RYPINS' INTENSIVE REVIEWS

SERIES EDITOR
Edward D. Frohlich

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Philip B. Conran
Peter J. Goldblatt

Pathology

Highlights key concepts you must learn and conquer for your examinations

Organizes information for course study

Prepares you for examinations by succinctly covering what you'll need to know

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Who Was "Rypins"?

Dr. Harold Rypins (1892–1939) was the founding editor of what is now known as the RYPINS' series of review books. Originally published under the title *Medical State Board Examinations,* the first edition was published by J. B. Lippincott Company in 1933. Dr. Rypins edited subsequent editions of the book in 1935, 1937, and 1939 before his death that year. The series that he began has since become the longest-running and most successful publication of its kind, having served as an invaluable tool in the training of generations of medical students. Dr. Rypins was a member of the faculty of Albany Medical College in Albany, New York, and also served as Secretary of the New York State Board of Medical Examiners. His legacy to medical education flourishes today in the highly successful *Rypins' Basic Sciences Review* and *Rypins' Clinical Sciences Review,* now in their 17th editions, and in the *Rypins' Intensive Reviews* series of subject review volumes. We at Lippincott–Raven Publishers take pride in this continuing success.

—The Publisher

Series Preface

These are indeed very exciting times in medicine. Having made this statement, one's thoughts immediately reflect about the major changes that are occurring in our overall health care delivery system, utilization-review and shortened hospitalizations, issues concerning quality assurance, ambulatory surgical procedures and medical clearances, and the impact of managed care on the practice of internal medicine and primary care. Each of these issues has had a considerable impact on the approach to the patient and on the practice of medicine.

But even more mind-boggling than the foregoing changes are the dramatic changes imposed on the practice of medicine by fundamental conceptual scientific innovations engendered by advances in basic science that no doubt will affect medical practice of the immediate future. Indeed, much of what we thought of as having a potential impact on the practice of medicine of the future has already been perceived. One need only take a cursory look at our weekly medical journals to realize that we are practicing "tomorrow's medicine today." And consider that the goal a few years ago of actually describing the human genome is now near reality.

Reflect, then, for a moment on our current thinking about genetics, molecular biology, cellular immunology, and other areas that have impacted upon our current understanding of the underlying mechanisms of the pathophysiological concepts of disease. Moreover, paralleling these innovations have been remarkable advances in the so-called "high tech" and "gee-whiz" aspects of how we diagnose disease and treat patients. We can now think with much greater perspective about the dimensions of more specific biologic diagnoses concerned with molecular perturbations; gene therapy not only affecting genetic but oncological diseases; more specific pharmacotherapy involving highly specific receptor inhibition, alterations of intracellular signal transduction, manipulations of cellular protein synthesis; immunosuppresive therapy not only with respect to organ transplantations but also of autoimmune and other immune-related diseases; and therapeutic means for manipulating organ remodeling or the intravascular placement of stents. Each of these concepts has become inculcated into our everyday medical practice within the past decade. The reason why these changes have so rapidly promoted an upheaval in medical prac-

tice is continuing medical education, a constant awareness of the current medical literature, and a thirst for new knowledge.

To assist the student and practitioner in the review process, the publisher and I have initiated a new approach in the publication of *Rypins' Basic Sciences Review* and *Rypins' Clinical Sciences Review.* Thus, when I assumed responsibility to edit this long-standing board review series with the 13th edition of the textbook (first published in 1931), it was with a feeling of great excitement. I perceived that great changes would be coming to medicine, and I believed that this would be one ideal means of not only facing these changes head on but also for me personally to cope and keep up with these changes. Over the subsequent editions, this confidence was reassured and rewarded. The presentation for the updating of medical information was tremendously enhanced by the substitution of new authors, as the former authority "standbys" stepped down or retired from our faculty. Each of the authors who continue to be selected for maintaining the character of our textbook is an authority in his or her respective area and has had considerable pedagogic and formal examination experience. One dramatic recent example of the changes in author replacement just came about with the 17th edition. When I invited Dr. Peter Goldblatt to participate in the authorship of the pathology chapter of the textbook, his answer was "what goes around, comes around." You see, Dr. Goldblatt's father, Dr. Harry Goldblatt, a major contributor to the history of hypertensive disease, was the first author of the pathology chapter in 1931. What a satisfying experience for me personally. Other less human changes in our format came with the establishment of two soft cover volumes, the current basic and clinical sciences review volumes, replacing the single volume text of earlier years. Soon, a third supplementary volume concerned with questions and answers for the basic science volume appeared. Accompanying these more obvious changes was the constant updating of the knowledge base of each of the chapters, and this continues on into the present 17th edition.

