferent output, the control mechanism, and finally, sensory processing. Vertigo symptoms can occur with lesions at all levels.

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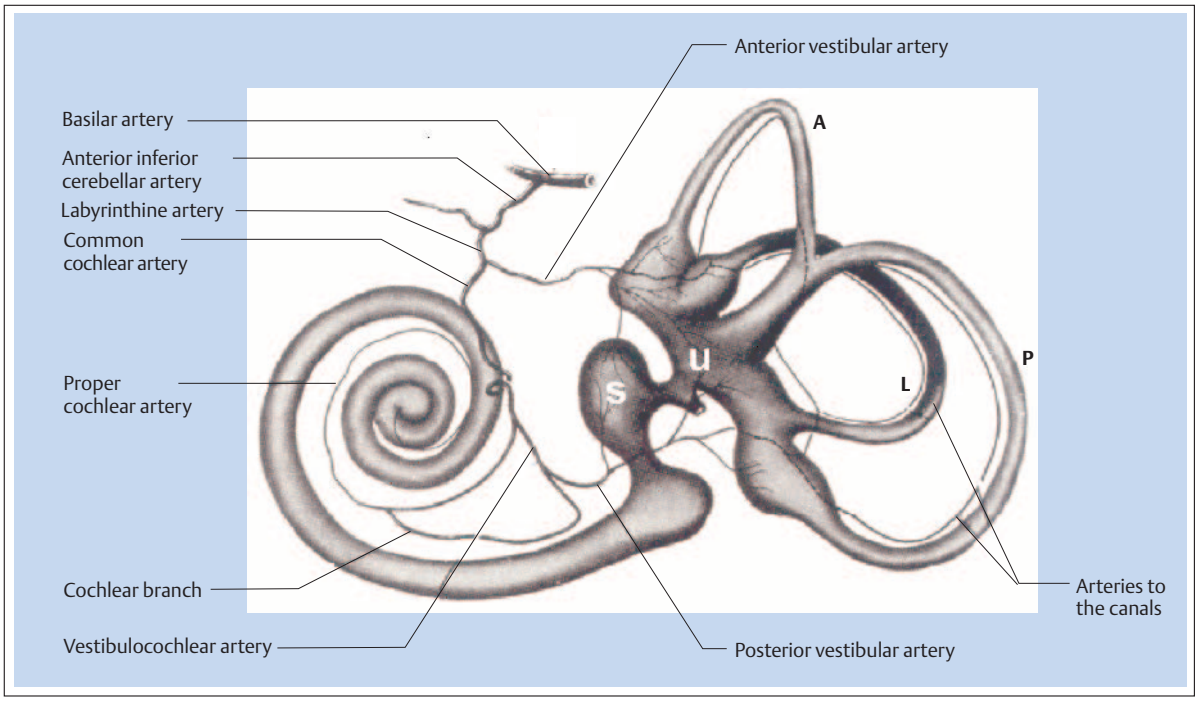

Fig. 31.**7** Arterial blood supply of the labyrinth. Occlusion of terminal branches can affect individual semicircular canals, the utricle, the saccule, and/or the cochlea and lead to highly varied peripheral vestibular and/or auditory disorders. A = anterior semicircular canal (SCC), L = lateral SCC, P = posterior SCC, u = utricle, s = saccule.

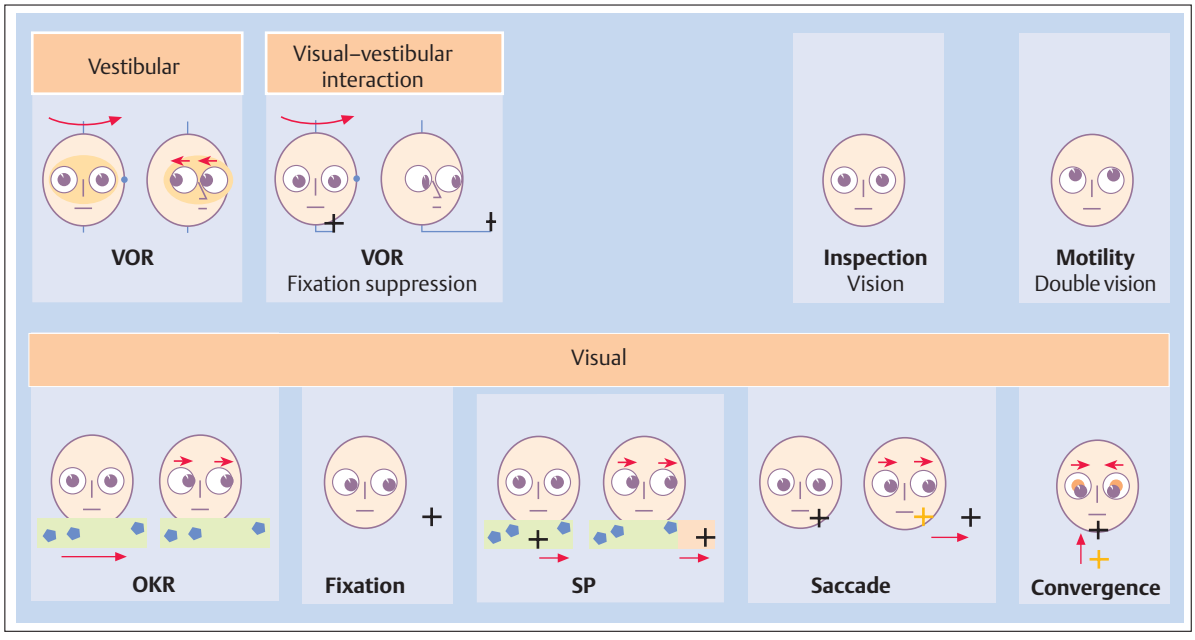

Fig. 31.**8** Examination of the oculomotor system. Visually and vestibularly generated eye movements are examined. **Inspection:** Ocular misalignment or spontaneous nystagmus is noted and vision is tested. **Motility:** The eyes should move freely in all directions. There must be no double vision. **VOR:** The patient is rotated wearing Frenzel spectacles (hatched surface). This produces physiologic vestibulo–ocular nystagmus. This is a test of the peripheral vestibular system. The purpose of the Frenzel spectacles is to eliminate fixation. **OKR:** A large visual stimulus pattern produces physiologic optokinetic nystagmus. This is a test of the integrity of subcortical visual systems in particular. In the VOR and OKR conjugated eye movements and normal saccades are noted. **Fixation:** The eyes must remain fixed quietly on an eccentric target. This can reveal gaze-evoked nystagmus. **VOR fixation suppression:** The patient fixates a point that can be moved while his head is stationary (e. g., outstretched arms and fixation of a thumbnail). When the head is rotated rapidly, it must be possible to

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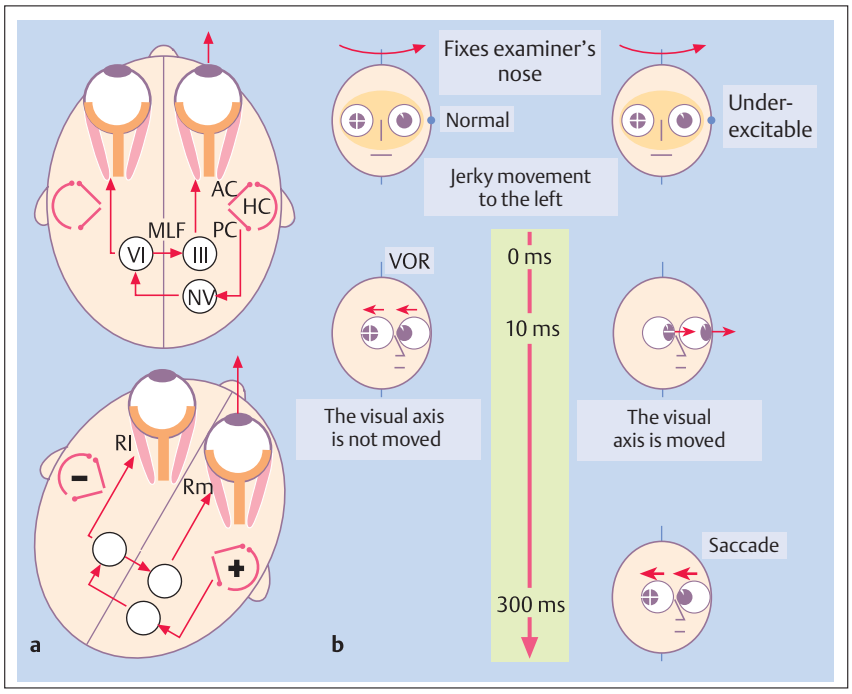

Fig. 31.**9** Head impulse test

a Eye movements with head movements triggered in the vestibule (VOR). When the head is rotated to the right, counterflow of endolymph is produced in the right horizontal semicircular canal (HC) with deflection of the cupula. There is an increase in the impulses in the right vestibular nerve and nucleus (VN), which stimulates neurons in the opposite abducens nucleus (VI) directly, leading to activation of the left lateral rectus muscle (RI). The abducens nucleus simultaneously activates the nucleus of the oculomotor nerve on the opposite side through the medial longitudinal fasciculus (MLF), so that the right medial rectus muscle also contracts. A rapid, compensatory, conjugated eye movement to the left results. Thus, the visual axis remains stable in space (arrow indicating the time axis). AC = anterior semicircular canal, HC = horizontal semicircular canal, PC = posterior semicircular canal, VN = vestibular nucleus, III = nucleus of the oculomotor nerve, VI = nucleus of the abducens nerve, MLF = medial longitudinal fasciculus, Rm = medial rectus muscle, RI = lateral rectus muscle.

b The function of the vestibular system is examined unilaterally with the head impulse test. When the peripheral vestibular apparatus functions normally, there is vestibular compensation with extremely short latency during a jerky movement. The examiner cannot find any gaze instability. If there is underfunction, the visual axis deviates in the direction of head rotation (arrows) and the patient has to make an adjustment saccade in order to reach the target again. This eye movement is seen by the examiner because of the longer latency of the saccade generator.

suppress the compensatory eye movements produced by the vestibulo–ocular reflex (VOR). Failure can be an indication of a cerebellar disorder. **SP (smooth pursuit):** In contrast to the OKR a small target is moved slowly against a stationary visual background. The resulting eye movements must be smooth. This tests cortical visual processing and cerebellar control of the movement. Noticeable jerking can be pathologic. **Saccades:** The patient is told to look rapidly from one eccentric point to another. Reaction time, speed, and precision are noted. Any abnormality may indicate a lesion in the brainstem or cerebellum. **Convergence:** The convergence reflex is a function of the oculomotor nerves alone and is normal in internuclear ophthalmoplegia. VOR = vestibulo–ocular reflex, OKR = opticokinetic reflex, SP = smooth pursuit eye movements (the band does not move in contrast to the OKR, only the target is moved across the background). VOR fixation suppression is a combination of the VOR and fixation, in which vestibular impulses must be suppressed.

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Paresis of the Nerves to the Ocular Muscles

Paresis of the nerves to the ocular muscles characteristically causes double vision, as long as one eye is not amblyopic (e. g., pre-existing strabismus). Fig. 31.**10** summarizes the most important clinical signs. Tabs. 31.**2** and 31.**3** show the varied etiology and the differential diagnosis of these peripheral pareses. Incipient myasthenia gravis should also always be ruled out in acute disorders because of the therapeutic consequences (Tab. 31.**4**).

Abducens Nerve Paresis (VI). Abducens nerve paresis (VI) results in weakness of the lateral rectus muscle with typical medial deviation of the paralyzed eye and uncrossed, horizontal double vision, which increases when looking to the paretic side. Additionally, lesions in the region of the abducens nucleus result in pontine gaze paresis for anatomic reasons, along with involvement of the facial nerve, as the nucleus contains a large number of neurons that are connected to the paramedian pontine reticular formation (PPRF) and are involved in supranuclear control of eye movement.

Trochlear Nerve Paresis (IV). Mild trochlear nerve paresis (IV) is often difficult to document. Because of the lack of intorsion of the eye by the *superior oblique muscle*, there is tilted double vision, which the patient notices, especially when looking downward and inward (e. g., reading, climbing stairs). If the paresis is marked, there is obvious compensation by tilting the head toward the side of the healthy eye (*Bielschowski sign*; see Fig. 31.**10**). Accordingly, the double vision increases markedly when the head is upright or tilted in the opposite direction. Distinction from oculomotor paresis (III) can be difficult.

Oculomotor Paresis (III). Complete internal and external oculomotor paresis (III) is characterized by *eye deviation* obliquely outward and slightly downward, *ptosis*, and *mydriasis* (involvement of autonomic fibers). Horizontal crossed double vision occurs. In addition to an infarct of the vasa nervorum in the diabetic or hypotensive patient (the most frequent causes), myasthenia gravis pseudoparalytica, as well as an aneurysm in the territory of the internal carotid artery (ICA), posterior communicating artery (PCoA), or posterior cerebral artery (PCA) must be considered in every paresis of the oculomotor nerve of acute onset (*ophthalmoplegic aneurysm*).

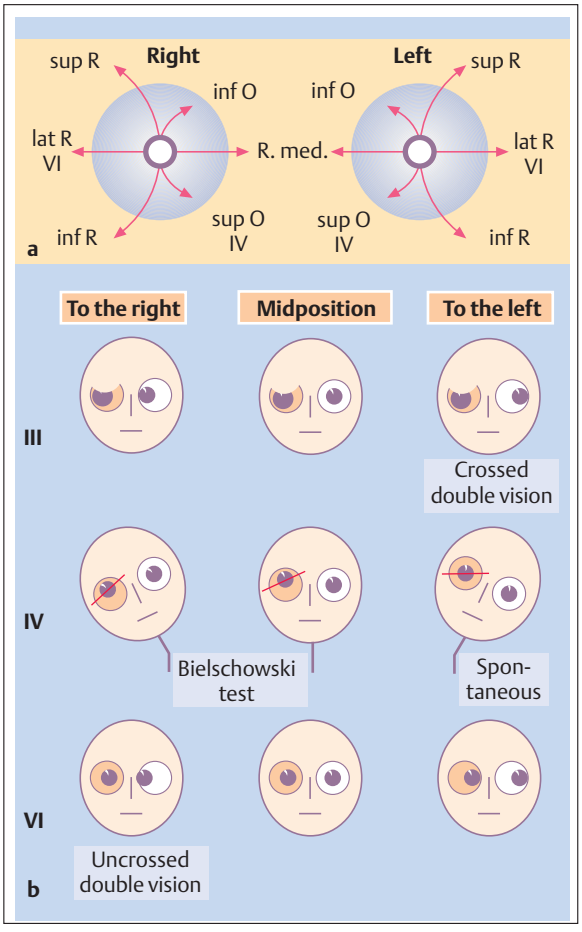

Fig. 31.**10** Synopsis of paresis of the nerves to the ocular muscles.

a The direction of pull of the ocular muscles. When the eyes are in midposition, the superior rectus and inferior oblique muscles work together during elevation and the inferior and superior rectus muscles during depression. A subsidiary function of the superior oblique muscle is to rotate the vertical meridian inwards (cycloinversion). R = rectus muscle, O = oblique muscle.

b Eye position and direction of double vision in isolated paresis of the right oculomotor nerve (III), trochlear nerve (IV), and abducens nerve (VI). Ptosis occurs with complete paresis of the oculomotor nerve. In paresis of the trochlear nerve, the head position, which compensates for the absence of inversion by the superior oblique muscle, is particularly striking. The line over the right eye marks the vertical meridian. The double vision increases on tilting to the opposite side (Bielschowski test). III = oculomotor nerve, IV = trochlear nerve, VI = abducens nerve.

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Table 31.**2** Etiology of ocular muscle nerve pareses

Classified according to anatomic segment in the course of the nerves. With the exception of paresis of the oculomotor nerve due to infarction of the vasa nervorum in the region of the superior orbital fissure and the cavernous sinus, lesions of the trochlear nerve and the abducens nerve of this etiology can usually not be classified topographically. Ophthalmoplegic migraine and immune-associated neuropathy can affect all the nerves along their entire infranuclear extracerebral course. III = oculomotor nerve, IV = trochlear nerve, VI = abducens nerve, ICA = internal carotid artery, AICA = anterior inferior cerebellar artery, PICA = posterior inferior cerebellar artery, PCoA = posterior communicating artery, x affects this nerve specifically or very frequently, + affects mainly this nerve, = usually affects several nerves simultaneously.

Location	III	IV	VI
Undetermined/multifocal			
– ophthalmoplegic migraine			+
– infarct (diabetes mellitus/ hypertension)			
– neuropathy (postinfectious/ postvaccinal)	=	=	=
Orbit			
– infection	=	=	=
– bacterial			
– fungal			
– infiltrate	=	=	=
– ocular muscle disease			
– granuloma			
– tumor			
– trauma		+	
Superior orbital fissure/ cavernous sinus			
– vasculitis (cranial arteritis)	=	=	=
– infarct (diabetes mellitus/ hypertension)	x		
– apoplexy of the hypophysis	+		
– thrombosis	=	=	=
– aneurysm/dissection of the ICA	=	=	=
– direct/dural arteriovenous fistula to the ICA	=	=	=
– infection			
– herpes zoster	=	=	= +
– sphenoidal sinusitis	+		
– mucocele	+		
– tumor			
– pineal gland		+	
– ependymoma		+	
– hypophyseal adenoma	+		+
– nasopharyngeal carcinoma	+		+
– meningioma	=	=	=
– metastasis/lymphoma	=	=	=
– paraneoplastic syndrome	=	=	=
– Tolosa–Hunt syndrome	=	=	=
Tentorium			
– raised intracranial pressure	=	=	=
– hydrocephalus			
– pseudotumor cerebri			+
– sinus vein thrombosis			+
– supratentorial/transtentorial herniation			
– trauma			

Location	III	IV	VI
Petrous bone			
– thrombosis of the inferior petrous sinus			x
– aneurysm			x
– arteriovenous malformation			x
– persistent trigeminal artery			x
– infection			x
– mastoiditis			
– tip of the petrous bone			
– foraminal herniation	=	=	= +
– trauma			x
– lumbar puncture			+
– spinal/epidural anesthesia			
– myelography			
– ventriculoatrial shunt			+
Subarachnoid space			
– hemorrhage			
– infarct (diabetes mellitus/ hypertension)	x		
– aneurysm of the PCoA	+		
– compression by AICA, PICA, basilar artery			x
– meningitis (infectious/ neoplastic)	=	=	=
– tumor			
Fascicular			
– multiple sclerosis			
– hemorrhage			
– infarct			
– tumor			
Nuclear			
– Wernicke encephalopathy			+
– infarct			
– infection			
– tumor			
– trauma			
– later, superior oblique myokymia		x	
– congenital hypoplasia			
– Möbius syndrome			x
– Duane syndrome			x

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Table 31.**3** Important differential diagnosis of ocular muscle nerve pareses

Concomitant strabismus
Vergence spasm
Brainstem lesion with supranuclear optomotor disorder – internuclear ophthalmoplegia (INO) – skew deviation – disorder of neuromuscular stimulus transmission – myasthenia gravis – Eaton–Lambert syndrome – botulism
Myopathy – chronic progressive external ophthalmoplegia (CPEO) – mitochondrial cytopathy – Kearns–Sayre syndrome – myotonic dystrophy – oculopharyngeal dystrophy – myotubular myopathy
Endocrine ophthalmopathy – Graves disease
Congenital muscle hypoplasia/muscle aplasia
Restrictive ophthalmopathy
Orbital tumor – metastasis – lymphoma
Trauma – blow-out fracture of the orbit

Table 31.**4** Clinical manifestation of ocular myasthenia gravis
The clinical signs and symptoms are highly variable, especially at the start of the illness, and typically increase toward evening or after physical exertion.

Ptosis – occasionally with twitching eyelids (Cogan eyelid twitch sign) – not pathognomonic
Fixation instability – with drift into the primary position and correction saccade – can simulate central gaze-evoked nystagmus
Double vision – can simulate strabismus – can simulate paresis of one or more ocular muscle nerves – can simulate ocular paresis (internuclear ophthalmoplegia, INO)
Saccade dysmetria – hypometria on large excursions – hypermetria on small excursions – often hypermetric after administration of edrophonium (Tensilon)
Slow saccades

Supranuclear Gaze Paresis

Medial Longitudinal Fasciculus. The nerves to the 6 ocular muscle nerves are linked by the supranuclear connections of their nuclei through the medial longitudinal fasciculus (MLF) so that the movements are coordinated (see Fig. 31.**4**; 31.**11**). The MLF passes dorsally along the pons to the pontomesencephalic junction and transmits the signals from both vestibular nuclei (VN) and the nucleus prepositus hypoglossi (PPH), as well as from the cerebellum and cortex to the motor nuclei. It also connects the PPRF and the rostral interstitial nucleus of the MLF (riMLF), which is located in the mesencephalic reticular formation (MRF), the upper visual center (Fig. 31.**11a**). Gaze paresis without double vision occurs with lesions of the PPRF or its cortical afferent supply (Fig. 31.**11b**).

Internuclear ophthalmoplegia (INO) occurs with a lesion of the MLF. In the typical case, ipsilateral adduction inhibition (medial rectus muscle) and contralateral abduction nystagmus are found as the abducens nerve, and therefore the lateral rectus muscle, receives the normal signal and attempts to look toward its own side unhindered. Convergence is preserved provided that the lesion does not also involve the nucleus of the oculomotor nerve (Fig. 31.**11**). The direction of the paresis and additional oculomotor signs generally allow the site of the lesion to be localized.

If, in addition to the supranuclear connections, there is also a disturbance of the nuclei or myelinated, intrapontine fascicles of the nerves (e. g., in multiple sclerosis), *complex oculomotor deficit syndromes* are found with central and peripheral participation. Clinically, only the most peripheral paresis can be localized with certainty. Tab. 31.**5** shows the most important causes of internuclear ophthalmoplegia.

Cortex. The motor and premotor cortices send binocular impulses to the supranuclear structures in the brainstem. When a deficit occurs there is gaze paresis to the contralateral side with *conjugate deviation*, as the eyes are tonically drawn to the side of the lesion (see Fig. 31.**11**). However, cortical irritation (epileptic seizure) causes conjugate turning of gaze to the side opposite the cortical lesion. Figs. 31.**11**, 31.**12** give a synopsis of the more important structures involved in the development of visually and vestibularly induced eye movements. Besides the motor areas, those visual and polysensory regions that carry out visuomotor transformation are particularly involved (v1, v5, ppc in Fig. 31.**12**).

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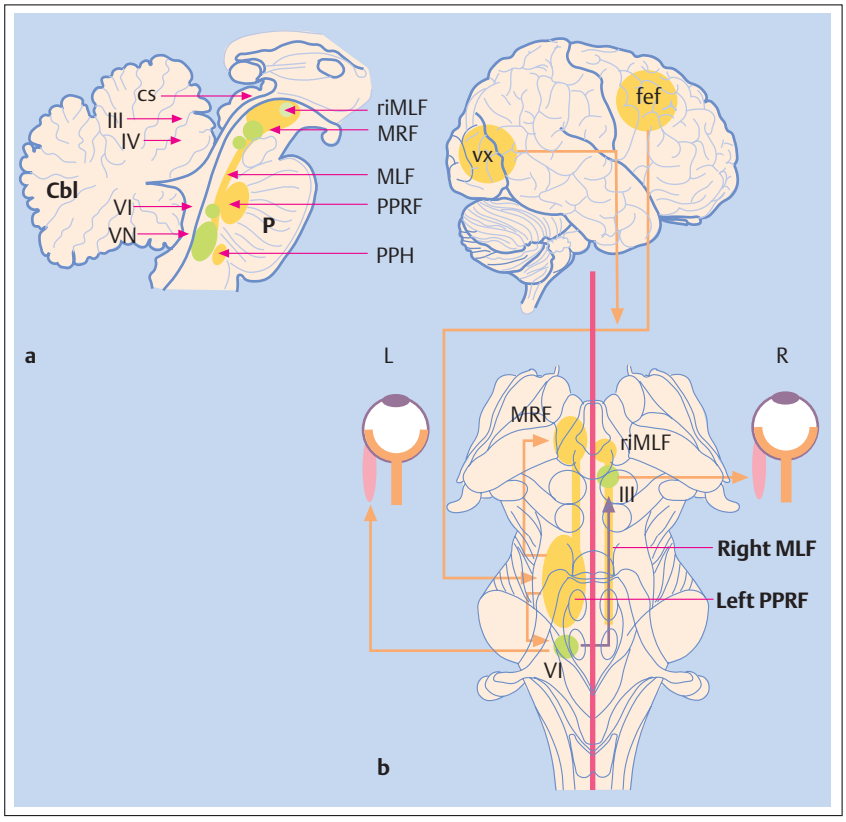

Fig. 31.**11** Important subcortical oculomotor structures and their connections.

a Diagram of the brainstem with supranuclear structures and ocular muscle nuclei that are important in the generation of eye movements. The medial longitudinal fasciculus (MLF) transmits both afferent visual and vestibular signals (cs, NV), and also signals from the oculomotor centers (PPRF, MRF) to the nuclei of the ocular nerves (III, IV, VI). The caudally located paramedian pontine reticular formation (PPRF) generates ipsilateral horizontal saccades. The interstitial nucleus of the MLF (riMLF), located in the rostral visual center (MRF), programs vertical and torsional saccades.

b Diagram of the control of voluntary ocular movements through the PPRF. The frontal eye field (fef) sends impulses to the opposite PPRF, where they are transmitted further to the mesencephalic reticular formation (MRF) and to the ipsilateral abducens nucleus (VI). The abducens nucleus, in turn, activates the lateral rectus muscle and after crossing through the opposite medial longitudinal fasciculus (MLF) it transmits the signal to the contralateral oculomotor nucleus, which innervates the medial rectus muscle. With a lesion of the eye field, there is ocular paresis to the opposite side and with a lesion of the PPRF there is ocular paresis to the same side without double vision. A lesion of the MLF causes internuclear ophthalmoplegia. Cbl = cerebellum, P = pons, III = oculomotor nerve, IV = trochlear nerve, VI = abducens nerve, sc = superior colliculus, VN = vestibular nucleus, riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus, MRF = mesencephalic reticular formation, MLF = medial longitudinal fasciculus, PPRF = paramedian pontine reticular formation, PPH = nucleus prepositus hypoglossi, fef = frontal eye field, vx = visual cortex.

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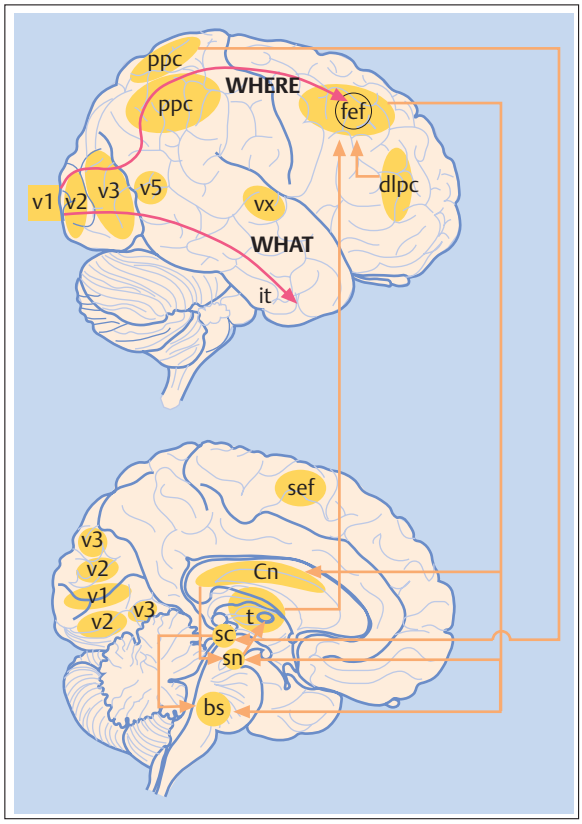

Fig. 31.**12** Important cortical oculomotor structures and their connections.
Diagram of the control of visually induced and voluntary ocular movements through the cortex and the extrapyramidal system. The primary visual cortex (v1) analyzes the signals from the thalamus (lateral geniculate body) and breaks the retinal image down into simple graphic elements such as shape, color, disparity, and movement, which are processed further through two fundamentally different pathways. In the WHAT pathway, the static elements (shape, color) are transmitted to the infratemporal cortex over v4 (not shown). In the WHERE pathway, the elements of position and speed that are important for eye movements are processed through the polysensory posterior parietal cortex (ppc) with other afferent input (vx) and transmitted to the frontal eye fields (fef) where cortical eye movements are finally generated. The fef activate oculomotor centers in the brainstem (bs) directly or indirectly through the superior colliculus (sc). At the same time, signals are sent to the substantia nigra (sn), which are led back again through the thalamus (t), and also reach the caudate nucleus (cn). Thus, the extrapyramidal system is activated with every eye movement. The dorsolateral prefrontal cortex (dlpc) and the supplementary eye field (sef) play an important part in the generation and memorization of saccades and are also activated through the frontal eye field. v1 = primary visual cortex, v2–v5 = extrastriate visual cortex, it = inferotemporal cortex, ppc = posterior parietal cortex, fef = frontal eye field, dlpc = dorsolateral prefrontal cortex, sef = supplementary eye field, vx = vestibular cortex, sc = superior colliculus, sn = substantia nigra, t = thalamus, cn = caudate nucleus, bs = oculomotor centers in the brainstem.

Table 31.**5** Etiology of internuclear ophthalmoplegia (INO)

Demyelination
– multiple sclerosis
– radiation-induced
Cerebrovascular lesion in the brainstem
– syphilis
Infection
– meningoencephalitis
– syphilis
Space-occupying lesion
– subdural hematoma
– hydrocephalus/syringobulbia
– Arnold–Chiari malformation
– supratentorial arteriovenous malformation
– neoplasm
– tumor in the brainstem and/or fourth ventricle
– infiltration
– paraneoplastic syndrome
Degenerative disease
– progressive supranuclear paresis (PSP)
– Steele–Richardson–Olszewski syndrome
Nutritional disorders
– Wernicke encephalopathy
– pernicious anemia
Metabolic disorders
– hepatic encephalopathy
– Fabry syndrome
– abetalipoproteinemia
Intoxications (examples)
– barbiturates
– lithium
– phenothiazine
– propranolol
– tricyclic antidepressants
Trauma
– cervical hyperextension
Pseudointernuclear ophthalmoplegia
– myasthenia gravis
– Fisher–Miller syndrome

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Saccades

Saccades are rapid and very precise conjugate eye movements that direct the fovea to a new object (see Fig. 31.**8**). They can be a reflex triggered by a new visual or auditory stimulus, and also voluntary (e. g., when reading). Supranuclear programming of the motor parameters (direction, speed) for the nerves to the ocular muscles is performed mainly by the *saccade apparatus*, which is located in the brainstem (see Fig. 31.**11**). It consists of the *PPRF*, which generates the horizontal saccades in the ipsilateral direction, and the *riMLF*, which generates vertical and torsional saccades (see Fig. 31.**11**).

When a deficit occurs, there is decay of the saccades in a direction corresponding to the site of the lesion (e. g., an expected nystagmus pattern can be absent). Depending on the stimulus, the eyes travel only into the end position and are then not moved back again, which can cause difficulties in the interpretation of oculomotor findings.

In a comatose patient, caloric testing can give false-positive results as the typical nystagmus pattern is absent if the saccade apparatus has been switched off by drugs (e. g., barbiturates).

Nystagmus and Ocular Tilt Reaction

Nystagmus is a jerky, back and forth movement of the eyes. Typically, it consists of a slow phase and a (physiologic) return saccade, provided that the saccade mechanism is intact. The direction and speed of the slow phase are determined by the natural stimulus or the pathologic stimulus combination.

Fig. 31.**13** shows an example of the development of vestibularly induced nystagmus. Physiologically, it occurs in all primates as vestibular nystagmus (rotation in the dark without visual stimulation or when wearing Frenzel spectacles) or as optokinetic nystagmus (optokinetic drum test). A typical nystagmus pattern can occur with a disorder of visual and/or vestibular stimulus processing and also of premotor control in the brainstem, which allows the site of the lesion to be narrowed down rapidly. Because of this diagnostic importance, two forms are discussed separately below. Tab. 31.**6** also lists the findings of other nystagmus patterns important in the investigation of vertigo.

Spontaneous Nystagmus. (Directional) spontaneous nystagmus is always pathologic and typically occurs in acute unilateral disorders of the peripheral or central vestibular type. The pathologic stimulus in the vestibular system simulates persistent linear (utricle, saccule) or angular (semicircular canals) head acceleration (see Fig. 31.**13**), which is subsequently processed at the premotor level to produce a compensatory eye movement (slow nystagmus phase) and changes in the postural reflexes (deviation when walking with eyes closed). Disabling vertigo occurs because of the (sensory) conflict that results from integration with the correct visual and proprioceptive stimuli, which do not validate the vestibular information centrally. The *caloric test* along with the *head impulse test* (see Fig. 31.**9**) is helpful in distinguishing between a peripheral and central vestibular lesion as it records underfunction on the affected side in the case of peripheral lesions.

Ocular Tilt Reaction. If, on the other hand, predominantly tonic vestibular structures are involved (utricle and/or saccule or their connections in the pons or mesencephalon to the thalamus and vestibular cortex), the ocular tilt reaction (OTR) occurs, which represents the physiologically expected response to pathologic neuronal impulses (Fig. 31.**14**).

In both cases observation, and if need be, documentation by means of *pure tone audiogram* (PTA), of any simultaneously occurring ipsilateral hearing loss can often point to a peripheral vestibular disorder.

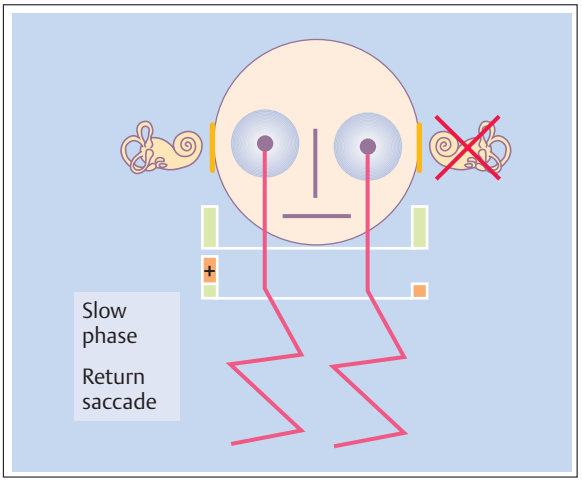

Fig. 31.**13** Development of peripheral vestibular spontaneous nystagmus.
Spontaneous nystagmus with deficit of the left labyrinth (X). There is a difference between the two sides in the neuronal discharge (+) in the peripheral vestibular system, which simulates head movement to the opposite side (see Fig. 31.**9 a**). Supranuclear control automatically generates a compensatory eye movement according to the combination of stimuli. This slow phase is interrupted by a rapid return saccade, so that the typical picture of directional spontaneous nystagmus arises, as it always moves in the same direction independently of the eye position.

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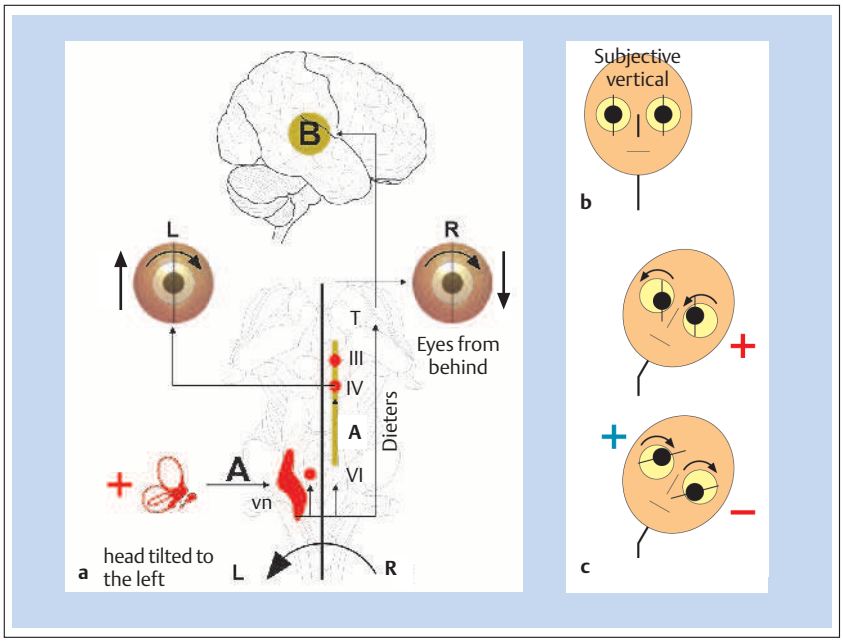

Fig. 31.**14** Generation of the ocular tilt reaction.
Tonic vestibular connections cause the eyes to roll back physiologically and keep the subjective visual vertical axis upright.

a Tilting the head to the left activates (+) the maculae of the ipsilateral utricle and saccule. Impulses from the vestibular nucleus (vn) reach the ipsilateral abducens nucleus (VI) and through the medial longitudinal fasciculus (MLF) they reach the contralateral oculomotor nucleus (III) and trochlear nucleus (IV), which in turn innervates the contralateral (!) superior oblique muscle. Thus, the eyes are rolled together to the opposite side, and in addition, the left eye is turned upward (elevation) and the right one downward (depression). In addition, impulses reach the thalamus (T) and the vestibular cortex through Deiters tract to generate the perception of the subjective visual vertical.

b Physiologic responses during head tilting to the left depend on normal relationships along the neuronal connections in **a**.

c A lesion along the connections in **a** leads to apparent head tilting to the right (!), and thus, to automatic counter-rolling of the eyes to the left, so that the subjective visual vertical deviates to the right. This virtual deviation is corrected by a further (paradoxical) head tilt to the left. The full clinical picture of the ocular tilt reaction (OTR) occurs with additional skew deviation (upward deviation of the higher and downward deviation of the lower eye). L = left, R = right, vn = vestibular nucleus, MLF = medial longitudinal fasciculus, III = oculomotor nucleus, IV = trochlear nucleus, VI = abducens nucleus, T = thalamus.

Gaze-Evoked Nystagmus. Gaze-evoked nystagmus is an expression of a disordered proprioceptive function of the eyes (fixation) and is always pathologic. It is most frequently due to drugs (sedatives, tranquilizers, antiepileptic drugs) or toxins (alcohol). Infratentorial, especially cerebellar or cerebellopontine, processes must be ruled out.

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Table 31.**6** Synopsis of the major types of nystagmus
Only the essential elements of the examination are indicated.

Directional spontaneous nystagmus of the peripheral vestibular type	
Mechanism	– imbalance of the peripheral signals from the vestibular nerves or labyrinths
Slow phase	– constant speed
Direction	– often mixed horizontal and torsional – occasionally also vertical
Fixation	– suppressible
Head shaking, position	– increased
Caloric testing	– can be pathologic
Slow pursuit	– normal
Saccades	– normal
Directional spontaneous nystagmus of the central vestibular type	
Mechanism	– imbalance of the central processing of signals from the semicircular canals and otoliths – disorder of vestibulo–cerebellar connections – disorder of fixation function also possible
Slow phase	– constant speed
Direction	– often purely horizontal, vertical or torsional – can also have several components
Fixation	– suppressible only with difficulty
Head shaking, position	– increased
Caloric testing	– normal or – with vertical component or – phase inversion
Slow pursuit	– often slowed
Saccades	– can be dysmetric and/or slowed
Gaze-evoked nystagmus	
Mechanism	– pathologic fixation mechanism – neuromuscular disorder (myasthenia gravis) – muscle weakness (myopathy)
Slow phase	– slow drift to central position with eccentric eye position followed by return saccade – often with rebound nystagmus
Slow pursuit	– often slowed and imprecise
Saccades	– can be dysmetric and/or slowed
Rebound nystagmus	
Mechanism	– compensation for persistent instability of fixation function (drift)
Direction	– after slower eccentric gaze there is transient nystagmus into the previous direction of gaze after return to the central position
Dissociated nystagmus	
Mechanism	many, e. g., – internuclear ophthalmoplegia (INO) – asymmetric gaze-evoked nystagmus
Slow phase or fast phase	– different eye speeds
See-saw nystagmus	
Mechanism	– possibly pathologic central processing of signals from the otoliths in the rostral mid-brain (Cajal interstitial nucleus)
Direction	– alternating with approx. 1 Hz in one eye vertically upward and vertically downward in the other eye

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31.3 Physiologic Stimulus-Induced Vertigo

Contradictory or prolonged unusual information from the visual, vestibular, and proprioceptive afferent nerve supply can, in principle, lead to a sensory conflict with diffuse vertigo and severe accompanying autonomic symptoms in any person. It can occur whenever there are motion and/or spatial situations in which the afferent modalities, which work optimally in different frequency regions (the visual system prefers low frequencies and the vestibular system high frequencies), are not stimulated to the same degree, and thus, generate (apparently) incongruent information for physiologic reasons, or when prolonged complex stimuli cannot be adapted peripherally or centrally because of their characteristics.

> Although many of these symptoms are not due to pathologic conditions, they have major and often disabling effects on persons who suffer from them.

Motion Sickness

The group of the *kinetoses* includes:

- *car sickness*, which arises because of conflicts between visual and vestibular stimuli
- *sea sickness*, which is triggered by prolonged, low-frequency, and thus only poorly adaptable, complex vestibular stimulus patterns
- *simulator sickness*, which is induced by optokinetic (whole-field) stimuli.

Besides mild vertigo, there are sometimes severe autonomic symptoms such as nausea and vomiting, cold sweats, headache, and impaired consciousness. The symptoms can occasionally persist for a few days in a mild form after cessation of the pathogenic stimulus (disembarkation sickness syndrome).

Height Vertigo

Height vertigo associated with fear and autonomic symptoms with crippling movement unsteadiness results from destabilization of the reconstruction (especially) in polysensory cortex areas (see Fig. 31.**12**) of the surrounding space, when it is not sufficiently filled with stable elements at varying distances from the observer. The important disparity stimuli are therefore lacking and the visually transmitted part of the *spatial representation* disintegrates. Ontogenetically, these disorders occur only when the visual cortex has fully matured.

Because of the generally obvious context (paucity of visual stimuli), the differential diagnosis of this form of vertigo is usually not difficult. However, individually and in its long-term course the threshold for destabilization varies, and physiologic vertigo can sometimes occur even in (geometrically) not immediately explicable situations (large, homogeneously colored wall). A behavior disorder (acrophobia) may be present if these symptoms occur inappropriately and are also associated with panic.

31.4 Peripheral Vestibular Vertigo

With acute dysfunction of the entire vestibular end organ (semicircular canals, saccule, utricle), vestibular nerve, or vestibular group of nuclei, the following clinical signs and symptoms are typically observed:

- severe rotational vertigo, swaying vertigo, vertical (elevator) vertigo
- nausea, vomiting
- a tendency to fall to one side
- directional, horizontal–torsional spontaneous nystagmus to the opposite side (see Fig. 31.**13**; Tab. 31.**6**), if the pontine saccade mechanism is not also previously or concurrently abnormal (e. g., multiple sclerosis, brainstem infarct).

Compensating and adapting mechanisms begin rapidly provided the structures of the vestibulocerebellum and the necessary pontine connections are not damaged (multiple sclerosis, brainstem and/or cerebellar infarcts), so that the direction of the pathologic nystagmus (and thus the rotational vertigo) and the tendency to fall may change over time and do not always point clearly to the affected side. Initially, however, directional *spontaneous nystagmus* is always towards the side opposite the affected organ (see Fig. 31.**13**).

Because of their diagnostic features, a number of forms are discussed separately below. Tab. 31.**7** lists the main causes of acute rotational vertigo.

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Benign Paroxysmal Positioning Vertigo (BPPV)

Clinical Features. The symptoms and clinical signs of benign paroxysmal positioning vertigo (BPPV) are so characteristic that the diagnosis seldom causes difficulty. It occurs in all periods of life but is more frequent from the sixth decade onward. Following a viral infection of the upper respiratory tract or a mild head injury, but usually without a clear history, immobilizing attacks of rotational vertigo lasting seconds occur without auditory symptoms, which are triggered consistently by certain head movements by the patient (turning in bed, lying down, bending the head backward). The patients are asymptomatic between attacks.

Diagnosis. The diagnosis is confirmed by *positional testing with Frenzel spectacles* (fixation eliminated):

- laying the head down rapidly when it is turned 45° toward the diseased side
- severe, mainly torsional and downward nystagmus with a latency of five to 10 seconds
- It increases somewhat in intensity and subsides again after approximately 30 s (these times reflect the dynamics of the cupulae and peripheral signal processing).
- The patient experiences the typical vertigo only during the nystagmus.
- After sitting up, weaker nystagmus in the opposite direction can occur briefly.

Pathophysiology. The disorder is due to inadequate stimulation in one of the three semicircular canals (usually the posterior one), which is due to:

- *cupulolithiasis:* particles (otoliths) shed from the saccule or utricle of the labyrinth, which adhere directly to the cupula and alter the characteristic signal processing of this organ, which normally reacts to head acceleration
- *canalolithiasis:* freely mobile otoliths in the endolymph, which bend the hair cells of the cupula on rapid changes of position, producing false stimuli.

Following a *positioning maneuver* (by the clinician) or with *positioning training* (by the patient), in which these particles are maneuvered out of the semicircular canal again, the patient usually becomes asymptomatic, although there may be *recurrences* (after variable intervals). However, if this rotational vertigo remains refractory to treatment then central postural nystagmus, in particular benign BPPV that is bilateral or interferes only with the horizontal semicircular canal, or other central nervous lesions must be considered in the differential diagnosis. The important distinction from central postural nystagmus can be made clinically and is summarized in Tab. 31.**8**.

Table 31.**7** Causes of acute rotational vertigo
Most of these types of vertigo can recur(●) In a few forms the symptoms are triggered or worsened by changes in position ($).

Benign paroxysmal positioning vertigo (BPPV) ● $

Acute unilateral partial deficit of the vestibular nerve ●
- labyrinthitis
- vestibular neuritis

Ménière disease ●

Basilar migraine ●

Multiple sclerosis ● $

Cerebral seizure ●

Posttraumatic vertigo

Other focal diseases
- ischemic hemorrhagic infarct ●
  - labyrinth/vestibular nerve: anterior inferior cerebellar artery (AICA)
  - ponto–cerebellar: posterior inferior cerebellar artery (PICA) $, Wallenberg syndrome
- venous outflow disorder ●
  - hyperviscosity syndrome
- valsalva-induced ●
  - Arnold–Chiari malformation $
- viral infection of the labyrinth/vestibular nerve:
  - herpes zoster
- bacterial infection of the labyrinth/vestibular nerve:
  - tuberculosis
- spirochetal infection of the labyrinth/vestibular nerve:
  - syphilis
  - borreliosis
- tumor
  - vestibulocochlear nerve, acoustic neuroma, neurofibromatosis 2
  - cerebellopontine $
  - glomus tumor
- autoimmune disease
  - Cogan syndrome I (vertigo, hearing loss, keratitis, often vasculitis) ●
- degeneration of the hair cells
- otosclerosis ●
- labyrinth fistula ●
- congenital anomaly of the labyrinths

Drug-induced vertigo
- antivertigo drugs
- antihypertensives
- antidepressants
- sedatives
- antiepileptics

Physiologic vertigo
- motion sickness ● $
- height vertigo ● $

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Table 31.**8** Characteristic differences between peripheral positional vertigo and central postural vertigo
Ageotropic = always away from the ground regardless of which side of the head.

Symptoms and Signs	Peripheral	Central
Latency	5–10 s	Begins immediately
Duration	< 30 s	Usually persists
Habituation	Yes	No
Nystagmus direction	Always the same Horizontal–torsional in the eyes' midposition	Can change Ageotropic nystagmus frequently
Intensity	With nausea Severe	Nausea rare Mild
Reproducibility	Inconsistent	Usually consistent

Acute Unilateral Partial Deficit of the Vestibular Nerve (Vestibular Neuritis)

Clinical Features. The cardinal symptoms of acute unilateral partial deficit of the vestibular nerve are:
- rotational vertigo lasting for days
- nausea
- a tendency to fall
- directional spontaneous nystagmus with a torsional component
- diminished excitability of the affected side on caloric testing.

If *hearing* is also impaired, the entire labyrinth is involved.

Differential Diagnosis. In the differential diagnosis, apart from *Ménière disease* and *labyrinth lesions* from other causes (syphilis, bacterial labyrinthitis [particularly tuberculous], rarely borreliosis, Cogan syndrome I [recurrent vertigo episodes, hearing loss, keratitis, often vasculitis, rarely aortic insufficiency]), *multiple sclerosis* with lesions at the myelinated zone where the vestibular nerve enters the pons or in the vestibular nuclei (without hearing impairment) and small, lacunar *cerebrovascular infarcts* in this region must be considered (see Tab. 31.**7**).

Epidemic and seasonal incidence and a preceding *viral infection* (mumps, measles, mononucleosis, viral infection of the upper respiratory tract) often suggest a specific infectious etiology, though this usually cannot be confirmed. *Herpes zoster oticus* can also lead to the clinical picture of acute labyrinth deficit. If the peripheral facial nerve is also involved, the condition is known as *Ramsay–Hunt syndrome*.

Ménière Disease

Clinical Features. The symptom triad of recurrent vertigo attacks, unilateral tinnitus, and unilateral hypacusis persisting after a prolonged illness, which subsides after minutes to hours and is associated with additional autonomic symptoms, including the occurrence of mild *impairment of consciousness* or occasional syncope, usually does not present difficulties in the differential diagnosis, although there are no confirmatory vestibular signs. In an attack there is usually directional *spontaneous nystagmus* because of the peripheral vestibular origin, which can change direction within hours.

Vascular Compression of the Vestibular Nerve

Vertigo attacks with unsteadiness on standing and walking can also occur with head movements or physical activity because of compression of the vestibular nerve by pulsating vessels close to the brainstem. This condition can be distinguished from BPPV by the following accompanying clinical signs and symptoms:
- hearing disturbance (dysacusis)
- pulsatile tinnitus
- pain in the territory of the trigeminal nerve and intermediate nerve
- possibly, other focal neurologic disorders.

It is assumed that this vertigo can be explained by a similar mechanism as that suggested for several forms of trigeminal neuralgia or facial nerve myokymia. However, compared to the frequently (incidentally) discovered vascular loops, this condition is rare.

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Perilymph Fistula

The presence of a perilymph fistula must be considered in vertigo that is partially dependent on head position, with the following clinical signs and symptoms:

- tinnitus
- sensorineural hearing loss
- stationary and gait unsteadiness
- attacks increased by pressure maneuvers (coughing, sneezing, playing a wind instrument).

This is due to an *abnormal communication* between the *endolymphatic tube* and the *inner ear*, which can occur after trauma, Valsalva maneuver, excessive physical training, inner ear operations (stapes), barotrauma after flying or diving, erosive lesions (tumor [cholesteatoma]) or inflammatory conditions (syphilis, *Yersinia*) in the petrous bone, as well as in congenital malformations (Mondini), or a large vestibulocochlear aqueduct.

Perilymph fistula is diagnosed on the basis of clinical findings and history. There are no definitive tests, and it may be difficult to diagnose.

Tullio phenomenon is related to the perilymph fistula. Vestibular symptoms (vertigo, oscillopsia, nystagmus) occur on purely acoustic stimulation, which can be attributed to abnormal transmission of sound oscillation to the vestibular apparatus.

Bilateral Vestibulopathy

The etiology of this syndrome with oscillopsia with head movements and gait ataxia in the dark, which can be attributed to chronic progressive disease of the labyrinths or vestibular nerves, is varied and sometimes overlaps with other peripheral vestibular diseases. *Oscillopsia* is perceived movement of objects, which occurs when compensation of intrinsic movements by the vestibular system is defective or absent so that the visual system cannot register high frequency disorders fast enough and the visual axis is therefore destabilized. Vertigo symptoms seldom predominate because of the simultaneous loss of both labyrinths and usually only occur temporarily at the start of the disease. The course of the disease is not uniform.

Table 31.**9** Ototoxic drugs (examples)

Aminoglycosides		
Amikacin	Gentamicin	Kanamycin
Neomycin	Netilmicin	Paromomycin
Streptomycin	Tobramycin	
Loop diuretics		
Bumetanide	Ethacrynic acid	Furosemide
Torsemide		
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Ibuprofen	Indomethacin	Naproxen
Salicylate		
Cytostatics		
Carboplatin	Cisplatin	Vincristine
Antibiotics		
Capreomycin	Erythromycin	Minocycline
Polymyxin e/b	Vancomycin	Viomycin
Chemicals		
Arsenic	Butyl nitrate	Co
Hexane	Lead	Manganese
Mercury	Strychnine	Styrene
Toluene	Trichlorethylene	Xylene
Zinc		

The following must be considered in the differential diagnosis:

- Ménière disease
- ototoxic substances (Tab. 31.**9**)
- autoimmune inner ear disorders
- familial vestibulopathies
- central vestibular disorders:
  - neuropathy
  - vascular anomalies in the vertebrobasilar territory
  - cerebellar degeneration of the most varied etiology
  - congenital malformations
  - history of meningitis

Traumatic Vertigo

Vertigo symptoms often occur, understandably, following head or cervical spine trauma, which, depending on the site of the disturbance, are associated with the corresponding oculomotor or other focal neurologic signs. This form of vertigo thus represents an artificial grouping.

The most frequent cause is injury of the labyrinth with shedding of otoliths, which leads to a temporary peripheral vestibular deficit syndrome. The deficit is fully compensated after days to a few weeks when brainstem and cerebellar structures are compensated, provided the patient is not (iatrogenically) immobilized.

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31.5 Central Vestibular Vertigo

In central vestibular forms of vertigo a distinction must be made in the differential diagnosis between *global* or *focal cerebral disorders* and *systemic diseases* with (temporary) co-impairment of cerebral functions, particularly cardiovascular and pulmonary diseases (hypoxic encephalopathy), as well as hepatopathies and nephropathies (toxic/metabolic encephalopathy).

Particular attention must be paid to the *drugs* used, as these are the most frequent cause of this form of vertigo. Transitions to psychiatric illnesses are fluid. With a careful history, these forms of vertigo can often be attributed to an episode (perhaps brief) with vestibular disorders, but which became established because of the patient's personality structure.

Cerebral Causes

Often, diffuse and fluctuating vertigo symptoms can occur in chronic, progressive diseases that affect the central nervous system either diffusely or (multi-) focally and with varying severity, (see History), which can be attributed to the dysfunction of cortical and subcortical structures and thus loss of spatial constancy (see Figs. 31.**1**, 31.**2**). The following manifestations are typical:

- vascular (subcortical arteriopathic encephalopathy)
- demyelinating (multiple sclerosis)
- nutritional (Wernicke–Korsakov syndrome)
- toxic/metabolic (Wilson disease)
- hereditary degenerative (Parkinson disease).

Lesions of central nervous system transmissions may be present, especially in the *central vestibular system* (see Figs. 31.**11**, 31.**12**). These lesions are found in the following forms:

- oculomotor efferent copies from supranuclear nuclei
- afferent signals that reach the cortex indirectly (thalamus), directly, or are sent to the vestibulocerebellum
- motor feedback signals from the cortex to the thalamus, basal ganglia, or substantia nigra.

Unlike the stereotypical peripheral vestibular disorders, the symptoms here are varied and the vertigo often does not predominate. The signs are marked by global or focal neurologic deficits depending on the underlying disease, with or without qualitative and/or quantitative disorders of consciousness. The oculomotor deficits are not always detectable. Often initially, complex functions of the visuomotor transformation disintegrate with predominant impairment of saccade control or slow pursuit movements. Because of their particular diagnostic features, a number of forms are presented below.

Basilar Migraine

In addition to peripheral or central vestibular vertigo there is usually a varied picture of (usually bilateral) focal neurologic deficits of the brainstem in basilar migraine. The vertigo is rarely a leitmotif in the differential diagnosis, and the possibility of *thrombosis of the basilar artery* must be considered in particular.

Vestibular Migraine

In this form of migraine, in which only vestibular structures are selectively affected, the clinical picture is one of acute peripheral vestibular deficit without hearing loss, which must be distinguished in the *differential diagnosis* especially from *Ménière disease*, which can also occur (very rarely) atypically without hearing impairment. Occasionally, focal neurologic disorders, especially oculomotor deficits (directional nystagmus, gaze-evoked nystagmus), can also be found between episodes.

Vestibular Epilepsy

Epileptic seizures, which have their origin in parietotemporal or parieto-occipital areas, can very rarely occur with vertigo and an aura. There are no diagnostic problems when there are typical seizure symptoms (visual illusions or hallucinations, motor automatisms, complex autonomic disorders with a drop in pulse or blood pressure, gastric discomfort, incontinence of urine and/or feces) or when there is secondary generalization of the seizure.

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Proprioceptive and Multisensory Vertigo

Clinical Features and Causes. In these forms of vertigo, sufficient compensation of the diminished, absent, or pathologically altered somatosensory signals by visual afferents is indicative. The vertigo, with sometimes immobilizing stationary and gait unsteadiness and falls, typically occurs only in darkness. The following clinical signs and symptoms predominate in the differential diagnosis and must be carefully sought and investigated.

- *Polyneuropathies:* (diabetes mellitus, alcoholism, paraneoplastic causes)
- *Polyradiculo-(neuro-)pathies:* (sensory Guillain–Barré syndrome)
- *Myelopathies with involvement of the posterior funiculus:* (trauma, extramedullary tumor, tabes dorsalis, funicular myelosis, Friedreich ataxia).

Multisensory Vertigo. Proprioceptive deficits are also one of the most important elements of so-called multisensory vertigo, which arises due to a summation effect of individually mild disorders of the afferents:

- ocular vertigo (refraction, diseases of the refractive media or retina)
- a peripheral vestibular vertigo (with hypacusis)
- proprioceptive vertigo in (sensory) polyneuropathy.

> Naturally, multisensory vertigo is one of the most frequent causes of restriction in the life of the elderly patient.

In this case, the individual elements must be investigated precisely as the patient can sometimes be helped substantially with only mild therapeutic intervention (e. g., new glasses, cataract operation, hearing aid, orthopedic aids).

Paroxysmal Dysarthrophonia and Ataxia

This disorder especially occurs in patients with a demyelinating disease (e. g., *multiple sclerosis*). Because of ephaptic excitation of partially myelinated axons, there are short attacks of swaying vertigo and limb ataxia during hyperventilation and/or on physical exertion. This mechanism may also be responsible for the vertigo attack occasionally observed with severe (psychogenic) hyperventilation with marked, but rapidly resolving, spontaneous nystagmus.

Psychogenic Vertigo

Both depressive moods and *schizoaffective psychoses* can be associated with diffuse or bizarre vertigo symptoms. The subgroup of phobic swaying vertigo is a clinically important psychosomatic disorder with vertigo.

Phobic Swaying Vertigo

In this condition, an individually stereotypical situation triggers an attack of swaying vertigo, as well as stationary and gait unsteadiness. Disabling avoidance behavior can occur increasingly as it progresses. Brandt and Dieterich, 1986, described this disorder and produced the following diagnostic observations:

- The patient complains of swaying vertigo and subjective stationary and gait unsteadiness with normal neurologic signs and normal balance test (otoneurologic examinations).
- The vertigo is described as a fluctuating unsteadiness when standing and walking with an attack-like feeling of falling and dropping, sometimes felt only as an involuntary body swaying for a fraction of a second.
- The attacks often occur in typical situations that are also known as triggers of other phobic syndromes.
- Generalization occurs later, with increasing avoidance behavior with regard to triggering stimuli. Fear and autonomic discomfort are reported during or shortly after these attacks (often only on questioning), although most patients also report vertigo attacks without fear.
- Patients with phobic swaying vertigo often have compulsive personality traits and symptoms of reactive depression.
- The onset of the disease can often be traced back to an initially organic vestibular disease or a particularly stressful situation.

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31.6 Diagnostic Evaluation of Syncope

Differential Diagnosis of Syncope

Cause. Syncope can be the result of cardiac (e. g., aortic stenosis), cardiovascular (e. g., *neurocardiogenic syncope*), or cerebral (e. g., *epilepsy*) diseases (Tab. 31.**10**). The forms due to structural heart disease, especially coronary heart disease, are particularly important, as they have a significantly higher mortality in the long term than all other forms of syncope.

> The most important aim of the diagnostic algorithm described below is the identification of cardiac syncope.

Independent of the etiology, any syncope of nonepileptic origin can cross over into *convulsive syncope*. There is brief tonic–clonic motor activity and very rarely also incontinence of urine and/or feces, which is often difficult to distinguish from an epileptic seizure. The diagnosis can be confirmed by means of a simultaneous EEG recording, which naturally is only rarely possible.

History. Taking an exact history, whenever possible with history from an *eyewitness*, is the most important diagnostic step in investigating syncope. A *family history* of sudden cardiac death suggests autosomal-dominant inherited conditions (e. g., hypertrophic obstructive cardiomyopathy, Brugada syndrome, right ventricular dysplasia). There is a greater incidence of the latter in patients from Northern Italy.
In the *personal history*, age < 50 years, female sex, and a history of numerous previous episodes of loss of consciousness suggest neurocardiogenic syncope. A history of myocardial infarction, on the other hand, suggests ventricular tachycardia as the cause of the syncope. Among the questions about the recent syncope, the period immediately before the loss of consciousness is important. In reflex vascular syncope, prodromes (e. g., nausea, sweating, an anticipated feeling of fainting) are nearly always reported. Conversely unconsciousness as a result of bradycardia always, and as a result of tachycardia usually, occurs without warning symptoms. Tongue biting, incontinence of urine and/or feces, and tonic–clonic seizures point to epilepsy. However, they can also be triggered by cardiac and vascular syncope through cerebral hypoxia; the diagnosis of epilepsy therefore must not be made based on the occurrence of a seizure only. An epileptic patient regains consciousness gradually, complains of headache, and can walk around before he is fully conscious again. In contrast, the patient with cardiac syncope is orientated immediately after the attack and rarely complains of headache.

Physical Status. Clinical examination initially includes recording of blood pressure and heart rate lying and standing (Shellong test), along with careful cardiac auscultation to seek evidence of a valvular lesion. Tachypnea and/or a pleural rub should also be noted as signs of pulmonary embolism. Finally, exact recording of the neurologic findings is important.

Additional Investigations. Of all the additional investigations, the *12-lead ECG* is both the most important, and the easiest test to perform. The ECG, which is usually recorded hours after the event, identifies the pathology leading to the syncope only in the rarest cases, but can provide evidence of cardiac disease underlying an arrhythmia (Tab. 31.**11**). It is of great practical relevance to look carefully for these signs in the ECG and to perform further investigations if the ECG result is positive.
The most important of the more complex methods are the *Holter monitor* and *echocardiography*. The former should be used especially in patients with known cardiac disease and a pathologic resting ECG (e. g., first degree AV block), which does not explain the syncope. Echocardiography is often of crucial importance in confirming or ruling out structural heart disease (particularly cardiomyopathies and valvular lesions) in patients with clinical or electrocardiographic signs of cardiac syncope.
All other investigations to clarify syncope (e. g., electrophysiologic tests, cardiac catheterization, EEG) should be performed only in selected cases. The use of a tilt-table, as recommended by various authors to identify neurocardiogenic syncope, requires considerable time and equipment and is, therefore, unsuitable for routine investigations.

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Table 31.**10** Possible causes of syncope

Cardiac syncope

Bradyarrhythmias

Tachyarrhythmias
- as part of structural heart disease
  - coronary heart disease
  - cardiomyopathies: dilated, hypertrophic and right ventricular arrhythmogenic cardiomyopathy
  - valvular heart disease
- without structural heart disease
  - long QT syndrome: congenital or acquired (drug-induced)
  - Brugada syndrome
  - idiopathic ventricular tachycardia
  - antidromic AV node re-entry tachycardia with accessory bundle

Disorders of left ventricular emptying
- aortic stenosis
- hypertrophic obstructive cardiomyopathy
- severe systolic heart failure

Filling disorders of the left ventricle
- pulmonary embolism
- chronic pulmonary hypertension
- mitral stenosis
- atrial myxoma
- pericardial effusion

Vascular syncope

Reflex
- neurocardiogenic syncope
- pressor–postpressor syncope
- carotid sinus syndrome
- orthostatic dysregulation
  - sympathicotonic
  - asympathitonic
- neurogenic syncope

Organic
- transient ischemic attack
- subclavian steal syndrome

Cerebral syncope

Epilepsy

Narcolepsy

Eclampsia

Behavior disorder

Table 31.**11** Cardiac syncope
Potential pathologic findings in the resting ECG and further diagnostic measures. RBB = right bundle block.

Cardiac syncope cause	EKG finding	Further investigation
Coronary heart disease with ventricular tachycardia	Signs of previous infarct	Echocardiography Coronary angiography
Acute ischemia with ventricular tachycardia	ST and T changes	Measure cardiac enzymes Coronary angiography
Aortic stenosis	Left ventricular hypertrophy	Echocardiography
Hypertrophic obstructive cardiomyopathy	Marked signs of hypertrophy, T-wave inversion	Family history Echocardiography
Right ventricular arrhythmogenic cardiomyopathy	rSR' in V_1, T-wave inversion in V_1–V_3	Family history Echocardiography
Congenital long QT syndrome	Prolonged QT interval	Family history
Acquired long QT syndrome	Prolonged QT interval	Drug history
Brugada syndrome	First degree AV block, partial RBB, ST elevation in V_1–V_3	Family history Provocation with flecainide
Pericardial effusion	Peripheral and precordial low voltage	Chest radiograph Echocardiography

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31.7 Cardiac Syncope

Bradyarrhythmias

Patients with bradycardia as the cause of syncope have a hemodynamically relevant pause (asystole), which leads to cerebral hypoperfusion. Sympathetic tone increases because of the abrupt drop in blood pressure, which is manifested as simultaneous sinus tachycardia in patients with AV block. Following the syncope, when the heart rate has been restored, the patients demonstrate a high to normal blood pressure and therefore have few symptoms.

The forms and differential diagnosis of bradyarrhythmias are discussed in detail in Chapter 22.

Tachyarrhythmias

As shown in Tab. 31.**10**, there are a large number of cardiac conditions that can lead to tachycardia-induced syncope. In these conditions, a fundamental distinction must be made between patients with and patients without structural cardiac disease, as the prognosis and, therefore, the therapy are different.

Tachyarrhythmias in the Setting of Structural Cardiac Disease

By far the most frequent, and therefore most important, structural cardiac disease associated with tachyarrhythmia is *coronary heart disease*. Dilated and hypertrophic obstructive cardiomyopathy, right ventricular arrhythmogenic cardiomyopathy associated with characteristic ECG changes (Fig. 31.**15**), and valvular disease must also be considered (see Tab. 31.**10**).

If a patient with known coronary heart disease suffers syncope, *ventricular tachycardia* must be assumed to be the cause until proven otherwise. The further diagnostic (Holter monitor, ergometry, electrophysiologic investigations) and therapeutic (antiarrhythmic agents, intracardiac defibrillator) steps depend substantially on the degree of left ventricular function, and must be determined in individual cases in close collaboration with a cardiologist.

Tachyarrhythmias without Structural Cardiac Disease

Several *hereditary syndromes*, usually autosomal dominant, with specific ECG changes, and which can lead to tachyarrhythmias as a result of abnormalities of the cardiac ion channels, are known. These tachycardias often occur in childhood or early adulthood. Sudden death of a child can also be a manifestation of such a mutation. It is therefore of great prognostic importance to analyze the resting ECG precisely for evidence of such a syndrome in young patients with possible tachycardia-induced syncope (see Tab. 31.**11**).

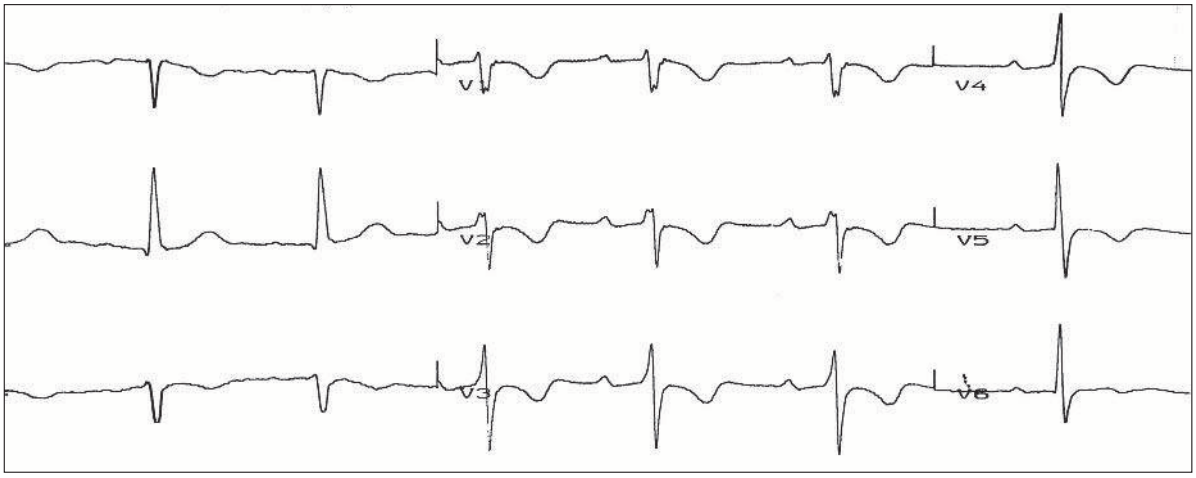

Fig. 31.**15** Typical ECG in right ventricular arrhythmogenic cardiomyopathy. Delayed conduction with widened QRS complex in V_1–V_3 and T-wave inversion in the right precordial leads.

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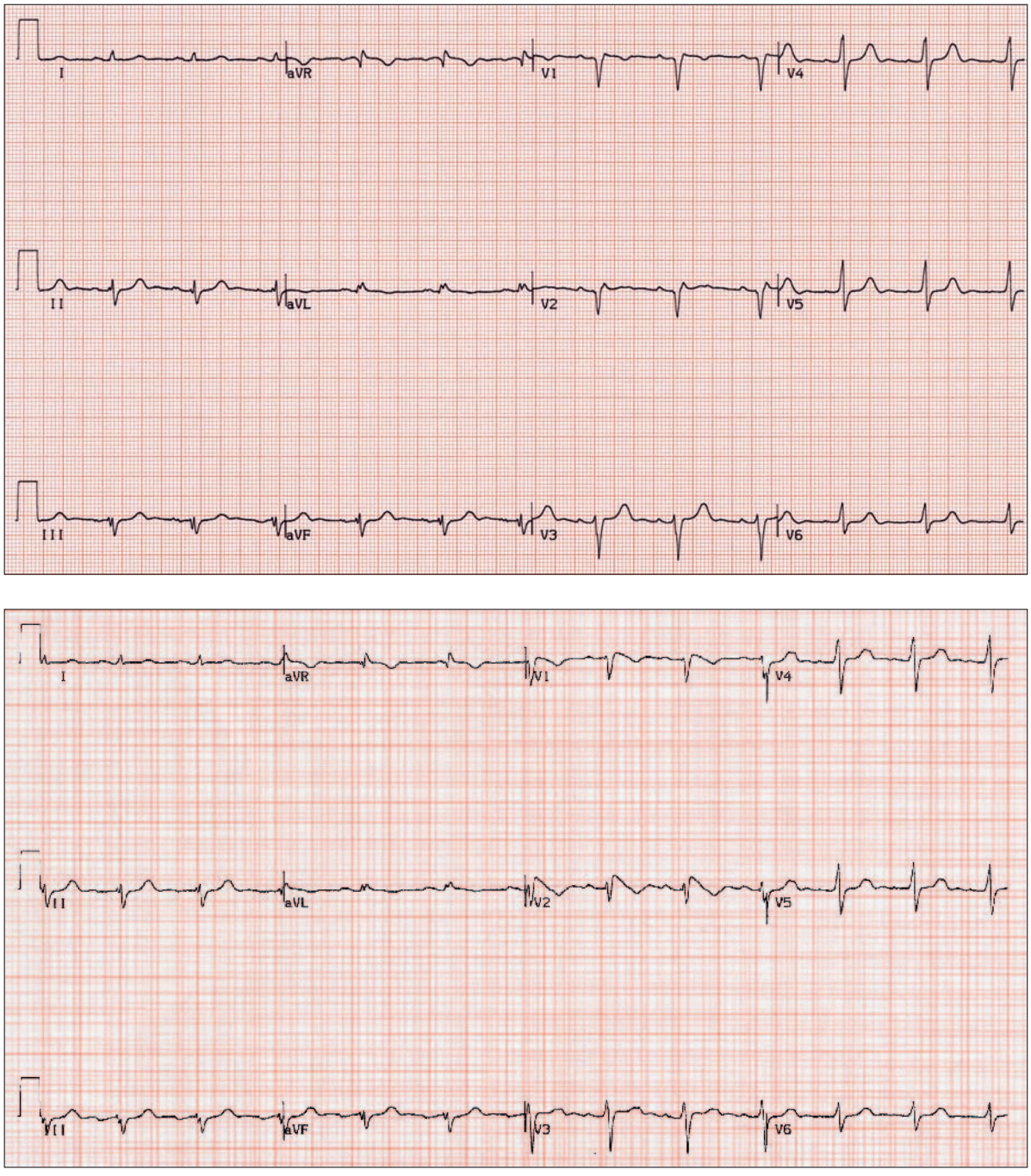

Fig. 31.**16** ECG in Brugada syndrome.
a Resting ECG with nonspecific changes: partial right bundle branch block and very slight ST elevation in V_1 and V_2.
b Specific ECG changes after provocation with flecainide: prolonged PQ, saddle-shaped ST elevation, right bundle branch block.

Long QT Syndrome. Apart from the congenital form, there is also a drug-induced acquired form. The *drug history* with enquiry about the use of anti-arrhythmic drugs (sotalol, amiodarone, procainamide, etc.), macrolide antibiotics, neuroleptic drugs, tricyclic antidepressants, and other drugs is decisive in this case.

Brugada Syndrome. Patients with Brugada syndrome (Fig. 31.**16**), which is thought to be responsible for about half of all sudden deaths when the heart is structurally normal, usually have a positive family history. In unclear cases, the arrhythmia can be provoked by administration of a sodium–potassium channel blocker (e. g., flecainide).

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Other Tachyarrhythmias. Apart from these syndromes, idiopathic ventricular tachycardias can also be observed in patients with a structurally normal heart. These are usually monomorphic, result more often in palpitations and dizziness than in syncope, and have a good prognosis.

Finally, it should be noted that supraventricular tachycardia can also lead to syncope in rare cases. For instance, atrial fibrillation can be conducted extremely quickly to the ventricle through the accessory bundle in antidromic AV node reentry tachycardia (see also Chapter 22).

Emptying Disorders of the Left Ventricle

Aortic Stenosis and Hypertrophic Obstructive Cardiomyopathy. Aortic stenosis and hypertrophic obstructive cardiomyopathy (see Chapter 23) can lead to syncope on physical exertion. These conditions must be sought carefully both clinically and with echocardiography in every case of exercise-induced syncope.

Heart Failure. Syncope can occur in heart failure from any cause. This is observed particularly when the failing left ventricle is no longer able to increase cardiac output on physical exertion or when there is an arrhythmia in addition (e. g., tachycardial atrial fibrillation).

Myocardial Infarction. Syncope can occasionally be the initial symptom of a myocardial infarction. Reduced cerebral perfusion can then be due to both the infarct-induced reduction in the ejection fraction and to an arrhythmia (AV block or ventricular tachycardia).

Filling Disorders of the Left Ventricle

Pulmonary Embolism and Pulmonary Hypertension. Both acute pulmonary embolism and chronic pulmonary hypertension of primary or secondary origin can lead to syncope because of diminished right ventricular output.

Mitral Stenosis and Atrial Tumors. In rare cases, syncope can be a symptom of mitral stenosis or an atrial myxoma.

31.8 Vascular Syncope

Reflex Vascular Causes

This term includes vasovagal reactions, orthostatic dysregulation, and neurogenic syncope.

Vasovagal (= Neurocardiogenic) Syncope

This is the most frequent form of syncope, particularly in the *younger age group*, and is characterized pathophysiologically by the combination of *diminished vascular tone* with a corresponding fall in systolic and diastolic pressure, and *increased vagal tone* with a consequent fall in heart rate. Since cardiac (left ventricular) receptors in particular play an important part, along with the autonomic nervous system, the term *neurocardiogenic* (no longer vasovagal) syncope is usually employed today. The autonomic nervous system functions according to the principle of reciprocal reinforcement (i. e., *increased sympathetic tone* potentiates vagal tone); this is why neurocardiogenic syncope often occurs in corresponding circumstances (e. g., pain, blood sampling, emotional excitement). Typically, the tendency to this form of reaction is increased further by preceding vasodilatation (e. g., warm shower, alcohol, vasodilating drugs [nitrates]) or hypovolemia (e. g., severe sweating, diuretics).

In most cases the diagnosis can be made based on an exact history, which details the accompanying circumstances and the presence of prodromes. In rare cases, a tilt-table test may be indicated, though this is limited by the difficulty of reproducing the symptoms and signs.

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Pressor–Postpressor Syncope

This form of syncope occurs after pressor efforts (e. g., coughing, laughing, micturition, defecation). Along with the diminished venous return due to the pressor activity, increased vagal tone with reflex vasodilatation also plays a part in pathogenesis.

Carotid Sinus Syndrome

Cardiac and vasomotor factors are also involved in carotid sinus syndrome. Under physiologic conditions, unilateral compression of the carotid sinus leads to a drop in blood pressure and heart rate. In cases of disease (particularly arteriosclerosis) this reflex can be so increased that symptoms such as dizziness, confusion, and even unconsciousness occur.

Clinically, a distinction is made between the cardioinhibitory type (with bradycardia and consequent drop in blood pressure), the vasodepressor type (with a fall in blood pressure without significant bradycardia), and mixed forms of the two types.

Orthostatic Dysregulation

In orthostasis syndrome a distinction is made between a sympathicotonic and a nonsympathicotonic form, depending on the behavior of the heart rate in the *Schellong test*.

Sympathicotonic Form. Sympathicotonic orthostatic collapse is characterized by excessive compensatory sympathetic activation, with a corresponding increase in heart rate, as a response to the drop in blood pressure induced by the change in position. Persons with a constitutional tendency to *hypotension* are particularly at risk. Symptoms of collapse are known to occur in hypotensive persons when they get up suddenly in the morning, and this can extend to syncope.

Conditions involving orthostatic collapse often occur in the initial phase of *antihypertensive therapy*, especially with peripherally-acting vasodilators. Inappropriate use of *diuretics* or laxatives can also give rise to an increased tendency to collapse because of the resulting hypovolemia, and often also hypokalemia. This situation is encountered frequently in young women.

Nonsympathicotonic Form. In nonsympathicotonic orthostatic collapse, in which there is no increase in heart rate despite the drop in blood pressure, primary and secondary (especially diabetic or alcoholic neuropathy) forms are distinguished.

Neurogenic Syncope

Various neurologic diseases, sometimes associated with a *functional or structural disorder* in the region of the *central and/or peripheral autonomic nervous system*, can lead to disabling syncope. These include:

- *multisystem atrophy (MSA):* including olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SN) and Shy–Drager syndrome, other Parkinson-plus syndromes, as well as Parkinson disease
- *myelopathies with involvement of the posterior funiculus:* (vasculopathy, tumor, trauma, tabes dorsalis, funicular myelosis, Friedreich ataxia)
- *polyradiculo-(neuro-)pathies:* (sensory Guillain–Barré syndrome)
- *polyneuropathies:* (diabetic, alcoholic, paraneoplastic).

Pathogenetically, the syncope is due to central autonomic dysregulation (e. g., in MSA) and/or cardiac deafferentation (e. g., in radiculoneuropathy). The deafferentation can be detected with the so-called *RR variance statistics*, which document inadequate or even absent heart rate variability in orthostasis, and essentially corresponds to a nonsympathicotonic orthostatic reaction.

Organic Vascular Causes (Cerebrovascular Causes)

Transient Ischemic Attacks (TIA)

Definition and Clinical Features. Syncope can occur as part of intermittent cerebrovascular insufficiency (transient ischemic attacks, TIA). These are brief ischemic attacks with reversible neurologic deficits, which typically are fully reversed after minutes to up to 24 hours (rare). Transient motor and sensory deficits, dysphasia, double vision, and amaurosis are frequent. When the territory of the vertebral and basilar arteries is involved (vertebral or basilar insufficiency), symptoms of dizziness, ataxia, and visual disorders predominate. However, when several arteries are involved, nearly any combination of neurologic symptoms is possible.

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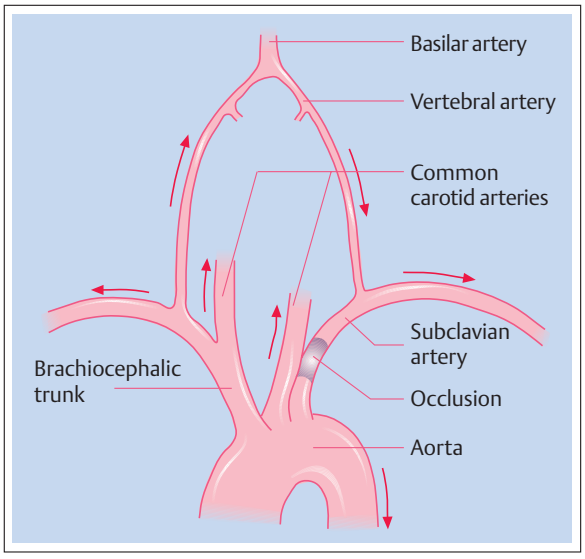

Fig. 31.**17** Subclavian steal syndrome with occlusion of the left subclavian artery.

Diagnosis. Intermittent cerebrovascular insufficiency is usually due to arteriosclerotic stenosis or occlusion of the extracranial or intracranial cerebral vessels. However, only the carotid arteries are readily accessible to clinical examination (palpation, auscultation). Other investigative methods (e. g., Doppler ultrasound, angiography) must often be used for further assessment. Because of the possibility of vascular surgical therapy, stenosis of the large cerebrobrachial arteries is of particular interest. Typical sites of arteriosclerotic stenosis include their origins from the aortic arch, and the internal carotid artery at the carotid bifurcation.

Aortic Arch Syndrome

In aortic arch syndrome the origins of the large vessels from the aortic arch can be narrowed or occluded by arteriosclerosis, and also more rarely by inflammatory conditions of the vessel walls (Takayasu syndrome), which is observed particularly in young women. Narrowing of these vessels can also occur with a dissecting thoracic aortic aneurysm. An additional triggering factor (e. g., drop in blood pressure, vasospasm in hypertensive crisis) is necessary for a TIA to occur.

Arterial Emboli

Arterio-arterial microemboli (thrombotic deposits on arteriosclerotic plaques in the arteries, or on myxedematous mitral valves in mitral valve prolapse syndrome) are held responsible to an increasing degree for temporary neurologic deficits.

In this context, saccular aneurysms of the carotid artery, which are detected as pulsating tumors in the neck, should be mentioned. These can also be the source of arterial emboli. The rare *carotid glomus tumors* should be considered in the differential diagnosis.

Microemboli can also originate in the heart when there are mural changes (e. g., after myocardial infarction) and are also possible in valvular heart disease (mitral stenosis, mitral valve prolapse syndrome, aortic stenosis, florid endocarditis on the mitral and/or aortic valves). Arrhythmias are frequently the probable immediate triggering factor.

Subclavian Steal Syndrome

In subclavian steal syndrome, the subclavian artery is occluded proximally to the origin of the vertebral artery. The blood flows to the arm through the vertebral artery on the opposite side and through the vertebral artery (retrograde) on the diseased side (Fig. 31.**17**). The cerebral circulation is deprived of blood in favor of the arm ("tapping" or steal syndrome). Dizziness, visual disorders, syncope, or other cerebral deficits are the result. Onset of the symptoms when working with the arm is typical.