And now we have introduced another major innovation in our presentation of the basic and clinical sciences reviews. This change is evidenced by the introduction of the *Rypins' Intensive Reviews* series, along with the 17th edition of *Rypins' Basic Sciences Review, Rypins' Clinical Sciences Review,* and the *Questions and Answers* third volume. These volumes are written to be used separately from the parent textbook. Each not only contains the material published in their respective chapters of the textbook, but is considerably "fleshed out" in the discussions, tables, figures, and questions and answers. Thus, the *Rypins' Intensive Reviews* series serves as an important supplement to the overall review process and also provides a study guide for those already in practice, in preparing for specific specialty board certification and recertification examinations.

Therefore, with continued confidence and excitement, I am pleased to present these innovations in review experience for your consideration. As in the past, I look forward to learning of your comments and suggestions. In doing so, we continue to look forward to our continued growth and acceptance of the *Rypins'* review experience.

Edward D. Frohlich, MD, MACP, FACC

Preface

This intensive review of pathology was written primarily for medical students preparing for USMLE Step 1. It is written in a narrative style for easy, rapid review. The review covers only the most important aspects of pathology, concentrating on the key concepts and cardinal diseases that, according to our experience, comprise approximately 90% of the pathology material tested in Step 1 of the USMLE. This approach reflects our philosophy that it is more important to know well the most important topics and to understand the basic concepts than it is to memorize hundreds of obscure facts about diseases that the student will almost never encounter on USMLE examinations nor in his or her practice of medicine.

We have included 220 questions, similar to USMLE format, dealing with the "high-yield" topics of pathology. These questions are accompanied by short discussions that provide students with rapid feedback as well as an assessment of their knowledge of pathology. We hope that this approach will be popular with students and that this book will be helpful to them in preparing for their examinations.

Ivan Damjanov, MD, PhD
Philip B. Conran, DVM, PhD
Peter J. Goldblatt, MD

Introduction

Preparing for the USMLE

UNITED STATES MEDICAL LICENSING EXAMINATION (USMLE)

In August 1991 the Federation of State Medical Boards (FSMB) and the National Board of Medical Examiners (NBME) agreed to replace their respective examinations, the FLEX and NBME, with a new examination, the United States Medical Licensing Examination (USMLE). This examination will provide a common means for evaluating all applicants for medical licensure. It appears that this development in medical licensure will at last satisfy the needs for state medical boards licensure, the national medical board licensure, and licensure examinations for foreign medical graduates. This is because the 1991 agreement provides for a composite committee that equally represents both organizations (the FSMB and NBME) as well as a jointly appointed public member and a representative of the Educational Council for Foreign Medical Graduates (ECFMG).

As indicated in the USMLE announcement, "It is expected that students who enrolled in U.S. medical schools in the fall of 1990 or later and foreign medical graduates applying for ECFMG examinations beginning in 1993 will have access only to USMLE for purposes of licensure." The phaseout of the last regular examinations for licensure was completed in December 1994.

The new USMLE is administered in three steps. Step 1 focuses on fundamental basic biomedical science concepts, with particular emphasis on "principles and mechanisms underlying disease and modes of therapy." Step 2 is related to the clinical sciences, with examination on material necessary to practice medicine in a supervised setting. Step 3 is designed to focus on "aspects of biomedical and clinical science essential for the unsupervised practice of medicine."

Today Step 1 and Step 2 examinations are set up and scored as total comprehensive objective tests in the basic sciences and clinical sciences, respectively. The format of each part is no longer subject-oriented, that is, separated into sections specifically labeled Anatomy, Pathology, Medicine, Surgery, and so forth. Subject labels are therefore missing, and in each part questions from the different fields are intermixed or integrated so that the subject origin of any

individual question is not immediately apparent, although it is known by the National Board office. Therefore, if necessary, individual subject grades can be extracted.

Step 1 is a two-day written test including questions in anatomy, biochemistry, microbiology, pathology, pharmacology, physiology, and the behavioral sciences. Each subject contributes to the examination a large number of questions designed to test not only knowledge of the subject itself but also "the subtler qualities of discrimination, judgment, and reasoning." Questions in such fields as molecular biology, cell biology, and genetics are included, as are questions to test the "candidate's recognition of the similarity or dissimilarity of diseases, drugs, and physiologic, behavioral, or pathologic processes." Problems are presented in narrative, tabular, or graphic form, followed by questions designed to assess the candidate's knowledge and comprehension of the situation described.

Step 2 is also a two-day written test that includes questions in internal medicine, obstetrics and gynecology, pediatrics, preventive medicine and public health, psychiatry, and surgery. The questions, like those in Step 1, cover a broad spectrum of knowledge in each of the clinical fields. In addition to individual questions, clinical problems are presented in the form of case histories, charts, roentgenograms, photographs of gross and microscopic pathologic specimens, laboratory data, and the like, and the candidate must answer questions concerning the interpretation of the data presented and their relation to the clinical problems. The questions are "designed to explore the extent of the candidate's knowledge of clinical situations, and to test his [or her] ability to bring information from many different clinical and basic science areas to bear upon these situations."

The examinations of both Step 1 and Step 2 are scored as a whole, certification being given on the basis of performance on the entire part, without reference to disciplinary breakdown. The grade for the examination is derived from the total number of questions answered correctly, rather than from an average of the grades in the component basic science or clinical science subjects. A candidate who fails will be required to repeat the entire examination. Nevertheless, as noted above, in spite of the interdisciplinary character of the examinations, all of the traditional disciplines are represented in the test, and separate grades for each subject can be extracted and reported separately to students, to state examining boards, or to those medical schools that request them for their own educational and academic purposes.

This type of interdisciplinary examination and the method of scoring the entire test as a unit have definite advantages, especially in view of the changing curricula in medical schools. The former type of rigid, almost standardized, curriculum, with its emphasis on specific subjects and a specified number of hours in each, has been replaced by a more liberal, open-ended curriculum, permitting emphasis in one or more fields and corresponding deemphasis in others. The result has been rather wide variations in the totality of education in different medical schools. Thus, the scoring of these

tests as a whole permits accommodation to this variability in the curricula of different schools. Within the total score, weakness in one subject that has received relatively little emphasis in a given school may be balanced by strength in other subjects.

The rationale for this type of comprehensive examination as replacement for the traditional department-oriented examination in the basic sciences and the clinical sciences is given in the National Board Examiner:

The student, as he [or she] confronts these examinations, must abandon the idea of "thinking like a physiologist" in answering a question labeled "physiology" or "thinking like a surgeon" in answering a question labeled "surgery." The one question may have been written by a biochemist or a pharmacologist; the other question may have been written by an internist or a pediatrician. The pattern of these examinations will direct the student to thinking more broadly of the basic sciences in Step 1 and to thinking of patients and their problems in Step 2.

Until a few years ago, the Part I examination could not be taken until the work of the second year in medical school had been completed, and the Part II test was given only to students who had completed the major part of the fourth year. Now students, if they feel they are ready, may be admitted to any regularly scheduled Step 1 or Step 2 examination during any year of their medical course without prerequisite completion of specified courses or chronologic periods of study. Thus, emphasis is placed on the acquisition of knowledge and competence rather than the completion of predetermined periods.