31.9 Cerebral Syncope

Cerebral Seizures and Epilepsy

Pathogenesis and Terminology

Pathogenesis. The common feature of epileptic seizures is sudden and simultaneously commencing excessive (*hypersynchronous*) discharges from certain groups of cerebral neurons, which can spread rapidly from the original focus to other regions of the brain. *Intracortical spreading* usually takes place along established anatomic connections. In the hippocampus, spreading is most likely also determined by extracellular ion alterations and the local current flow. This disorder of neu-

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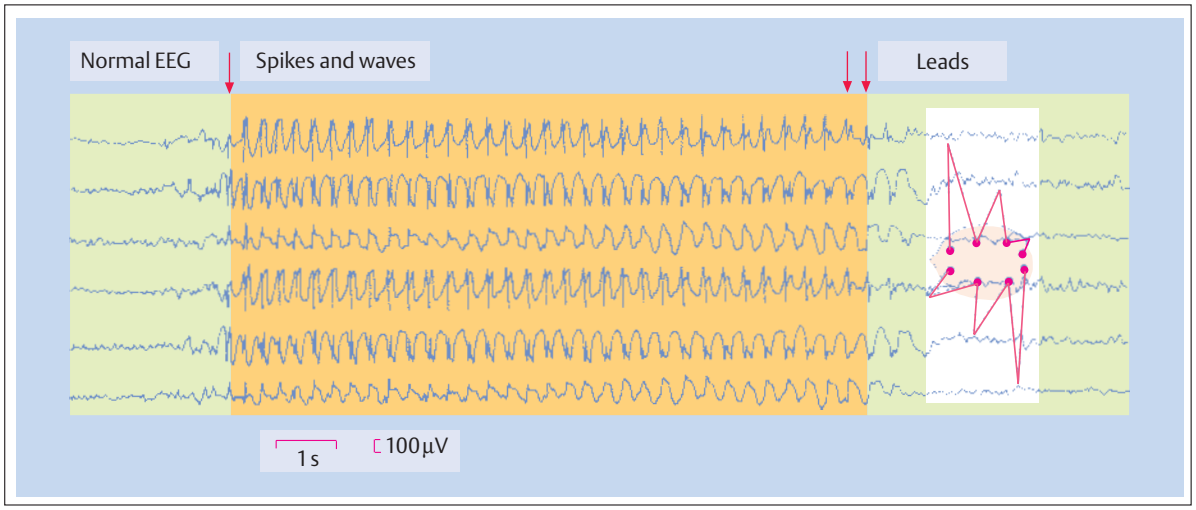

Fig. 31.**18** Epileptic absence on EEG.
The spike waves typical of this form of epilepsy start at ↓. They end at ↓↓. The section of the graph before the first arrow corresponds to a normal EEG. The recording sites belonging to the graphs are entered in the last part of the graph.

ronal processing of excitation always arises in the region of the nerve cells of the *cerebral cortex*, or more deeply located gray nuclei, and not in the white matter.

Symptomatic Epilepsy. This does not always indicate a cerebral lesion (e. g., intracranial tumors, brain trauma, pre- or perinatal brain damage, meningoencephalitis, congenital dysplasias, cerebral lipidoses, degenerative brain diseases, multiple sclerosis). Exogenous intoxications (e. g., alcohol, excitatory drugs, neuroleptics), withdrawal of sedatives following chronic abuse, hypoxia, and metabolic and endocrine disorders (e. g., uremia, porphyria, hypoglycemia, severe hepatic disease, water intoxication, hypocalcemia, etc.) can also lead to seizures.

Cryptogenic Epilepsy. If the epilepsy is presumably symptomatic but there is presently no known specific etiology, it is also called cryptogenic.

Idiopathic Epilepsy. The diagnosis of idiopathic epilepsy (i. e., a disease of unknown cause) is permissible only after exclusion of the aforementioned factors, and thus, also of symptomatic epilepsy.

Epileptic Aura. Aura is essentially a *simple, partial seizure*. However, it is often interpreted by the affected patient as a warning sign before the actual seizure and can also occur in isolation as part of epilepsy. The nature of the aura (elementary sensory perceptions, complex changes in state such as *dreamy states*, *alienation*, *simple or polymodal hallucinations*) is of particular importance in localization as it points to the site of seizure origin.

Classification and Clinical Features of Types of Epilepsy

The classification of epilepsies and their nomenclature can be made from various criteria (etiology, EEG appearance, type and age at primary manifestation, etc.; Tab. 31.**12**). A phenomenological classification of seizures is preferred here.

Primary, generalized seizures are epileptic seizures in which a disorder of excitation spreading diffusely through both hemispheres is assumed clinically (major seizure) or from the EEG (e. g., absence; Fig. 31.**18**). They are usually associated with a sudden loss or impairment of consciousness.

In *focal seizures*, the expression of the seizure symptoms is restricted clinically (e. g., jacksonian motor seizure with twitching of the fingers of one hand, possibly spreading to the arm) or electroencephalographically to a distinct focus. A focal seizure can be associated with or without (jacksonian seizure) impairment of consciousness and is always symptomatic. The term *minor seizure* is used for both EEG generalized seizures (Fig. 31.**18**), as well as for focal seizures without a generalized convulsion.

Focal Seizures

Localization and Symptoms. In focal seizures the symptoms are determined by the function of the affected brain area. Thus they include the entire range of motor, sensory, and at times even cognitive and mnestic brain activity.

Accordingly, a focus in the precentral motor region is expressed as a jacksonian motor seizure and one in the

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Table 31.**12** International classification of epilepsies, epilepsy syndromes, and related seizure disorders

1.	**Localized (local, focal, partial) epilepsies and syndromes**
1.1	**Idiopathic (with age-dependent onset)** – benign epilepsy in childhood with centrotemporal spike focus – epilepsy in childhood with occipital seizures – primary reading epilepsy
1.2	**Symptomatic** – temporal lobe epilepsies – frontal lobe epilepsies – parietal lobe epilepsies – occipital lobe epilepsies – chronic progressive continuous partial epilepsy – syndromes characterized by specific seizure triggers
1.3	**Cryptogenic**
2.	**Generalized epilepsies and syndromes**
2.1	**Idiopathic (with age-dependent onset)** – benign neonatal familial seizures – benign neonatal seizures – benign myoclonic epilepsy in infants – absences in childhood – absences in adolescents – myoclonic epilepsy in adolescents – epilepsy with grand mal on waking (GTCS) – other generalized idiopathic epilepsies – epilepsies with seizure triggered by special activation forms
2.2	**Cryptogenic or symptomatic** – West syndrome – Lennox–Gastaut syndrome – epilepsy with myoclonic–astatic seizures – epilepsy with myoclonic absences
2.3 *2.3.1* *2.3.2*	**Symptomatic** *Nonspecific etiology* – early myoclonic encephalopathy – early infantile epileptic encephalopathy with intermittent discharge salvos – other symptomatic generalized epilepsies *Specific syndromes* – epileptic seizures as a complication of other diseases
3.	**Epilepsies and syndromes, that cannot be classified as either focal or generalized**
3.1	**With both generalized and focal seizures** – seizures in neonates – severe myoclonic epilepsy in infants – epilepsy with continuous spike wave potentials during sleep – acquired epileptic aphasia – other unclassifiable epilepsies
3.2	**Epilepsies without clear generalized or focal signs**
4.	**Special syndromes**
4.1	**Occasional seizures ("situation-related seizures")** – febrile convulsions – isolated seizures or isolated status epilepticus – seizures only as a result of acute metabolic or toxic causes

postcentral sensory region as a contralateral sensory seizure. Disorders of excitation in brain regions, combined with a primary sensory function (e. g., visual, acoustic, vestibular, olfactory, gustatory), lead to the occurrence of photopsia, noises, sudden vertigo, and smell and taste perceptions.

A focus in *brain regions with a higher integrative function*, such as the limbic structures (amygdala, hippocampus, cingulate gyrus, etc.), causes complex partial seizures with motor automatisms, scenic experiences (dreamy states, déjà vu, jamais vu), usually of a negative, but occasionally also of a positive, emotional tinge, and

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also autonomic symptoms along with olfactory and gustatory hallucinations.

However, partial seizures with complex symptoms cannot simply be interpreted as limbic or temporal lobe epilepsy, as they can also occur with parietal and frontobasal foci.

Seizure Course. The focal seizure can remain localized or produce *secondary generalization*. Both types of seizure can occur in the same patient. If generalization is delayed, memorization is possible and the onset is recalled as an *aura*. When there is rapid spread, the memory of commencing focal symptoms is erased. A focal onset can then only be discovered from eyewitnesses in the case of motor seizures with a focal onset or, if isolated sensory auras occur, it can be concluded from the description of these equivalents. An aura or focal onset of a major seizure usually indicates circumscribed brain injury (i. e., *symptomatic epilepsy*). Occasionally, an otherwise clinically silent brain lesion can reach a threshold as part of a nonspecific triggering mechanism and mimic a primary epileptic focal seizure (e. g., complex partial seizure as a result of cerebral hypoxia in Adams–Stokes attacks).

Because of its significance for localization, the aura is crucial in diagnosis and is more important than the subsequent, clinically more impressive, major seizure.

Generalized Seizures

The major convulsive seizure begins suddenly with a general tonic muscle spasm, which lasts about half a minute. The clonic stage then begins, with violent spasms of the entire body. As a result of the tonic innervation of the diaphragm and the vocal cords, it is often initiated by an inspiratory cry. The skin color is typically cyanotic. Tongue biting is frequent. The forced respiration and whipping up of saliva with the tongue in the clonic stage then lead to blood-stained foam at the mouth. There is often incontinence of urine and feces. Lateral tongue biting and urinary and/or fecal incontinence and postictal drowsiness or sleep suggest an epileptic seizure in cases of doubt. Major seizures can occur in isolation during a period of sleep deprivation, intoxication, and sometimes also without a recognizable external cause, as *occasional seizures*.

Status Epilepticus. If seizures follow one another rapidly, without recovery of consciousness (serial seizures), or if the seizure lasts longer than *30 minutes*, this constitutes status epilepticus, a condition that is always life-threatening. Statuslike occurrence of absences over days and weeks occasionally present as *petit mal status*. In these states, the patients walk around, have delayed reactions, and merely give an impression of psychomotor slowing.

Special Seizure Types

- In the *akinetic–astatic seizure* there is a sudden fall, from which the patient immediately rises, and occasionally only the hint of a fall.
- *Myoclonic attacks* show sudden, uncontrolled flailing movements of the arms and legs and very abrupt flexion movements of the trunk, particularly in the morning after rising. Later, major seizures usually also occur.
- *Mesial temporal lobe syndrome* is characterized by the frequent occurrence of febrile convulsions in early childhood, a seizure-free interval until puberty followed by renewed manifestation of seizures in the form of complex partial seizures, which have their origin in the amygdala and/or other hippocampal formations.
- *Saalam convulsions* can be classified by their typical appearance.
- The great variability of the *focal minor seizures* was mentioned already. However, the manifestation of a focal seizure can be not only excitatory (e. g., convulsions of a limb) but also inhibitory, e. g., transient blocking of a movement. Accordingly, brief transitory aphasia can occur as a seizure equivalent along with disordered vocalization.
- *Kozhevnikov epilepsy* is a continuous focal epilepsy lasting days and months (e. g., with repetitive clonic twitches in the facial nerve region on one side). Generalized seizures also occur occasionally.

Diagnosis and Differential Diagnosis

Diagnosis. As the anticonvulsant drug is determined by the seizure form, each seizure disorder requires *neurologic and internist examination* with an EEG. With the exception of the symptomatic epilepsies, the majority of patients in the interictal state have no identifiable abnormalities so the *detailed history* is of the greatest importance, and must include, in particular, a precise family history, the course of pregnancy and the birth history and also psychomotor development (ideally compared with siblings). Whenever possible, the seizure history should be supplemented by asking an eyewitness. The seizure history includes:

- *semiology*, including its constancy
- frequency
- severity
- temporal pattern (possibly clusterlike)
- provocation factors, including circadian or *menstrual* associations.

As a further investigation, the *electroencephalogram* (EEG) is crucial. There are characteristic changes in individual epilepsies both ictally and interictally (e. g., the spike and wave pattern of absence; see Fig. 31.**18**). However, a normal EEG in the interval between episodes does not rule out epilepsy (especially posttraumatic forms).

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Table 31.**13** Neurologic diseases in which seizure-like attacks can occur

- Transient ischemic attack (TIA)
- Migraine accompagnée, basilar migraine
- Ménière disease, vestibular drop attack, Tumarkin otolithic crisis
- Paroxysmal dyskinesia
- Extrapyramidal seizures: drug dyskinesia, acute dystonic reaction after administration of dopamine receptor antagonists
- Tonic brainstem seizures: especially in multiple sclerosis
- Tumors of the posterior cranial fossa
- Colloid cysts of the third ventricle
- Extension synergies: in severe diffuse brain damage or coning of the brainstem
- Somnambulism

Differential Diagnosis. The differential diagnosis with nonepileptic attacks includes all other types of syncope listed in Tab. 31.**10**, as well as attacks associated with endocrine disorders listed below:

- hypoglycemic shock (insulinoma)
- pheochromocytoma crisis
- Addison disease
- hypothyroidism
- tetany
- hypercalcemia
- seizures associated with a disturbed sleeping and waking rhythm, particularly in narcolepsy
- other neurologic diseases (Tab. 31.**13**) and functional disorders.

While the major seizure (*grand mal*) poses little diagnostic difficulty, the diagnosis of minor seizures can often only be made with the EEG.

A *simple absence* is characterized by absence and staring lasting for seconds, and often also by tonic upward deviation of gaze with blinking. However, it can also occasionally be associated with stereotypies, which resemble the motor automatisms of complex partial seizures (oral–alimentary, gestural), and which no longer allow the most important distinction between a generalized idiopathic seizure form (absence) and a focal symptomatic epilepsy to be made without an EEG.

Differentiation from *frontal lobe epilepsy* can be particularly difficult. Neurologic examination during the seizure (pupil reactions, possibly positive Babinski sign, withdrawal reflexes) and increased serum CPK and prolactin levels can be useful here.

Narcolepsy

Clinical Features. Narcolepsy is a form of *hypersomnia* (increased daytime drowsiness) with characteristic pathophysiologic and biochemical abnormalities. Recently, the neurotransmitter *hypocretin* (*orexin*) has been gaining in importance in diagnosis and therapy. It is often regarded as an autoimmune disease because of its known association with the human leukocyte antigen HLA DQB1 0602.

The full picture of *narcoleptic–cataplectic syndrome*, which, however, occurs in only about 10% of cases, consists of the following tetrad of clinical signs and symptoms.

- *Sleep attacks (principal and primary symptom):* uncontrollable attacks of falling asleep for one to many minutes, which can occur several times daily and from which those affected awaken refreshed.
- *Cataplectic attacks (affective loss of muscle tone) for seconds to minutes (in 70–90%, pathognomonic):* can involve all muscles (patients collapse while remaining fully conscious) or only individual muscles (e. g., chin or leg).
- *Sleep paralysis (dissociated waking):* The affected person is awake mentally but can neither speak nor move for a short period.
- *Hypnagogic hallucinations:* vivid, dreamlike, visual or acoustic impressions when falling asleep or during sleep paralysis.

Diagnosis. Narcoleptic–cataplectic syndrome can be diagnosed relatively easily from the history, though only individual elements may occur (monosymptomatic form) or dominate the picture. This leads to numerous semiological varieties, and distinguishing other syncopal disorders or *paroxysmal losses of consciousness* can be problematic. The symptoms are often triggered by positive or negative *emotional factors*. Narcolepsy occurs more often in men than in women and there is an increased familial incidence in about 30%. The onset is usually before the age of 30. Early *REM stages* (rapid eye movement) can often be identified on the EEG without preceding deep sleep.

Cause. Most cases of narcolepsy are *idiopathic*. They can rarely be attributed to preceding severe brain trauma, encephalitis, or tumors in the posterior hypothalamus.

There is *no connection* with epilepsy, Pickwick syndrome hypersomnia, compensatory hypersomnia in episodic sleep apnea as a result of respiratory obstruction, or Kleine–Levin syndrome with periodic hypersomnia and megaphagia in young men.

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Eclampsia

Preeclampsia and eclampsia are still the most frequent cause of maternal death during pregnancy in Western countries.

Preeclampsia is characterized by increased blood pressure and proteinuria. In the much rarer *eclampsia* cerebral manifestations such as headache, tinnitus, visual disorders and amaurosis, and tonic–clonic convulsions and unconsciousness also occur.

In the differential diagnosis, epilepsy, the seizures of which do not differ from those of eclampsia, must always be considered.

Women with pre-existing renal disease (primary glomerulopathy or renal disease in conjunction with diabetes mellitus or systemic vasculitis) are particularly at risk of preeclampsia. As there is no specific test for early recognition, monitoring the blood pressure and urine is of great importance.

Abnormal Mental Status Due to a Behavioral Disorder

Impaired or disordered consciousness as part of a *temporary hysterical state* is not rare. It is usually easy to differentiate (e. g., when resistance is felt on attempting to open the eyelids, or provided the lids can be raised, the eyes stare rigidly straight ahead or move like a pendulum with *intact pupil reactions* and *preserved corneal reflexes*).

Psychogenic seizures with genuine loss of consciousness in emotionally triggered vagal syncope are more difficult to differentiate. *Hyperventilation tetany* is usually easy to distinguish clinically.

In contrast, so-called major hysterical attacks occasionally cause problems in differential diagnosis, particularly when both electroencephalic and hysterical attacks occur alternately in the same patient (*hystero-epilepsy*). The actual hysterical attack usually occurs under stereotypical conditions and when it can be observed. Injuries (tongue biting) are rare. Urinary and/or fecal incontinence can occur. *Myoclonus* often makes a less uncoordinated impression and lasts significantly longer, with short interruptions, than epileptic seizures. Actual cyanosis as after a major epileptic seizure is absent. The attacks can sometimes merge with a *psychogenic stupor* lasting hours, which should not be mistaken for the postictal sleep after a (major) epileptic seizure.

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32 Coma and Other Disturbances of Consciousness

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32.1 Consciousness: Definition

Consciousness: Anatomic, Physiologic, and Neurochemical Fundamentals

The notion of *consciousness* evades a simple definition. Consciousness can be understood as an individual experience, which, on the one hand, necessitates the existence of a "self," and on the other hand, originates from the interaction of the self with its inner and outer world. Pragmatically, *quantitative and qualitative aspects* of consciousness can be distinguished. Alertness and attention (synonyms: vigilance, arousal), the quantitative dimensions of consciousness, are the absolute prerequisites, whereas the sum of the objects or contents of consciousness, the presence of mind (synonyms: lucidity, awareness), corresponds to the qualitative dimensions of consciousness. Normal vigilance is an indispensable precondition for clear comprehension and thoughtful acting.

Vigilance. Normal activity in the so-called ascending reticular activation system (ARAS) is necessary for normal alertness (vigilance; Fig. 32.**1**). This system consists of projections from aminergic and cholinergic neurons, which are localized in the rostral (upper) pons, in the tegmental (dorsal) mesencephalon, and in the posterior hypothalamus. The ARAS activates the entire neocortex through a thalamic interconnection (in particular through the intralaminar nuclei) and through the basal forebrain. Among the aminergic population of the ARAS, the noradrenergic, dopaminergic, serotoninergic, and histaminergic neurons are particularly noteworthy. The most important cholinergic neurons of the ARAS are located at the ponto–mesencephalic junction in the lateral dorsal tegmental and pedunculopontine nuclei. These different neurons of the ARAS are responsible for the regulation of various aspects of alertness (mental, motor, electroencephalographic, etc) and for the emergence of the three states of being (alertness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep; Fig. 32.**2**; Tab. 32.**1**). These processes can be impaired in various degrees by pathologic processes. The activity of the ARAS is modulated by sensory stimuli (pain, light, noise, and body position, among others), by corticofugal efferences, as well as by the only recently discovered hypocretin (orexin) neurons, which are located in the lateral hypothalamus. The decrease in activity of the ARAS when falling asleep is furthered by an inhibitory GABAergic (GABA: γ-aminobutyric acid) influence from the ventral preoptic nucleus in the anterior hypothalamus, among others.

Lucidity. Currently it is believed that normal lucidity depends on sufficient tonic activity of the ARAS and cortical regions as well as "phasic" (i. e., short lasting), synchronized activation (i. e., binding) of thalamo–cortico–thalamic and cortico-cortical networks in a frequency range of 30–70 Hz (gamma rhythm).
Synchronized activation of thalamo-prefrontal, as well as thalamo–temporo–parietal, networks seems to be the basic requirement for focussed and sustained attention.

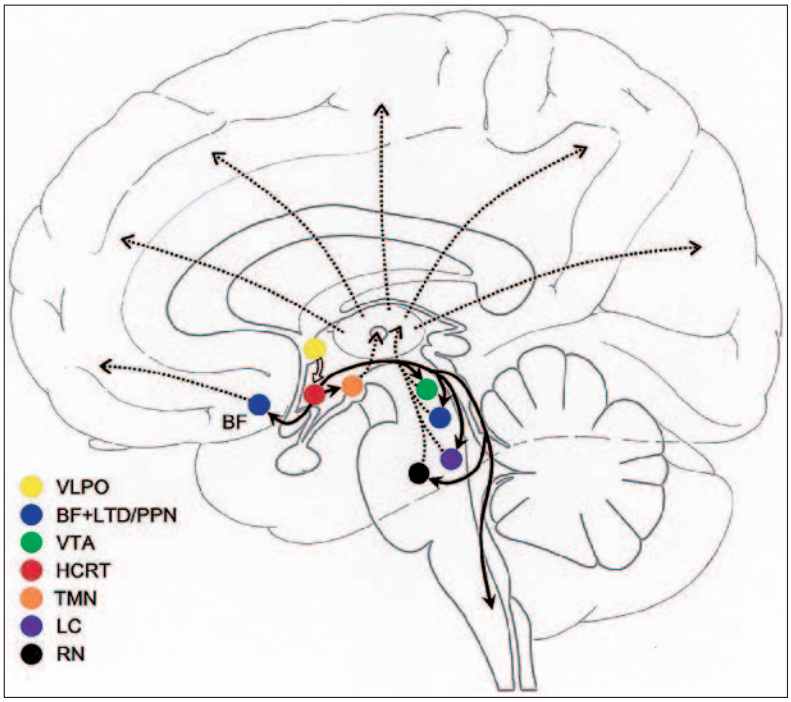

Fig. 32.**1** Neuroanatomy, neurophysiology, and neurochemistry of vigilance.The ascending reticular activation system (ARAS) consists of projections (dotted lines) from neurons that are located in the brain stem. The ARAS activates the entire neocortex through the thalamus and the basal forebrain (cholinergic, BF). The aminergic population of the ARAS are noradrenergic (dorsal raphe nucleus, RN), dopaminergic (ventral tegmental area, VTA), serotonergic (locus coeruleus, LC), and histaminegic (tuberomamillary nucleus, TMN). The cholinergic neurons of the ARAS are located at the ponto–mesencephalic junction (lateral dorsal tegmental and pedunculopontine nuclei, LTD/PPN). The activity of the ARAS and most of the aminergic/cholinergic neurons in the brain stem is modulated by hypocretin neurons in the lateral hypothalamus (HCRT) among others. The decrease in activity of the ARAS, when falling asleep, is furthered by inhibitory influences from the "sleep-onset center" (ventral preoptic nucleus, VLPO), among others.

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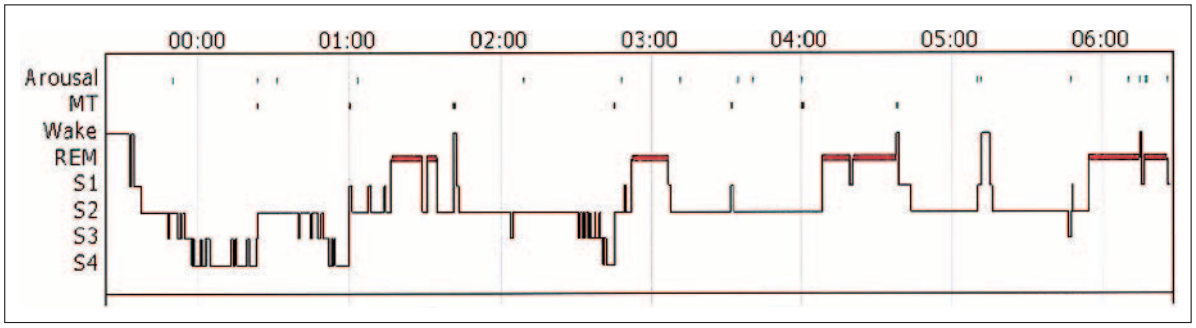

Fig. 32.**2** Normal sleep pattern. Normal sleep starts after 10–30 minutes with the superficial NREM sleep stages (S1–S2, NREM: nonrapid eye movements). The deep NREM sleep (S3–S4) is reached after 40–50 minutes. The first REM sleep cycle occurs after 60–90 minutes. During the night, these sleep cycles are repeated 3–5 times. Deep NREM sleep dominates the first half of the night (aproximately 10–20 % of the entire sleep time), whereas REM sleep (20–25 % of the entire sleep time) dominates the second half.

Table 32.**1** Alertness, NREM and REM sleep
Three physiological variables (electroencephalogram, muscle tone, eye movements) can be used to characterize the main states of being (alertness, NREM sleep, REM sleep), which emerge from the interrelation of different neuronal populations of the ventral lateral preoptic nucleus (VLPO, transmitter: γ-aminobutyric acid = GABA), lateral dorsal tegmental and pedunculopontine nuclei, LTD/PPN, acetylcholine), dorsal raphe nucleus (RN, norepinephrine), ventral tegmental area (VTA, dopamine), locus coeruleus (LC, serotonin), tuberomamillary nucleus (TMS, histamine), and lateral hypothalamus (HCRT, hypocretin). See also Fig. 32.**1**.

	Alertness	NREM sleep	REM sleep
Mental activity	Thinking	–*	dreaming
Electroencephalogram (EEG)	Fast	Slow	Fast
Muscle tone (EMG)	Normal	Reduced	Minimal
Eye movements	Variable	Slow	Rapid
VLPO	Inactive	Active	??
LDT/PPT	Active	Inactive	Very active
LC/TMN/VTA	Very active	Barely active	Inactive
HCRT	Very active	?	Active?

* Fractions of dreams are possible after arousal from NREM sleep 3.

Disturbances of Consciousness: Pathophysiology

Quantitative Disturbances of Consciousness. These may be explained by a bilateral dysfunction of the ARAS or the various centers that modulate it (see above).

Three main mechanisms can be distinguished in the clinical routine:

- *diffuse, bilateral, or multifocal cortical diseases* (e. g., in the context of metabolic–toxic encephalopathies)
- *focal, supratentorial diseases with space-occupying effects, transtentorial herniation, and brain stem compression* (e. g., in the context of a cerebral infarct)
- *focal, infratentorial diseases* (e. g., in the context of a cerebral infarct).

Severe and, in particular, persistent quantitative disturbances of consciousness (sopor and coma) are most often caused by bilateral processes in the brain stem (rostral pons, mesencephalon, thalamus), which result in a significant dysfunction of the ARAS. Due to the redundancy of activating systems (thalamic and extrathalamic pathways of cortical activation, see above), a coma typically persists only for days to a few weeks. After awakening from a coma, patients may exhibit hypersomnia with a greater tendency to fall asleep during daytime and an increased sleep requirement (see below, Fig. 32.**3**).

Qualitative Disturbances of Consciousness. These may be caused by unilateral or partial lesions of the ARAS as well as focal lesions of the cortex. In this context, partial deficits of the consciousness with disturbances (e. g., in the perception of the self or the outer world [with illusions and hallucinations]) may develop.

In the *acute confusional state*, one assumes a disturbance of oriented attention, or rather of the aforementioned fronto–thalamic or thalamo–temporo–parietal neural networks (Fig. 32.**4**). However, the emergence of

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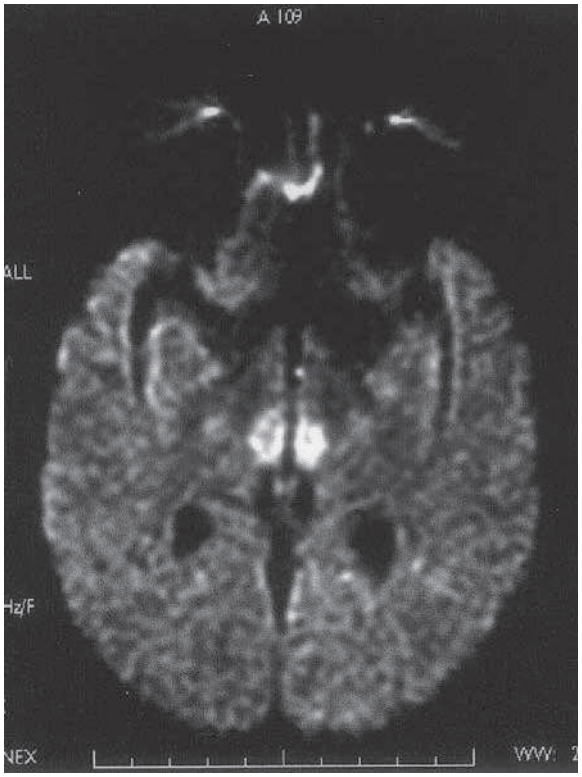

Fig. 32.**3** Initial coma followed by severe hypersomnia for a month in a 58-year-old man with bilateral paramedian thalamus infarcts (diffusion-weighted MRI).

Fig. 32.**4** Acute confusional state in a 71-year-old woman with a frontal cerebral infarct (diffusion-weighted MRI).

confusional states from focal lesions of other brain areas (e. g., the parietal or occipital lobe, see below) indicates that focussed and sustained attention depends on the integrity of multiple cortical regions.

Disturbances of Consciousness: Clinical Features

Somnolence, Sopor, and Coma (Quantitative Disturbances of Consciousness)

Somnolence. Somnolence (drowsiness) is the mildest form of a quantitative disturbance of consciousness. Simple external stimulations make the patient who appears slow and often falls asleep, react adequately.

Sopor. In sopor (stupor) the patient can only be awakened temporarily and incompletely by very strong and repeated stimulations (pain, among others).

Coma. Coma corresponds to a complete state of unconsciousness with closed eyes and without any comprehensible reaction to external stimulations, intelligible verbal expression, or goal-directed motor resistance (pain reaction).

Increased Vigilance. Incidentally, a quantitative disturbance of consciousness may present with heightened alertness including sleeplessness (insomnia) and often (psycho-) motor agitation (e. g., alcohol withdrawal syndrome).

Somnolence, Sleepiness, and Hypersomnia. Somnolence (drowsiness) denotes the first stage of a continuum ending with coma, while sleepiness denotes the first stage of a continuum ending with normal sleep. Somnolence and pathologic sleepiness (hypersomnia, see below) are often not distinguishable on clinical grounds.

Differential Diagnosis. The following conditions could be misinterpreted as a *coma*:

- *Akinetic mutism* is characterized by extraordinary apathy and abulia. The patients, however, can be forced to talk and make goal-directed movements upon intense and repeated stimulations. Frequently, the neurologic examination reveals pathologic signs (hyperreflexia or lateralized reflexes, positive Babinski reflex). Most often, this condition is observed in fronto–basal, more rarely in thalamo–mesencephalic, lesions (infarct, trauma sequels, neoplasia).
- In *catatonic stupor* the patient remains mute and motionless with open eyes for a long time without responding to external stimulations. All vital functions and the neurologic findings are normal. Frequently, the patients exhibit catalepsy (the limbs remain in a passively induced position, "flexibilitas cerea" or waxy flexibility). The most frequent cause is a psychogenic disturbance. Certain intoxications (e. g.,

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benzodiazepines, disulfiram) may cause a similar picture.

- Patients in the *locked-in syndrome* are completely paralyzed, and therefore, unable to speak or move their limbs. However, they have a normal consciousness, which can be documented by nonverbal communication with the eyelids and vertical eye movements. The most frequent cause of a locked-in syndrome is a bilateral pontine cerebral infarct.
- The *persistent vegetative state* (PVS, synonyms: vigil coma, apallic syndrome, α-coma) denotes the most extreme form of a qualitative disturbance of consciousness. The patient shows a normal sleep–wake pattern, or rather preserved vigilance, but no signs of cognitive awareness or any goal-directed verbal or motor reactivity ("awake but unaware").

Acute Confusional State and Other Qualitative Disturbances of Consciousness

Acute Confusional State. The most frequent qualitative disturbance of consciousness is the acute confusional state (delirium). This state is characterized by a disturbance of awareness and an attention deficit and is often associated with disorientation, amnestic disturbances, and incoherent thought and action. Despite its various etiologies, the signs of the acute confusional state do not vary, typically evolve within a short time-span, and usually fluctuate during the course of the day.

Twilight States and Delirium. Hypovigilant, inhibited confusional states, where the patient is in a "dreamlike" state, are also referred to as twilight states. Agitated, often hypervigilant confusional states with perceptive disorders are called delirium.

Differential Diagnosis. States that can be misinterpreted as being confusional include:

- The so-called *amnestic episode (transient global amnesia)* is characterized by an acute loss of the anterograde memory and a retrograde amnesia for weeks to months. Memory, as well as recall is blocked. However, the patients show no attention deficit (immediate memory).
- In *dementias* the onset is insidious, the course not fluctuating, and vigilance and attention are often normal in contrast to the acute confusional state.
- Patients with a sensory aphasia (*Wernicke aphasia*) initially are often misinterpreted as being "confused" due to their disturbed speech comprehension and speech production with paraphasias.

Disturbances of Consciousness: Clinical Examination, Signs, and Symptoms

Clinical Examination. The examination of a patient with somnolence, sopor, or coma begins with a check of the *vital functions* (see Tab. 32.**2**) (respiration, temperature, blood pressure, pulse) and the documentation of any current *drugs* (sedatives, muscle relaxants). Internal medical findings may indicate the origin of the disturbance of consciousness.

Next, the *level of vigilance* is evaluated. The remaining neurologic examination includes the examination of eye movements (spontaneous, during head rotation [oculo–cephalic reflex] and after ice water irrigation [so-called vestibulo–ocular reflex]), pupillary reflexes, corneal reflexes, limb movements (spontaneous and on painful stimulation), muscle tone, muscle reflexes, Babinski reflex, and meningeal signs (the latter can be a false negative with a deep coma).

> The meticulous neurologic examination is of utmost importance for the topical diagnosis and any subsequent procedure.

Table 32.**2** Examination protocol in disturbances of consciousness

Date, time of day
Medication (sedatives, muscle relaxants, etc.)
Vital signs and internal medical findings: – temperature – blood pressure, pulse – respiration – general internal status
Inspection: – body position – movements of the eyelids, eyes, limbs
Level of consciousness: Glasgow Coma Scale
Attention: – forward digit span (repeat 5–6 single numbers) – "100 minus 7" test – spell the word "flower" in reverse
Mental status examination*: – orientation (in time, in space, autopsychic) – memory (recall of 4–10 words after 10 minutes) – speech (fluency, comprehension, paraphasias, repetitions, writing, reading) – neglect – redrawing of a cube – archaic reflexes
Brain stem functions: – spontaneous eye movements – corneal reflexes – pupillary reflexes – oculo–cephalic and vestibulo–ocular reflexes – protective reflexes
Signs of lateralization: – muscle tone, muscle reflexes, long tract signs
Meningeal signs

* Only if sufficiently alert and attentive

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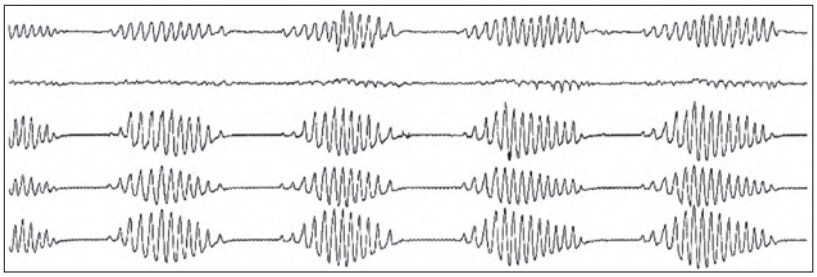

Fig. 32.**5** Cheyne–Stokes respiration. Cheyne–Stokes respiration in a 49-year-old man after a left frontal cerebral infarct. Note periodic changes between increasing and decreasing tidal volumes (upper two channels) and breathing effort (lower three channels) interspersed with periods of central apnea.

Additional Diagnostic Procedures. First, vital functions must be evaluated and ensured in the emergency unit. The additional diagnostic procedures encompass an *extensive laboratory work-up* (hemogram, blood glucose, electrolytes, and kidney and liver parameters), urinalysis, ECG, and chest radiograph. Moreover, blood gas analysis, thyroid parameters, serologies, and thiamine level should be requested if there is an urgent suspicion. A *cranial computed tomography (CT) scan* is required quickly in sopor and coma with focal neurologic signs. With fever and meningeal signs (the latter may be missing in comatose patients!) the CSF analysis is most important and, in the absence of focal neurologic signs, may be performed before the brain scan.

In sopor and coma without focal neurologic deficits and a normal CCT, a *very long EEG recording* can be helpful (even 30 minutes of recording may yield a false negative in a fluctuating epileptic state). The EEG can indicate a clinically unobvious epileptic state or encephalitis (among others, a herpes simplex encephalitis, see below). Moreover, it allows one to estimate the severity in toxic- or medicamentous encephalopathies, and thus can be a helpful parameter in the follow-up examination.

Respiration

Normal breathing indicates a supratentorial or psychogenic origin of a coma. *Hypoventilation* is suggestive of intoxication with opiates, among others. *Cheyne–Stokes periodic breathing* is most often observed in somnolence and sopor in supratentorial, as well as infratentorial processes (Fig. 32.**5**). *Hyperventilation* only rarely is purely neurogenic (so-called neurogenic hyperventilation). *Apneustic breathing* (apneusis) and the *ataxic* (Biot) *respiration* can be found in pontine and medullary lesions and prognostically are bad signs.

Table 32.**3** Glasgow Coma Scale

Score	Eye opening	Verbal response	Best motor reaction
6			Obeys commands
5		Oriented	Localizes pain
4	Spontaneous	Confused	Withdraws from pain
3	Only on command	Inappropriate words	Flexion on pain
2	Only with pain	Incomprehensible	Extension on pain
1	None	None	None

Vigilance, Attention, and Mental State

Glascow Coma Scale. The level of vigilance is gradually measured by arousal, as well as behavioral reactions to acoustic and nociceptive stimulations of various kinds and intensities. The examination always starts by inspecting and addressing the patient. The "Glasgow Coma Scale" is the most often used instrument, which can be helpful in the judgment of the prognosis of traumatic and nontraumatic disturbances of consciousness (Tab. 32.**3**).

Attention. If vigilance is normal, then attention can be examined. An attention deficit is the hallmark of the acute confusional state, the most common qualitative disturbance of consciousness. Here, the patient is not able, for instance, to recall series of numbers (so-called "forward digit span"), to correctly complete the "100 minus 7" test (i. e., five times without error), or to spell a short word in reverse (e. g., "flower"). Disturbances in vigilance (somnolence or insomnia), thinking (formal and in content), perception (illusions, hallucinations), orientation, memory, psychomotility (inhibited or uninhibited), and the sleep–wake cycle are often observed.

Cognitive Functions. Cognitive functions (mental status) can only be examined after normal vigilance and attention have been established. For this reason the diagnosis of a dementia cannot be made in a patient with a disturbed consciousness or in a confused state.

Eyes

- *Bilaterally normal reactive pupils* are more likely in a coma of metabolic–toxic origin.
- A *unilaterally large and nonreactive pupil* in a comatose patient is indicative of a transtentorial herniation due to a supratentorial space-occupying lesion (so-called uncal syndrome, see below; Fig. 32.**7**). *Bi-*

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laterally nonreactive pupils with bilateral ptosis can occur in mesencephalic lesions (Fig. 32.**6**), oculomotor lesions (frequently by compression), and intoxications (anticholinergics, barbiturates, sympathicomimetics).

- *Pinpoint pupils* occur in intoxications with opiates and in pontine lesions. An *anisocoria* of more than 1 mm and/or a *unilaterally delayed light reaction* may indicate a lesion of the midbrain or oculomotor nerve, frequently in connection with a supratentorial space-occupying lesion (Fig. 32.**7**).
- *Bilaterally absent corneal reflexes* can be caused by pontine lesions, intoxications, or are due to insufficient stimulation of the cornea during clinical examination.
- *Spontaneous, conjugate, horizontally and vertically drifting eye movements* (roving eye movements) likely eliminate an infratentorial or psychogenic origin of a coma.
- *Spontaneous, strictly vertical eye movements* (ocular bobbing, dipping, reverse bobbing, or see-saw nystagmus) are most often seen in infratentorial lesions, rarely in diffuse metabolic–toxic encephalopathies.
- *Normal oculo–cephalic reflexes* (OCR) or *vestibulo–ocular reflexes* (VOR, doll eye sign) are indicative of an undamaged brain stem. OCR should not be tested if cervical spine fracture is suspected, and VOR should not be tested if a perforation of the eardrum is suspected. OCR and VOR can be suppressed not only by brain stem lesions but also by drugs and intoxications.
- *In a comatose patient, the occurrence of nystagmus* after ice water irrigation (caloric test, 50–100 mL ice water, head raised to 30°) indicates a psychogenic origin of the altered consciousness.
- On the other hand, *reflex closure of the eye* after passive opening and *gazing in the direction of a passive head rotation* can be observed in a nonpsychogenic (light) coma.
- A *horizontally divergent bulbar position* can be observed in a light coma as well as during sleep.
- A conjugate horizontal deviation of the eyes (*déviation conjugée*) can be observed in supratentorial (towards the side of the lesion) and infratentorial (towards the other side of the lesion) lesions. Rarely, the eyes can drift in the "wrong" direction (wrong-way eyes), for example, during an epileptic seizure or in thalamic lesions.
- *Conjugate vertical eye deviations* (upward or downward) are seen in structural (mostly infratentorial), as well as in metabolic–toxic comas.