Candidates are eligible for Step 3 after they have passed Steps 1 and 2, have received the M.D. degree from an approved medical school in the United States or Canada, and subsequent to the receipt of the M.D. degree, have served at least six months in an approved hospital internship or residency. Under certain circumstances, consideration may be given to other types of graduate training provided they meet with the approval of the National Board. After passing the Step 3 examination, candidates will receive their diplomas as of the date of the satisfactory completion of an internship or residency program. If candidates have completed the approved hospital training prior to completion of Step 3, they will receive certification as of the date of the successful completion of Step 3.

The Step 3 examination, as noted above, is an objective test of general clinical competence. It occupies one full day and is divided into two sections, the first of which is a multiple-choice examination that relates to the interpretation of clinical data presented primarily in pictorial form, such as pictures of patients, gross and microscopic lesions, electrocardiograms, charts, and graphs. The second section, entitled Patient Management Problems, utilizes a programmed-testing technique designed to measure the candidate's clinical judgment in the management of patients. This technique simulates clinical situations in which the physician is faced with the problems of patient management presented in a sequential programmed pattern. A set of four to six problems is related to each of a series of patients. In the scoring of this section, candi-

dates are given credit for correct choices; they are penalized for errors of commission (selection of procedures that are unnecessary or are contraindicated) and for errors of omission (failure to select indicated procedures).

All parts of the USMLE are given in many centers, usually in medical schools, in nearly every large city in the United States as well as in a few cities in Canada, Puerto Rico, and the Canal Zone. In some cities, such as New York, Chicago, and Baltimore, the examination may be given in more than one center.

The examinations of the National Board have become recognized as the most comprehensive test of knowledge of the medical sciences and their clinical application produced in this country.

THE NATIONAL BOARD OF MEDICAL EXAMINERS

For years the National Board examinations have served as an index of the medical education of the period and have strongly influenced higher educational standards in each of the medical sciences. The Diploma of the National Board is accepted by 47 state licensing authorities, the District of Columbia, and the Commonwealth of Puerto Rico in lieu of the examination usually required for licensure and is recognized in the American Medical Directory by the letters DNB following the name of the physician holding National Board certification.

The National Board of Medical Examiners has been a leader in developing new and more reliable techniques of testing, not only for knowledge in all medical fields but also for clinical competence and fitness to practice. In recent years, too, a number of medical schools, several specialty certifying boards, professional medical societies organized to encourage their members to keep abreast of progress in medicine, and other professional qualifying agencies have called upon the National Board's professional staff for advice or for the actual preparation of tests to be employed in evaluating medical knowledge, effectiveness of teaching, and professional competence in certain medical fields. In all cases, advantage has been taken of the validity and effectiveness of the objective, multiple-choice type of examination, a technique the National Board has played an important role in bringing to its present state of perfection and discriminatory effectiveness.

Objective examinations permit a large number of questions to be asked, and approximately 150 to 180 questions can be answered in a 2½-hour period. Because the answer sheets are scored by machine, the grading can be accomplished rapidly, accurately, and impartially. It is completely unbiased and based on percentile ranking. Of long-range significance is the facility with which the total test and individual questions can be subjected to thorough and rapid statistical analyses, thus providing a sound basis for comparative

studies of medical school teaching and for continuing improvement in the quality of the test itself.

QUESTIONS

Over the years, many different forms of objective questions have been devised to test not only medical knowledge but also those subtler qualities of discrimination, judgment, and reasoning. Certain types of questions may test an individual's recognition of the similarity or dissimilarity of diseases, drugs, and physiologic or pathologic processes. Other questions test judgment as to cause and effect or the lack of causal relationships. Case histories or patient problems are used to simulate the experience of a physician confronted with a diagnostic problem; a series of questions then tests the individual's understanding of related aspects of the case, such as signs and symptoms, associated laboratory findings, treatment, complications, and prognosis. Case-history questions are set up purposely to place emphasis on correct diagnosis within a context comparable with the experience of actual practice.

It is apparent from recent certification and board examinations that the examiners are devoting more attention in their construction of questions to more practical means of testing basic and clinical knowledge. This greater realism in testing relates to an increasingly interdisciplinary approach toward fundamental material and to the direct relevance accorded practical clinical problems. These more recent approaches to questions have been incorporated into this review series.

Of course, the new approaches to testing add to the difficulty experienced by the student or physician preparing for board or certification examinations. With this in mind, the author of this review is acutely aware not only of the interrelationships of fundamental information within the basic science disciplines and their clinical implications but also of the necessity to present this material clearly and concisely despite its complexity. For this reason, the questions are devised to test knowledge of specific material within the text and identify areas for more intensive study, if necessary. Also, those preparing for examinations must be aware of the interdisciplinary nature of fundamental clinical material, the common multifactorial characteristics of disease mechanisms, and the necessity to shift back and forth from one discipline to another in order to appreciate the less than clear-cut nature separating the pedagogic disciplines.

The different types of questions that may be used on examinations include the completion-type question, in which the individual must select one best answer among a number of possible choices, most often five, although there may be three or four; the completion-type question in the negative form, in which all but one of the choices is correct and words such as *except* or *least* appear in

the question; the true-false type of question, which tests an understanding of cause and effect in relationship to medicine; the multiple true-false type, in which the question may have one, several, or all correct choices; one matching-type question, which tests association and relatedness and uses four choices, two of which use the word, *both* or *neither;* another matching-type question that uses anywhere from three to twenty-six choices and may have more than one correct answer; and, as noted above, the patient-oriented question, which is written around a case and may have several questions included as a group or set.

Many of these question types may be used in course or practice exams; however, at this time the most commonly used types of questions on the USMLE exams are the completion-type question (one best answer), the completion-type negative form, and the multiple matching-type question, designating specifically how many choices are correct. Often included within the questions are graphic elements such as diagrams, charts, graphs, electrocardiograms, roentgenograms, or photomicrographs to elicit knowledge of structure, function, the course of a clinical situation, or a statistical tabulation. Questions then may be asked in relation to designated elements of the same. As noted above, case histories or patient-oriented questions are more frequently used on these examinations, requiring the individual to use more analytic abilities and less memorization-type data.

For further detailed information concerning developments in the evolution of the examination process for medical licensure (for graduates of both U.S. and foreign medical schools), those interested should contact the National Board of Medical Examiners at 3750 Market Street, Philadelphia, PA 19104; telephone 215-590-9500; or http://www.usmle.org.

FIVE POINTS TO REMEMBER

In order for the candidate to maximize chances for passing these examinations, a few common sense strategies or guidelines should be kept in mind.

First, it is imperative to prepare thoroughly for the examination. Know well the types of questions to be presented and the pedagogic areas of particular weakness, and devote more preparatory study time to these areas of weakness. Do not use too much time restudying areas in which there is a feeling of great confidence and do not leave unexplored those areas in which there is less confidence. Finally, be well rested before the test and, if possible, avoid traveling to the city of testing that morning or late the evening before.

Second, know well the format of the examination and the instructions before becoming immersed in the challenge at hand. This information can be obtained from many published texts and

brochures or directly from the testing service (National Board of Medical Examiners, 3750 Market Street, Philadelphia, PA 19104; telephone 215-590-9500). In addition, many available texts and self-assessment types of examination are valuable for practice.

Third, know well the overall time allotted for the examination and its components and the scope of the test to be faced. These may be learned by a rapid review of the examination itself. Then, proceed with the test at a careful, deliberate, and steady pace without spending an inordinate amount of time on any single question. For example, certain questions such as the "one best answer" probably should be allotted 1 to 1½ minutes each. The "matching" type of question should be allotted a similar amount of time.

Fourth, if a question is particularly disturbing, note appropriately the question (put a mark on the question sheet) and return to it later. Don't compromise yourself by so concentrating on a likely "loser" that several "winners" are eliminated because of inadequate time. One way to save this time on a particular "stickler" is to play your initial choice; your chances of a correct answer are always best with your first impression. If there is no initial choice, reread the question.