Fig. 32.**6** Bilateral ptosis with nonreactive pupils after bilateral midbrain infarct.

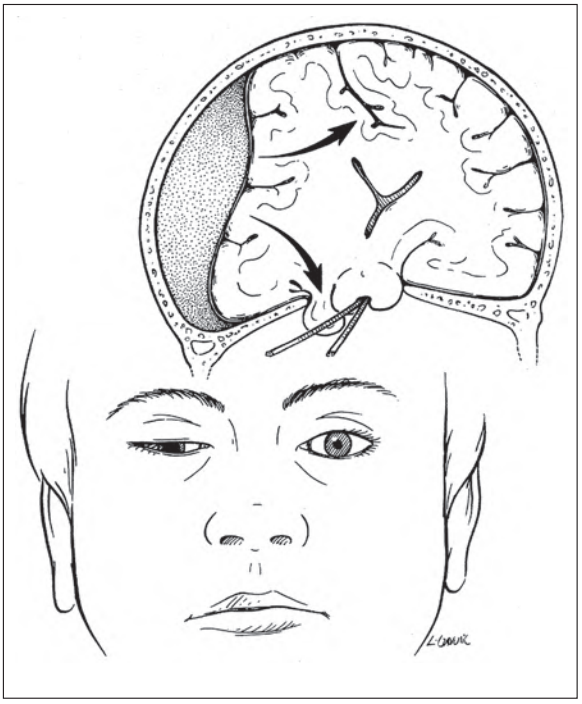

Fig. 32.**7** Oculomotor palsy after transtentorial herniation in a supratentorial space-occupying lesion (hemorrhage). A unilateral, large, nonreactive pupil with ptosis (III-palsy) in a patient with a disturbance of consciousness is indicative of a so-called uncal syndrome (e. g., in the context of a traumatic hemorrhage).

Motor Functions

Yawning, sighing, blinking, sneezing, and stretching are compatible with a light coma, whereas hiccupping and spontaneous swallowing can be observed even in a deep coma. A normal or sleeplike body posture is compatible with a supratentorial (in particular thalamic–hypothalamic) or psychogenic origin of a coma. *Limb movements in flexion or extension*, which occur spontaneously or after painful stimuli, can be seen in a structural, as well as in a metabolic coma. Therefore, terms like "decortication seizures" or "decerebration seizures" are not recommended.

The association of a hemiparesis, possibly with flexion in the arm and extension in the leg, with a contralateral, upon light exposure nonreactive, large pupil with ptosis (III-paresis) and an increasing quantitative disturbance of consciousness, corresponds to a so-called *uncal syndrome* and indicates herniation of a supratentorial space-occupying lesion, which is ipsilateral to the pupillary dysfunction. Respiratory disturbances (Cheyne–Stokes respiration or hyperventilation) are often observed as well. Rarely, the hemiparesis is ipsilateral and the pupillary dysfunction is contralateral to the herniation ("false localizing signs").

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A *Babinski reflex* can be observed in a coma (as well as during sleep) and must not be considered at all to be proof of a structural lesion. Flexions of the extremities and the trunk, more rarely of the head, in particular on painful stimulation, may be demonstrated in a brain dead individual and reflect *spinal reflexes*.

Differential Diagnosis of Coma and Other Disturbances of Consciousness

In principle, causes of a disturbance of consciousness are either primarily extracerebral or primarily intracerebral diseases (Tab. 32.**4**). Similar diseases can cause quantitative and/or qualitative disturbances of consciousness (hence they shall not be discussed separately in this context).

Table 32.**4** Causes of coma, acute confusional state, and other disturbances of consciousness

Primarily noncerebral causes (neuroimaging [CCT/MRI] negative)
- hypoxia (cardiac arrest, etc.)
- uremia, hepatic insufficiency
- hypoglycemia, hyperglycemia
- hyperosmolality, hypoosmolality, myelinolysis
- hyperthyroidism, hypothyroidism, Hashimoto encephalopathy
- hyperthermia, hypothermia
- deficiencies (vitamin B_{12}, vitamin B_1: Wernicke encephalopathy)
- drugs, toxins (intoxication, withdrawal)
- porphyria
- multifactorial (especially in the elderly)

Primarily cerebral causes
- diffuse (multifocal) diseases/lesions of the CNS
  - neuroimaging positive:
  - subarachnoid hemorrhage
  - multiple (including septic) embolisms
  - hypertensive encephalopathy
  - sinus vein thrombosis
- neuroimaging (often) negative:
  - infectious and inflammatory diseases of the CNS
  - epilepsy
  - migraine

Focal diseases
- neuroimaging positive:
- ischemic cerebral infarct, intracerebral hemorrhage
- brain trauma (subdural/epidural hematoma, contusion)
- neoplasia
- brain abscess

Psychogenic disorders

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32.2 Coma with Primarily Cerebral Causes

A distinction is made between diffuse and focal diseases of the central nervous system (CNS).

Diffuse (or Multifocal) Diseases/Lesions of the Central Nervous System

These conditions are characterized by the following findings:

- A subacute course is most frequent.
- Focal neurologic signs are often not present.
- Frequently, normal brain stem reflexes are observed.
- Neuroimaging (CCT/brain MRI) can be either positive or negative.

Diseases with Positive Neuroimaging

Subarachnoid Hemorrhage. In the primary subarachnoid hemorrhage due to rupture of a congenital, arterial, or mycotic aneurysm, patients usually complain of a sudden ("lancinating"), very severe headache, which often radiates into the back of the head or the neck. Meningism, which may be the only objective sign, develops quickly. Initially, about half of the patients lose consciousness. Qualitative (e. g., confusion) and quantitative disturbances of consciousness are often observed, whereas coma and focal neurologic deficits are rare (15–20% of cases, Hunt and Hess scale IV, V). Meningism decreases as the coma becomes deeper.

Multiple Brain Embolisms. Hemogenic encephalitis or brain abscess in bronchiectasia, abscesses of the lung, endocarditis, or actinomycoses are frequently multifocal and may mimic a diffuse disease of the central nervous system.

Hypertensive Encephalopathy. An acute confusional state and quantitative disturbances of consciousness may express a hypertensive encephalopathy. Headaches, visual disturbances, and high blood pressure are almost always present.

Sinus Vein Thrombosis (SVT). SVTs are responsible only for approximately 1% of all strokes. Among others, its cause may be a coagulopathy (hereditary or acquired), infections of facial regions by contiguity, or Behçet disease. Often, however, the origin remains unknown. Headaches (90% of cases) and epileptic seizures (50%) are the most frequent symptoms. Disturbances of consciousness, either acute confusional states or quantitative forms, are observed in 25–50% of all cases. These disturbances are almost mandatory in thromboses of the deep cerebral veins. Focal neurologic deficits (sensory and motor hemisyndromes) may fluctuate or even change sides in SVTs and are absent in up to 70% of all patients.

Diseases with (Mostly) Negative Neuroimaging

Infections and Inflammatory Diseases of the CNS. Fever, headaches, disturbances of consciousness, and focal neurologic irritation and loss symptoms are the landmarks of *encephalitis*.

Herpes simplex encephalitis is the most frequent sporadic encephalitis. Acute confusion with hallucinations (olfactory, gustatory), personality changes, and bizarre behavior are characteristic. In comatose patients, the prognosis is unfavorable even with treatment. Lymphocytic pleocytosis and raised CSF protein levels, (asymmetric, enhancing) MRI alterations in the frontal and temporal lobes, and a temporal focus with periodic epileptic potentials in the EEG (even with a normal MRI) are all typical associated findings. The season, geographic region, age, and immune status of the patient, concomitant internal medical effects, and specific neurologic findings may be indicative of nonherpetic viral encephalitis.

In so-called *lethargic encephalitis*, within the scope of an influenza infection, there is a hypothalamic and subcortical involvement, which clinically manifests itself by quantitative disturbances of consciousness, insomnia or hypersomnia, extrapyramidal signs, and oculomotor disturbances. Formerly, the disease broke out epidemically (e. g., after World War I), currently it occurs only sporadically. Hypersomnia may also occur in infections with trypanosomes ("sleeping sickness").

The course of the measles-associated, *subacute sclerosing panencephalitis* (SSPE) is subacute to chronic. As with the herpes simplex encephalitis, CSF PCR examinations, as well as blood and CSF serology, are critical for the exact diagnosis.

Other nonviral infectious CNS diseases, such as bacterial *meningitis* (in particular meningococcus, pneumococcus) and *meningoencephalitis* (e. g., *Borrelia*, *Listeria*, *Brucella*), tuberculosis, neurosyphilis, parameningeal infections, Whipple disease, fungal infections, and opportunistic infections (toxoplasmosis in AIDS) may mimic encephalitis. Clinical and laboratory findings, as well as the brain MRI, determine the correct diagnosis. In bacterial meningitis, the disturbance of consciousness may evolve unusually fast, so that the differential diagnosis of subarachnoid hemorrhage may be excluded only by the CSF analysis. In tuberculosis, borreliosis, brucellosis, syphilis, and HIV infections, the course of the encephalitis may be subacute to chronic.

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Postinfectious Diseases of the CNS. In postinfectious diseases of the CNS (acute demyelinating encephalomyelitis [ADEM], Weston Hurst acute necrotizing hemorrhagic encephalitis), somnolence (and other disturbances of consciousness), fever, headaches, fulminant course, and CSF pleocytosis occur similar to infectious diseases of the CNS. An MRI examination is diagnostically critical for the detection of either demyelinating or hemorrhagic lesions.

Paraneoplastic Diseases of the CNS. Paraneoplastic diseases of the CNS, such as the so-called limbic encephalitis, may lead to confusion and other qualitative/quantitative disturbances of consciousness as well as CSF pleocytosis. Here, disturbances of memory and other mental functions are characteristic. The course is mostly subacute and the brain MRI may either be normal or reveal signal alterations (in the limbic region). The detection of an underlying neoplasia as well as antineuronal antibodies is diagnostic.

Noninfectious Inflammatory Diseases of the CNS. Noninfectious inflammatory diseases of the CNS, such as neurosarcoidosis, Behçet disease, CNS lupus, and CNS vasculitis (among others, Wegener granulomatosis, panarteritis nodosa, Sjögren syndrome) may lead to disturbances of consciousness with CSF pleocytosis. Systemic signs and symptoms or inflammatory signs are diagnostic.

Metabolic–Toxic Encephalopathies. Metabolic–toxic encephalopathies (see below) may lead to focal neurologic irritation or losses, particularly in older patients. Usually, there is no significant (cell count > 50) pleocytosis or alteration of the brain in the MRI.

Epilepsy. Brief disturbances of consciousness are the cardinal symptom of epileptic seizures. A protracted impairment in connection with epileptic seizures is also possible and may be encountered in three situations (see also Chapter 31):

- **Postictal State.** Following generalized tonic–clonic seizures, patients may appear somnolent, confused, and show psychomotor slowing for hours (rarely for more than one day).
- **Focal Nonconvulsive Epileptic State (Partial Complex State).** This epileptic activity originates mostly from the frontal or temporal lobe. The patients present usually with a hypovigilant (somnolent), dreamlike confusional state (trance, see above). Stereotypical motor activities (automatisms) like fumbling, rubbing the hands, smacking, and chewing movements are typical. Certain patients may also perform complex actions, for which there is later amnesia. The differential diagnosis of automatic actions (among others, in the form of the so-called "fugue epileptique") in connection with hypersomnia (see below), metabolic disorders (among others, hypoglycemia), or a primary psychiatric affection may be difficult under certain circumstances. The EEG documents focal, epileptic activity.
- **Generalized Nonconvulsive Epileptic State (Petit Mal/Absence State).** This state may continue for days to weeks. The etiology may be a petit mal epilepsy known since childhood; frequently, however, it is a "de novo" first manifestation in (older) adults. In these instances, benzodiazepine/alcohol withdrawal, metabolic disturbances, toxic–medicamentous influences, and brain trauma may be triggering factors. Clinically, variable somnolence, confusional state with psychomotor slowing and hallucinations are predominant. Severe fluctuations of the conscious state and generalized and ocular myoclonias may be indicative of an epileptic origin. The EEG reveals generalized epileptiform (mostly spike or spike-wave) activity.
  Protracted disturbances of consciousness in epileptic patients may occur in connection with therapy associated, metabolic disturbances (among others, hyponatremia).

Migraine. Brief (syncopelike), as well as protracted disturbances of consciousness may appear in connection with migraine attacks of the so-called "basilar type." Patients present with a variable combination of bilateral/side changing/crossed sensorimotor signs/deficits, visual field deficits, dizziness, drop attacks, and hearing, as well as speech disturbances. The accompanying qualitative (in particular, confusional state) and quantitative disturbances of consciousness (including comatose state) may persist for hours to days. This kind of migraine is frequently familial (autosomal dominant), the main clinical feature is often a motor hemisyndrome ("hemiplegic migraine"), and mild CSF pleocytosis is possible ("meningitic migraine"). Whether the underlying dysfunction is located in the brain stem or both cerebral hemispheres is still disputed. A gene locus has been identified for approximately half of the patients. In some cases, these are patients with a progressive vascular encephalopathy (CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) with a mutation of the *Notch3* gene (so-called CADASIL coma).

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Focal Diseases/Lesions of the Central Nervous System

These conditions are characterized by the following findings:

- often acute course
- focal neurologic signs often predominant
- brain stem reflexes primarily normal in supratentorial, primarily abnormal in infratentorial processes
- mostly positive neuroimaging (CCT/brain MRI).

Ischemic Stroke

A brief or transient loss of consciousness is observed in the carotid and vertebro-basilar territory, although it is rarely seen in connection with transient ischemic attacks (TIAs).

Qualitative Disturbances of Consciousness. Qualitative disturbances of consciousness and, in particular, acute confusional states are observed in at least 10–20% of all stroke patients. In some patients, hallucinations, aggressive behavior, or a schizophreniclike syndrome may be observed. Advanced age, more severe strokes, temporo–parieto–occipital, thalamo–mesencephalic, and right hemispheric strokes are risk factors for such complications. Associated metabolic disturbances, fever, sleep-associated breathing disturbances, and epileptic seizures may also play a role.

Marked Quantitative Disturbances of Consciousness (Sopor and Coma). These are observed in 20–30% of patients. Large, space-occupying hemispheric strokes or bilateral strokes in the thalamus, mesencephalon, or upper pons are the most frequent causes. In space-occupying, hemispheric strokes, the comatose state develops progressively within 1–2 days after onset of the signs via a so-called undefined syndrome (Fig. 32.**8**). In brain stem strokes, however, quantitative disturbances of consciousness often occur at the onset. Patients with a basilar thrombosis or occlusion typically present with bilateral or crossed sensorimotor deficits, speech and swallowing difficulties, and oculomotor disturbances (spontaneous vertical eye movements, pathologic oculo-cephalic or vestibulo-ocular reflexes, divergent eye position, etc.). Acutely, a coma may also occur in rare cases of simultaneous, bilateral hemispheric strokes (often the sign of a cardioembolic event).

Mild Quantitative Disturbances of Consciousness. These often occur with initial sopor or somnolence, followed by hypersomnia and apathy, may also occur in non space-occupying, cortical and subcortical hemispheric strokes. Most marked is hypersomnia after bilateral, paramedian thalamic strokes (see below). In these patients, the triad of hypersomnia, vertical gaze palsy, and amnesia can usually be found.

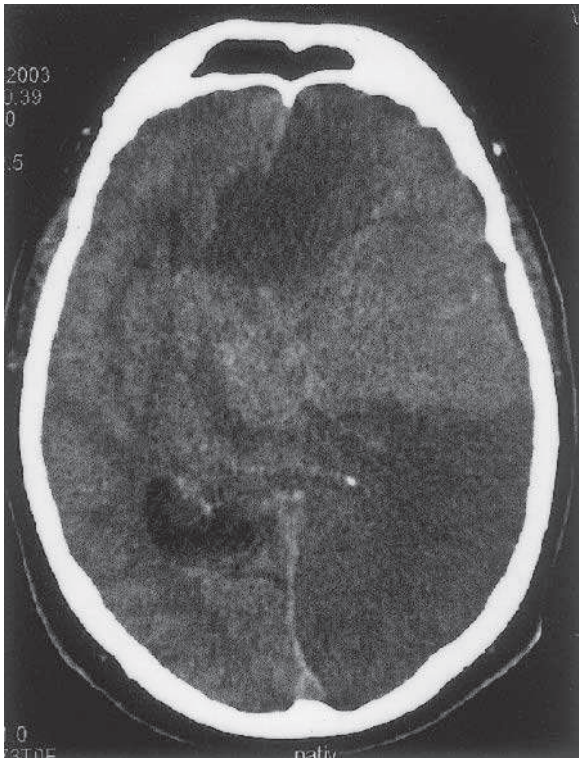

Fig. 32.**8** Malignant medial anterior infarct. Malignant infarct in the territory of the right middle and anterior cerebral arteries after intracranial occlusion of the right carotid bifurcation due to atrial fibrillation. Clinical signs: somnolence, deviation conjugée to the right, and severe sensorimotor hemisyndrome left. 12 hours after onset coma with undefined syndrome (see above) and a clear space-occupying effect (midline shift to the left side, subfalcine herniation) in the CCT (figure). Death despite an initial intravenous thrombolysis and craniotomy.

Intracerebral Hemorrhage

The signs and symptoms occur abruptly and mostly during wakefulness (possibly during exertion). Since ischemic stroke may manifest with a similarly sudden onset, the differentiation between hemorrhage and ischemia is not possible on clinical grounds alone (i. e., without neuroimaging).

The severity of the disturbance of consciousness and of the accompanying clinical signs is determined by the extent and localization of the hemorrhage. Up to 50% of patients present with sopor or coma. In these patients, body temperature and blood pressure are significantly raised at admission.

Hypertensive hemorrhages (approximately 50–60% of all hemorrhages) originate predominantly from the medial cerebral artery and cause lesions in the internal capsule as well as the basal ganglia, which explain the often complete hemiplegia. Less frequent are hemorrhages in the cerebellum, thalamus, or pons.

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In *nonhypertensive hemorrhages* (e. g., vascular malformations, anticoagulation, vasculitis, drug abuse, etc.), other locations are more frequent. A protracted onset with focal neurologic deficits is possible even with smaller intracerebral hemorrhages, due to the development of perifocal edemas. Intraventricular bleeding causes augmentation of the clinical deficits. The coma becomes deeper, the breathing irregular, and the temperature rises. Some patients may show areflexia, whereas others may present with tonic convulsions.

The concurrence of headaches with visual disturbances and eye muscle palsies is characteristic of the so-called *pituitary apoplexy* (stroke or hemorrhage in an adenoma).

Traumatic Brain Injury

Brain lesions after trauma are classified according to their localization (diffuse, focal, multifocal), time course (immediate, delayed), and severity (initial Glasgow Coma Scale, duration of unconsciousness, duration of amnesia).

Cerebral Concussion. Uncomplicated cerebral concussion is characterized by a very brief unconsciousness and a usually short retrograde amnesia (a few minutes, at most a few hours). The unconsciousness may last seconds to at most one hour. Subsequent vomiting is frequent. The initial unconsciousness is thought to be caused by a transient dysfunction of the ARAS. A cerebral concussion leaves no neurologic deficits and shows no neuroimaging alterations (CCT/MRI).

Cerebral Contusion. If either focal neurologic signs or epileptic seizures occur after brain injury, or the CCT/MRI reveals focal lesions after regaining consciousness, it is considered a cerebral contusion. The protracted disturbance of consciousness in this context is thought to be due to acute, diffuse axonal lesions, which are caused by acceleration-deceleration forces and are accompanied by characteristic changes in the MRI. The cerebral contusion may be without concomitant unconsciousness, and absence of neurologic signs or symptoms does not exclude a contusion in a neurologically silent brain region. Since the CCT/MRI changes may regress and often no imaging is available at the onset, this diagnosis may be problematic at times. Hence, we assume this diagnosis if unconsciousness exceeded one hour or amnesia lasted several hours/days. With protracted amnestic intervals for days or continuing changes in consciousness, the diagnosis is certain.

In children, in particular, severe encephalopathy with impaired consciousness may ensue in the context of even a minor trauma after an unremarkable interval.

Epidural and Acute Subdural Hematoma. If the coma deepens within hours after a brain injury or there is a new impairment of consciousness with a latency of hours to days after awakening from a previous unconsciousness, an epidural hematoma must be suspected, which may be due to bleeding from torn branches of the meningeal arteries (fracture), or a *peracute subdural hematoma* due to arterial bleedings from vessels of the brain surface after extensive destruction of parenchyma and concurrent lesion of the arachnoid.

> Continuing observation (blood pressure, breathing, pupils) of unconscious patients is mandatory, since both forms of hematoma are treatable surgically. The diagnosis must be made by CCT before the development of pupillary areflexia and tonic convulsions due to mesencephalic herniation.

Subdural hematomas, which develop after tearing of bridging veins, usually show protracted to chronic signs and symptoms. The *acute subdural hematoma* ensues from the brain contusion with a latency of days, and changes in consciousness may be difficult to differentiate from a postcontusional psychosis.

Chronic Subdural Hematoma. This may occur after mild traumas in older patients and, in particular, in alcoholics or people using anticoagulants. As with the epidural hematoma, there may not be a free interval in the chronic subdural hematoma. In both cases, the increasing clouding of consciousness is frequently the leading sign. Chronic subdural hematomas are regularly accompanied by mostly unilateral, increasing headaches, and characterized by often fluctuating changes in consciousness with mild forms of somnolence and intermittent phases of wakefulness (Fig. 32.**9**). Often during those episodes, the patient seems strangely indifferent to the condition and sullen towards other people. Even without an additional hemisyndrome, a CCT should be performed with such a history.

Most subdural hematomas are located at the brain's convexity. Frontal and occipital hematomas, however, do occur. Moreover, there are rare subdural hematomas above the cerebellum, which manifest themselves with the signs and symptoms of a tumor in the posterior cranial fossa. In its subsequent time course, the subdural hematoma causes hemiparesis and, rarely, aphasia. Papilloedema and epileptic seizures are more frequent in the chronic subdural hematoma than in the acute one. Moreover, subdural hematomas are often bilateral (Fig. 32.**9**).

Neoplasias

Hemorrhages in tumors may occasionally mimic a vascular stroke or true intracerebral hemorrhage by the acute onset of the signs and symptoms. Usually, however, intracranial space-occupying lesions end in a coma after a slowly increasing impairment of consciousness with signs and symptoms of raised intracere-

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bral pressure (papilloedema, vomiting, headache, later in the course psychomotor slowing and affective leveling) as well as progressive neurologic deficits or focal or generalized epileptic seizures. The transition into the comatose state may occur rather acutely in sudden herniation of the mesencephalon. "*Cerebellar fits*" denote brief episodes with headache, loss of consciousness and extension posture of the head and extremities, which are observed in herniation of cerebellar tumors through the foramen magnum.

Cerebral Abscess

Focal encephalitis and brain abscesses may have similar signs and symptoms to brain tumors and are clinically hard to differentiate, since the diagnostic triad of headache, fever, and focal neurologic deficits are observed in less than 50% of these patients. Cerebral abscesses are more frequent in patients suffering from HIV, bronchiectasia, cardiac abnormalities, and Osler disease.

Disturbances of consciousness and the aforementioned triad are more frequent in subdural or epidural abscesses (subdural empyema, epidural empyema), which often originate from otogenic infections or per continuitatem.

Some focal diseases can mimic the clinical picture of a diffuse encephalopathy.

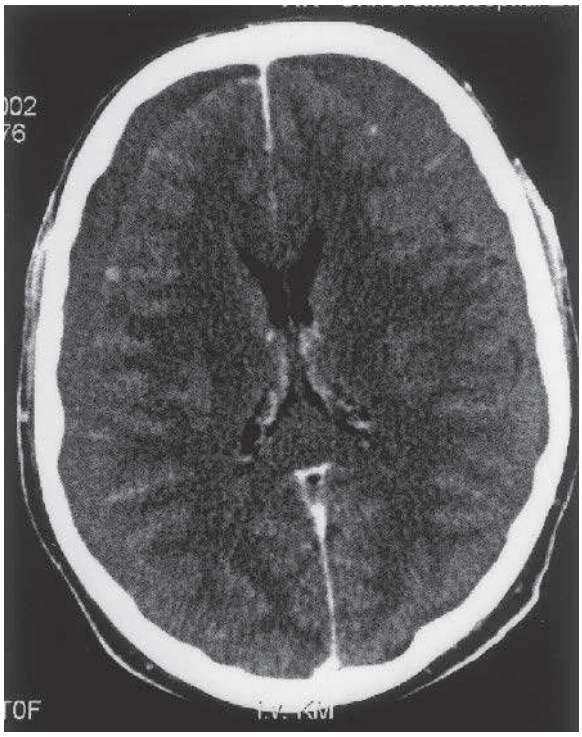

Fig. 32.**9** Somnolence, confusional state, and headaches in a patient with chronic bilateral subdural hematoma. Bilateral, in the CCT almost isodense, subdural hematoma at the brain's convexity (arrows) in a 72-year-old man with bilateral headaches, fluctuating somnolence, psychomotor slowing, confusional state, and gait disturbance of the frontal type. Two severe falls whilst skiing two weeks previously and anticoagulation because of a TIA 10 years previously are in his medical history.

32.3 Psychogenic Coma

Psychogenic states of emergency may present as brief syncopelike episodes, as automatism behaviors (possibly as "fugue"), as catatonic stupor (see above), and as continuing sopor or coma. In the psychogenic coma, a typical nystagmus is observed after caloric stimulation. Patients may also show involuntary eyelid closure after passive opening of the eyes, as well as gazing in the direction of a passive head movement. A normal EEG and normal motor-evoked potentials may be helpful in recognizing a psychogenic coma with missing motor responses.

32.4 Coma Due to Metabolic Disorders

Hypoglycemic Coma

Glucose in the bloodstream is basically the only available energy source for cerebral metabolic activity. The blood glucose concentration remains within a narrow range (3.3–5.6 mmol/L, or 60–100 mg/dL) in healthy individuals with an uninterrupted food supply. If the blood glucose concentration falls below a specific threshold value and hypoglycemic symptoms arise, counter-regulatory hormones are released to return it to the normal range.

Clinical Features. Hypoglycemia causes clinical symptoms of two types:

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Table 32.**6** Differential diagnosis of hypoglycemia

Cause	Mechanism of hypoglycemia
Pancreatic Insulinoma: benign, malignant Nesidioblastosis (persistent hyperinsulinemic hypoglycemia of infancy, PHHI)	Insulin secretion by tumor Mutation of the sulfonylurea receptor (SUR) (defective K^+ channel of the pancreatic β cells) → cell membrane depolarization → Ca^{2+} influx
Extrapancreatic tumors Mesenchymal tumors, hemangiopericytoma, hepatocellular carcinoma	Secretion of IGF-II by the tumor
Autoimmune Autoimmune insulin syndrome (AIS): insulin auto-antibodies	Insulin bound by antibodies and suddenly released
Toxic and drug-induced Insulin, sulfonylureas, glinides, insulin secretagogues Pentamidine Salicylates Quinine, quinidine, chloroquine Alcohol in large amounts Ackee fruit	Stimulation of insulin secretion Insulin release by cytolysis Inhibition of hepatic gluconeogenesis Inhibition of hepatic insulin degradation Inhibition of gluconeogenesis Hypoglycine A inhibits hepatic gluconeogenesis
Reactive Postgastrectomy status, after alcohol, postprandial (functional)	Rapid gastric emptying followed by hyperinsulinism and hypoglycemia
Hepatic and renal disease Hepatocellular diseases, end-stage renal failure	Inhibition of gluconeogenesis, impaired insulin degradation
Endocrinopathies Pituitary insufficiency (partial/total) Adrenocortical insufficiency	ACTH deficiency, GH deficiency cortisol deficiency
Congenital metabolic diseases Glycogenoses Hereditary fructose intolerance	Defect of glycogenolytic enzymes Fructose-1,6-diphosphatase deficiency (severe hypoglycemia!) → defective gluconeogenesis
Miscellaneous causes Sepsis, anorexia, prolonged fasting, excessive physical activity	

- *adrenergic manifestations* (activation of the sympathetic nervous system), including sweating, tremulousness, craving, palpitations, anxiety, pallor, and nausea
- *neuroglycopenic manifestations* (due to an inadequate energy supply to the brain, with consequent impairment of cortical and subcortical function), including headache, blurred vision, diplopia, weakness, dizziness, confusion, abnormal behavior, aggressiveness, transient hemiparesis, aphasia, paresthesia, epileptic seizures, and coma.

Hypoglycemia can arise in a number of different situations: spontaneously or in the *fasting state* because of an underlying organic illness, as a *reactive* phenomenon after eating, or as a result of exogenous factors (Tab. 32.**6**). A further important clinical distinction is between hypoglycemic events in patients with and without diabetes mellitus.

Patients with Diabetes Mellitus

Among patients with diabetes mellitus, hypoglycemic coma occurs mainly in those being treated with insulin. The most common situation is that a patient with type 1 diabetes has injected too much insulin in relation to the amount of carbohydrates consumed, or has not reduced the insulin dose despite increased physical activity, concurrent illness, etc. There are also rarer cases of hypoglycemic coma among patients with type 2 diabetes being treated with insulin alone or in combination with sulfonylureas, glinides, and/or thiazolidinediones (insulin sensitizers). Hypoglycemia can take a protracted or even fatal course, particularly in elderly patients being treated with long-acting sulfonylureas.

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Whenever a patient with diabetes presents with a neurologic disturbance, hypoglycemia must be considered in the differential diagnosis.

Differential Diagnosis. Coma in a diabetic patient may be due to hypoglycemia, but the alternative diagnoses of *hyperglycemic* and *ketoacidotic diabetic coma* must always be considered. Hypoglycemic coma is usually easy to distinguish from the other two conditions because of the lack of ketoacidotic hyperpnea or dehydration, which can be observed in the skin, mucous membranes, and eyes. In hypoglycemic patients, the intravenous injection of 20–40 mL of a highly concentrated glucose solution causes rapid, though often only transient, improvement. Hyperglycemic and ketoacidotic coma do not improve upon glucose injection.

Patients without Diabetes Mellitus

The disorders causing hypoglycemia in patients without diabetes mellitus are classified into two categories: *reactive postprandial hypoglycemia* and *fasting hypoglycemia*.

Reactive Postprandial Hypoglycemia

Reactive postprandial hypoglycemia manifests with signs and symptoms of autonomous hyperactivity as described above without any impairment of consciousness or other disturbances of cerebral function. The affected patients are often asthenic persons or individuals with rapid gastric emptying after gastrectomy, gastroenterostomy, or vagotomy ("late dumping syndrome"). Hypoglycemia occurs 1–3 hours after ingestion of meals rich in carbohydrates. It can be diagnostically reproduced with a glucose load (glucose tolerance test): 2 hours after the oral administration of glucose, marked reactive hypoglycemia occurs, with blood glucose values below 3.3 mmol/L (60 mg/dL), while a fasting test does not cause any significant drop in blood glucose.

Fasting Hypoglycemia

Hypoglycemia due to an underlying organic disorder tends to occur in the fasting state, i. e., in the morning, after prolonged abstinence from food, or after increased physical activity (e. g., sports). The cause may be any of the following:

- excessive endogenous insulin production by *insulinomas*
- secretion of insulinlike substances (IGF-II), or increased utilization of glucose, by an *extrapancreatic tumor*
- impaired gluconeogenesis in *adrenocortical insufficiency*
- diminished glycogen reserves and gluconeogenesis in *hepatic and renal diseases*
- *enzyme defects* impairing glycolysis or gluconeogenesis

Insulinoma. Seventy to eighty percent of cases of endogenous hyperinsulinism are due to a single, insulin-secreting β-cell adenoma of the pancreas (insulinoma). The remainder are due to multiple adenomas, carcinomas, or rarely, diffuse hyperplasia (nesidioblastosis, persistent hyperinsulinemic hypoglycemia of infancy). The hypoglycemic attacks generally occur in the fasting state or after exercise. They tend to become more frequent and more severe over time.

If an insulin-secreting tumor is suspected, a prolonged fast test should be performed. Blood samples are drawn every six hours and whenever hypoglycemic manifestations occur, for determination of plasma glucose, insulin, and C-peptide concentrations. The prolonged fast should be continued for 72 hours, or until hypoglycemia arises. In the presence of an insulin-secreting tumor, endocrine insulin production will not be suppressed during the prolonged fast, and plasma insulin concentrations will remain inappropriately high in relation to plasma glucose. The simultaneous measurement of C-peptide concentrations provides information about endogenous insulin production and is useful in differentiating endogenous from exogenous hyperinsulinism (e. g., factitious hypoglycemia due to surreptitious self-administration of insulin).

Once the presence of endogenous hyperinsulinism has been biochemically confirmed, further test(s) are necessary to *localize* the underlying abnormality. The tests listed below complement each other. Often, more than one test will have to be applied to establish the diagnosis.

- The method with the highest yield is arterial stimulation and venous sampling (ASVS), whereby calcium gluconate is injected into the pancreatic artery, and the insulin concentration is then measured in blood sampled from the veins that drain different regions of the pancreas. An elevated insulin concentration in a single vein implies the presence of an insulin-secreting tumor in the region that it drains.
- *Ultrasonography* and MRI are often performed before ASVS, but these methods have less than 50 % sensitivity and specificity because the tumors being sought are usually small (< 1 cm in diameter). *Endoscopic sonography* has a diagnostic yield of up to 70 % in experienced hands.

Extrapancreatic Tumors. Hypoglycemia can, on rare occasions, be caused by extrapancreatic tumors, which either secrete IGF-II, metabolize large amounts of glucose, or inhibit hepatic glucose production. These tumors are easy to find because of their large size (several kilograms in weight). They are generally of hepatocellular or mesenchymal origin (fibroma, fi-

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brosarcoma, sarcoma) and are usually located retroperitoneally or within the liver itself.

Adrenocortical Insufficiency. Hypoglycemia due to cortisol deficiency in primary or secondary (pituitary) adrenocortical insufficiency is usually easy to distinguish from hypoglycemia of other causes because of these patients' characteristic addisonian appearance and other specific clinical findings. Latent adrenocortical insufficiency sometimes becomes clinically overt when longstanding treatment with pharmacologic doses of glucocorticoids is stopped. Additional stress can then precipitate acute adrenocortical failure and hypoglycemia. The same may occur in patients receiving cortisone replacement after adrenalectomy.

Fructose Intolerance. This is a familial disorder of autosomal recessive inheritance whose principal manifestation is hypoglycemia. The affected persons generally avoid all foods containing fructose.

Other Causes of Hypoglycemia

- Growth hormone deficiency can disturb glucose homeostasis, producing hypoglycemia.
- Insulin (auto-)antibodies are another rare cause of hypoglycemia. They can arise in the setting of an autoimmune syndrome or be produced by a lymphoma.
- A more common situation is exogenous, i. e., toxic or drug-induced, hypoglycemia. Erroneous or excessive dosing of insulin, sulfonylureas, and/or glinides (and combinations of these substances with thiazolidinediones) were already mentioned above as a possible cause. Alcohol intoxication in poorly nourished individuals is another possible cause (alcohol inhibits hepatic gluconeogenesis). There have been a few reports of hypoglycemia after the use of salicylates, pentamidine, quinine, chloroquine, and other drugs (for mechanisms see Tab. 32.**6**), as well as after the consumption of ackee fruit, which contains hypoglycine A, an inhibitor of hepatic gluconeogenesis.

Diabetic Coma

Diabetic coma, an acute metabolic decompensation due to insulin deficiency, is fatal unless correctly treated. It is divided into two types, ketoacidotic diabetic coma and hyperglycemic hyperosmolar nonketotic coma.

Ketoacidotic Coma

Pathogenesis. Ketoacidotic decompensation results from an acute (absolute) insulin deficiency combined with the secretion of counter-regulatory hormones. In acute insulin deficiency, the body's metabolism shifts to an uncontrollable catabolic state. Hyperglycemia ensues, with osmotic diuresis, dehydration, and loss of electrolytes, as well as hyperketonemia with metabolic acidosis. Extracellular hyperosmolality causes cerebral dysfunction and in severe cases, coma. Ketoacidotic coma is most commonly seen in persons with type 1 diabetes, developing over hours or days as a consequence of insufficient insulin supplementation (forgotten injections, pump defects), gastrointestinal disturbances (vomiting, diarrhea), stressful events causing elevation of catabolic hormone levels, acute infection, etc.

Clinical Features. The major clinical features of diabetic ketoacidosis are polyuria, thirst, fatigue, anorexia, weight loss, and weakness. Patients sometimes complain of severe epigastric pain (pseudoperitonitis). Vomiting is also a common manifestation, and the combination of pain and vomiting can create the misleading impression of an "acute abdomen." The major clinical findings of ketoacidotic coma are:

- deep, rapid breathing (Kussmaul respiration), which is a physiologic attempt to compensate for metabolic acidosis
- dehydration, with dry, flaccid skin, sunken eyes, and flat neck veins

Laboratory Tests. The urine test for glucose is strongly positive (+++). The plasma glucose concentration is typically between 20–30 mmol/L (360–540 mg/dL) but may be as high as 50 mmol/L (900 mg/dL) or more, particularly when thirst is quenched with drinks containing sugar. The arterial pH is typically below 7.3, and the anion gap exceeds 12 mmol/L (Tab. 32.**7**). Dehydration manifests itself as hemoconcentration and moderately severe prerenal azotemia. Renal calcium loss is often masked by an intracellular to extracellular shift of calcium ions due to acidosis. The severity of impairment of consciousness or coma is not correlated with the blood glucose level but rather with the extent of ketoacidosis.

Differential Diagnosis. Ketoacidotic coma must be differentiated from hyperglycemic hyperosmolar nonketotic coma and from lactic acidosis (see below).

Hyperglycemic Hyperosmolar Nonketotic Coma

Pathogenesis. In hyperosmolar diabetic coma, a certain amount of insulin secretion and insulin activity is still present and prevents the occurrence of excessive lipolysis, ketogenesis, and acidosis. Hyperosmolar coma mainly occurs in patients with type 2 diabetes, oc-

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Table 32.**7** The differential diagnosis of ketoacidotic and hyperosmolar coma

	Ketoacidotic coma	Hyperglycemic hyperosmolar nonketotic coma
Age	Any	Usually > 50 years
Patients	Diabetes mellitus type 1	Diabetes mellitus type 2
Onset	1–24 hours	1 day to 2 weeks
History	– polyuria, polydipsia – vomiting – weight loss	– polyuria, inadequate fluid intake – steroids, diuretics
Presenting features	– somnolence ranging to coma – Kussmaul respiration	– dehydration – somnolence ranging to coma – normal respiration
Course	– coma – hyporeflexia – pseudoperitonitis	– coma – hyporeflexia – seizure tendency
Plasma glucose	> 15 mmol/L (> 270 mg/dL)	> 33.3 mmol/L (> 600 mg/dL)
Arterial pH	< 7.30	> 7.30
Serum bicarbonate	< 15 mmol/L	> 15 mmol/L
Serum osmolality	< 320 mmol/kg	> 320 mmol/kg
Anion gap	> 12 mmol/L	Variable
Ketone bodies in serum	Moderate to high	–/trace
Ketone bodies in urine	Moderate to high	–/trace

casionally as the presenting manifestation of previously undiagnosed disease. The metabolic decompensation can be triggered by an infectious illness (in 20–25 % of cases), myocardial infarction, stroke, mesenteric infarction, gastrointestinal bleeding, acute pancreatitis, or the therapeutic administration of glucocorticoids, thiazide diuretics, calcium antagonists, β-blockers, protease inhibitors, etc.

Clinical Features. In these usually elderly patients, the impairment of consciousness tends to progress slowly toward coma over the course of several days or weeks. It may be accompanied by other neurologic abnormalities (seizures, transient hemiparesis). In hyperosmolar coma, there is no ketoacidosis, and therefore no Kussmaul respiration, yet most of the clinical findings of hyperosmolar coma resemble those of diabetic ketoacidosis, namely polyuria, severe dehydration, hyperosmolality with hemoconcentration and hypernatremia, moderately severe azotemia, and, usually, severe hyperglycemia, with blood glucose levels exceeding 30 mmol/L (540 mg/dL). As a rule, no more than a trace of acetone (+) is found in the urine.

Coma Due to Lactic Acidosis

Pathogenesis. Lactic acidosis occurs in situations of diminished tissue perfusion (e. g., as a result of heart failure, hypovolemia, or sepsis). It can also be an accompanying manifestation of certain diseases in which there is no systemic tissue hypoxia (Tab. 32.**8**). Thus, congenital enzyme defects, severe hepatic failure, malignancy, and poorly controlled diabetes mellitus can all cause lactic acidosis.

Lactic acidosis is particularly likely to occur as a complication of antidiabetic therapy with biguanides in patients with poor renal function.

Table 32.**8** Differential diagnosis of lactic acidosis

- Tissue hypoxia due to circulatory shock
- Congenital enzyme defects
- Accompanying manifestation of severe hepatic failure or malignant disease
- Biguanide therapy (particularly in the setting of renal failure)
- Salicylate intoxication
- Alcohol intoxication

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Salicylate overdose and alcohol intoxication are further causes of lactic acidosis.

Clinical Features. Patients complain of loss of appetite, abdominal discomfort, nausea, and vomiting and may suffer impairment of consciousness or coma. Metabolic acidosis leads to hyperventilation. The condition is diagnosed by measurement of the serum lactate concentration.

Other Types of Metabolic Coma

Hepatic Coma

Hepatic coma is an extreme form of hepatic encephalopathy, which manifests itself initially as confusion and cognitive impairment, and later as delirium, before the final transition to coma.

Among the conditions entering into its differential diagnosis, alcoholic encephalopathy is often the most difficult to distinguish from hepatic encephalopathy (or coma), particularly because both illnesses tend to affect the same group of patients. A further possible cause of impaired consciousness or coma in an alcoholic patient, which must not be overlooked, is subdural hematoma.

The pathogenesis and clinical findings of hepatic encephalopathy are described in detail in Chapter 25.