Fifth, allow adequate time to review answers, to return to the questions that were unanswered and "flagged" for later attention, and check every *n*th (e.g., 20th) question to make certain that the answers are appropriate and that you did not inadvertently skip a question in the booklet or answer on the sheet (this can happen easily under these stressful circumstances).

There is nothing magical about these five points. They are simple and just make common sense. If you have prepared well, have gotten a good night's sleep, have eaten a good breakfast, and follow the preceding five points, the chances are that you will not have to return for a second go-around.

Edward D. Frohlich, MD, MACP, FACC

Series Acknowledgments

In no other writing experience is one more dependent on others than in a textbook, especially a textbook that provides a broad review for the student and fellow practitioner. In this spirit, I am truly indebted to all who have contributed to our past and current understanding of the fundamental and clinical aspects related to the practice of medicine. No one individual ever provides the singular "breakthrough" so frequently attributed as such by the news media. Knowledge develops and grows as a result of continuing and exciting contributions of research from all disciplines, academic institutions, and nations. Clearly, outstanding investigators have been credited for major contributions, but those with true and understanding humility are quick to attribute the preceding input of knowledge by others to the growing body of knowledge. In this spirit, we acknowledge the long list of contributors to medicine over the generations. We also acknowledge that in no century has man so exceeded the sheer volume of these advances than in the twentieth century. Indeed, it has been said by many that the sum of new knowledge over the past 50 years has most likely exceeded all that had been contributed in the prior years.

With this spirit of more universal acknowledgment, I wish to recognize personally the interest, support, and suggestions made by my colleagues in my institution and elsewhere. I specifically refer to those people from my institution who were of particular help and are listed at the outset of the internal medicine volume. But, in addition to these colleagues, I want to express my deep appreciation to my institution and clinic for providing the opportunity and ambience to maintain and continue these academic pursuits. As I have often said, the primary mission of a school of medicine is that of education and research; the care of patients, a long secondary mission to ensure the conduct of the primary goal, has now also become a primary commitment in these more pragmatic times. In contrast, the primary mission of the major multidisciplinary clinics has been the care of patients, with education and research assuming secondary roles as these commitments become affordable. It is this distinction that sets the multispecialty clinic apart from other modes of medical practice.

Over and above a personal commitment and drive to assure publication of a textbook such as this is the tremendous support and loyalty of a hard-working and dedicated office staff. To this end, I am tremendously grateful and indebted to Mrs. Lillian Buffa and Mrs. Caramia Fairchild. Their long hours of unselfish work on my behalf and to satisfy their own interest in participating in this major educational effort is appreciated no end. I am personally deeply hon-

ored and thankful for their important roles in the publication of the Rypins' series.

Words of appreciation must be extended to the staff of Lippincott–Raven Publishers. It is more than 25 years since I have become associated with this publishing house, one of the first to be established in our nation. Over these years, I have worked closely with Mr. Richard Winters, not only with the Rypins' editions but also with other textbooks. His has been a labor of commitment, interest, and full support—not only because of his responsibility to his institution, but also because of the excitement of publishing new knowledge. In recent years, we discussed at length the merits of adding the intensive review supplements to the parent textbook and together we worked out the details that have become the substance of our present "joint venture." Moreover, together we are willing to make the necessary changes to assure the intellectual success of this series. To this end, we are delighted to include a new member of our team effort, Ms. Susan Kelly. She joined our cause to ensure that the format of questions, the reference process of answers to those questions within the text itself, and the editorial process involved be natural and clear to our readers. I am grateful for each of these facets of the overall publication process.