Uremic Coma

Uremic coma is rarely seen at present because of the widespread use of dialysis to treat end-stage renal failure. Renal disease usually manifests itself with many other symptoms and signs (see Chapter 29) before uremic encephalopathy can arise and progress to coma. Typically, the impairment of consciousness worsens slowly over a long period of time. The condition is easy to diagnose on the basis of the markedly elevated serum creatinine concentration.

Differential Diagnosis. Hypertensive encephalopathy, water intoxication, and metabolic acidosis of other causes (ketoacidosis, lactic acidosis, exogenous intoxications) all enter into the differential diagnosis of uremic coma. Water intoxication and metabolic acidosis are easily detected by laboratory tests, but hypertensive encephalopathy can be more difficult to diagnose. Elevation of the serum creatinine concentration and of arterial blood pressure is evidence for this condition.

Coma Due to Adrenal Insufficiency

Clinical Features. Primary adrenal insufficiency is a rare cause of coma, either in the setting of a hypoglycemic episode or in an actual addisonian crisis heralded by nausea, vomiting, diarrhea, and cramping abdominal pain. The blood pressure, already low, sinks further as the patient becomes increasingly lethargic, and then comatose. The typical hyperpigmentation of the skin (palmar creases, nipples, scars) and mucous membranes aids in the differential diagnosis. This condition usually arises in situations of stress that overtax the insufficient reserves of the dysfunctional adrenal cortex (febrile illness, vomiting/diarrhea, surgery, heat exposure, overexertion). The patient is dehydrated, with oliguria and mild azotemia.

Diagnosis. The serum sodium level may remain normal because of concomitant hemoconcentration. The cortisol deficiency is reflected by a low plasma glucose concentration and eosinophilia.

An addisonian crisis is definitively diagnosed by the finding of a markedly low plasma cortisol level despite a simultaneously elevated concentration of ACTH. The diagnosis must be made on clinical grounds first, however, because cortisol measurement takes time, and the necessary treatment measures must be initiated without waiting for the test results.

Coma Due to Pituitary Insufficiency

So-called "lethargia pituitaria" is an extremely rare condition, in which simultaneous deficiencies of thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH), and therefore also of thyroxine and cortisol, produce coma. Patients have prodromal gastrointestinal symptoms at first, then develop a progressively hypodynamic circulatory state, with bradycardia and hypotension, as well as a tendency to hypothermia. The plasma glucose level is often low. Coma usually arises only after longstanding panhypopituitarism. Physical findings in affected patients may thus include a waxen pallor, myxedematous skin changes, loss of secondary sexual hair, and signs of an endocrine psychosyndrome.

Potential causes include pituitary tumors, necrosis of the anterior pituitary lobe (Sheehan syndrome, pituitary apoplexy), or cessation of pituitary hormone supplementation in panhypopituitarism. The diagnosis is established by measurement of low levels of peripheral hormones and simultaneously low levels of the corresponding anterior pituitary hormones.

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Myxedema Coma

The clinical picture of myxedema coma, which is hardly ever encountered at present, may be thought of as a kind of endogenous hibernation, sometimes so marked as to resemble death. The respirations are infrequent and shallow, the circulation is hypodynamic with bradycardia and hypotension, and the body temperature is low, as long as there is no concurrent infection (pneumonia is a frequent complication). This condition can be triggered in severely hypothyroid individuals by sedatives (barbiturates, phenothiazines, morphine, etc.), general anesthesia, infections, trauma, or stress. The diagnosis is strongly suggested by a myxedematous appearance of the skin and tongue, a scar indicating prior thyroidectomy, radioiodine treatment, an enlarged heart, markedly slowed or absent intrinsic muscle reflexes, and markedly low thyroid hormone levels.

Coma Due to Vitamin B1 (Thiamine) Deficiency, i. e., Wernicke Encephalopathy

Wernicke encephalopathy, or pseudoencephalitis hemorrhagica superior, as it was originally named, is characterized histopathologically by perivascular hemorrhages and hyperplasia of the vascular connective tissue in the midbrain, hypothalamus, and mamillary bodies. It is caused by a deficiency of vitamin B1 (thiamine). This deficiency is often due to alcoholism but can also arise in the setting of chronic dialysis, hyperemesis gravidarum, and wasting illnesses of various kinds. Somnolence may be accompanied by ophthalmoplegia, ataxia, and frequently, confusion with amnesia and confabulation (Korsakoff syndrome), though the full-blown classical triad (ophthalmoplegia, ataxia, confusion) is rare. Coma indicates a poor prognosis.

Coma in Hyperviscosity Syndrome (Paraproteinemic Coma)

This type of coma occurs in patients with IgM paraproteinemia (Waldenström disease). The clinical manifestations are due to microcirculatory disturbances caused by the elevated viscosity of the serum. The most prominent manifestations are usually neurologic, including headache, dizziness, confusion, coma, and epileptic seizures.

Coma in Severe Systemic Illness

Severe systemic illnesses of many types, including infectious diseases (particularly sepsis) and malignancies, can produce coma as they progress, or as a preterminal phenomenon. It is important to recognize the cases where coma is actually due to a secondary complication of the underlying disease (e. g., meningitis, diabetic or hypoglycemic coma) rather than to the disease process itself.

Coma Due to Disturbances of Fluid, Electrolyte, and Acid–Base Homeostasis

These conditions are discussed in Chapter 30.

32.5 Intoxication-Induced Coma

Decreased levels of consciousness are frequently seen in intoxicated patients. Among 14567 toxic exposures reported to the Swiss Toxicological Information Centre (STIC) from 1998–2000, the prevalence of coma was 7%.

Toxic effects on the central nervous system (CNS) include quantitative and qualitative changes in CNS function. The grades of severity of CNS depression are *somnolence*, *sopor*, and *frank coma*, and the grade is most frequently expressed using the Glasgow Coma Scale. *Agitation*, *hallucinations*, *confusion*, or *delirium* are qualitative changes in CNS function and are often associated with seizures, headaches, respiratory depression, and disturbed thermoregulation (hypothermia or hyperthermia).

CNS changes due to poisoning are not basically different from CNS changes from nontoxic causes. Depressed level of consciousness, agitation, and fluctuating delirium suggest a toxic etiology.

Causes. Illicit drugs and medications play the most important role among the causes of toxic coma. The circumstances under which the patient is found may give important clues on the toxic substance involved. As no history can be taken from a comatous patient, information from relatives or bystanders is particularly helpful. Important causes of exogenous toxic coma are summarized in Tab. 32.**9**.

Clinical Features and Diagnosis. Clinical symptoms (Tab. 32.**10**) suggesting a toxic etiology often appear as toxic syndromes (so-called "toxidromes"). In multi-substance poisoning the clinical appearance may be

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Table 32.**9** Medications, drugs, and poisons as a cause of coma

Mechanism	Substances or substance class
Generalized CNS depression	Anticholinergics, antihistamines, barbiturates, meprobamate, methaqualone, benzodiazepines, carbamazepine, alcohols (ethanol, methanol, isopropanol, ethylene glycol), γ-hydroxybutyric acid, phenothiazines, tricyclic antidepressants, valproic acid
Sympatholytic effects	Clonidin, imidazoline (tetrahydrozoline, oxymetazoline), methyldopa, opiates
Cellular hypoxia	Carbon monoxide, cyanides, hydrogen sulfide, methemoglobin, sodium azide
Other	Bromides, diquat, disulfiram, antidiabetics, lithium, phencyclidine, phenylbutazone and other enolic acid derivatives, salicylates, mefenamic acid, cholinesterase inhibitors

Table 32.**10** Symptoms and findings in illicit drug intoxication

	CNS	Pupils	Respiration	Circulation
Opiates	Somnolence, coma	Miosis	Respiratory depression, pulmonary edema	Circulatory depression, right-sided endocarditis
Cocaine	Euphoria, delirium	Mydriasis	Increase of respiratory rate	Increase of heart rate and blood pressure, coronary spasm
Amphetamines	Excitation	Mydriasis	Increase of respiratory rate	Increase of heart rate and blood pressure
Barbiturates	Somnolence, coma	Fluctuating state	Respiratory depression	Decrease of blood pressure
γ-Hydroxybutyric acid	Coma, agitation		Rarely, respiratory depression	Bradycardia
Anticholinergics	Coma, delirium, agitation, hallucinations, seizures	Mydriasis	No change	Tachycardia
Hallucinogens	Hallucinations	Mydriasis	No change	Increase of heart rate and blood pressure
Cannabis	Euphoria	Mydriasis	Bronchial hyperreactivity	

Fig. 32.**10** γ-Hydroxybutyrate (GHB) is sometimes sold in capsules, but usually in 5 mL plastic tubes as colored liquid.

blurred, and a diagnosis will be dependent on analytical toxicology with identification of substances in body fluids. Therefore, the first clinical decisions about patient management depend on history, with treatment being supportive. Although the causative agent can be elucidated during the course of illness, its exact dose remains indetermined in most cases.

Illicit Drugs

Narcotic drugs lead to CNS depression in a dose-dependent manner, whereas stimulants first cause CNS excitation, which turns into coma only after high doses.

Poisoning with *opiates* and *barbiturates* is typically associated with respiratory depression. *Cannabinoids* lead to somnolence, occasionally with psychotic reactions (mainly in high doses and oral administration). *Stimulants* and *sympathomimetic drugs* cause a syndrome that includes CNS excitation, agitation, hypertension, and tachycardia, with delirium, hallucinations, seizures, and hyperthermia in high doses.

γ-Hydroxybutyric acid (GHB; Fig. 32.**10**) and its chemical derivatives γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), which are being abused at techno raves and among body builders, causes coma due to its structural analogy with the inhibitory neurotransmitter

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γ-aminobutyric acid (GABA). It causes only moderate respiratory depression, and patients awake after 3–4 hours without rebound hypersomnia or "hang-over." *Cocaine* leads to vasospasms with hypertension and end organ ischemia (brain, heart, intestine) or hemorrhage. Pulmonary edema and acute abdominal pain can be seen in *heroin* toxicity. The most significant symptoms and findings are summarized in Tab. 32.**10**.

Differential Diagnosis. The reaction to a diagnostic dose of an opiate antagonist (naloxone) may be helpful in the differential diagnosis of a coma of unknown origin. The administration of the benzodiazepine antagonist flumazenil, on the other hand, bears the risk of seizures after cessation of the anticonvulsant effect of the benzodiazepines. In states of an increased propensity for seizures, as is the case in severe tricyclic antidepressant poisoning, convulsions may be triggered.

Sedatives and Hypnotics

Poisoning with *benzodiazepines* is associated with its typical CNS depression, minor hypotension with bradycardia, and decreased muscular tone. Dizziness, ataxia, and slurred speech are signs of mild poisoning. Whereas respiratory depression is rare in pure benzodiazepine poisoning in patients without cardiopulmonary compromise, it is a regular feature of *barbiturate intoxication*, in association with severe hypotension. Typical findings in chloral hydrate and methaqualone poisoning are increased tendon reflexes, myoclonus, and seizures.

Drugs Acting on the Central Nervous System

Antidepressants and *neuroleptics* in high doses have a marked depressant effect on the CNS, partly due to their central anticholinergic properties, which are also the reason for their proconvulsant action. The tricyclic antidepressants, more than neuroleptics, through their quinidinelike effects on the myocardium, inhibit sodium influx leading to a widening of the QRS complex in the ECG, to a decrease of myocardial contractility with arterial hypotension, and ventricular arrhythmias. The QT interval in the ECG may be prolonged.

Anticholinergics

The most important anticholinergic drugs are tricyclic antidepressants, antihistamines (especially diphenhydramine), antiparkinson medications, scopolamine, and atropine (also from plants such as *Atropa belladonna*, *Datura* species).

Anticholinergic effects include CNS depression, agitation, hallucinations, seizures, and peripheral anticholinergic symptoms such as dry mouth, mydriasis, tachycardia, dry and warm flushed skin, urinary retention, and enteral atonia. In the most severe or fatal cases delirium with major agitation progresses rapidly to deep coma.

Analgesics and Antipyretics

Many drugs for pain and fever contain more than one active substance, the most significant of them from a toxicologic point of view being *acetylsalicylic acid*, *paracetamol* (acetaminophen), *mefenamic acid*, and *pyrazole derivatives*. Ingestion of high enough doses of each of these drugs may lead to coma.

- Symptoms of *mild salicylate poisoning* include nausea, vomiting, abdominal pain, tinnitus, elevated temperature, and lethargy. With increasing severity hearing loss, agitation, confusion, and fever are seen, followed by coma, convulsions, pulmonary edema, coagulopathy, and electrolyte disturbances. Mild poisoning shows respiratory stimulation due to a direct effect on the CNS medullary respiratory centre, with typical findings in the arterial blood gases (mixed respiratory alkalosis with metabolic acidosis). In advanced, severe salicylate poisoning, decompensated metabolic acidosis prevails, and is an ominous sign.
- The most important toxic effect of *paracetamol* (acetaminophen) is hepatocellular injury which may eventually lead to hepatic coma. This is invariably associated with other signs of hepatic failure. There are no or few symptoms during the early stage of poisoning, when antidotal treatment with N-acetylcysteine is still effective.
- *Pyrazol derivatives* may cause seizures.
- Among nonsteroidal antiinflammatory drugs (NSAIDs) *mefenamic acid* has exceptionally toxic properties. This substance leads to coma, seizures, and metabolic acidosis even in low doses (> 3.5 g).

Alcohols

Deep coma is rare in acute ethanol intoxication. The signs of vasodilation including flushed face, tachycardia with hypotension, and cool moist skin are the hallmarks. The mental state is frequently fluctuating. The combination of ethanol with tranquilizers or narcotics is not rare and leads to rapidly progredient decrease of consciousness. Additionally, hypoglycemia and alcoholic ketoacidosis are frequently seen.

Differential Diagnosis. Emergency physicians must consider chronic subdural hematoma, cranial trauma, or Wernicke syndrome if patients present with altered mental state.

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Methanol and Ethylene Glycol. Intoxications with methanol or ethylene glycol are more dangerous than ethanol poisoning. Both substances are widely used as technical solvents or defrosters. Early after ingestion they lead to a state of inebriation, decreased level of consciousness, and an increased osmotic gap. Later, when metabolism is advanced, severe metabolic acidosis and an increased anion gap ensue. In ethylene glycol poisoning there are oxalate crystals in the urine sediment.

Solvents

Solvents have a low viscosity and a high volatility. Alcohols, ethers, and esters are more hydrophilic and less toxic than aliphatic, aromatic, or halogenated low-molecular hydrocarbons. Aliphatic hydrocarbons are the least toxic, whereas halogenated hydrocarbons are highly toxic. Toxicity is dependent on the means of exposure. If low-viscosity hydrocarbons (gasoline, naphtha, lamp oil) are ingested, there is a high risk for tracheobronchial aspiration with subsequent chemical pneumonitis. If large volumes of low-viscosity hydrocarbons are orally ingested, or if they are heavily inhaled, CNS depression or cardiac arrhythmias may ensue. Hydrocarbons are abused by *inhalation* ("glue sniffing") due to their effects on the CNS. Some of the halogenated hydrocarbons are hepatotoxic (e. g., carbon tetrachloride). Nonhalogenated hydrocarbons have a smell like gasoline, halogenated hydrocarbons have a chloroform-like odor.

Carbon Monoxide

Pink skin discoloration is described as the typical sign of acute severe carbon monoxide (CO) poisoning, but is not detectable in the majority of cases.

There is rather a cyanotic or livid skin discoloration with increasing duration of exposure and degree of cardiovascular depression. The incidence of carbon monoxide (CO) poisoning has decreased markedly since the detoxification of cooking gas. Currently, important sources of carbon monoxide are defective heating systems, smoke, and engine exhaust.

Clinical symptoms are headache, fatigue, dizziness, nausea, and with continued exposure, disturbances in consciousness and concentration, shortness of breath, syncope, coma, seizures, and cardiac arrhythmias. Laboratory detection is performed with arterial blood gas analysis (co-oximetry). Severe cases also show lactic acidosis.

Cyanides and Hydrogen Sulfide

The most important sources of *cyanide poisoning* are smoke, gas inhalation and occupational exposure (especially in galvanization). Suicide attempts and criminal poisoning are less frequent. The course of cyanide poisoning is more rapid after exposure to hydrogen cyanide and simple cyanide salts (potassium or sodium cyanide) than after exposure to more complex cyanide salts such as silver cyanide. Even slower symptom emergence is seen after exposure to cyanogenic glycosides or organic cyanide compounds (nitriles).

Clinical Features. Typical symptoms in mild, nonlethal cyanide poisoning are a scratchy sensation in the throat, shortness of breath, headache, blurred vision, dizziness, palpitation, vomiting, defecation, anxiety, cramping, paralysis, weakness, syncope, flushed face, and a feeling of suffocation. Laboratory tests show lactic acidosis. In severe cases, rapid loss of consciousness ensues, with tachycardia, seizures, dilated pupils, and death. Sudden death can occur.

Poisoning with *hydrogen sulfide* (especially from manure pits) leads to a state similar to cyanide poisoning.

32.6 Hypersomnia and Excessive Tendency to Fall Asleep/ Daytime Sleepiness

Hypersomnia corresponds to an excessive tendency to fall asleep/daytime sleepiness (i. e., abnormal difficulty to stay awake). Increased sleep behavior (i. e., prolongation of the total amount of sleep) with napping during daytime and/or prolonged nocturnal sleep may, but do not have to, be present. Several authors reserve the label of hypersomnia for an increase in the sleep duration over 24 hours. Occasionally, hypersomnia is accompanied by a shortened latency to fall asleep, an increased depth of sleep, and difficulties awakening (sleep drunkenness). There is a fluid transition between a physiologic/mild and a pathologic/excessive tendency to fall asleep.

Clinical Features. The *physiologic/mild tendency to fall asleep* typically occurs in the early afternoon, after alcohol intake, in a warm environment, during boring activities (e. g., car passengers during a long ride). The cognitive performance is not impaired and the frequency of accidents is not increased.

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The *pathologic/excessive tendency to fall asleep* may occur during physical activities (speaking, eating, walking, and even during sexual intercourse) and result in unwanted sleep episodes. A pathologic tendency to fall asleep should be suspected if the Epworth sleepiness scale score is > 10–12 (Tab. 32.**5**) and an impairment of cognitive performance, as well as an increased frequency of accidents, must be assumed in the clinical history.

Automatic ("nonsense") behaviors (e. g., putting clothes into the refrigerator, pouring salt into coffee, driving to the wrong place, "fugues," etc.) may occur in the context of "microsleep" episodes in patients with hypersomnia (independent of its etiology) and result in accidents, among other consequences. Differentiation of disturbances of consciousness of epileptic origin (see above) may be difficult at times.

Table 32.**5** Epworth Sleepiness Scale
How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you. (**0** would never doze, **1** slight chance of dozing, **2** moderate chance of dozing, **3** high chance of dozing):

Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e. g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
Total:__/24 (normal = 3–10)	

Narcolepsy

The frequency of narcolepsy in the population is comparable to the incidence of multiple sclerosis (0.05%). The disease typically starts in the second to third decade of life. Its biological markers are the HLA-haplotype DQB1*0602 (positive in 95% of Caucasian patients), the occurrence of REM sleep 10–20 minutes after falling asleep (so-called SOREM, sleep onset REM, 70–80% of patients; Fig. 32.**11**), and a low/unmeasurable CSF level of the peptide hypocretin-1/orexin A (90% of patients, see also Fig. 32.**1**), which is synthesized in the lateral hypothalamus. The origin of narcolepsy is explained by a (possibly autoimmune-mediated) loss of hypocretin neurons in the lateral thalamus.

The main, and often first, symptom of narcolepsy is excessive daytime sleepiness (hypersomnia), which typically is fluctuant and accompanied by sleep attacks (mostly occurring several times per day or per week), from which the patient awakes refreshed after a few minutes.

Cataplexy is present in 70–90% of cases and is, in its classic presentation, pathognomonic for the narcolepsy. The typical appearance of cataplexy is a usually partial, bilateral loss of tone in the knees, arms, neck, and chin muscles, which is caused by sudden emotions (mostly by laughing) and last for seconds to minutes while the consciousness is not altered. Classic cataplexy occurs regularly (at least a few times per month) and can be well distinguished by the clinical history from cataplexylike symptoms, which also may occur in healthy individuals (the state of being "weak with laughter").

Sleep paralysis (general palsy of the voluntary muscles with normal consciousness) and (often visual) hallucinations occur at the onset of sleep or during awakening in approximately half of narcoleptic patients. However, they may also occur in other sleep disorders.

Other Hypersomnias

Sleep apnea syndrome (SAS) has a prevalence of 2–5% in the normal population and is the most frequent cause of excessive daytime sleepiness (hypersomnia). Male sex, narrow pharynx/double chin, overweight, and arterial hypertension are frequently seen in patients with SAS. Landmarks of the sleep-associated respiratory disturbance are loud, habitual snoring (occurring almost every night), and observed apnea as well as a restless and nonrefreshing sleep. Only a minority of patients suffer from hypersomnia. Patients with SAS have a higher risk for accidents and cardiovascular diseases.

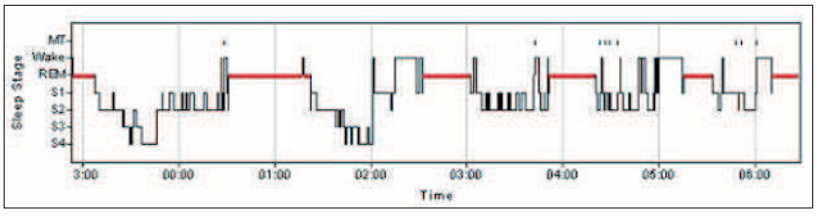

Fig. 32.**11** Narcolepsy. Occurrence of REM sleep shortly after onset of sleep (and not 60–90 minutes later, as in healthy individuals, see Fig. 32.**2**) in a polysomnography of a 17-year-old patient with narcolepsy tetrad (hypersomnia, cataplexy, sleep palsy, and hallucinations).

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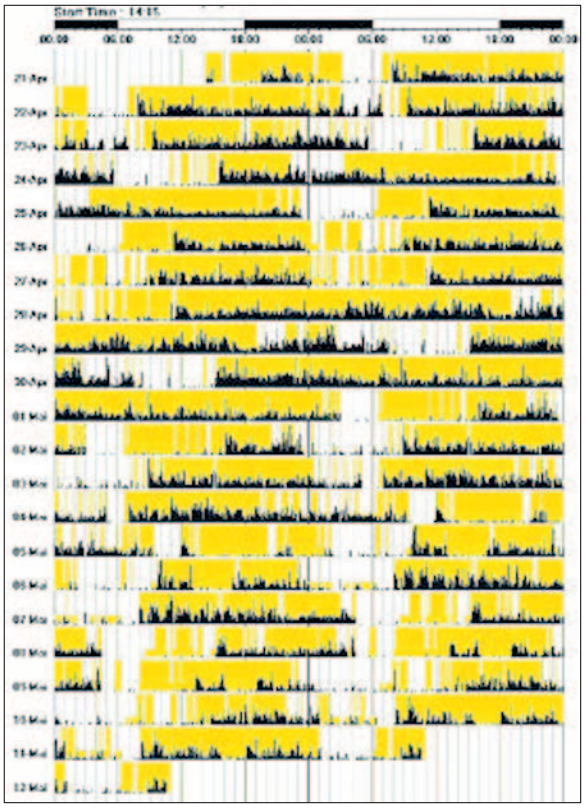

Fig. 32.**12** Sleep deficit as a cause for hypersomnia. This actigraphy over 3 weeks shows irregular sleep–wake cycles (with reactive sleep deficit) as a cause of hypersomnia of "unknown origin" in a 40-year-old man. Yellow indicates the exposure to light.

A *chronic sleep insufficiency* must be assumed in hypersomnic patients, who sleep discrepantly less (> 2–3 hours) on workdays than at the weekend or during vacations. After an increase in sleep duration for several days, the hypersomnia improves. Monitoring the activity with actigraphy (carried on the wrist for 2–3 weeks) may be diagnostically helpful (Fig. 32.**12**).

An *idiopathic hypersomnia* (IH) is approximately 10 times rarer than a narcolepsy. Its pathogenesis is not known. Besides the hypersomnia, a prolonged nocturnal sleep (up to 13–16 hours) and marked sleep drunkenness in the morning are typical. Often, the symptoms appear in the second to third decade of life and, occasionally, the family history is positive. The hypersomnia remains unchanged even after an increase in the sleep duration over several days.

In *restless legs/periodic limb movement in sleep* (RLS/PLMS) syndrome, which affects approximately 5 % of the adult population, insomnia at the onset and during sleep is more frequent than hypersomnia (only 10–20 % of the patients). The hypersomnia is thought to be due to repeated awakening resulting the periodic movements of the extremities. It still remains unclear, however, whether the hypersomnia may be explained by isolated PLMS (without RLS).

Psychogenic hypersomnia occurs in the context of neuroses and depressions with a typical discrepancy between subjective and objective (see below) severity of the hypersomnia. Often, these patients also show fluctuations in their symptoms (possibly seasonal), as well as eating disorders.

Other Neurologic Diseases. Hypersomnias in other *neurologic disorders* are generally recognizable and diagnosable in their respective contexts. In these patients, the distinction between hypersomnia and somnolence (see disturbances of consciousness) may be difficult.

- In particular, severe hypersomnias are observed in bilateral thalamic, hypothalamic, and mesencephalic lesions (strokes, traumatic lesions, tumors, abscesses, granulomas). In thalamus infarcts, the patients may remain in a sleeplike state for 16–20 hours.
- Hypersomnia and sleep–wake disturbances are also characteristic of CNS infections with influenza virus and trypanosomes (see above).
- Hypersomnia is particularly frequent in myotonic dystrophies and certain Parkinson syndromes (e. g., the so-called diffuse Lewy body disease).
- A decompensated hydrocephalus may manifest itself with increasing hypersomnia.
- Rare causes of hypersomnia are abuse of medications or drugs, and hypothyroidism. Periodic hypersomnias, including the so-called Kleine–Levin syndrome, associated with megaphagia and conspicuous behavior, are very rare.

Differential Diagnosis. A hypersomnia must be distinguished from pseudohypersomnia or fatigue ("lack of energy," for instance in "*chronic fatigue*" or "*adynamia–myalgia*" syndrome). Here, the desire to sleep is high, while the tendency to fall asleep is mostly normal or even low.

Long sleepers are normal individuals who need more than 9–10 hours of sleep per day. With insufficient duration of sleep, they may be misdiagnosed as suffering from hypersomnia.

Diagnostic Confirmation of Hypersomnia. Besides the clinical history, the physical examination, and several laboratory tests (hemogram, kidney, liver, and thyroid parameters), polysomnography (PSG) is usually necessary in the evaluation of a hypersomnia. In the PSG special attention must be given to the occurrence of a PLMS and sleep associated respiratory disorders. In addition, the multiple sleep latency test (MSLT) may, on the one hand, document the sleepiness, and on the other hand, support the diagnosis of narcolepsy in the presence of REM sleep in two or more of five sleep onset episodes. A normal MSLT in a subjective severe hypersomnia may be indicative of a pseudohypersomnia (psychogenic causes, see above). The actigraphy allows one to recognize lack of sleep hygiene with insufficient sleep, among other patterns. A toxic screening, brain MRI, and psychiatric evaluation should be considered in selected cases.

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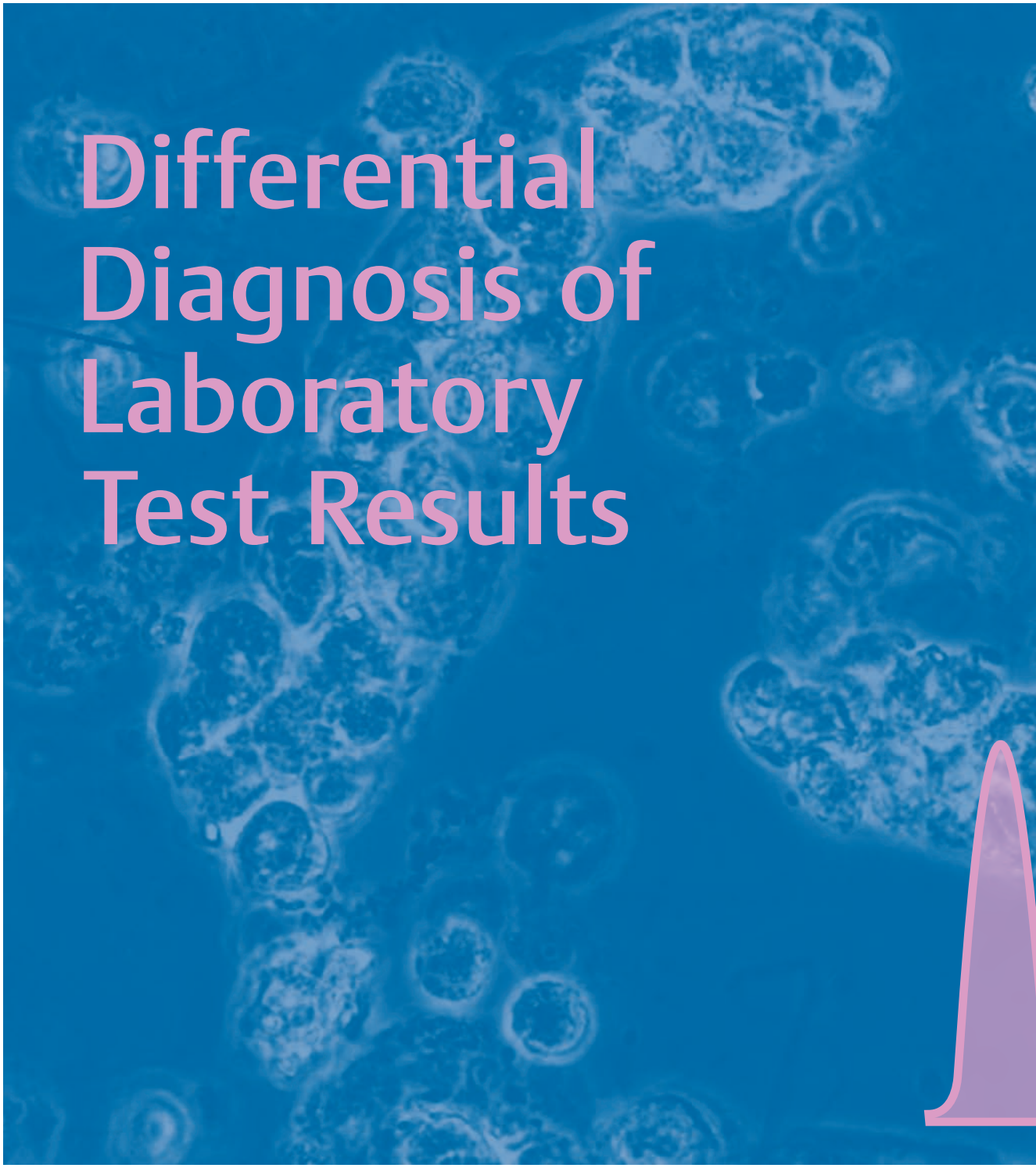

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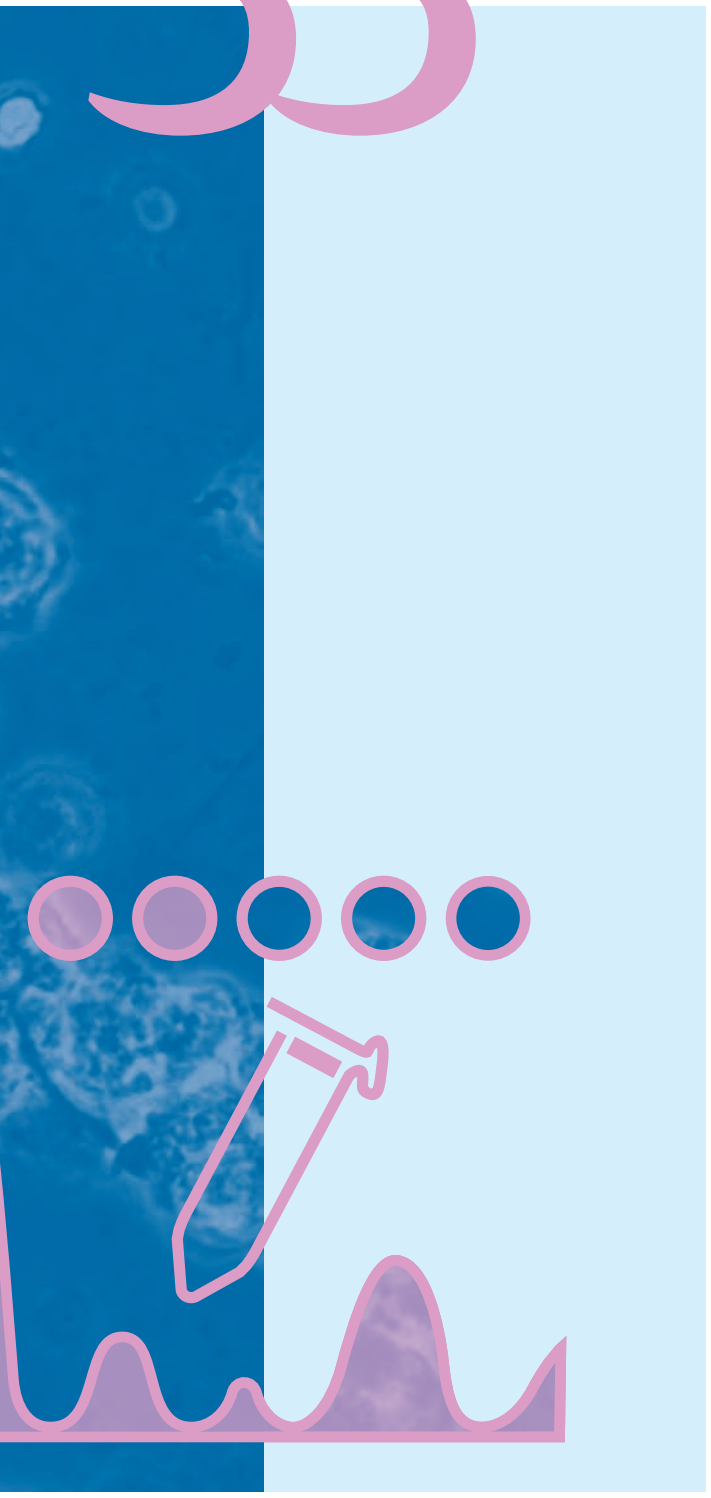
33 Differential Diagnosis of Laboratory Test Results

A. von Eckardstein



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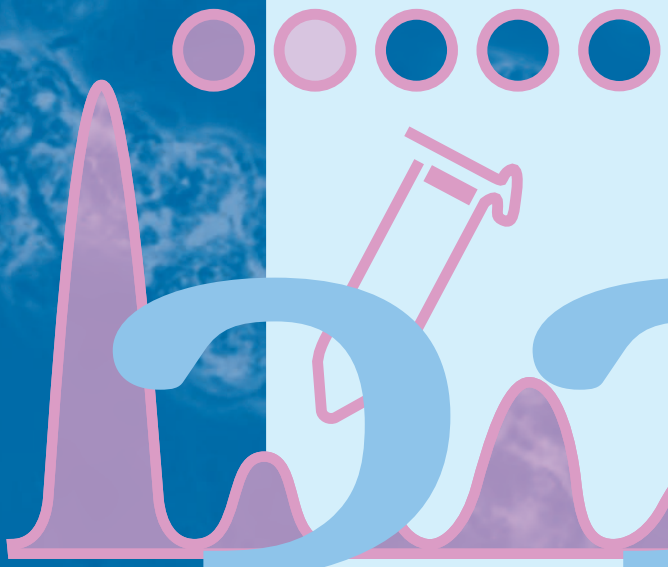

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33.1 Introduction 1017

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Zinc 1066

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33.1 Introduction

This chapter presents differential diagnoses of selected laboratory parameters. In view of the multitude of laboratory tests existing today and the limited space offered within a single textbook, the chapter encompasses only the laboratory tests that the University Hospital Zürich performs most frequently and the laboratory parameters that are part of primary healthcare in Switzerland. Urine analysis and tests or tests to examine the cellular components of blood are described in other chapters of this volume (see Chapters 13, 14, and 29).

To efficiently use the limited space in this chapter, information on each parameter is presented in tables, preceded by relevant indications, reference ranges, and the most important Factors that may influence results. In-depth information on pre-analytical and analytical issues are omitted; for further information the reader is kindly asked to refer to specialized and more exhaustive literature (see Appendix).

Reference ranges often depend on the method chosen. For this reason, the reader is explicitly urged not to simply adopt the reference ranges valid for the University Hospital Zürich, but to view them with a critical eye and to primarily apply the reference ranges of the laboratory with which he or she is collaborating.

The Factors that may influence results mentioned in the chapter were selected according to their pre-analytical relevance, i. e., factors were chosen that are therefore checked by the physician.

The supplementary tests given in this chapter may help to continue differential diagnostics or are relevant for follow-up or therapy monitoring. The parameters put in parentheses are additional voluntary tests.

33.2 Laboratory Parameters

Acid–Base Balance

Indication. Ventilation disorders, parenchymal lung diseases and impairment of pulmonary perfusion, circulatory insufficiency, shock, hypovolemia, renal insufficiency, renal failure, tubular renal diseases, decompensated diabetes mellitus, intoxications, coma, vomiting, diarrhea, pancreatic and biliary fistulas, hypokalemia and hyperkalemia, hypochloremia and hyperchloremia, impairment of adrenal function, all forms of intensive therapeutic interventions (e. g., infusions, artificial ventilation, dialysis, massive blood transfusion).

Normal values:
Arterial blood:
pH: 7.37–7.45
PC_{O_2} in men: 4.7–6.1 kPa (35–46 mmHg)
PC_{O_2} in women: 4.3–5.7 kPa (32–43 mmHg)
Standard bicarbonate (current HCO_3^-):
21–26 mmol/L
Total CO_2: 23–28 mmol/L
Base excess: -2–+3 mmol/L

Mixed venous blood:
pH: 7.35–7.43
P_{CO_2}: 4.9–6.7 kPa (37–50 mmHg)
Standard bicarbonate (current HCO_3^-):
21–26 mmol/L
Total CO_2: 22–29 mmol/L
Base excess: -2–3 mmol/L

Plasma, serum:
Standard bicarbonate (current HCO_3^-):
21–26 mmol/L
Total CO_2: 22–29 mmol/L

Factors that may influence results. The possibility of inappropriate test material makes this test highly error-prone (vein instead of artery, pressure exerted during capillary blood withdrawal, contact with air, heparin excess, cell metabolism, clotting, insufficient resuspension); body temperature of the patient.

Metabolic acidosis (base deviation and standard bicarbonate decreased, pH decreased, or normal [if compensated], P_{CO_2} normal or decreased [if compensated])		
Differential diagnosis	**Supplementary tests**	**See Chapter**
With enlarged anion gap		
Ketoacidosis (diabetic coma, starvation, high body temperature, thyrotoxicosis)	See Glucose, Anion Gap; sodium, chloride, osmolality, potassium, ketone bodies in urine; see CRP, TSH	2–4, 16, 30, 32
Lactic acidosis (for causes see Lactate)	See Lactate	30

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Metabolic acidosis (base deviation and standard bicarbonate decreased, pH decreased, or normal [if compensated], P_{CO_2} normal or decreased [if compensated]) (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
With enlarged anion gap Intoxications (salicylate, methanol, paraldehyde, ethylene glycol)	See Anion Gap	30, 32
Acute and chronic renal failure	See Creatinine	29, 30
With normal anion gap Bicarbonate loss (pancreatic and biliary fistulas, diarrhea, reactive after hyperventilation)	Potassium	17, 27, 30
Increased chloride uptake (infusions, ammonium chloride, ureteroenterostomy, etc.)		2, 3, 30
Renal tubular acidoses (proximal, type II: hereditary [Fanconi] or symptomatic in several hereditary metabolic disorders, in plasmacytoma, amyloidosis, nephrotic syndrome, collagen diseases, calcium metabolism disorders, or certain drugs)	See Potassium, Calcium, Phosphate, Albumin, Immunoglobulins; urinary pH (normally < 5.3), urinary phosphate (increased)	29, 30
Renal tubular acidoses (distal, type I: hereditary or symptomatic in several hereditary metabolic disorders, in plasmacytoma, amyloidosis, nephrotic syndrome, collagen diseases, nephrocalcinoses, or certain drugs)	See Potassium, Calcium, Phosphate, Albumin, Immunoglobulins, PTH, 25-OH vitamin D_3; urinary pH (normally > 6), urinary phosphate (normal)	29, 30
Renal tubular acidoses resulting from impaired aldosterone action	See Potassium, Aldosterone	23, 29, 30

Metabolic alkalosis (base deviation and standard bicarbonate increased, pH increased or normal [if compensated], PCO_2 normal or increased [if compensated])		
Differential diagnosis Chloride loss (vomiting, aspiration of gastric juice)	**Supplementary tests** See Chloride, Anion Gap	**See Chapter** 26, 30
Increased supply of alkali (sodium bicarbonate infusion, antacids, citrate, lactate), milk-alkali syndrome, diuretics	See Chloride	2, 3, 30
Status after hypoventilation	See Oxygen (PO_2)	17
Hypokalemia	See Potassium	30
Primary and secondary hyperaldosteronism	See Aldosterone	23, 29, 30
Hypercortisolism (Cushing syndrome, therapy with corticosteroids, paraneoplastic)	See Cortisol	

Respiratory acidosis (PCO_2 increased, pH decreased or normal [if compensated], base deviation and standard bicarbonate normal or increased [if decompensated])		
Differential diagnosis Alveolar hypoventilation due to chronic obstructive bronchopulmonary diseases and restrictive pulmonary diseases, respiratory failure due to mechanical obstruction (neuromuscular and skeletal obstruction, diaphragmatic elevation, pleural effusion, hemopneumothorax and pneumothorax), or central respiratory paralysis (drugs, diseases of the CNS)	**Supplementary tests** P_{O_2}	**See Chapter** 17, 31, 32

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Respiratory alkalosis (PCO_2 decreased, pH increased or normal [if compensated], base deviation and standard bicarbonate normal or decreased [if compensated])		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hyperventilation (anxiety, excitement, fever, diseases of the CNS, pregnancy, thyreotoxicosis, liver cirrhosis, drugs, incorrect mechanical ventilation)	PO_2; see CRP, Albumin, TSH	16, 17, 30
Reflex-induced respiration due to impaired diffusion, distribution, and perfusion (see Oxygen [PO_2])	See Oxygen (PO_2)	17, 30

Albumin

Indication. Differential diagnosis of edema, follow-up of acute liver diseases and liver cirrhosis, nephrotic syndrome, shock, burn injuries, index of nutritional status of patients in intensive care.

Normal values:
< 15 years: 38–54 g/L
15–60 years: 35–52 g/L
> 60 years: 32–46 g/L

Factors that may influence results. False-high values, up to 10%, due to hemoconcentration if patient is not in a supine position or has been sitting for 15 minutes.

Values decreased, up to 20%, due to pregnancy, infusion therapy, polydipsia (pseudohypoproteinemia, hematocrit as control parameter), pseudohyperalbuminemia due to dehydration (hematocrit as control parameter), radiograph contrast medium, ampicillin.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Liver cirrhosis	Complete blood count, sodium, potassium, calcium, bilirubin, ALT, GGTP; ChE, Quick test, (ammonia, AFP)	12, 25
Protein-deficient nutrition (e. g., starvation, anorexia, gastrointestinal tumors, long-term amino acid-free infusion therapy)	Complete blood count, sodium, potassium, calcium, osmolality, acid–base balance, glucose, creatinine, urea, lactate, lipid profile, total protein, Quick test, PTT, TSH (magnesium, urinary sodium, ammonia, retinol binding protein, prealbumin, transferrin, vitamin level)	2, 3, 7, 12, 26, 28
Malassimilation syndrome (e. g., sprue, cystic fibrosis)	Complete blood count, sodium, potassium, calcium, osmolality, lipid profile, total protein, serum protein electrophoresis, CRP, ALT, AST, GGTP, alkaline phosphatase, amylase, lipase, Quick test, folic acid, vitamin B_{12}, (phosphate, magnesium, zinc, β-carotene, 25-OH vitamin D_3, parathyroid hormone, ferritin, immunoglobulins, antibodies to endomysium, gliadin, mitochondria [AMA] and nuclei [ANA], xylose absorption test and other function tests, fecal fat and fecal pancreatic elastase, stool culture)	27, 28
Protein-losing enteropathy (e. g., ulcerative colitis, Crohn disease, polyposis)	Complete blood count, sodium, potassium, serum protein electrophoresis, CRP, ESR, GGTP, alkaline phosphatase, amylase, ferritin (see Malassimilation Syndrome, above; fecal calprotectin)	7, 27, 28
Nephrotic syndrome	Blood count, sodium, potassium, calcium, phosphate, creatinine, urea, lipid profile, total protein, serum protein electrophoresis, CRP, ESR, Quick test, PTT, complement C3 and C4, urinalysis and urinary sediment including erythrocyte morphology, protein in urine, differentiation of proteinuria	12, 29
Chronic hemodialysis	See Creatinine	29
Skin diseases (e. g., burn injuries, oozing eczemas, bullous dermatoses)	Blood count, potassium, sodium, chloride; see CRP	2, 3
Chronic inflammation	See CRP	4, 7, 10, 11, 17
Monoclonal gammopathy (multiple myeloma)	See Immunoglobulins	14
Analbuminemia	Total protein, serum protein electrophoresis	11

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Aldosterone

For the assessment of the renin–angiotensin–aldosterone system, especially the differentiation between primary and secondary forms of hyperaldosteronism, it is important to know the sodium and potassium balance (serum/plasma concentration and urinary excretion) as well as the renin concentration and activity.

Indication. Hyperaldosteronism, mineralocorticoid deficiency.

Normal values:
Supine position: 80–400 pmol/L (30–150 ng/L)
Upright position (2 hours): 200–800 pmol/L (75–300 ng/L)

Factors that may influence results. Drugs, body position, time of the day, sodium and potassium balance.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Aldosterone decreased, renin increased		
Primary adrenocortical insufficiency	Complete blood count, sodium, potassium, calcium, acid–base balance, creatinine, glucose, urea, cortisol, ACTH, ACTH stimulation test	24, 30
Congenital defects in steroid synthesis (adrenogenital syndrome)	Sodium, potassium, cortisol, DHEA(S), androstenedione, 17-OH progesterone	2, 3, 30
Aldosterone decreased, renin decreased		
Pseudohyperaldosteronism (syndrome of apparent mineralocorticoid excess, Liddle syndrome, Cushing syndrome, syndrome of cortisol resistance, 11-deoxycortisol producing tumors)	Sodium and potassium in serum and urine, acid–base balance; see Cortisol; 11-deoxycortisol	23, 29, 30
Negative sodium balance	Sodium in serum and urine	30
Positive potassium balance	Potassium in serum and urine	30
Excessive licorice intake (glycyrrhizic acid)	Sodium and potassium in serum and urine	2
Drugs (beta-blockers, reserpine, α-methyldopa, clonidine, carbenoxolone, cardiac glycosides, antiphlogistics, heparin, vasopressin, corticosteroids, low-dose lithium)	Sodium and potassium in serum and urine	2

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Aldosterone increased, renin decreased or normal and cannot be stimulated		
Primary hyperaldosteronism (adrenocortical adenoma or hyperplasia, idiopathic, glucocorticoid-suppressible hyperaldosteronism)	Sodium, potassium, renin, orthostatic test, aldosterone-18-glucuronide, (cortisol 11-deoxycorticosterone, 18-OH deoxycorticosterone, 18-OH corticosterone, corticosterone in serum and urine, potassium in urine, acid–base balance)	23, 30
Aldosterone increased, renin increased		
Renovascular hypertension, renal parenchymatous hypertension	Potassium, sodium, creatinine, urea, renin, CRP, urinalysis, (captopril test, renal vein renin test)	23, 30
Renin-producing tumors	Potassium, sodium, renin	23
Bartter syndrome	Potassium, sodium, calcium, magnesium, chloride, acid–base balance, uric acid, glucose tolerance test, renin, chloride in urine	30
Pheochromocytoma	Catecholamines and metanephrines in plasma or 24 h urine	23
Panarteritis nodosa	See ANCA	29

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Increased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Aldosterone increased, renin increased		
Pregnancy, hormonal contraceptives	Pregnancy test	2, 3
Hyperthyroidism	See TSH	16
Negative sodium balance	Sodium in serum and urine	30
Positive potassium balance	Potassium in serum and urine	30
Edema (heart failure, nephrotic syndrome, liver cirrhosis, protein-losing enteropathy)	See Albumin, BNP	6, 7, 12, 20, 27–29
Drugs (calcium antagonists, spironolactone, diuretics, laxatives, beta-adrenergic agonists, high-dose lithium, aminoglycosides)	Sodium and potassium in serum and urine	2

Alkaline Phosphatase (AP)

The total activity of alkaline phosphatase (AP) in serum and plasma is a result of the particular activities of 17 different isoenzymes (e. g., liver AP, bone AP, placental AP, small intestinal AP), which can be differentiated by electrophoresis.

Indication. Diagnosis and course of liver diseases, diseases of the bile ducts, skeletal diseases.

Normal values:
Women: 30–104 U/L
Men: 30–129 U/L
Children and adolescents: strikingly increased and highly dependent on age!

Factors that may influence results. False-high values due to hyperbilirubinemia (> 250 μmol/L).
False-low values due to lipemia and hemolysis, citrated plasma or EDTA plasma; induced (increased activity) and suppressed (decreased activity) by various drugs.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Wilson disease	See Copper	25
Protein deficiency (liver cirrhosis, nephrotic syndrome, protein-losing enteropathy)	See Albumin	29
Hypothyroidism	See TSH	16
Magnesium deficiency	See Magnesium	30
Vitamin C deficiency		
Familial hypophosphatasia		

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Various diseases of the liver and the bile ducts	See GGTP, Aminotransferases	25
Paget disease	Calcium, pyridinium crosslinks	3, 11
Osteomalacia (vitamin D deficiency or metabolic disorders caused by vitamin D deficiency, various renal tubular defects)	Calcium and phosphate in serum and urine, 25-OH vitamin D, 1,25- $(OH)_2$ vitamin D, PTH	3, 11, 29, 30
Renal osteodystrophy	Calcium and phosphate in serum and urine, 25-OH vitamin D, 1,25- $(OH)_2$ vitamin D, PTH	11, 29, 30
Bone tumors and metastases	Calcium, search for primary tumor (e. g., serum electrophoresis especially in case of plasmacytoma), tumor markers in the course of the disease (e. g., PSA in case of carcinoma of the prostate, CA 15–3 or CEA in case of breast cancer)	11

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Increased (continued)		
Differential diagnosis Bone fracture	**Supplementary tests**	**See Chapter** 11
Primary hyperparathyroidism	See PTH	11, 29
Acromegaly and growth hormone therapy (slightly increased)	Glucose, GH (basal level and in glucose tolerance test), IGF-I, IGFBP-3	11
Hyperthyroidism	See TSH	16
Diabetes mellitus	See Glucose	
Pregnancy	Pregnancy test	
Drugs (anticonvulsants)		

α-Fetoprotein (AFP)

Indication. Diagnosis, differential diagnosis, and follow-up of hepatocellular carcinoma and germ cell tumors (also early recognition of these tumors in high-risk groups), prenatal screening during pregnancy (Down syndrome, neural tube defects).

Normal values: < 10 μg/L

Factors that may influence results. Significantly higher concentrations during pregnancy (depending on the week of pregnancy; interpretation in the context of risk assessment for Down syndrome and neural tube defects by multifactorial algorithms), hemolysis, hyperbilirubinemia, lipemia, other clouding of the sample (e. g., by fibrin).

Increased		
Differential diagnosis Hepatocellular carcinoma	**Supplementary tests** bilirubin, albumin, GLDH, ALT, GGTP, (GGTP/ALT > 6), GLDH ([ALT+AST]/GLDH < 20), ChE, Quick test (ammonia)	**See Chapter** 25
Germ cell tumors – yolk sac tumors always positive – embryonic carcinomas sometimes positive – seminomas, dysgerminomas, teratomas, and dermoid cysts usually negative	β-HCG (mandatory)	
Various carcinomas especially of the gastrointestinal tract and the lungs, particularly if liver metastases are present		6, 17, 18, 25–28
Acute and chronic hepatitides	See Aminotransferases	25
Liver cirrhosis	See Albumin	25

Aminotransferases (Transaminases: ALT/GPT and AST/GOT)

The two enzymes most important for diagnostics, i. e., alanine aminotransferase (ALT; = glutamic pyruvate transaminase [GPT]) and aspartate aminotransferase (AST; = glutamic oxalacetic transaminase [GOT]) differ by their quantitative tissue distribution, subcellular localization, and plasma half-life. Activity ratios can therefore help in differential diagnosis and staging. ALT is primarily expressed in the liver and the bile ducts, can be found in both the cytoplasm and mitochondria, and has a plasma half-life of 48 hours. AST is primarily expressed in cardiac and skeletal muscle, located exclusively in the cytoplasm, and has a plasma half-life of 17 hours.

Indication. (Differential) diagnosis and follow-up of liver diseases and diseases of the bile ducts (ALT/GPT) and of cardiac and skeletal muscle (AST/GOT).

diagnostic cut-offs: < 50 U/L

Factors that may influence results. Hemolysis (ALT and AST), macroenzymes (AST), aging of the specimen (ALT).

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Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Diseases of the liver and the bile ducts (typically ALT >AST)		
Acute, chronic aggressive and persisting viral hepatitides	Bilirubin (direct), GGTP (GGTP/ALT < 1), alkaline phosphatase, GLDH ([ALT+AST]/GLDH > 50), hepatitis serology (screening procedures with anti-HAV, anti-HBc, anti-HCV)	25
Concomitant hepatitis (e. g., mononucleosis)	Complete blood count (smear), bilirubin (direct), serology for CMV, EBV, etc.	4, 14, 25
Hepatic abscess	Complete blood count, bilirubin, alkaline phosphatase, GGTP, GLDH, CRP, albumin, immunoglobulins, microbiology (blood and stool cultures, serology), parasitology	25
Autoimmune hepatitis	GGTP, bilirubin, serum protein electrophoresis, ANA, liver-specific autoantibodies (SMA, SLA, LKM, ASGPR), HLA-A1, HLA-B8, HLA-DR3, HLA-DR4	25
Primary biliary cirrhosis	See AMA	25
Primary sclerosing cholangitis	See ANCA	25
Alcoholic and other toxic hepatopathies	Complete blood count, sodium, potassium, bilirubin, creatinine, urea, lipid profile, alkaline phosphatase, GGTP, ChE, Quick test, albumin, carbohydrate-deficient transferrin	25
Nonalcoholic fatty liver disease (NAFLD, steatosis hepatis), fatty liver hepatitis (NASH)	Sodium, potassium, bilirubin, creatinine, urea, lipid profile, alkaline phosphatase, GGTP, ChE, Quick test, albumin, carbohydrate-deficient transferrin	25
Drug-induced jaundice	See Bilirubin	25
Liver cirrhosis	GGTP (GGTP/ALT = 1–6); see Albumin	25
Intrahepatic and extrahepatic cholestasis	GLDH ([ALT+AST]/GLDH = 20–50); see Bilirubin, GGTP	25
Hypoxic hepatopathy	GLDH; ([ALT+AST]/GLDH < 20)	25
Liver carcinoma and liver metastases	GGTP (GGTP/ALT > 6), GLDH ([ALT+AST]/GLDH < 20), AFP	25
Pregnancy (cholestasis, HELLP, eclampsia, hyperemesis gravidarum)	Blood count, creatinine, glucose, uric acid, total protein, albumin, AP, GGTP, ALT, D-dimers, Quick test, pregnancy test, urinalysis and urinary sediment	25
Diseases of cardiac and skeletal muscle (AST >ALT)		
Diseases of cardiac muscle (AST >ALT) (myocardial infarction, myocarditis)	See CK, Troponin	6, 20, 21, 22
Diseases of skeletal muscle (AST >ALT) (myositis, muscular dystrophy, trauma, rhabdomyolysis, exertion, etc.)	See CK	8, 10, 11, 31, 32
Other disorders		
Malignant hyperthermia	See CK	
Hypothyroidism	See TSH	16
Embolism of the pulmonary artery (AST)	See D-Dimers	6, 9

Ammonia

Indication. Follow-up of hepatopathy, chemotherapy, valproate therapy, especially congenital metabolic disorders in neonates and children.

Normal values: 9–33 μmol/L (15–56 μg/100 mL)

Factors that may influence results. Test material other than EDTA blood, specimen transport too long and without cooling, increased GGTP activity (formation of ammonia), thrombocytosis, polycythemia, hemolysis (in all cases false-high values).

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Increased		
Differential diagnosis Acute liver dystrophy, terminal liver cirrhosis	**Supplementary tests** See Quick Test, ChE, Albumin	**See Chapter** 25
Portocaval anastomoses		25
Reye syndrome	ALT, AST, Quick test, acid–base balance, glucose, ketone bodies	
Multiple myeloma	See Immunoglobulins	14
Urinary tract infections	Complete blood count, CRP, urinalysis and urinary sediment, urine culture	3, 29
Various congenital hyperammonemias (urea cycle defects, organoacidopathies, fatty acid oxidation disorders, disorders of pyruvate metabolism)	Glucose, lactate, ketone body, acid–base balance, chloride, sodium, bicarbonate (anion gap), amino acids, organic acids in urine	30, 32
High-dose chemotherapy	Drug level	
Valproate therapy	Valproate level	
Infusion of ammonium chloride	Acid–base balance	

Amylase and Pancreatic Amylase

Indication. Diagnosis of acute pancreatitis, relapsing chronic pancreatitis, evidence for pancreatic involvement in abdominal diseases; follow-up after abdominal surgery and endoscopic retrograde cholangiopancreatography (ERCP), parotitis.

Normal values: Highly dependent on method.

Factors that may influence results. Macroamylase, EDTA, hemolysis.

Increased		
Differential diagnosis Acute pancreatitis and acute bouts of chronic pancreatitis	**Supplementary tests** Complete blood count, sodium, potassium, calcium, bilirubin, glucose, urea, creatinine, acid–base balance, CRP, lipase, LDH, GGTP, AP, Quick test, PTT	**See Chapter** 7
Obstruction of pancreatic duct (calculus, carcinoma, stricture)	GGTP, AP, bilirubin (direct), lipase	7
After endoscopic retrograde pancreatography	GGTP, AP, bilirubin (direct), lipase, CRP	7, 25
Concomitant pancreatitis in abdominal diseases (gastric ulcer perforation, ileus, mesenteric infarction, peritonitis, salpingitis, extrauterine gravidity)	Complete blood count, sodium, potassium, calcium, bilirubin, glucose, urea, creatinine, acid–base balance, CRP, lipase, LDH, GGTP, AP, Quick test, PTT, pregnancy test	7, 25, 27, 28
Diseases of the salivary glands (parotitis, salivary calculus, etc.)	Blood count, CRP, mumps serology	5
Renal insufficiency	See Creatinine	29
Malignant tumors (bronchial carcinoma, ovarian carcinoma, thyroid carcinoma, colon carcinoma, carcinoma of the prostate)	Differentiation of amylase	
Liver diseases (viral hepatitis, liver cirrhosis)	Differentiation of amylase, see Aminotransferases, Albumin	28
Alcoholism (acute intoxication)	See GGTP, Osmolality, Anion Gap, Acid-Base Balance	32
Diabetic ketoacidosis	See Glucose, Acid-Base Balance	32
Opiate therapy, opiate abuse	Opiate testing	

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Anion Gap

The anion gap corresponds to the difference sodium – (chloride + bicarbonate).

Normal values: 8–16 mmol/L

Indication. Differentiation of metabolic acidosis.

Factors that may influence results. See Sodium, Chloride, and Acid–Base Balance.

Increased		
Differential diagnosis Diabetic ketoacidosis	**Supplementary tests** Blood count, potassium, sodium, osmolality, acid–base balance, urea, creatinine, glucose, CRP, urinalysis (ketone body)	**See Chapter** 32
Lactic acidosis	See Lactate	32
Uremia	See Creatinine	29
Alcoholism	Blood count, potassium, sodium, osmolality (osmotic gap), acid–base balance, urea, glucose, alcohol, GGTP, carbohydrate-deficient transferrin, CRP, urinalysis (ketone body)	32
Salicylate intoxication	Creatinine, acid–base balance, salicylate	32
Methanol or ethylene glycol intoxication	Acid–base balance, osmolality (osmotic gap), methanol, oxalate in urine	32

Antineutrophil Cytoplasmic Antibodies (ANCA)

Antineutrophil cytoplasmic antibodies (ANCA) are directed toward cytoplasmic enzymes. Using immunofluorescence, cytoplasmic ANCA (c-ANCA = classic or cytoplasmic ANCA), which recognizes proteinase 3 as the antigen, is distinguished from perinuclear ANCA (p-ANCA), which primarily recognizes myeloperoxidase as the antigen. Immunoassays and blotting methods which identify antibodies to proteinase 3 or myeloperoxidase directly are also employed. In addition, there are atypical ANCA whose target antigens are not known.

Indication. Suspected vasculitis, primary sclerosing cholangitis.

Normal values: Negative, not detectable.

Factors that may influence results. Dependent on method.

Increased		
Differential diagnosis Vasculitis of large vessels (giant cell arteritis, Takayasu arteritis)	**Supplementary tests** Blood count, CRP, erythrocyte sedimentation rate, complement factors	**See Chapter** 9
Vasculitis of medium-size vessels (classic panarteritis nodosa, Kawasaki disease) (p-ANCA)	Antibodies to endothelial cells, HBs Ag, blood count, CRP, erythrocyte sedimentation rate, complement factors	
Wegener granulomatosis (c-ANCA)	Anti-proteinase 3 antibodies, blood count, CRP, erythrocyte sedimentation rate, complement factors	29
Churg–Strauss syndrome (c-ANCA, p-ANCA)	Anti-myeloperoxidase antibodies, blood count (eosinophilia), CRP, erythrocyte sedimentation rate, complement factors	4, 18
Microscopic panarteritis (c-ANCA, p-ANCA)	Anti-proteinase 3 antibodies, anti-myeloperoxidase antibodies, blood count, CRP, erythrocyte sedimentation rate, complement factors	4
Idiopathic glomerulonephritis (p-ANCA)	Anti-proteinase 3 antibodies, anti-myeloperoxidase antibodies, creatinine, urinalysis, urinary sediment, blood count, CRP, erythrocyte sedimentation rate, complement factors	29

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Increased (continued)		
Differential diagnosis Henoch–Schönlein purpura	**Supplementary tests** Blood count, CRP, erythrocyte sedimentation rate, complement factors	**See Chapter** 15
Cryoglobulinemia-associated vasculitis	Cryoglobulins, serum protein electrophoresis, blood count, CRP, erythrocyte sedimentation rate, complement factors, hepatitis C antigen	14, 29
Primary sclerosing cholangitis (atypical ANCA)	Bilirubin (direct), ALT, GGTP	25
Autoimmune hepatitis (atypical ANCA)	See ANA	25
Primary biliary cirrhosis (atypical ANCA)	See Bilirubin	25
Crohn disease, ulcerative colitis (atypical ANCA)	See Albumin	7, 27
Rheumatoid arthritis (p-ANCA, atypical ANCA)	See Rheumatoid Factor	10
Systemic lupus erythematosus	See ANA	10, 29

Antinuclear Antibodies (ANA)

Antinuclear antibodies should be evaluated by performing step by step diagnostic assessment, i. e., by starting with immunofluorescence followed by confirmation by ELISA and ending with the differentiation of antibodies to particular nuclear antigens. Especially in the case of suspected systemic lupus erythematosus (SLE), antibodies to dsDNA are also sought.

Indication. Suspected collagen diseases (SLE, Sjögren syndrome, dermatomyositis), suspected drug-induced lupus erythematosus (LE), suspected autoimmune hepatitis.

Normal values: Positive, from titer 1:160.

Factors that may influence results. Depending on method.

Increased		
Differential diagnosis Systemic lupus erythematosus (SLE)	**Supplementary tests** Blood count including LE cells, protein in urine, antibodies to dsDNA, differentiation of ANA (Sm antibodies, SS-A, histone antibodies), antiphospholipid antibodies	**See Chapter** 2, 3, 6, 8–10, 12, 13, 15, 29 31, 32
Asymptomatic relatives of SLE patients		
Drug-induced LE	Differentiation of ANA (histone antibodies)	2, 3
Discoid LE		2, 3
Subacute cutaneous LE		2,3
Mixed connective tissue disease	Differentiation of ANA (U1 RNP)	2, 3
Systemic sclerosis	Differentiation of ANA (Scl-70, centromere)	2, 3, 26
Sjögren syndrome	Differentiation of ANA (SS-A, SS-B)	10
Polymyositis, dermatomyositis	Differentiation of ANA (Jo-1)	8
Rheumatoid arthritis	See Rheumatoid Factor	10
Felty syndrome		10, 15
Juvenile chronic arthritis		10
Autoimmune hepatitis	GGTP, bilirubin, serum protein electrophoresis, ANA, liver-specific autoantibodies (SMA, SLA, LKM, ASGPR), HLA-A1, HLA-B8, HLA-DR3, HLA-DR4	25
Various noninflammatory diseases (neoplasias, sarcoidosis) and healthy individuals (especially older people)	Blood count, erythrocyte sedimentation rate, sodium, potassium, calcium, creatinine, CRP, total protein, serum protein electrophoresis, GGTP, AST, ALT, urinalysis	

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Bicarbonate

See Acid–Base Balance, Anion Gap.

Bilirubin

The serum level is determined by the formation of bilirubin, primarily from hemoglobin, by the ability of the liver to conjugate bilirubin, and by the excretion into an open biliary duct system. Correspondingly, prehepatic jaundice (increased availability of bilirubin: increase in indirect or unconjugated bilirubin), intrahepatic jaundice (impaired uptake of bilirubin into the liver or impaired conjugation in the liver: increase in direct and indirect bilirubin), and cholestatic jaundice (impaired intra- or posthepatic excretion of bilirubin: increase in direct or conjugated bilirubin) are distinguished.

Total and direct bilirubin levels are measured, and the indirect bilirubin level is determined arithmetically (total bilirubin minus direct bilirubin). Some methods allow direct determination of conjugated and nonconjugated bilirubin.

Indication. Diagnosis and differential diagnosis of jaundice.

Normal values:
Total bilirubin: up to 17 μmol/L (1.0 mg/100 mL)
Direct conjugated bilirubin: up to 3 μmol/L (0.2 mg/100 mL)
Indirect bilirubin: total minus direct bilirubin

Factors that may influence results. Light, massive hemolysis, drugs (aminosalicylic acid, levodopa, methyldopa, methotrexate, nitrofurantoin, propranolol).

Increased "direct" (unconjugated) bilirubin		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hepatocellular jaundice		
Viral hepatitides and other hepatitides	See Aminotransferases	25
Liver cirrhosis (posthepatic, alcoholic)	See Albumin	25
Primary biliary liver cirrhosis	Total blood count, lipid profile, AMA, ANCA; see Albumin	25
Toxic liver damage	See Aminotransferases	25
Hypoxic hepatopathy, congestion of liver, right-sided heart failure	GLDH	25
Hereditary impaired excretion of conjugated bilirubin (Dubin–Johnson syndrome, Rotor syndrome, progressive familial intrahepatic cholestasis, etc.)	GGTP, coproporphyrins in urine, phenobarbital test, genetic analyses (MRP2, BSEP, MDR3)	25
Drug-induced jaundice	GGTP, AP, ALT, AST, hepatitis serology, opiate testing	25
Fatty liver	See Aminotransferases	25
Pregnancy (cholestasis, HELLP, eclampsia, hyperemesis gravidarum)	Blood count, creatinine, glucose, uric acid, total protein, albumin, AP, GGTP, ALT, D-dimers, Quick test, pregnancy test, urinalysis, urinary sediment	25
Liver cell carcinoma, liver metastases	See AFP	25
Extrahepatic cholestasis		
Obstructive jaundice of variable etiology (e. g., bile duct or carcinomas of pancreatic head, cholelithiasis, pancreatitis)	GGTP, AP, ALT; see Amylase	7, 25
Cholangitis	Complete blood count, CRP, GGTP, AP, ALT, microbiology of blood and bile	4, 7, 25
Benign intrahepatic cholestasis	GGTP, AP	25

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Increased "indirect" (unconjugated) bilirubin (hemolytic jaundice)		
Differential diagnosis Hemolytic anemia and toxic hemolysis	**Supplementary tests** See Haptoglobin	**See Chapter** 13, 14
Increased degradation of blood due to lung infarction, intestinal bleeding, and resorption of hematoma	LDH, CK, haptoglobin	25
Polycythemia	Blood count	13, 14, 25
Shunt hyperbilirubinemia (= degradation of erythrocyte precursors in bone marrow)	Blood count, reticulocytes	13, 25
Gilbert disease	ChE, genetic polymorphisms of UGT	25

Blood Count

See Chapters 13, 14.

Brain Natriuretic Peptide (BNP), NT-Pro-Brain Natriuretic Peptide (NT-proBNP)

Indication. Differential diagnosis of dyspnea (exclusion of heart failure).

Normal values:
BNP: dependent on method
NT-proBNP:
Women < 50 years: < 153 ng/L
Women > 50 years: < 334 ng/L
Men < 50 years: < 88 ng/L
Men > 50 years: < 227 ng/L

Factors that may influence results. Blood drawn in supine position.

Increased		
Differential diagnosis Heart failure	**Supplementary tests** Blood count, potassium, sodium, creatinine, urea, bilirubin, albumin	**See Chapter** 20, 24
Valvular heart defect		20, 21, 24
Myocardial infarction	Troponins, CK-MB, myoglobin	6
Tachycardia (eg., fever, hyperthyroidism)	See TSH, CRP	22
Renal insufficiency (especially NT-proBNP)	See Creatinine	22
Sepsis	See CRP, Procalcitonin	3

CA 15–3

Indication. Therapy and monitoring of breast cancer.

Normal values: < 30 kU/L

Factors that may influence results. Change of assays.

Increased		
Differential diagnosis Breast cancer	**Supplementary tests** CEA	**See Chapter** 6, 11, 25
Renal insufficiency	See Creatinine	29
Mastopathy, fibroadenoma of the breast		6

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Increased		
Differential diagnosis Acute pancreatitis	**Supplementary tests** See Amylase	**See Chapter** 7
Cholelithiasis, cholecystitis	See Bilirubin, GGTP	7, 25
Liver cirrhosis	See Albumin	25
Diseases of the respiratory tract	See PO_2, Acid-Base Balance	17
Autoimmune diseases	See CRP, ANA, Rheumatoid Factor	2, 3, 4, 9, 10, 14, 17, 29, 31, 32

CA 19–9

Indication. Therapy and monitoring of pancreatic carcinoma, hepatobiliary carcinoma, and of gastric carcinoma (primary marker), as well as of colorectal carcinoma and ovarian carcinoma (secondary marker).

Normal values: < 40 kU/L

Factors that may influence results. Can only be found in carriers of the Lewis antigen; beware contamination caused by secretion; change of assays, high-dose hook effect, human anti-mouse CA-125 antibodies (HAMA).

Increased		
Differential diagnosis Pancreatic carcinoma	**Supplementary tests** CA 125 and CEA as secondary tumor markers; see Amylase	**See Chapter** 7
Primary liver cell carcinoma	See AFP	25
Cholangiocarcinoma	See Bilirubin, GGTP	25
Gastric carcinoma	CEA, CA72–4	7
Ovarian carcinoma	CA 125 as primary marker	7
Colorectal carcinoma	CEA	7
Acute pancreatitis	See Amylase	7
Cholelithiasis, cholecystitis	See Bilirubin, GGTP	7, 25
Liver diseases	See Bilirubin, Albumin, Aminotransferases, GGTP	25

CA-125

Indication. Therapy and follow-up of ovarian carcinoma (primary marker) and pancreatic carcinoma (secondary marker).

Normal values: < 35 kU/L

Factors that may influence results. Change of assays, high-dose hook effect, human anti-mouse CA-125 antibodies (HAMA).

Increased		
Differential diagnosis Ovarian carcinoma	**Supplementary tests** CA 19–9, CA 72–4	**See Chapter** 7
Pancreatic carcinoma	CA 19–9 as primary tumor marker; See Amylase	7, 25
Carcinomas of the breast, cervix, endometrium, and of the gastrointestinal tract	More suitable primary tumor markers	7
Adnexitis, adnexal tumors, leiomyoma	Blood count, CRP	7

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Increased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Endometriosis		7
Acute pancreatitis	See Amylase	7
Cholelithiasis, cholecystitis	See Bilirubin, GGTP	7, 25
Liver diseases	See Bilirubin, Albumin, Aminotransferases, GGTP	25
Renal insufficiency	See Creatinine	29

Calcium

Investigation of disorders of calcium metabolism should always include additional tests: calcium in urine, phosphate in serum and urine, total protein, albumin, creatinine, alkaline phosphatase, chloride, sodium, potassium, magnesium. The tables below list only specific additional tests.

Indication. Tetany, bone and renal diseases, gastrointestinal, pulmonary (Boeck), thyroid diseases, etc., tumors, certain drugs.

Normal values:
Total calcium: 2.10–2.60 mmol/L
Ionized calcium: 1.10–1.30 mmol/L

Factors that may influence results. The calcium level is increased by upright body position and physical activity and is decreased by food intake. Pseudohypocalcemia due to protein deficiency (affects total calcium), specimen transport of long duration (ionized calcium), EDTA, citrate, oxalate.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Vitamin D deficiency	$1,25\text{-}(OH)_2$ vitamin D_3, 25-OH vitamin D_3	11
Hypoparathyroidism and pseudohypoparathyroidism	See PTH	16, 29, 30
Renal insufficiency	See Creatinine	29
Nephrotic syndrome	See Albumin	29
Liver cirrhosis	See Albumin	25
Malassimilation syndrome	See Albumin	27
Tumors and carcinomas (e. g., of the breast, prostate, thyroid, and bronchial)	See PSA, CEA, CA 15–3, CA 125, CA 19–9	6, 7, 11, 14, 17, 18
Acute pancreatitis	See Amylase	7
Hypercortisolism	See Cortisol	
Magnesium deficiency	See Magnesium	
Certain drugs (loop diuretics, anticonvulsants, glucocorticoids, cytostatics, citrate)		

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Malignant neoplasms (e. g., of the breast, bronchial, renal, pancreatic or prostatic; multiple myeloma)	See Alkaline Phosphatase	6, 7, 11, 14, 17, 18
Sarcoidosis and other granulomatoses (Wegener disease, tuberculosis, berylliosis, etc.)	angiotensin converting enzyme, $1,25\text{-}(OH)_2$ vitamin D_3	17–19
Acute renal failure	See Creatinine	29
Primary hyperparathyroidism	See PTH	16, 30
Hyperthyroidism	See TSH	16
Acromegaly	GH (basal level and in oral glucose tolerance test), IGF1	16

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Increased		
Differential diagnosis Pheochromocytoma	**Supplementary tests** Catecholamines, metanephrines	**See Chapter** 23
Addison disease	See Cortisol	
Familial hypocalciuric hypercalcemia	PTH, calcium and magnesium in urine, magnesium in serum	
Immobilization		11
Paget disease	Phosphate, PTH, 25-OH vitamin D_3, alkaline phosphatase (bone), pyridinium crosslinks	11
Vitamin D and vitamin A overdose	25-OH vitamin D_3, vitamin A	
Thiazide diuretics, lithium, theophylline intoxication, milk alkali syndrome	Drug level, chloride, acid–base balance	

Carcinoembryonic Antigen (CEA)

Indication. Monitoring the effectiveness of colorectal cancer therapy, follow-up of colorectal carcinomas.

Normal values:
Nonsmokers: < 5 mg/L
Smokers: < 10 mg/L

Factors that may influence results. Smokers show increased values; values in serum and plasma can be discrepant; human anti-mouse CA-125 antibodies (HAMA).

Increased		
Differential diagnosis Colorectal carcinoma	**Supplementary tests** CA 19–9 as secondary tumor marker	**See Chapter** 7
Pancreatic carcinoma	CA 125 as primary and CA 19–9 as secondary tumor marker; see Amylase	7
Gastric cancer	CA 19–9, CA 72–4 as primary tumor markers	7
Breast cancer	CA 15–3 as primary marker	7
Ovarian carcinoma	CA 125 as primary marker	7
Cervical carcinoma	SCC as primary marker	7
Small cell bronchial carcinoma	NSE as primary marker	7
Acute pancreatitis	See Amylase	7
Cholelithiasis, cholecystitis	See Bilirubin, GGTP	7, 25
Liver diseases	See Bilirubin, Albumin, Aminotransferases, GGTP	25
Inflammatory intestinal diseases	See Albumin, CRP	7
Inflammatory pulmonary diseases	See CRP, PO_2	17

Chloride

The assessment of the chloride level often requires knowledge of the anion gap and acid–base balance.

Normal values: 95–105 mmol/L

Indication. Acid–base imbalance and abnormalities of the sodium and water balance.

Factors that may influence results. Bromide and iodide, effect of volume displacement in chylomicronemia.

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Decreased		
Differential diagnosis Vomiting	**Supplementary tests** Acid–base balance, potassium in serum, potassium and chloride in urine	**See Chapter** 2, 3, 26, 30
Hyperaldosteronism, hypercortisolism	See Aldosterone, Cortisol	30
Milk alkali syndrome	Acid–base balance, calcium	
Chronic respiratory insufficiency (respiratory acidosis)	See Acid-Base Balance, PO_2	17, 30
Bartter syndrome	Potassium, sodium, calcium, magnesium, acid–base balance, uric acid, glucose tolerance test, aldosterone, renin, chloride in urine	30
Diuretics	Chloride and sodium in urine	2, 30

Increased		
Differential diagnosis Renal tubular acidoses	**Supplementary tests** Acid–base balance, potassium, sodium, potassium and chloride in urine, urinary pH, alkaline phosphatase	**See Chapter** 29, 30
Primary hyperparathyroidism	See PTH	11, 16
Renal insufficiency	See Creatinine	29
Ureterosigmoidostomy	Bicarbonate, anion gap	27
Diarrhea	Acid–base balance	27
Chronic hyperventilation	Acid–base balance, see PO_2	17, 30, 31
Exogenous addition of chloride ions		2, 3, 30
Therapy with carbonic anhydrase inhibitors		

Cholesterol

See Lipid Profile.

Cholinesterase (ChE)

The etiological classification of decreased cholinesterase activity into hepatic and nonhepatic diseases is facilitated by the simultaneous determination of albumin and ALT.

Indication. Evaluation of synthesis function of the liver; exclusion or evaluation of suspected cholinesterase deficiency (if muscle relaxants are administered); pesticide intoxication.

Normal values:
Dependent on method (the following values are given for the butyrylthiocholine method).
Women < 16 years and > 40 years;
Men: 5.3–12.9 kU/L
Women 16–40 years: 3.7–11.3 kU/L

Factors that may influence results. Hyperestrogenism (pregnancy, oral contraceptives); albumin > 70 g/L (false-high), citrate, fluoride.

Decreased		
Differential diagnosis Impaired liver function due to cirrhosis, hepatitis, liver failure, hypoxia, tumors, transplantation	**Supplementary tests** See Albumin, Aminotransferases, Bilirubin	**See Chapter** 25
(Septic) shock	See CRP	3, 4, 24
Chronic inflammatory intestinal diseases	See Albumin	2, 3, 7, 27

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Decreased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Muscular dystrophy, myotonia congenita (Thomson)	See CK	2, 3
Hereditary deficiency and variance	Dibucaine number	2, 3
Cholinesterase inhibitor intoxication (e. g., pesticides, E605)		2, 3
Hyperestrogenism (pregnancy, oral contraceptives)	Pregnancy test; see HCG	2, 3

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Diabetes mellitus	See Glucose	2, 3
Hypertriglyceridemia	Triglycerides	6
Fatty liver	See GGTP, Aminotransferases	25
Protein-losing enteropathy	See Albumin	27
Nephrotic syndrome	See Albumin	29
Gilbert disease	See Bilirubin	25

Complement C3 and C4

Indication. Evaluation of suspected immune-complex diseases (SLE, vasculitis, glomerulonephritis, cryoglobulinemia) and follow-up, suspected complement deficiency (e. g., due to relapsing infections).

Normal values:
C3: 0.80–1.70 g/L
C4: 0.15–0.49 g/L

Factors that may influence results. EDTA plasma should be used in order to avoid in vitro activation; acute phase reactions lead to elevated C3 and C4, which conceals consumption by immune-complex diseases (simultaneous determination of CRP recommended).

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Immune-complex diseases		
SLE (C3 and C4)	See ANA	2–4, 10, 29
Membranoproliferative glomerulonephritis (C3, rarely C4)	Creatinine, electrolyte, urinary proteins, urinary sediment, C3 nephritic factor	12, 29
Postinfectious glomerulonephritis (C3, rarely C4)	Creatinine, electrolyte, urinary proteins, urinary sediment, evidence for infection (ASL, etc.)	4, 12, 29
Cryoglobulinemia (C3, C4)	Evidence for cryoglobulins	2, 3, 9, 10, 29
Hereditary immunoglobulin A deficiency (C4)	IgA	
(Autoimmune) thyroiditis (C3, C4)	ESR, CRP, blood count, TSH, LATS	16
AIDS (C3, C4)	Total blood count, aminotransferases, protein, protein electrophoresis, LDH, CRP, ESR; HIV serology, HIV load, lymphocyte subpopulations (CD4, CD8)	2–4, 14, 17, 18, 32
Multiple myeloma (C4)	See Immunoglobulins	2–4, 11, 13–15, 29
Diseases without immune-complex formation		
Embolization (spontaneous and iatrogenic)	See D-Dimers	9, 15
Hemolytic–uremic syndrome and thrombotic–thrombocytopenic purpura (C3, rarely C4)	Creatinine, total blood count including fragmentocytes; see Haptoglobin; blood culture, Quick test, PTT, fibrinogen, D-dimer	13, 29

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Decreased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Diseases without immune-complex formation		
Sepsis (C3, C4)	See CRP, Procalcitonin	4
Acute pancreatitis (C3, C4)	See Amylase	7
Liver failure (C3, C4)	See ChE, Albumin, Ammonia	2, 3, 12, 15, 25
Malnutrition	See Albumin	2, 3
Extensive burn injuries (C3, C4)	See Albumin	2, 3
Malaria (C3, C4)	Blood count, blood smear, thick smear, potassium, sodium, blood gases, acid–base balance, glucose, lactate, creatinine, Quick test, PTT, fibrinogen, D-dimers	2, 4
Erythropoietic porphyria (C3)	Protoporphyrinogen and uroporphyrinogen in stool, (total porphyrins in urine)	2, 3
Hereditary complement deficiency (C3 and/or C4, depending on defect)	CH50, C1 esterase inhibitor, C2, factor B	2–4, 12

Copper

Indication. Suspected Wilson disease or Menkes syndrome, unclear refractory iron deficiency anemia, long-term parenteral feeding.

Factors that may influence results. Excessive application of tourniquet.

Normal values:
Women: 12–19 μmol/L (70–120 μg/dL)
Men: 12–21 μmol/L (70–130 μg/dL)

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Wilson disease	Complete blood count, CRP, ceruloplasmin, copper in urine, copper in liver tissue; see Albumin, Aminotransferases	25, 32
Menkes syndrome	Complete blood count, CRP, ceruloplasmin, copper in urine, copper in liver tissue; see Albumin, Aminotransferases; copper incorporation into cultivated skin fibroblasts	25, 32
Nutritional copper deficiency, intestinal malabsorption	Blood count, copper in urine; see Albumin	13
Zinc overdose	Blood count, copper in urine	13

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Liver cirrhosis	See Albumin	25
Hemochromatosis	See Transferrin Saturation	25
Obstructive jaundice	See Bilirubin (direct)	25
Acute and chronic infection	See CRP	4
Leukemias, lymphomas, and other malignant neoplasms		14
Influence of estrogen (pregnancy, oral contraceptives)	Pregnancy test	

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Cortisol

The usual tests measure the total cortisol concentration.