Not the least is my everlasting love and appreciation to my family. I am particularly indebted to my parents who inculcated in me at a very early age the love of education, the respect for study and hard work, and the honor for those who share these values. In this regard, it would have been impossible for me to accomplish any of my academic pursuits without the love, inspiration, and continued support of my wife, Sherry. Not only has she maintained the personal encouragement to initiate and continue with these labors of love, but she has sustained and supported our family and home life so that these activities could be encouraged. Hopefully, these pursuits have not detracted from the development and love of our children, Margie, Bruce, and Lara. I assume that this has not occurred; we are so very proud that each is personally committed to education and research. How satisfying it is to realize that these ideals remain a familial characteristic.

Edward D. Frohlich, MD, MACP, FACC
New Orleans, Louisiana

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My thanks to Ms. Beverli Isidore, my secretary, who helped me in compiling this book. The support and patience of Andrea Damjanov, my life companion, cannot be measured nor acknowledged adequately.

Ivan Damjanov, MD, PhD

I wish to thank my wife, Phyliss, who, in spite of her busy life and illness, gave me unconditional support. Thanks also to my children who gave me a computer so that I could work at home. Last, but certainly not least, my gratitude is extended to Ms. Monika DeGregorio for her uncanny ability to accurately interpret illegible handwriting and her indefatigable efforts in typing the manuscript.

Philip B. Conran, DVM, PhD

I cannot but reminisce about my father, Harry, one of the contributors to the original Rypins' Review series. In addition, he was a very early candidate for certification by the National Board of Medical Examiners, but after completing Part I, he waited for more than 15 years to complete the other parts because, at that time, a license was not required for the practice of pathology in Ohio. He also graded the pathology sections of the National Boards, which, at that time, were lengthy essays. He carried parts of exams with us on our fishing trips and graded them while we ate our "shore" lunch, which most often included freshly caught bass. If I remember correctly, he was paid $0.50 per exam.

My acknowledgments are extended also to Ms. Marilyn Cline, who interpreted my scrawls and Dr. Damjanov's explosive editorial comments; Ms. Catharine Harman; and my wife, Anna Lou, who kept me from straying too far off.

Peter J. Goldblatt, MD

Contents

Chapter 20

Chapter 21

Chapter 1

Cell Pathology

All diseases ultimately can be traced to cellular responses to injury. Each cell is in an equilibrium with its environment **(homeostasis)**, and its activity varies within a narrow range that reflects its overall physiology. In general, the specialized parenchymal cells are more susceptible to perturbations in their microenvironment than stromal elements.

Any disturbance of the environment can be potentially injurious and could cause cellular changes, either irreversible or reversible. **Irreversible cell injury** results in cell death, or necrosis. **Reversible** changes induced by acute injury change cell functions and typically change the cell shape (e.g., causing cell swelling [hydropic swelling]). Chronic stress or injury results in adaptations in cell functions and morphology. The most important forms of adaptations are **atrophy, hypertrophy, hyperplasia,** and **dysplasia.** All of these changes are reversible and, on cessation of stress, the cell reverts to normal. In some instances, however, the cell may remain permanently changed and transform into a neoplastic cell.

The injurious stimuli are grouped into several categories. Causes of cell injury also can be considered as endogenous or exogenous, albeit most often they interact with each other. The outcome of cell injury depends on the intensity, duration of adverse influences, and the capacity of cells to respond (i.e., adapt).

REVERSIBLE ACUTE CELL INJURY

The initial response to a potentially lethal stimulus is reversible if the proper remedial steps are taken before the point of no return. If the stimulus exceeds the capacity of the cell to maintain its function and integrity, the changes become irreversible, and cell death occurs.

The injured cell cannot maintain the selective permeability of its plasma membrane, resulting in a loss of volume control. This