Indication. Diagnosis of hypo- and hypercortisolism.

Normal values:
Morning: 171–540 nmol/L (60–200 μg/L)
Afternoon: 64–340 nmol/L (28–125 μg/L)
Midnight: < 138 nmol/L (< 50 μg/L)

Factors that may influence results. Circadian rhythm, food intake.

Increased		
Differential diagnosis Primary or secondary (Cushing syndrome) hypercortisolism	**Supplementary tests** Potassium, glucose (oral glucose tolerance test), cortisol in 24 h urine or salivary free cortisol (best test for screening); dexamethasone suppression test; cortisol diurnal profile, ACTH, CRH test	**See Chapter** 2, 3
Iatrogenic (drug-induced)		2, 3
Paraneoplastic	ACTH	
Severe acute and chronic general diseases	Blood count, erythrocyte sedimentation rate, sodium, potassium, calcium, creatinine, CRP, total protein, serum protein electrophoresis, GGTP, AST, ALT, urinalysis	2, 3
Anorexia nervosa	Blood count, potassium, sodium, lipid profile; see Albumin; dexamethasone suppression test (cortisol often not suppressible); CRH test	2, 3
Obesity	Free cortisol in serum or saliva (usually normal), glucose, lipid profile	2, 3
Endogenous depression	Dexamethasone suppression test (cortisol usually suppressible)	2, 3
Chronic alcoholism	Dexamethasone suppression test (cortisol often not suppressible); See GGTP	2, 3
Hyperestrogenism (pregnancy, oral contraceptives)	Free cortisol in serum or saliva, pregnancy test	2

Decreased		
Differential diagnosis Primary (Addison disease) or secondary hypocortisolism	**Supplementary tests** Complete blood count, sodium, potassium, calcium, acid–base balance, creatinine, glucose, urea, ACTH, ACTH test, CRH test, aldosterone, renin	**See Chapter** 2, 3

C-Peptide and Insulin

Indication. Residual secretion of insulin by beta cells, differential diagnosis of hypoglycemia.

Normal values:
C-peptide: 1.1–5.0 μg/L (0.3–1.5 nmol/L)
Insulin: 6–25 mU/L (36–150 pmol/L)

Factors that may influence results. Cross reactivity of some insulin tests with proinsulin, hemolysis.

Increased		
Differential diagnosis Insulinoma	**Supplementary tests** Glucose, starvation test	**See Chapter** 31, 32
Factitious hypoglycemia	Glucose, high insulin and suppressed C-peptide levels	31, 32
Insulin autoimmune hypoglycemia	Glucose, high insulin and suppressed C-peptide levels	31, 32

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C-Reactive Protein (CRP)

Indication. Identification and monitoring of inflammatory diseases.

Normal values: < 5 mg/L

Factors that may influence results. Lipemia.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Infections	Blood count, procalcitonin, urinalysis, determination of focus and pathogens (urine culture, blood culture, stool culture, diagnostic cerebrospinal fluid examination, smear, sputum, etc.)	2–11, 16–18, 20, 27, 29, 31, 32
Rheumatic diseases	See Rheumatoid Factor	2–4, 9–11, 13, 17, 18, 25, 29, 31, 32
Acute pancreatitis	See Amylase	7
Necroses, tissue damage (e. g., trauma, surgery, myocardial infarction)	Depending on the situation (CK, CK-MB, troponins)	6
Malignant tumors	Tumor screening	2, 3, 13, 14, 16–19, 25–28

Creatine Kinase (CK and CK-MB)

Creatine kinase (CK) activity increases with either myocardial or skeletal muscle etiology can be differentiated by the determination of isoenzyme CK-MB. Detection and exclusion of cardiac etiology is facilitated by the determination of troponin I or T.

Indication. Diseases of cardiac muscle (especially exclusion/detection or follow-up of myocardial infarction), diseases of skeletal muscle.

Normal values:
Total CK: Men: < 190 U/L; Women: < 170 U/L
CK-MB: < 24 U/L (men and women)

Factors that may influence results. Hemolysis, macro CK (affects total CK and CK-MB), mitochondrial CK, presence of CK-BB in craniocerebral trauma, uterine trauma, birth (only CK-MB is affected).

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Myocardial diseases (CK-MB)		
Acute myocardial infarction	Troponins, myoglobin (blood count, sodium, potassium, calcium, magnesium, glucose, creatinine, urea, CRP, Quick test, PTT)	6
Myocarditis, endocarditis, pericarditis	Blood count, CRP, procalcitonin, blood cultures, virus serology; see ANA	4, 6, 20, 21, 22
Diagnostic and therapeutic cardiac interventions (e. g., surgery, defibrillation, cardiac massage)	Troponins, myoglobin	2, 3
Diseases of skeletal muscle		
Traumas (accident, injections, surgery, intramuscular injections, etc.)	Sodium, potassium, calcium, creatinine, urea, myoglobin in serum and urine, urinalysis	2
Rhabdomyolysis	Sodium, potassium, calcium, creatinine, urea, myoglobin in serum and urine, urinalysis	2, 3, 8
Myositis	Blood count, CRP; see ANA; virus serology, bacteriology	8
Exertion (sports, epileptic seizure, labor)		2
Myasthenia gravis	Autoantibodies to acetylcholine receptors	8

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Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Diseases of skeletal muscle Congenital muscle diseases (Duchenne muscular dystrophy, Becker muscular dystrophy, McArdle disease, Kugelberg–Welander syndrome, Aran–Duchenne disease)		2
Secondary myopathies (hyperthyroidism, hypothyroidism, hypokalemia, pheochromocytoma, intoxications, etc.)	See TSH, Potassium; catecholamines and their metabolites in urine	2, 3, 16, 23
Malignant hyperthermias	Sodium, potassium, chloride, acid–base balance, creatinine, urea, lactate, myoglobin, AST	
Diseases affecting other organs Pulmonary embolism	See D-Dimers	2, 3, 6, 9, 15, 17, 20, 21
Gastrointestinal disorders (especially mesenteric infarction, liver necrosis, acute pancreatitis)	See Amylase, Aminotransferases, GGTP, Bilirubin	2, 3, 7, 25, 27, 28
Malignant tumors	See Amylase, LDH, Aminotransferases, GGTP, GLDH, Bilirubin, Serum Protein Electrophoresis	2, 3, 13, 14, 16–19, 25–28
Hemolysis and myeloproliferative syndrome	See LDH, Haptoglobin	13, 14
Neurological diseases with blood-brain barrier damage (craniocerebral trauma, subarachnoid hemorrhage, stroke, brain tumor, meningoencephalitis)		5, 31, 32

Creatinine

Creatinine is the most important parameter to estimate renal function. Optimal diagnosis of renal function requires the determination or estimate of creatinine clearance.

Simplified MDRD formula (for Caucasian men):
eGFR [ml/min/1.73 m^2] =
175 × (serum creatinine [µmol/dL]/88.4)$^{-1.154}$ × Age [years]$^{-0.0203}$

or

eGFR [ml/min/1.73 m^2] =
175 × serum creatinine [µmol/dL]$^{-1.154}$ × Age [years]$^{-0.0203}$

For women: eGFR men × 0.742
For Black people: eGFR Caucasians × 1.212

Indication. Assessment of renal function e. g., in preliminary examinations, acute and chronic renal diseases, pathological findings in urine examination, hypertension, any acute disease, metabolic disorders, pregnancy, therapeutic use of renally excreted drugs.

Normal values:
Jaffé:
Women: < 100 µmol/L (< 1.1 mg/dL)
Men < 50 years: < 110 µmol/L (< 1.25 mg/dL)
Men > 50 years: < 125 µmol/L (< 1.45 mg/dL)
Enzymatic:
Women: < 80 µmol/L (< 0.9 mg/dL)
Men: < 100 µmol/L (< 1.0 mg/dL)
Creatinine clearance:
95–160 ml/min./1.73 m^2 body surface

Factors that may influence results. Jaffé method is disturbed by many factors, e. g., by bilirubin, ketone bodies, glucose, and several drugs (false-high values, by 5%–20%). Creatinine and creatinine clearance are influenced by muscle mass (beware age, cachexia, muscularity); increased glomerular filtration rate during pregnancy (consequently, lower cut-off) and early stage of diabetes mellitus.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Acute renal failure	Blood count, potassium, sodium, chloride, calcium, phosphate, acid–base balance, urea, uric acid, Quick test, PTT, CRP, urinalysis, urinary sediment (erythrocyte morphology), differentiation of proteinuria	29
Chronic renal insufficiency	Blood count, potassium, sodium, chloride, calcium, phosphate, acid–base balance, uric acid, alkaline phosphatase, protein (lipid profile, ferritin, PTH, 25-OH vitamin D)	29

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D-Dimers

D-dimers are fibrinolytic degradation products composed of crosslinked fibrin, which are released in response to prior disseminated intravascular coagulation or local activation of coagulation (thrombosis). They must be differentiated from fibrinogen degradation products that develop in the course of primary fibrinolysis, i. e., without prior activation of coagulation.

Indication. Ruling out venous thrombosis or pulmonary embolism; diagnosis and monitoring of disseminated intravascular coagulation, monitoring of fibrinolytic therapy.

Normal values:
Dependent on method; cut-off of most tests: 0.5 mg/L

Factors that may influence results. Material other than citrate plasma, incorrect blood withdrawal (see Quick Test), thrombolysis therapy.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Venous thrombosis (deep vein thrombosis of the leg)	(Quick test, PTT and fibrinogen to monitor therapy; screening for thrombophilic risk factors: APC resistance, protein deficiency, protein C and S deficiency, antithrombin deficiency; prothrombin gene mutations, factor V gene mutations, homocysteine, Lp[a])	9, 15
Pulmonary embolism	PO_2, acid–base balance (Quick test, PTT and fibrinogen to monitor therapy; screening for thrombophilic risk factors: APC resistance, protein deficiency, protein C and S deficiency, antithrombin deficiency; prothrombin gene mutations, factor V gene mutations, homocysteine, Lp[a])	6, 9, 15, 17
Disseminated intravascular coagulation	Thrombocytes, fibrinogen, antithrombin	15
Arterial thrombosis (e. g., myocardial infarction)	See Troponins, CK	6, 9
Carcinomas		

Erythrocytes

See Chapter 13.

Ferritin

Indication. Diagnosis of iron deficiency anemia and of storage iron deficiency, differential diagnosis of anemias, iron overload, monitoring of iron substitution and iron mobilization.

Normal values:
Women < 60 years: 10–150 µg/L
Women > 60 years; Men: 30–400 µg/L

Factors that may influence results. Normal values are highly dependent on age and gender; beware increased concentration in inflammation (acute phase protein), massive hemolysis.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Iron deficiency (iron storage deficiency, chronic blood loss, status after acute blood loss, functional iron deficiency resulting from erythropoietin therapy for renal anemia, hemodialysis, impaired iron absorption, dietary iron deficiency, pregnancy)	Blood count including determination of erythrocyte coefficients and of relative distribution width, fraction of hypochromic reticulocytes, soluble transferrin receptor	13

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Increased		
Differential diagnosis Anemias without iron deficiency	**Supplementary tests** Blood count including determination of erythrocyte coefficients and relative distribution width, fraction of hypochromic reticulocytes, soluble transferrin receptor, reticulocytes, bilirubin, haptoglobin, vitamin B_{12}, folic acid	**See Chapter** 13
Anemias in chronic diseases (infection- or tumor-related anemia) (also in infections, tumors, or chronic inflammation without manifest anemia)	Blood count including determination of erythrocyte coefficients and relative distribution width, fraction of hypochromic reticulocytes, soluble transferrin receptor; see CRP, Rheumatoid Factor, ANA	13
Hereditary hemochromatosis	Ferritin, HFE genotyping, ALT, GGTP, bilirubin, ChE, Quick test, albumin	25
Secondary hemochromatosis (anemia due to ineffective erythropoiesis, e. g., sideroblastic anemia; liver diseases, e. g., hepatitis)	Ferritin, blood count, ALT, GGTP, bilirubin, ChE, Quick test, albumin	13, 25
Liver cirrhosis	See Albumin	25
Alcoholism	See GGTP	25

Fibrinogen

Indication. Congenital or acquired fibrinogen deficiency, monitoring of fibrinolytic therapies, disseminated intravascular coagulation.

Normal values: 1.5–4.0 g/L

Factors that may influence results. Heparin and fibrin(ogen) degradation products lead to false-low fibrinogen concentrations; acute phase (inflammation) increases fibrinogen concentration.

Decreased		
Differential diagnosis Disseminated intravascular coagulation (e. g., in shock, sepsis, transfusion incidence)	**Supplementary tests** See D-Dimers	**See Chapter** 15
Hyperfibrinolysis (e. g., following extensive surgery, leukosis)	See D-Dimers	15
Severe damage of liver parenchyma	See Albumin, Aminotransferases	25
Cachexia	See Albumin	2, 3
Congenital Afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia		15
Drugs (fibrinolytic agents, ancrod, defibrase, asparaginase)		15

Increased		
Differential diagnosis Infections	**Supplementary tests** See CRP, Procalcitonin	**See Chapter** 2–11, 16–18, 20, 27, 29, 31, 32
Inflammatory and rheumatic diseases	See CRP, Rheumatoid Factor, ANA, Uric Acid, ANCA	2–4, 9–11, 13, 17, 18, 25, 29, 31, 32
Necroses, tissue damage (e. g., trauma, surgery, myocardial infarction, burn injuries, radiation therapy)	Depending on situation; see CK, LDH	6
Malignant tumors	See Amylase, LDH, Aminotransferases, GGTP, GLDH, Bilirubin, Serum Protein Electrophoresis	2, 3, 13, 14, 16–19, 25–28
Nephrotic syndrome	See Albumin	29

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Folic Acid

Indication. Macrocytic anemia, peripheral neuropathy, alcoholism, hyperhomocysteinemia, malabsorption syndrome, reduced nutritional status in elderly patients, certain drugs, planning of pregnancy (prevention of neural tube defects).

Factors that may influence results. Blood drawn from non-fasting patient, hemolysis, drugs (methotrexate or leucovorin therapy [cross reaction], ampicillin, chloramphenicol, penicillin, tetracyclines).

Normal values:
In plasma: 2.5–9.0 μg/L (5–20 nmol/L)
In erythrocytes: > 165 μg/L (> 350 nmol/L)

Decreased		
Differential diagnosis Macrocytic anemia	**Supplementary tests** Blood count including determination of erythrocyte coefficients, vitamin B_{12}	**See Chapter** 13
Folate malabsorption	Xylose test, see Albumin	27, 28
Chronic alcoholism	See GGTP; carbohydrate-deficient transferrin	2, 3
Malnutrition, especially in old age	See Albumin, Homocysteine	2, 3
Smokers		2, 3
Drugs (methotrexate, trimethoprim, anticonvulsants)		2, 3
Inborn errors of folate metabolism	MTHFR genotyping	

Follicle Stimulating Hormone (FSH)

See Gonadotropins.

Gamma-Glutamyl Transpeptidase (GGTP)

Indication. Diagnosis and monitoring of liver diseases and bile duct disorders.

Factors that may influence results. Hemolysis, citrate, oxalate.

Normal values:
Women: < 39 U/L
Men: < 66 U/L

Increased		
Differential diagnosis Acute, chronic aggressive and persisting viral hepatitides	**Supplementary tests** See Aminotransferases	**See Chapter** 25
Concomitant hepatitis (e. g., mononucleosis)	See Aminotransferases	4, 14, 25
Liver abscess	See Bilirubin	25
Autoimmune hepatitides	See ANA, ANCA, Bilirubin	25
Alcoholic and other toxic hepatopathies	See Aminotransferases	25
Liver cirrhosis	See Albumin	25
Hypoxic liver disease, congestion of liver	See GLDH	25
Liver carcinoma and metastases	See AFP	25
Fatty liver (alcohol, metabolic syndrome, diabetes mellitus, hypertriglyceridemia)	See Aminotransferases	2, 3

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Increased		
Differential diagnosis Intrahepatic and extrahepatic cholestasis	**Supplementary tests** See Bilirubin	**See Chapter** 25
Acute pancreatitis	See Amylase	7
Myocardial infarction	See CK, Troponins	6
Alcoholism	ALT, carbohydrate-deficient transferrin, mean corpuscular erythrocyte volume, folic acid	2, 3
Pharmaceuticals and xenobiotics		2, 3

Glucose

Indication. Screening, diagnosis, monitoring of therapy and course of diabetes mellitus; assessment of carbohydrate metabolism in many conditions and during various therapies; evaluation of symptoms of hypoglycemia.

Normal values:
Conventional (fasting):
Capillary: 3.9–5.5 mmol/L (70–100 mg/dL)
Venous whole blood: 3.3–5.5 mmol/L (60–100 mg/ dL)
Venous plasma: 3.9–6.4 mmol/L (70–115 mg/dL)

ADA criteria for using plasma glucose:
Normal: < 5.5 mmol/L (< 100 mg/dL)
Impaired fasting glucose: 5.5–7.0 mmol/L (100–126 mg/dL)
Diabetes mellitus:
> 7.0 mmol/L (> 126 mg/dL) (fasting);
> 11.1 mmol/L (> 200 mg/dL) (spontaneous)

Factors that may influence results. Testing material (see reference ranges, which depend on testing material), food intake, glucose consumption by blood cells, ascorbic acid, uric acid, creatinine.

Decreased		
Differential diagnosis Inadequate therapy for diabetes mellitus (insulin overdose, antidiabetics; insufficient carbohydrate uptake, acute secondary diseases, etc.)	**Supplementary tests** Blood count, sodium, potassium, chloride, osmolality, acid–base balance, glucose, lactate, creatinine, urea, CRP, urinalysis (ketone bodies)	**See Chapter** 2, 3, 31, 32
Insulinoma	C-peptide, insulin, starvation test	2, 3, 31, 32
Other large tumors, leukemias, polycythemia vera	Blood count, C-peptide, insulin, starvation test, tumor screening	2, 3, 13, 14
Alcohol-induced hypoglycemia	Blood count, sodium, potassium, chloride, osmolality, acid–base balance, glucose, lactate, alcohol, β-hydroxybutyrate, free fatty acids, creatinine, urea, C-peptide, insulin	2, 3, 31, 32
Drug-induced hypoglycemia (oral antidiabetics, salicylates, ACE inhibitors, quinine, pentamidine, disopyramide)	Drug screening	2, 3, 31, 32
Factitious hypoglycemia	C-peptide, insulin	2, 3, 31, 32

Increased		
Differential diagnosis Diabetes mellitus type 1 and type 2	**Supplementary tests** For first diagnosis: HbA_{1c}, lipid profile, creatinine, urinary albumin, urinalysis, (in some cases autoantibodies [IA, ICA, GADA] to differentiate between type 1 and type 2); for follow-up: HbA_{1c}, lipid profile, urinary albumin	**See Chapter** 2, 3, 6, 8, 29–32
Gestational diabetes	HbA_{1c}, creatinine, uric acid, urinalysis, protein, quantitative determination of albumin in urine, (prenatal screening, [AFP, free β-HCG, PAPP-A])	2, 3, 29
Diabetic coma	Blood count, sodium, potassium, chloride, osmolality, acid–base balance, lactate, creatinine, urea, CRP, urinalysis	2, 3, 30–32

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Gonadotropins

Indication. Women: menstrual cycle disturbances, fertility testing; men: hypogonadism, fertility testing.

Normal values:		
Women:	**LH**	**FSH**
proliferative stage	3–15 U/L	2–10 U/L
periovulatory phase	20–200 U/L	8–20 U/L
luteal phase	5–10 U/L	2–8 U/L
postmenopause	> 20 U/L	> 20 U/L

Normal values:	**LH**	**FSH**
Men:	2–10 U/L	1–7 U/L

Factors that may influence results. Insufficient standardization results in method-dependent reference intervals.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hyperprolactinemia	See Prolactin	2, 3
Hypopituitarism (tumor, trauma, necrosis, empty sella syndrome)	Blood count, glucose, prolactin, TSH, GH, IGF-I, IGFBP-3, ACTH, cortisol, cortisol in 24 hour urine, gonadotropin-releasing hormone tests (global pituitary stimulation test)	2, 3
Anorexia nervosa	Blood count, potassium, sodium, lipid profile; see Albumin, Cortisol	2, 3
Kallmann syndrome	Men: testosterone, women: estradiol	2, 3
Suppression by use of sex steroids and androgenic anabolic steroids		2, 3

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Menopause	Estradiol, (lipid profile, glucose)	2, 3
Precocious menopause	Estradiol, (lipid profile, glucose)	2, 3
Hyperandrogenemic ovarian failure, polycystic ovary syndrome (LH/FSH ratio > 2)	Testosterone, SHBG, DHEAS, androstenedione, (lipid profile, glucose)	2, 3
Resistant ovary syndrome	Estradiol	2, 3
Sex chromosome disorders (Turner syndrome, Swyer–James syndrome, Klinefelter syndrome)	Karyogram	2, 3

Haptoglobin

Indication. Diagnosis and follow-up of hemolytic anemias.

Normal values: 0.3–2.0 g/L

Factors that may influence results. Inflammations (acute phase).

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hemolytic anemia	Blood count, reticulocytes, bilirubin (indirect), LDH, urinalysis, (hemopexin, hemoglobin in plasma, examinations to determine the etiology of hemolytic anemia [direct and indirect Coombs tests, erythrocyte morphology, osmotic resistance, sugar water test, Hb electrophoresis, erythrocyte enzymes, CD59])	13, 25
Acute and chronic liver diseases	See ALT, GGTP, Bilirubin (direct), ChE, Quick Test, Albumin	25
Malabsorption syndrome	See Albumin	27
Congenital haptoglobin deficiency	Haptoglobin electrophoresis or haptoglobin genotyping	

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Increased		
Differential diagnosis Acute phase (acute and chronic inflammations, necroses, tumors)	**Supplementary tests** See CRP	**See Chapter** 2–11, 13, 16–18, 20, 27, 29, 31, 32
Cholestasis	See ALT, Bilirubin (direct)	25
Iron deficiency anemia	See Ferritin	29
Plasmocytoma, amyloidosis	See Immunoglobulins	11, 13–15, 29
Nephrotic syndrome	See Albumin	12, 29

HDL Cholesterol

Indication. Assessment of cardiovascular risk.

Normal values:
Conventional:
Women: 0.90–2.20 mmol/L (35–85 mg/dL)
Men: 0.75–1.70 mmol/L (29–66 mg/dL)

Risk cut-off level:
Women: 1.15 mmol/L (45 mg/dL)
Men: 0.90 mmol/L (35 mg/dL)

Factors that may influence results. Hemolysis, lipemia, jaundice.

Decreased		
Differential diagnosis Severe damage of liver parenchyma (liver cirrhosis, hypoxic liver damage)	**Supplementary tests** See ALT, GGTP, Bilirubin, ChE, Albumin	**See Chapter** 6, 25
Inflammatory bowel diseases	See Albumin	27
Acute phase (acute and chronic inflammations, infections, necroses)	See CRP	2–11, 13, 16–18, 20, 27, 29, 31, 32
Insulin resistance and diabetes mellitus type 2	See Glucose, HbA_{1c}	2, 3, 6
Hypertriglyceridemia	See Lipid Profile	2, 3, 6
Hypothyroidism	See TSH	6, 16
Drugs and hormones (androgens, gestagens, beta-blockers, thiazides, probucol)		2, 6
Rare familial HDL deficiency syndromes (apo A-I deficiency, LCAT deficiency, Tangier disease) or lipid storage diseases (Gaucher disease, Niemann–Pick disease type A, B, or C, Wolman disease, Refsum disease)	Apo A-I, creatinine, ALT, GGTP, bilirubin, ChE, Quick test, albumin, proteinuria, genetic analysis of candidate genes	2, 3, 6, 12–14, 25, 29

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Rare familial hyperlipoproteinemia syndromes (CETP deficiency, hepatic lipase deficiency)	Lipid profile	6
Drugs and hormones (estrogens, fibrates, nicotinic acid)		2, 6

Hematocrit

See Chapter 13.

Hemoglobin

See Chapter 13.

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Homocysteine

Indication. Assessment of cardiovascular risk and risk of thrombophilia, especially in high-risk patients, global test to evaluate the supply of vitamin B_{12} and folic acid (especially in the elderly).

Normal values:
Conventional: < 20 mmol/L
Risk cut-off level: < 12 mmol/L

Factors that may influence results. Methionine-rich foods (animal products must be avoided 24 hours prior to blood withdrawal), long storage period (erythrocyte metabolism).

Increased		
Differential diagnosis Deficiency of certain B vitamins	**Supplementary tests** Folic acid, vitamins B_6, B_{12}, methylmalonic acid	**See Chapter**
Renal insufficiency	See Creatinine	29
Hypothyroidism	See TSH	16
Homocystinuria		
Drugs (methotrexate, sulfonamides, anticonvulsants, fibrates)		

Human Chorionic Gonadotropin (HCG)

Human chorionic gonadotropin (HCG) consists of two peptide chains (α-chain and β-chain). Depending on the indication, different test formats are used. The pregnancy test recognizes intact HCG, the tumor marker recognizes intact HCG and the free β-chain, and the test for prenatal diagnostics recognizes only the free β-chain.

Indication. Pregnancy test; diagnosis, differential diagnosis, and follow-up of hepatocellular carcinoma and germ cell tumors (also early recognition of these tumors in risk groups); prenatal diagnostics during pregnancy (Down syndrome, neural tube defects).

Normal values:
HCG (β-HCG and free β-HCG):
Premenopausal women; Men: < 5 U/L
Postmenopausal women: < 10 U/L

β-HCG:
Premenopausal women: < 3 U/L
Postmenopausal women: < 6 U/L
Men: < 2 U/L

Free β-HCG: < 0.2 U/L

Factors that may influence results. Nicked HCG forms in some trophoblastic tumors, which are not recognized by all immunoassays, high-dose hook effect if HCG concentration is very high (false-low).

Increased		
Differential diagnosis Pregnancy	**Supplementary tests**	**See Chapter** 2, 3
Germ cell tumors, seminomas, teratomas partly positive, dermoid cysts, yolk sac tumor always negative	AFP (mandatory)	
Terminal renal insufficiency	See Creatinine	29

Immunoglobulins A, G, and M

Indication. Diagnosis and monitoring of antibody deficiency; differential diagnosis of monoclonal and polyclonal gammopathies.

Factors that may influence results. Hypertriglyceridemia, bilirubin.

Normal values:
IgA: 0.7–5.0 g/L
IgG: 7.0–16.0 g/L
IgM: 0.4–2.8 g/L (women); 0.4–2.3 g/L (men)

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Decreased (all or selectively decreased)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Primary immunodeficiencies		
B-cell defects (e. g., Bruton type agammaglobulinemia, selective deficiencies of IgA, IgG, or IgM; light- or heavy-chain deficiency)	Complete blood count, lymphocyte subclasses (CD3, CD4, CD8, CD20), CRP, ESR, complement factors, provocation testing (protein)	2–4, 14
T-cell defects (e. g., Di George syndrome, mucocutaneous candidiasis)		2–4, 14
Combined immunodeficiencies (e. g., Nezelof syndrome, Wiskott–Aldrich syndrome)	Blood count	2–4, 14
Secondary immunodeficiencies		
Malignant tumors (all Ig)	See CRP	2, 3, 13, 14
Lymphatic leukemias, Hodgkin and non-Hodgkin lymphomas (especially IgA and IgM)	Complete blood count, genetic and immunologic characterization	2, 3, 13, 14
Malignant monoclonal gammopathies (especially suppression of nonaffected Ig and loss of affected Ig)	Complete blood count, calcium, phosphate, creatinine, alkaline phosphatase, serum and urinary protein electrophoresis; immunofixation electrophoresis of serum and urine, urinalysis, quantitative urinary protein excretion	2, 3, 13, 14
Nephrotic syndrome (primarily IgG)	See Albumin	12, 29
Protein-losing enteropathy (all Ig)	See Albumin	27
Burn injuries (all Ig)	See Albumin	2, 3
Viral infections (e. g., measles, rubella, EBV)	Blood count, virus serology	2, 3, 4, 14
Drugs (immunosuppressants, glucocorticoids, cytostatics)		2, 3

Increased (all or selectively increased)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Malignant monoclonal gammopathies (multiple myeloma/plasmacytoma, Waldenström disease, cryoglobulinemia, amyloidosis [IgA, IgG, or IgM])	Complete blood count, calcium, phosphate, creatinine, alkaline phosphatase, serum and urinary protein electrophoresis; immunofixation electrophoresis of serum and urine, urinalysis, quantitative urinary protein excretion	2, 3, 13, 14
Benign monoclonal gammopathies or monoclonal gammopathies of unclear significance (IgA, IgG, or IgM)	Complete blood count, calcium, phosphate, creatinine, alkaline phosphatase, serum and urinary protein electrophoresis; immunofixation electrophoresis of serum and urine, urinalysis, quantitative urinary protein excretion	2, 3, 13, 14
Acute hepatitis (IgM first, then IgG)	See Aminotransferases	25
Chronic persisting hepatitis (IgM and IgG)	See Aminotransferases	25
Primary biliary cirrhosis (IgM)	See Bilirubin	25
Liver cirrhosis (IgA, IgG, and IgM)	See Albumin	25
Infections (viruses, parasites, [first IgM then IgG])	blood count; see CRP; serology (if indicated)	4
Rheumatic diseases, collagen diseases (IgM and IgG)	See Rheumatoid Factor, ANA, ANCA	2–4, 9–11, 13, 17, 18, 25, 29, 31, 32

Immunoglobulin E

Indication. Allergy, parasitosis.

Factors that may influence results. Smoking.

Normal values: < 120 kU/L

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Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Allergy, atopic dermatitis	Blood count (eosinophils), specific IgE	2, 3, 12, 17, 27
Parasitosis	Blood count (eosinophils)	4, 8, 25, 27, 28
Congenital and acquired disorders of T-cell function (Wiskott–Aldrich syndrome, Nezelof syndrome, AIDS, non-Hodgkin lymphomas)	See Immunoglobulins	2–4, 13–15
Malignant tumors	See CRP	
Hyper-IgE syndrome		

Iron

Iron is an unsuitable parameter for diagnosis of iron deficiency. In addition to the blood count, ferritin is the most important parameter to evaluate iron deficiency. The determination of iron is only suitable for evaluation of transferrin saturation (see Transferrin Saturation) and (in this context) for the diagnosis and follow-up of iron overload (hemochromatosis).

Lactate

Indication. Prognosis and monitoring of shock and intoxications, evaluation of metabolic acidosis, identification of tissue hypoxia if P_{O_2} is normal.

Normal values:
Arterial: < 1.8 mmol/L (< 16.0 mg/dL)
Venous: 0.5–2.2 mmol/L (4.5–20.0 mg/dL)

Factors that may influence results. Preference should be given to arterial samples, withdrawal of venous blood samples should be without tourniquet application; cell metabolism if specimen transport or storage period are long (reduced impact if potassium oxalate or sodium fluoride are added).

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Without acidosis		
Hyperventilation	See Acid–Base Balance	17, 20
Muscular activity (sports, grand-mal seizure)	See CK	
Infusions of sodium bicarbonate, pyruvate, lactate, glucose, fructose, sorbite, or xylitol		
High-dose insulin therapy		
Administration of catecholamines or catecholaminergic substances (theophylline, cocaine, ether)		
Postoperatively	See CRP	
With acidosis		
Shock, cardiac arrest	Blood count, potassium, sodium, chloride, osmolality, blood gases, acid–base balance, glucose, bilirubin, Quick test, PTT, fibrinogen, D-dimers, CRP	3, 24, 30
Sepsis	See CRP, Procalcitonin	4, 30
Infections (HIV, malaria)	See Complement C3 and C4	4, 30
Anaerobic bacterial overgrowth of the small intestine	Microbiology	27, 28
Acute hepatic failure	See Albumin, ChE, Ammonia	25, 30
Leukemias and lymphomas	Hemogram	13, 14, 30
Biguanide-induced lactic acidosis	Glucose, acid–base balance, ketone bodies, creatinine	30, 32

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Increased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
With acidosis		
Diabetic or alcoholic ketoacidosis	See Glucose; acid–base balance, ketone bodies, osmotic gap, alcohol	30, 32
Alcohol intoxication, methanol intoxication, salicylate intoxication, acetaminophen intoxication	See Osmotic Gap; detection of intoxication	25, 30–32
CO intoxication	Blood gases, CO hemoglobin	30–32
Thiamine deficiency (alcoholics, beriberi, intensive care patients)	vitamin B_1	2, 3, 30, 32
Isoniazide therapy, nicotinic acid therapy, lactulose therapy, therapy with L. acidophilus		2, 3, 30
Congenital lactic acidoses (mitochondrial myopathies, glycogen storage disease, enzyme defects in glucose degradation)	Pyruvate, CK, myoglobin in urine, ammonia, test for McArdle disease	8

Lactate Dehydrogenase

Indication. Suspected hemolytic anemia, differentiation of jaundice, diagnosis of organ damage (isoenzymes), monitoring of hematologic and oncologic diseases.

Normal values: 150–420 U/L

Factors that may influence results. Hemolysis, unstable at low temperatures, production stimulated by various drugs.

Increased		
Differential diagnosis Shock	**Supplementary tests** Blood count, potassium, sodium, chloride, osmolality, blood gases, acid–base balance, glucose, lactate, bilirubin, Quick test, PTT, fibrinogen, D-dimers, CRP	**See Chapter** 3, 24, 30
Heart muscle damage (myocardial infarction, myocarditis, trauma, surgery) (LDH1)	See CK	2–4, 6
Diseases of skeletal muscle (trauma, myositis, vigorous exertion)	See CK	8
Pulmonary embolism (LDH3)	See D-Dimers	6, 17, 21
Damage of liver parenchyma (e. g., hepatitis, tumors, abscess) (LDH5)	See Aminotransferases, GGTP, Bilirubin	25
Hemolytic anemia (LDH1 and LDH5)	See Haptoglobin	13
Megaloblastic anemia	See Vitamin B_{12}	13
Thrombotic thrombocytopenic purpura	See Haptoglobin, Complement C3 and C4	13, 15
Mononucleosis	See Aminotransferases	14, 25
Acute leukemia, chronic myeloid leukemia	Complete blood count, aminotransferases, genetic and immunologic characterization, EBV serology	14
Malignant neoplasms (e. g., liver metastases, non-Hodgkin lymphoma)	CRP, aminotransferases, GLDH, tumor screening	2, 3

LDL Cholesterol

See Lipid Profile.

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Leukocytes

See Chapter 14.

Lipase

Indication. Diagnosis of acute pancreatitis, relapsing chronic pancreatitis, evidence of pancreatic involvement in abdominal diseases.

Normal values: Higly dependent on method

Factors that may influence results. Intravenous heparin, macrolipase.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Acute pancreatitis and acute episodes in the course of chronic pancreatitis	See Amylase	7
Obstruction of pancreatic duct (calculus, carcinoma, stricture)	See Amylase	7
After endoscopic retrograde cholangiopancreatography (ERCP)	See Amylase	7, 25
Concomitant pancreatitis in abdominal diseases (ulcer perforation, ileus, mesenteric infarction, peritonitis, salpingitis, extrauterine gravidity)	See Amylase	7, 25, 27, 28
Renal insufficiency	See Creatinine	29

Lipid Profile

The most important indication is the determination of cardiovascular risk. To assess this risk, it is necessary to include other risk factors such as age, sex, patient's history and family history of arteriosclerotic diseases, diabetes mellitus, smoking, and blood pressure. These factors, together with the lipid profile, allow the assessment of the risk of myocardial infarction through algorithms, scores, or tables available on the internet (e. g., www.chd-taskforce.com). Ideal values and target values have to be seen from this angle. Most often, hyperlipidemias are of multifactorial or of polygenetic origin. Monocausal hyperlipidemias, either of genetic origin or based on an underlying disease, often manifest through extreme dyslipidemias. Therefore, from the point of view of differential diagnosis, conventional reference ranges (i. e., defined by percentiles) are relevant. Particularly if the values determined fall below or exceed the reference ranges, screening for primary and secondary causes of dyslipidemia should be performed. Hypolipidemias are diagnostically relevant only in special situations and if characteristic symptoms are present.

Normal values (ideal values):
Total cholesterol:
5th and 95th percentiles:
3.9–7.8 mmol/L (150–300 mg/dL)
Ideal value: < 5.2 mmol/L (< 200 mg/dL)

LDL cholesterol:
5th and 95th percentiles:
2.3–5.2 mmol/L (90–200 mg/dL)
Ideal values, target values:
secondary prevention, high risk: < 2.6 mmol/L (< 100 mg/dL)
intermediate risk: < 3.4 mmol/L (< 130 mg/dL)
moderate risk: < 4.2 mmol/L (< 160 mg/dL)

Triglycerides:
5th and 95th percentiles:
Women: 0.6–2.1 mmol/L (50–180 mg/dL)
Men: 0.6–4.1 mmol/L (50–360 mg/dL)
Ideal value, target value: < 1.7 mmol/L (< 150 mg/dL)

HDL cholesterol: See HDL Cholesterol.

Indication. Assessment of cardiovascular risk, therapy monitoring of detected dyslipidemia and dyslipidemia-associated disorders (e. g., diabetes mellitus, renal insufficiency, nephrotic syndrome), diagnosis of dyslipidemia if typical clinical symptoms are present (e. g., early onset of arteriosclerosis, xanthomas, arcus cornea, steatorrhea, hepatomegaly, neuropathy).

Factors that may influence results. Food intake (triglycerides, calculated LDL cholesterol), excessive application of a tourniquet, upright body position versus supine position, acute phase (decreased lipoprotein concentration), hemolysis, hyperbilirubinemia.

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Isolated hypercholesterolemia (type IIa, according to Fredrickson)		
Differential diagnosis Familial hypercholesterolemia	**Supplementary tests** LDL receptor, apo B defects	**See Chapter** 6
Sitosterolemia	Phytosterols	6
Hypothyroidism	TSH	16
Anorexia	Albumin	2, 3
Acute intermittent porphyria	Complete blood count, sodium, potassium, creatinin, aminotransferases, indirect bilirubin, total porphyrins, δ-aminolevulinic acid, urinary porphobilinogen	7
Drugs (gestagens, protease inhibitors)		2, 3

Isolated hypertriglyceridemia (type I or IV, according to Fredrickson)		
Differential diagnosis Chylomicronemia (type I)	**Supplementary tests** Lipoprotein lipase, apo C-II	**See Chapter** 6
Diabetes mellitus	See Glucose	2, 3, 29, 30, 32
Glycogen storage disease, type I		
Renal insufficiency	See Creatinine	29
Acute hepatitis	See Aminotransferases	25
Acute inflammations	See CRP	4
Monoclonal gammopathy	See Immunoglobulins	14
Debilitating diseases (e. g., AIDS)	See Complement C3 and C4, CRP	2, 3
Estrogens (pregnancy, contraception, hormone replacement therapy)	Pregnancy test	2, 3
Alcoholism (Zieve syndrome)	See GGTP; thrombocytes	2, 3, 25
Gaucher disease		
Drugs (diuretics, beta-blockers without ISA, retinoids, cimetidine, tamoxifen, glucocorticoids, protease inhibitors) (type IV)		

Mixed hyperlipidemia (type IIb, III, and V, according to Fredrickson)		
Differential diagnosis Familial hypercholesterolemia (type IIb)	**Supplementary tests** LDL receptor, apo B defects	**See Chapter** 6
Remnant hyperlipidemia (type III)	Apo E polymorphism, VLDL cholesterol, lipoprotein electrophoresis	6
Other rare genetic hyperlipidemias (hepatic lipase deficiency, cholesterol ester storage disease [type IIb, III])	Hepatic lipase, acid lipase	6
Cholestatic diseases (type IIb)	See GGTP, Bilirubin	25
Biliary cirrhosis (type IIb)	See Bilirubin	25
Nephrotic syndrome (type IIb, V)	See Albumin	12, 29
Renal insufficiency (type IIb)	See Creatinine	29
Consumptive diseases (e. g., AIDS) (type IIb, V)	See Complement C3 and C4, CRP	2–4
Hypothyroidism (type IIb)	See TSH	16
Hypercortisolism (type IIb, V)	See Cortisol	2, 3
Acromegaly	Glucose, GH (basal level and in glucose tolerance test), IGF-1	2, 3
Estrogens (pregnancy) (type IIb, V)	Pregnancy test, HCG	2, 3
Alcoholism (type V)	See GGTP	2, 3, 25, 32
Diabetes mellitus (type IIb, V)	see Glucose	2, 3, 29, 30, 32
Drugs (diuretics, retinoids, glucocorticoids, protease inhibitors) (type IIb, V)		

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Hypolipidemia (particularly manifests as hypocholesterolemia)		
Differential diagnosis Marked HDL deficiencies	**Supplementary tests** See HDL Cholesterol	**See Chapter** 6
Abetalipoproteinemia, hypobetalipoproteinemia	Apo B, lipoprotein electrophoresis, stool fat	6, 27
Liver cirrhosis	See Albumin	12, 25
Debilitating diseases	See Complement C3 and C4, CRP	2–4

Luteinizing Hormone (LH)

See Gonadotropins.

Magnesium

Indication. Evaluation of cardiac conduction disturbances, disturbances of neuromuscular transmission, and gastrointestinal complaints; monitoring of treatment with diuretics and nephrotoxic drugs, intestinal malabsorption, alcohol withdrawal, parenteral feeding, renal insufficiency; magnesium intoxication.

Normal values: 0.70–01.00 mmol/L

Factors that may influence results. Extended application of a tourniquet, hemolysis.

Decreased		
Differential diagnosis Insufficient magnesium supply (alcoholism, malassimilation)	**Supplementary tests** See GGTP, Albumin	**See Chapter** 26, 27, 30
Gastrointestinal loss (vomiting and aspiration of gastric juice, diarrhea, steatorrhea, inflammatory intestinal diseases, laxative abuse, villous adenomas, celiac disease, short bowel syndrome)	Potassium, sodium, chloride, osmolality, acid–base balance, urinary potassium	26, 27, 30
Familial tubular absorption defects	See Potassium, Acid-Base Balance	29, 30
Bartter syndrome	See Potassium	23, 30
Primary and secondary hyperaldosteronism	See Aldosterone	23, 30
Liddle syndrome	See Potassium	23, 30
Diabetic and alcoholic ketoacidosis	See Glucose, Acid-Base Balance	29, 30
Primary hyperparathyroidism	See PTH	16, 30
Osteolysis due to bone metastases or plasmacytoma	See Alkaline Phosphatase, Immunoglobulins	11
Hyperthyroidism	See TSH	16
Familial hypomagnesemia	Potassium, sodium, chloride, osmolality, acid–base balance, urinary potassium	29, 30
Drugs (diuretics, penicillin, aminoglycosides, cisplatin, methotrexate, etc.)	Potassium in serum and urine	2, 3, 30

Increased		
Differential diagnosis Acute and chronic renal insufficiency	**Supplementary tests** See Creatinine	**See Chapter** 29, 30
Milk alkali syndrome	See Potassium	30
Tumor lysis syndrome	See LDH	
Magnesium-containing drugs (antacids, magnesium-containing enemas), theophylline, lithium		2, 3

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Myoglobin

Indication. Early diagnosis of myocardial infarction, follow-up of diseases of skeletal muscle.

Normal values:
Women: 25–58 μg/L
Men: 28–72 μg/L

Factors that may influence results. Hemolysis, lipemia; intramuscular injections.

Assessment. See Creatine Kinase.

Osmolality and Osmotic Gap

Osmolality can be assessed analytically and also calculated. Calculating facilitates the determination of the osmotic gap in suspected intoxication with nonionic, low molecular substances (e. g., methanol or ethanol):

mosmol/kg H_2O = 1.86 x sodium (mmol/L)
+ glucose (mmol/L) + urea (mmol/L) + 9 (mmol/L)

or

mosmol/kg H_2O = 1.86 x sodium (mmol/L)
+ glucose/18 (mg/dL) + urea/9 (mg/dL) + 9 (mmol/L)

Indication. Disorders of water and sodium balance, suspected intoxication with nonionic, low molecular substances, identification of pseudohyponatremia.

Normal values: 280–300 mosmol/kg H_2O

Factors that may influence results. Long specimen or storage period transport.

Increased osmotic gap		
Differential diagnosis Intoxication with nonionic low molecular substances (ethanol, methanol)	**Supplementary tests** Ethanol, methanol	**See Chapter** 30, 32
Lactic acidosis, ketoacidosis	See Acid–Base Balance, Glucose, Lactate	30, 32
Hemorrhagic shock	Blood count, electrolytes, blood gases, acid–base balance, glucose, Quick test, PTT, fibrinogen, D-dimers, CRP, lactate	30, 32
Pseudohyponatremia (hyperlipidemia, hyperproteinemia)	Measurement of sodium with direct ion-selective electrode, protein, lipid profile	30

Oxygen (Oxygen Partial Pressure [P_{O_2}]; Oxygen Saturation [S_{O_2}]; Oxyhemoglobin Fraction [FHb_{O_2}]; Oxygen Content [Ct_{O_2}])

Indication. Ventilation disorders, diseases of pulmonary parenchyma and impairment of pulmonary perfusion.

Normal values:
Arterial blood:
P_{O_2}: 9.5–13.9 kPa (71–104 mmHg)
S_{O_2}: 95 %–98.5 %
FHb_{O_2}: 94 %–98 %
Ct_{O_2}: 180–230 mL/L

Mixed venous blood:
P_{O_2}: 4.8–5.9 kPa (36–44 mmHg)
S_{O_2}: 70 %–80 %
FHb_{O_2}: 70 %–80 %
Ct_{O_2}: 130–180 mL/L

Factors that may influence results. The risk of using inappropriate test material inherent to this test makes it highly error-prone (vein instead of artery, pressure exerted during capillary blood withdrawal, contact with air, heparin excess, cell metabolism, clotting, insufficient resuspension); body temperature of patient.

Decreased		
Differential diagnosis Restrictive ventilation disorder (partial pulmonary resection, compression caused by pleural effusion or tumor, pneumothorax)	**Supplementary tests** Acid–base balance (in most cases, PCO_2 is normal)	**See Chapter** 17

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Decreased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Impaired diffusion (early stages of ARDS, sarcoidosis, pulmonary hemosiderosis)	Acid–base balance (in most cases, PCO_2 is normal or decreased)	17
Impaired distribution (bronchial asthma, emphysema, pneumonia, atelectasis, tumor, thoracic deformation)	Acid–base balance (in most cases, PCO_2 is normal or decreased); see CRP, IgE	17
Impaired perfusion (right-left shunt, pulmonary edema)	Acid–base balance (in most cases, PCO_2 is normal or decreased), BNP	17, 20
Alveolar hypoventilation in chronic obstructive bronchopulmonary and restrictive pulmonary diseases, respiratory embarrassment following mechanical obstruction (neuromuscular, osseus, diaphragmatic elevation, pleural effusion, hemo- and pneumothorax) or central respiratory paralysis (drugs, diseases of the CNS)	Acid–base balance	17
Decreased atmospheric pressure (respiration at high altitudes, insufficient oxygen supply during artificial respiration)	Acid–base balance	17

Parathyroid Hormone (PTH) (Intact PTH, iPTH)

Indication. Differential diagnostics of hypocalcemia and hypercalcemia; osteopathy; renal insufficiency, nephrolithiasis and nephrocalcinosis; malabsorption syndrome; evaluation of suspected hyperparathyroidism (HPT); localization of adenoma in primary HPT.

Normal values: 15–65 ng/L

Factors that may influence results. Slight pulsatility of PTH, blood withdrawal should therefore be performed in the morning.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
(Autoimmune) hypoparathyroidism	Calcium and phosphate in serum and urine, autoantibodies to parathyroid gland	16
Hypercalcemias without involvement of the parathyroid gland (vitamin D and AT10 overdose, milk alkali syndrome, Boeck disease, hyperthyroidism, tumor hypercalcemia)	Calcium and phosphate in serum and urine, 25-OH vitamin D_3, PTH-related peptide	2, 11, 18

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Primary hyperparathyroidism	Calcium and phosphate in serum and urine	7, 11, 16, 29
Secondary hyperparathyroidism	Calcium and phosphate in serum and urine, creatinine (clearance)	16, 29
Pseudohypoparathyroidism	Calcium, phosphate in serum and urine; urinary cAMP	29
Malabsorption syndrome	Calcium, phosphate, 25-OH vitamin D_3, stool fat; see Albumin	11, 27

(Activated) Partial Thromboplastin Time (PTT, aPTT)

Indication. Screening test for suspected hemorrhagic diathesis (e. g., hemophilia) or evaluation of the risk of bleeding; to monitor heparin therapy; evaluation of suspected presence of anticoagulants (e. g., lupus anticoagulant).

Normal values: 25–40 s

Factors that may influence results. Incorrect blood withdrawal (e. g., wrong test material, excessive application of a tourniquet, test tube is not completely filled); drugs (valproate, penicillin), heparin.

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Increased		
Differential diagnosis Therapy with unfractionated heparin	**Supplementary tests**	**See Chapter**
Congenital deficiency of factors I, II, VIII (hemophilia A or von Willebrand disease), IX (hemophilia B), X, XI, XII, prekallikrein, high molecular kininogen	Analysis of single factors	15
Inhibitors of the above-mentioned coagulation factors		15
Lupus anticoagulant	Phospholipid antibodies	15
Disseminated intravascular coagulation	D-dimers, antithrombin, fibrinogen, thrombocytes	15

P_{CO_2}

See Acid–Base Balance.

pH

See Acid–Base Balance.

Phosphate

Indication. Bone diseases, renal diseases (especially insufficieny, dialysis, and calculi), disorders of parathyroid gland, suspected vitamin D deficiency, alcoholism, after thyroid surgery, intensive care medicine.

Normal values: 0.85–1.45 mmol/L (2.6–4.6 mg/dL)

Factors that may influence results. Food intake, circadian rhythm, test material (serum > plasma), release from blood cells (caution: specimen transport and storage; hemolysis), hyperbilirubinemia and hyperlipidemia; pseudohyperphosphatemia due to monoclonal gammopathy.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Gastrointestinal causes Gastrointestinal loss (vomiting and aspiration of gastric juice, diarrhea, steatorrhea, inflammatory intestinal diseases, laxative abuse, villous adenomas, celiac disease, short bowel syndrome)	Potassium, sodium, chloride, osmolality, acid–base balance, urinary potassium	26, 27, 30
Intestinal malabsorption	See Albumin, PTH	27
Alcoholism	See GGTP, Osmolality, Anion Gap, Acid-Base Balance	30, 32
Antacid therapy		2
Vitamin D deficiency (rickets)	Calcium, 25-OH vitamin D_3, 1,25 $(OH)_2$ vitamin D_3, PTH	11
Renal causes Primary hyperparathyroidism	See PTH	7, 11, 16, 29
Renal tubular defects		29
Acidosis	See Acid–Base Balance	30
Diuretics		
Distribution disorders Hyperalimentation; particularly carbohydrate-rich diet after long fast period		

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Decreased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Distribution disorders		
Tumor-induced osteopathy	Calcium, alkaline phosphatase, 25-OH vitamin D_3, 1,25-$(OH)_2$ vitamin D_3, PTH, phosphate clearance	11
Postoperatively	Blood count, potassium, sodium, osmolality, CRP	2, 30
Severe burn injuries	Potassium, sodium, osmolality; see Albumin	2, 30
Sepsis	See CRP	4
Competitive sports	CK, lactate	2
Respiratory alkalosis	See Acid–Base Balance	30
Insulin therapy of diabetic ketoacidosis	See Glucose, Acid–Base Balance	30
Familial hypophosphatemia	Phosphate clearance	

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Renal causes		
Renal insufficiency	See Creatinine	11, 29
Hypoparathyroidism	See PTH	16
Pseudohypoparathyroidism	See PTH	16, 29
Increased release of intracellular phosphate		
Tumor cell death (chemotherapy, radiation therapy)	See Uric Acid LDH	2
Massive muscle cell death (trauma, crush syndrome, hemolysis, rhabdomyolysis)	See CK, LDH, Haptoglobin	2, 8, 13
Catabolism	See Urea	
Distribution disorders and other causes		
Acute metabolic acidosis	See Acid–Base Balance	30
Acromegaly	GH (basal level and after OGTT), IGF-I, IGFBP3	30
Increased supply of phosphate (e. g., laxatives, infusions)	Sodium, potassium, osmolality	
Vitamin D supply		

P_{O_2}

See Oxygen.

Potassium

Indication. High blood pressure, cardiac arrhythmias, renal insufficiency, diarrhea, vomiting, disorders of electrolyte and acid–base balance, monitoring of patients in intensive care.

Normal values: 3.6–4.8 mmol/L

Factors that may influence results. Hemolysis, unstable leukocytes in mononucleosis and leukemias, thrombocytosis, excessive application of tourniquet (false-high), extreme leukocytosis in leukemic patients, hypertriglyceridemia (false-low).

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Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Gastrointestinal loss Diarrhea, villous adenomas, secretion loss through enteral fistulas, laxative abuse, therapy with cation exchangers	Sodium, chloride, osmolality, acid–base balance, urinary potassium	27, 30
Vomiting, aspiration of gastric juice (pseudo-Bartter syndrome)	Potassium, sodium, chloride, calcium, magnesium, acid–base balance, uric acid, glucose tolerance test, aldosterone, renin, urinary chloride	26, 30
Renal loss Renal tubular acidosis	Sodium, chloride, osmolality, acid–base balance, urinary potassium	29, 30
Bartter syndrome	Sodium, chloride, osmolality, magnesium, acid–base balance, urinary potassium and urinary chloride, ADH	23, 30
Liddle syndrome	Sodium, chloride, osmolality, magnesium, acid–base balance, urinary potassium, desoxycortisone	23, 30
Polyuria after acute renal failure	See Creatinine	29, 30
Primary and secondary hyperaldosteronism	See Aldosterone	23, 30
Hypomagnesemia	See Magnesium	29, 30
Drugs (diuretics, penicillins, steroids, aminoglycosides, cisplatin, glycyrrhizic acid)	Urinary potassium	2, 3, 30
Loss through the skin Burn injuries, excessive perspiration	Sodium, chloride, osmolality, acid–base balance, urinary potassium	30
Insufficient potassium supply Anorexia and undernourishment, potassium-free parenteral feeding	Sodium, chloride, osmolality, acid–base balance, urinary potassium	30
Disorders of internal balance Metabolic alkalosis	See Acid–Base Balance	30
Familial hypokalemic periodic paralysis		
Insulin therapy	See Glucose	
Intensive therapy for vitamin B_{12} deficiency and folic acid deficiency	See Folic Acid, Vitamin B_{12}	
β_2 stimulation		

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Decreased renal excretion Acute and chronic renal insufficiency	See Creatinine	29, 30
Addisonian crisis	See Cortisol, Aldosterone	29, 30
Aldosterone deficiency (adrenogenital syndrome, hyporeninemic hypoaldosteronism)	See Cortisol, Aldosterone	29, 30
Renal tubular acidosis	Sodium, chloride, osmolality, acid–base balance, glucose, urinary potassium and urinary ketone bodies	29, 30
Drugs (spironolactone, sulfonamides, cyclosporin A, lithium, ACE inhibitors and angiotensin II receptor antagonists, NSAIDs)		2, 3
Increased supply Drugs (potassium infusion, succinylcholine, digitalis intoxication)	Digoxin, digitoxin	2, 3

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Increased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Disorders of internal balance Massive cell death (rhabdomyolysis, trauma, tumor cell death, hemolysis)	See CK, LDH, Aminotransferases	
Diabetic and alcoholic ketoacidosis	See Glucose, Acid–Base Balance	29, 30
Hyperkalemic periodic paralysis		
Drugs (beta-blockers, α-adrenergic agonists, digoxin, digitoxin, succinylcholine, somatostatin, diazoxide)		2, 3

Procalcitonin

Indication. Differentiation between bacterial and non-bacterial infections, parameter to monitor the course of bacterial infection (e. g., sepsis, peritonitis) or patients with increased risk of bacterial infections (e. g., intensive care patients, postoperative patients, patients with multiple trauma).

Normal values: < 0.5 μg/L

Factors that may influence results. Bilirubin, hemolysis, lipemia.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Bacterial infections (sepsis, meningitis, peritonitis, pneumonia, etc.)	See CRP	4, 5, 7, 10, 11, 14, 17, 18, 20, 22, 29, 31, 32
Fungal infections (candida, aspergillosis)	Blood count, CRP, urinalysis, urinary sediment, microbiological testing cultures	4, 5, 7, 14, 17, 18, 29, 31, 32
Protozoa infections (malaria)	See Complement C3 and C4	4, 14, 17, 18, 27, 29, 31, 32
Acute pancreatitis of biliary etiology	See Amylase	7
C-cell carcinoma, paraneoplastic in small cell bronchial carcinoma	Calcitonin, NSE	16–18

Prolactin

Indication. Women and men: galactorrhea; women: menstrual cycle disturbances, infertility, virilization, mastodynia, mastopathy; men: hypogonadism, gynecomastia, reduced libido, impotence.

Normal values:
Women: 3.4–24.1 μg/L (82–578 mIU/L)
Men: 4.1–18.4 μg/L (98–442 mIU/L)

Factors that may influence results. Stress (caution with blood withdrawal, preceding physical examination), circadian rhythm, macroprolactinemia.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Prolactinoma with or without pituitary tumor	Prolactin stimulation test	5, 31
Impaired dopamine transmission (prolactin-inhibiting factor), (pituitary tumors, suprasellar tumors, meningeal sarcoidosis, pituitary stalk section)	Prolactin stimulation test	5, 31
Hypothyroidism	See TSH	16
Renal insufficiency	See Creatinine	29
Drugs (several neuroleptics, metoclopramide, α-methyldopa, reserpine, cimetidine, high-dose estrogens)		

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Prostate-Specific Antigen (PSA; Free, Total)

Indication. Prostate cancer: screening, staging, and follow-up.

Normal values: Total PSA: < 4 μg/L
If total PSA level in the "gray area" (2.5–10.0 μg/L): free PSA/total ratio x 100 %): > 19 %

Factors that may influence results. Irritation or manipulation of the prostate prior to blood withdrawal (prostatic massage, digital rectal examination, sexual intercourse, biopsy, bicycling); administration of testosterone; change of method.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Prostate cancer	Free PSA	2
Prostatic hypertrophy	Free PSA	
Prostatitis	Free PSA, CRP, blood count	4, 29
Testosterone therapy, androgen therapy	Free PSA, testosterone, LH, hematocrit	

Protein (Total)

Indication. Differential diagnosis edema, monitoring of acute liver diseases and liver cirrhosis, of nephrotic syndrome, index of nutritional status, shock, burn injuries, intensive care patients.

Normal values: 65–82 g/L

Factors that may influence results. False-high values, up to 10 %, due to hemoconcentration if patient is not in a supine position or has been sitting for 15 minutes.

Values reduced, up to 20 % due to pregnancy, infusion therapy, polydipsia (pseudohypoproteinemia); pseudohyperalbuminemia due to dehydration (control of hematocrit); lipemia, hemolysis.

Evaluation. Decreased: see Albumin. Increased: see Protein Electrophoresis (γ-Globulins), Immunoglobulins.

Protein Electrophoresis

Indication. Diagnosis and monitoring of inflammations, protein loss (renal, intestinal, dermal, exudates and transudates), monoclonal gammopathy; differential diagnosis of hypoproteinemia and hyperproteinemia.

Normal values: Albumin: 35.2–50.4 g/L (52 %–65 %)
α1-globulins: 1.3–3.9 g/L (2 %–5 %)
α2-globulins: 5.4–9.3 g/L (11 %–15 %)
β-globulins: 5.9–11.4 g/L (6 %–13 %)
γ-globulins: 5.8–15.2 g/L (10 %–19 %)

Factors that may influence results. Impaired coagulation or plasma instead of serum (fibrinogen peak in β-globulins).

α_1-globulins and α_2-globulins increased (possibly β-globulins are also increased), albumin decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Acute inflammations (e. g., pneumonia, urinary tract infections)	See CRP	4, 5, 7, 10, 11, 14, 17, 18, 20, 22, 29, 31, 32
Malignant tumor	See CRP, LDH	
Obstructive jaundice	See Bilirubin (direct)	25

α_2-globulins and β-globulins increased, albumin and γ-globulins decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Nephrotic syndrome	See Albumin	12, 29

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α_2-globulins and γ-globulins increased, albumin decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Chronic inflammation (e. g., rheumatoid arthritis)	See CRP, Rheumatoid Factor, ANA, ANCA	

γ-globulins increased, albumin decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Monoclonal gammopathy/M-gradient (multiple myeloma, Waldenström disease, cryoglobulinemia)	See Immunoglobulins	14, 29
Polyclonal gammopathy (liver cirrhosis, hepatitis)	See Albumin, Aminotransferases	25

Quick Test (Prothrombin Time [PT]; Thromboplastin Time; International Normalized Ratio [INR])

Indication. Screening test for suspected hemorrhagic diathesis or evaluation of the risk of bleeding; to direct coumarin or warfarin therapy; monitoring of vitamin K deficiency (e. g., liver cirrhosis).

Normal values:
PT, Quick test: 70 %–130 %
INR: 2.0–3.5 (depending on indication of anticoagulant therapy)

Factors that may influence results. Incorrect blood withdrawal (e. g., wrong testing material, insufficient mixing, test tube is not completely filled, withdrawal from infusion catheter with hypertonic NaCl); hemolysis, insufficient centrifugation, drugs (heparin, penicillin).

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Therapy with warfarin or coumarins		15
Disturbances of the synthesis function of the liver (liver cirrhosis)	See Albumin, ChE	25
Vitamin K deficiency	Vitamin K	15
Congenital factor I, II, and V deficiency	Analysis of each single factor	15
Inhibitors of the above-mentioned coagulation factors		15
Lupus anticoagulant	Phospholipid antibodies	15
Disseminated intravascular coagulation	D-dimers, antithrombin, fibrinogen, thrombocytes	15

Renin

For the assessment of the renin-angiotensin-aldosterone system, especially the differentiation between primary and secondary forms of hyperaldosteronism, it is important to know the sodium and potassium balance (serum/plasma concentration and urinary excretion) as well as the renin concentration and activity.

Indication. Differential diagnosis of hyperaldosteronism, detection of a renin-producing tumor, diagnosis of malignant hypertension, diagnosis of mineralocorticoid deficiency.

Normal values:
Mass concentration:
Supine position: 3–19 ng/L
Upright position: 5–40 ng/L

Activity:
Supine position: 0.5–1.6 µg/L/h
Upright position: basal level increased two- to fivefold

Factors that may influence results. Drugs, body position, time of the day, sodium and potassium balance.

Assessment. See Aldosterone.

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Rheumatoid Factor (RF)

Indication. Evaluation of suspected rheumatoid arthritis; cryoglobulinemia.

Normal values: Dependent on method.

Factors that may influence results. Endogenous IgG, prozone phenomenon if titer is very high (false-negative); rheumatoid factor itself is a disturbing factor in many tests.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Cryoglobulinemia type II	IgM rheumatoid factor, cryoglobulinemia, immunofixation electrophoresis	
Rheumatoid arthritis	Ig classification of RF, CRP, erythrocyte sedimentation rate, blood count	10
Collagen diseases (Sjögren syndrome, mixed connective tissue disease, SLE)	See ANA	10
Vasculitides (Wegener granulomatosis, panarteritis nodosa)	See ANCA	10
Chronic liver diseases (e. g.,chronic hepatitis, primary biliary cirrhosis)	See Bilirubin, Aminotransferases, GGTP	25
Chronic pulmonary diseases (e. g., fibrosis, silicosis, asbestosis)	Blood gases	
Bacterial infections (e. g., mycobacteria, spirochetes, various species of *Brucella* and *Salmonella*)	See CRP	4
Parasitic infections (e. g., various species of trypanosoma and plasmodium)	See IgE	4
Viral infections (e. g., EBV, CMV, HIV)	Blood count, serology; see Aminotransferases, Complement C3 and C4	4

Selenium

Indication. Suspected selenium deficiency (especially if parenteral feeding is administered) or selenium intoxication.

Normal values: 0.8–1.1 μmol/L (63–87 μg/L)

Factors that may influence results. Age, sex, nutrition, alcohol, smoking.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Nutritional deficiency (parenteral feeding, Keshan disease and Kashin–Beck disease)	Glutathione peroxidase activity of erythrocytes, vitamin E, albumin	8, 10, 20, 22
Renal insufficiency, hemodialysis	See Creatinine	29
Cardiomyopathy, heart failure, arrhythmia	See BNP, TSH	20–22
Liver cirrhosis	See Albumin	25
Carcinomas	See CRP, LDH, Aminotransferases	
Rheumatoid arthritis	See Rheumatoid Factor	10

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Intoxication (occupation-associated intoxication, overdose caused through inappropriate self-medication, antiseborrheics)	Chloride	

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Sodium

In hospitalized patients, hypo- and hypernatremia are mostly iatrogenic. In most cases, the etiological assessment of equivocal disturbances of sodium balance requires the determination of osmolality in order to evaluate tonicity (evaluation of water distribution between intra- and extracellular space).

Indication. Disorders of water, electrolyte or acid–base balance, polyuria and renal diseases, hypertension, monitoring of intensive care patients.

Normal values: 135–145 mmol/L

Factors that may influence results. Hypertriglyceridemia (pseudohyponatremia).

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hypo-osmolar dehydration		
Salt-losing nephritis	Creatinine, urinary sodium, potassium in serum and urine	29, 30
Renal tubular acidosis	See Potassium	29, 30
Polyuria due to acute renal failure	See Creatinine, urinary sodium, potassium in serum and urine	29, 30
Hypoaldosteronism, hypocortisolism	See Aldosterone, Cortisol	30
Osmotic diuresis (e. g., diabetics with glucosuria or ketonuria, urea diuresis)	glucose in serum and urine, urinalysis, urinary osmolality	2, 30
Diuretics		2, 29, 30
Low-salt diet	Urinary sodium; potassium in serum and urine	2, 30
Vomiting (pseudo-Bartter syndrome)	Potassium, sodium, calcium, magnesium, acid–base balance, uric acid, glucose tolerance test, aldosterone, renin, urinary chloride	2, 26, 30
Diarrhea, steatorrhea	Acid–base balance, potassium, stool fat	2, 27, 30
Fluid loss into the third space (e. g., pancreatitis, peritonitis, ileus)	Blood count, CRP, potassium, calcium, Quick test, PTT, creatinine, glucose, amylase, lipase, AST, ALT, GGTP, bilirubin, blood gases, urinalysis, acid–base balance	7, 30
Perspiration (physical exertion, fever), burn injuries		2, 30
Hypo-osmolar hyperhydration (slight)		
Inadequate ADH secretion	See Potassium	30
Excessive water intake	Potassium, sodium, urinary osmolality	2, 30
Postoperatively	Potassium, sodium, urinary osmolality	2, 30
Drugs (nicotine, isoproterenol, morphine, carbamazepine, chlorpropamid, antidepressants, indometacin, trimethoprim)		2, 30
Hypo-osmolar hyperhydration (pronounced)		
Generalized edema (nephrotic syndrome, heart failure, liver cirrhosis)	See Albumin; urinary sodium	12, 20, 25, 29, 30
Chronic renal insufficiency and oliguric phase of acute renal failure	See Creatinine	29, 30

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hyperosmolar hyperhydration		
High salt diet, drinking of sea water, infusion of hyperosmolar NaCl	Creatinine, urinary sodium; potassium in serum and urine	30
Hyperaldosteronism	See Aldosterone	30

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Increased (continued)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Osmotic diuresis (e. g., diabetics with glucosuria or ketonuria, urea diuresis)	glucose in serum and urine, urinalysis, urinary osmolality	2, 30
Perspiration (physical exertion, fever), burn injuries		2, 30
Hyperosmolar hyperhydration Acute renal failure	See Creatinine	29, 30
Hyperosmolar dehydration Diabetes insipidus	Urinary volume, urinary osmolality, urinary density, water deprivation test, ADH	2, 30
Insufficient fluid supply (thirst)	Urinary volume, urinary osmolality, urinary density	2, 30

Testosterone

Indication. Women: virilization, polycystic ovary syndrome; men: hypogonadism, evaluation of symptoms of androgen deficiency.

Normal values:
Sexually mature women: < 2.1 nmol/L (< 0.6 μg/L)
Postmenopausal women: < 2.8 nmol/L (< 0.8 μg/L)
Men: 12–30 nmol/L (3.5–8.6 μg/L)

Factors that may influence results. Diurnal rhythm, extended exertion, medication and illicit drugs (e. g., ketoconazole, heroin, methadone). Beware pseudohypoandrogenemia and pseudohyperandrogenemia, especially in obese patients due to low and high sex hormone-binding globulin (SHBG) concentration, respectively (determination of free testosterone or calculation of testosterone index).

Decreased (men)		
Differential diagnosis Primary impairment of GnRH secretion (Kallmann syndrome, Prader–Willi syndrome, fertile eunuch syndrome; idiopathic hypogonadotropic hypogonadism)	**Supplementary tests** LH, FSH, GnRH test, HCG test, SHBG	**See Chapter**
Secondary impairment of GnRH secretion (hyperprolactinemia, hypopituitarism due to/after tumor, surgery, trauma, etc.)	LH, FSH, GnRH test, prolactin, ACTH, TSH, GH	
Congenital or acquired anorchidism (surgery, trauma, torsion, tumor, infection), gonadal dysgenesis	LH, FSH, GnRH test, HCG test, SHBG	
Genetic impairment of testicular function (Klinefelter syndrome, Leydig cell hypoplasia, hermaphroditism, defects of steroid synthesis) (pseudohermaphroditism)	LH, FSH, GnRH test, HCG test, SHBG, karyogram	
Testicular tumors	LH, FSH, GnRH test, HCG test, SHBG, placental alkaline phosphatase	
Androgen deficiency caused by exogenous factors (drugs, radiation, toxic substances) or general diseases (andropause, obesity, renal insufficiency, liver cirrhosis, heart failure, in oncology patients, AIDS)	LH, FSH, GnRH test, HCG test, SHBG	

Increased (women)		
Differential diagnosis Polycystic ovary syndrome	**Supplementary tests** LH, FSH, DHEAS, androstenedione, glucose, lipid profile	**See Chapter**
Ovarian hyperthecosis	LH, FSH, DHEAS, androstenedione, glucose, lipid profile, insulin (insulin resistance indices)	
Adrenogenital syndrome (late onset)	Aldosterone, 17-OH progesterone (basal level and ACTH test), cortisol, DHEAS, deoxycorticosteroids, genetic analysis of the 17β-HSD gene	30

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Increased (women)		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Androgen producing tumors of the ovary or the adrenal gland	DHEAS	
Formation of ACTH or HCG by pituitary adenomas or paraneoplastic formation of ACTH or HCG	DHEAS, ACTH, HCG, GH, IGF1, prolactin, testosterone in the dexamethasone suppression test	
Iatrogenic (androgens, anabolics, gestagens [nortestosterone derivatives], glucocorticoids, diuretics, antirheumatics)		

Thrombocytes

See Chapter 15.

Thyrotropin, Thyroid Stimulating Hormone (TSH)

Indication. Exclusion of thyroid malfunction (hyperthyroidism or hypothyroidism), differential diagnosis of hypothyroidism, monitoring of substitution or suppression therapy in treatment of thyroid diseases.

Normal values: 0.27–4.2 mU/L

Factors that may influence results. Nonthyroidal diseases in hospitalized patients, pregnancy.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Primary hyperthyroidism (autonomous adenoma, Graves disease)	Free T_4, free T_3, TSH receptor antibodies	16
Secondary hypothyroidism (pituitary adenoma, craniopharyngioma)	Free T_4, free T_3, TRH test, GH, ACTH, LH, FSH	16
Therapy with thyroid hormones (substitution in patients with euthyroid goiter, suppression in thyroid carcinoma patients)	free T_4, free T_3	16
Pregnancy	Pregnancy test (HCG)	
Hospitalized, seriously ill patients		
Dopaminergic drugs		

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Primary hypothyroidism (autoimmune forms of thyroiditis, in some cases infectious thyroiditis)	Free T_4, free T_3, anti-TPO antibodies	16
Thyroid hormone resistance	Free T_4, free T_3, antibodies to thyroid hormones	16
TSH resistance	Free T_4, free T_3	16
TSH producing pituitary adenomas	Free T_4, free T_3	
Hospitalized, seriously ill patients	Free T_4, free T_3	

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Thyroxine, Triiodothyronine (Free and Total; fT3, T3), Tetraiodothyronine (Free and Total; fT4, T4)

Indication. Diagnosis of hyperthyroidism and hypothyroidism with abnormal TSH, assessment of substitution and suppression therapy for thyroid diseases.

Normal values:
Total T4: 77–142 nmol/L (55.0–110.0 μg/L)
Free T4: 12–22 pmol/L (9.4–17.0 ng/L)

Total T3: 1.3–3.1 nmol/L (0.9–2.0 μg/L), dependent on method
Free T3: 2.8–7.1 pmol/L (1.8–4.6 ng/L), dependent on method

Factors that may influence results. Age, pregnancy, severe illnesses, heparin, T4 antibodies.

Decreased		
Differential diagnosis Primary hypothyroidism (autoimmune forms of thyroiditis, some cases of infectious thyroiditis) (T_3, fT_3, T_4, fT_4)	**Supplementary tests** Anti-TPO antibodies	**See Chapter** 16
Secondary hypothyroidism (pituitary adenoma, craniopharyngioma) (T_3, fT_3, T_4, fT4)	Free T_4, free T_3, TRH test, GH, ACTH, LH, FSH	16
TSH resistance (T_3, fT_3, T_4, fT_4)	TSH	16
Hospitalized, seriously ill patients (low T_3 syndrome) (T_3, T_4)	TSH, reverse T_3	
Acute hepatitis (T_3, fT_3)	See Aminotransferases	25
Liver cirrhosis (T_3, T_4, fT_3)	See Albumin	25
Renal insufficiency (T_3, T_4)	TSH normal; see Creatinine	29
Protein loss (nephrotic syndrome, protein-losing enteropathy) (T_3, T_4)	See Albumin	25, 29
Pregnancy (fT_4)	pregnancy test	
Diabetic ketoacidosis (T_3, T_4)	See Glucose, Acid–Base Balance	32
Acetylsalicylic acid (T_3, T_4)		
Anticonvulsants (phenytoin, phenobarbital, carbamazepine) (T_3, fT_3, T_4, fT_4)		

Increased		
Differential diagnosis Primary hyperthyroidism (autonomous adenoma, Graves disease) (T_3, fT_3, T_4, fT_4)	**Supplementary tests** TSH, TSH receptor antibodies	**See Chapter** 16
TSH producing pituitary adenomas (T_3, fT_3, T_4, fT_4)	TSH	
Thyroid hormone resistance (T_3, fT_3, T_4, fT_4)	TSH, antibodies to thyroid hormones	16
Systemic diseases and neuropsychiatry patients (T_3, fT_3, T_4, fT_4)	TSH	
Acute hepatitis (T_4, fT_4)	See Aminotransferases	25
Pregnancy (T_3, T_4)	Pregnancy test	
Diabetic ketoacidosis, starvation (fT_3, fT_4)	See Glucose, Acid–Base Balance	32
Therapy with thyroid hormones (substitution in patients with euthyroid goiter, suppression in thyroid carcinoma patients)	TSH	16
Oral contraceptives (T_3, T_4)	TSH	16
Acetylsalicylic acid (fT_3, fT_4)		
Amiodarone (T_3, fT_3, T_4, fT_4)		

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Transaminases

See Aminotransferases.

Transferrin Saturation

Transferrin saturation is calculated from the serum concentrations of iron and transferrin:

Transferrin saturation (%)
= iron (mmol/L)/transferrin (mg/dL) x 398

or

Transferrin saturation (%)
= iron (μg/dL)/transferrin (mg/dL) x 70.9

Normal values:
Women: 15 %–50 %
Men: 20 %–55 %

Indication. Diagnosis and follow-up of iron overload.

Factors that may influence results. Strong diurnal rhythm of iron concentration, increased transferrin concentration in the presence of inflammation (acute phase protein) and damage of liver parenchyma; hemolysis.

Decreased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Iron deficiency	See Ferritin	13
Anemia in chronic diseases	See Ferritin	13
Renal anemia	Creatinine, ferritin, blood count including determination of the erythrocyte coefficients and the relative distribution width, erythropoietin	13

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Hereditary hemochromatosis	Ferritin, HFE genotyping, ALT, GGTP, bilirubin, ChE, Quick test, albumin	
Symptomatic hemochromatosis (anemia due to ineffective erythropoiesis, e. g., sideroblastic anemia; liver diseases, e. g., hepatitis)	Ferritin, blood count, ALT, GGTP, bilirubin, ChE, Quick test, albumin	13, 25

Triglycerides

See Lipid Profile.

Troponin I and Troponin T

Indication. Diagnosis and monitoring of acute myocardial infarction, prognosis of unstable angina pectoris.

Normal values:
Troponin T: < 0.1 μg/L
Troponin I: dependent on method

Factors that may influence results. Hemolysis.

Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Acute myocardial infarction	See CK	6
Unstable angina pectoris		6
Myocarditis, endocarditis, pericarditis	CK-MB, blood count, CRP, procalcitonin, blood cultures, virus serology, autoantibodies	4, 6, 20, 21, 22
Diagnostic and therapeutic interventions in the heart (e. g., surgery, defibrillation, cardiac massage)	See CK	2, 3
Renal insufficiency (especially troponin T)	See Creatinine	29

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Urea

The urea/creatinine ratio should be calculated to differentiate between prerenal und postrenal azotemia.

Indication. Differentiation between prerenal and postrenal azotemia; monitoring of renal insufficiency and its treatment.

Normal values:
Women < 50 years: 2.6–6.7 mmol/L (15–40 mg/dL)
Women > 50 years: 3.5–7.2 mmol/L (21–43 mg/dL)

Normal values:
Men < 50 years: 3.2–7.3 mmol/L (15–40 mg/dL)
Men > 50 years: 3.0–9.2 mmol/L (18–55 mg/dL)

Factors that may influence results. False-high values if ascorbic acid, guanethidine, thiazides, sulfonamides, chloramphenicol, or dextrans are administered.

Increased		
Differential diagnosis Acute renal failure	**Supplementary tests** See Creatinine	**See Chapter** 29
Chronic renal insufficiency	See Creatinine	29
Prerenal azotemia (reduced extracellular volume due to bleeding, vomiting, diarrhea, burn injuries, insufficient fluid supply)	Creatinine to calculate the urea/creatinine ratio (> 40 mmol/L, > 35 mg/dL); electrolytes, acid–base balance, blood count	30
Postrenal azotemia (obstruction of the lower urinary tract system due to calculi, tumors, diseases of the prostate)	Creatinine to calculate the urea/creatinine ratio (> 40 mmol/L, > 35 mg/dL); urinalysis and urinary sediment, CRP, blood count, PSA	30
High protein supply, especially if combined with insufficient fluid supply	Electrolytes, osmolality	2, 3

Uric Acid

Indication. Screening for hyperuricemia; diagnosis, therapy, and monitoring of gout; differential diagnosis of nephrolithiasis; monitoring of diseases and therapies involving a risk of hyperuricemia.

Normal values:
Women: 150–350 μmol/L (2.5–6.0 mg/dL)
Men: 210–420 μmol/L (3.5–7.0 mg/dL)

Factors that may influence results. Ascorbic acid, EDTA, citrate.

Decreased		
Differential diagnosis Xanthinuria	**Supplementary tests** urinary uric acid	**See Chapter**
Severe damage of liver parenchyma	See ALT, Bilirubin, ChE, Albumin	25
Renal tubular diseases (renal tubular acidosis/Fanconi syndrome, syndrome of inadequate secretion of antidiuretic hormone [ADH])	Acid–base balance, potassium, sodium in serum, urinary potassium and chloride, urinary pH, alkaline phosphatase, ADH	29, 30
Malignancies	See CRP	
AIDS	Complete blood count, aminotransferases, protein, protein electrophoresis, LDH, CRP, ESR; HIV serology, HIV viral load, lymphocyte subpopulations (CD4, CD8)	4
Wilson disease	See Copper	
Heavy-metal intoxications	Lead, copper, cadmium	
Allopurinol overdose or overdose of uricosuric agents		2, 3
Other drugs (salicylates, radiographic contrast medium, phenylbutazone, estrogens)		2, 3

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Increased		
Differential diagnosis Primary hyperuricemia (acute gout, nephrolithiasis, urate nephropathy)	**Supplementary tests** Blood count, creatinine, urea, CRP, erythrocyte sedimentation rate, uric acid crystals in joint aspirate, urinalysis, urinary uric acid	**See Chapter** 10, 29
Renal insufficiency	See Creatinine	29
Malignant tumors, leukemias, polycythemia vera	Blood count; see CRP; tumor screening	2, 3, 13, 14
Psoriasis		2, 3
After extensive muscle damage (trauma, surgery, grand mal seizure)	See CK	2, 3
Starvation	Creatinine, urea, urinary ketone bodies; see Albumin	2, 3
Chronic alcohol consumption	See GGTP	2, 3
Chemotherapy and radiation therapy for tumor treatment		
Tubular toxins	Urinary uric acid, lead, cadmium, beryllium, urinalysis and urinary sediment	2, 3
Drugs (diuretics, cyclosporin A, cytostatics)		2, 3
Lesch–Nyhan syndrome	Blood count, genetic diagnostics	

Urinalysis

See Chapter 29.

Urinary Sediment

See Chapter 29.

Vitamin B_{12} (Cobalamin)

Indication. Suspected vitamin B_{12} deficiency due to chronic atrophic gastritis, diseases of the terminal ileum, peripheral neuropathy, macrocytic anemia, long-term vegetarianism or use of proton pump inhibitors, alcoholism, AIDS, old age.

Normal values: 135–560 pmol/L (180–900 ng/L)

Factors that may influence results. Hemolysis, lipemia.

Increased		
Differential diagnosis Intrinsic factor deficiency (pernicious anemia, neuropathy, autoimmune gastritis)	**Supplementary tests** Blood count, antibodies to intrinsic factor and parietal cells, Schilling test	**See Chapter** 7, 8, 13
Achlorhydria (e. g., in old age, AIDS)		7
Intestinal malabsorption	See Albumin; Schilling test	27
Vegetarian lifestyle		

Zinc

Indication. Impaired wound healing, inflammatory skin diseases, susceptibility to infection, hypogonadism.

Normal values:
Serum, plasma: 9–21 μmol/L (0.6–1.4 mg/L)
Whole blood: 60–115 μmol/L (4.0–7.5 mg/L)

Factors that may influence results. Hospitalization, pregnancy, contaminations.

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Increased		
Differential diagnosis	**Supplementary tests**	**See Chapter**
Malnutrition	See Albumin	7
Malassimilation	See Albumin, Vitamin B_{12}	7
Alcoholism	See GGTP	
Diabetes mellitus	See Glucose	2
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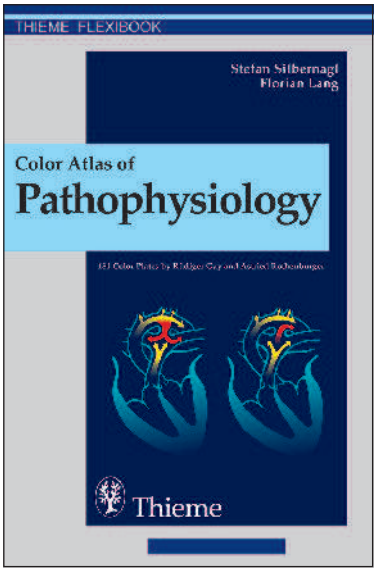

Color Atlas of Pathophysiology

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