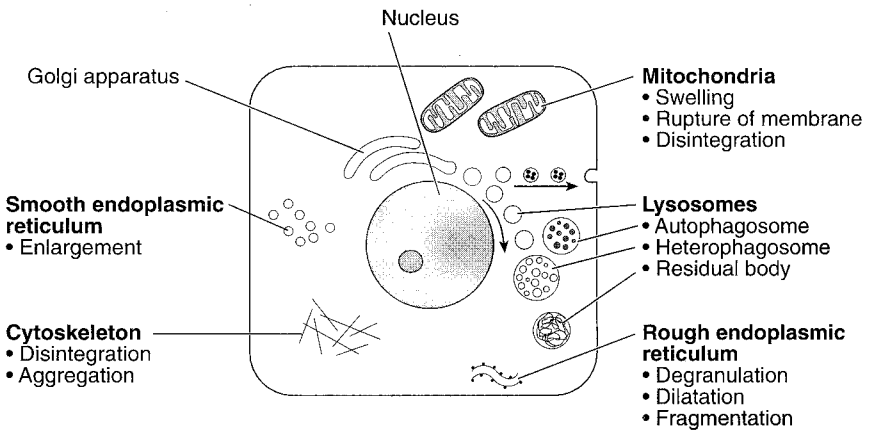


Figure 1-1.
The response of organelles to acute cell injury. By electron microscopy, changes are seen in the nucleus, mitochondria, lysosome, rough endoplasmic reticulum, smooth endoplasmic reticulum, and cytoskeleton.

hydropic swelling of cells is marked by an increased influx of Na^+ and H_2O into the cell and efflux of K^+, related to a dysfunction of the Na^+/K^+-ATPase and inadequate supply of energy (adenosine triphosphate [ATP]). The swollen cell has a vacuolated cytoplasm and may appear more pale or eosinophilic (pink) due to decreased basophilia (bluish staining with hematoxylin that binds to DNA and RNA).

Morphologic Changes of Cellular Organelles

Hydropic swelling of the cell produces no obvious nuclear changes. The cytoplasmic changes are reversible and are best seen with the electron microscope (Fig. 1-1).

Mitochondria are double membrane–bound organelles that serve as primary sources of energy. Their size is approximately at the limits of resolution of light microscopy, but they are readily visualized by electron microscopy. In acute cell injury, mitochondria swell. Initially, ions such as Ca^{2+} and Mg^{2+}, which are stored in mitochondria, leave the mitochondria and enter the cytoplasm. Adenosine diphosphate (ADP) accumulates as electron transport is uncoupled and ATP production is depressed. Lactic acid accumulates, and the intracellular pH decreases. Progressive swelling of mitochondria leads to widening of the spaces between the cristae, the inner and outer membranes, and the rupture of the membranes. The membranes of ruptured mitochondria calcify or are digested in lysosomes (autophagosomes). Mitochondrial injury impairs energy production in the cell.

Rough endoplasmic reticulum (RER) is composed of cisterns lined by membranes that are studded with ribosomes. Most proteins destined for export from the cell are synthesized in the RER. Among the

earliest changes in response to injury is the detachment of ribosomes from the membranes, which leads to a loss of cytoplasmic basophilia. The cisternae of the RER progressively dilate as Na^+ and H_2O accumulate in its lumen. This dilation is accompanied by fragmentation. Loss of RER is accompanied by decreased protein synthesis.

Smooth endoplasmic reticulum (SER) is composed of membrane-bound vesicles rich in enzymes, which participate in intermediary metabolism or catabolism of drugs, toxins, and hormones. SER is prominent in metabolically active cells such as liver cells. Prolonged exposure to drugs (e.g., barbiturates) causes enlargement of SER in liver cells. SER is also abundant in corticosteroid hormone–synthesizing cells such as Leydig cells. Increased SER in these cells reflects increased corticosteroid hormone synthesis.

Lysosomes are membrane-bound organelles rich in hydrolytic enzymes. Primary lysosomes, which are derived from the vesicles of the Golgi apparatus, fuse with pinocytotic or phagocytotic vesicles derived from the invaginations of the plasma membrane and form secondary lysosomes or heterophagosomes. Autophagosomes are secondary lysosomes filled with fragments of damaged organelles. Secondary lysosomes digest their contents. Undigested material remains as residual bodies rich in lipid (lipofuscin).

The **cytoskeleton** consists of a mesh of filaments divided into three groups: (1) microtubules composed of tubulin, (2) microfilaments composed of actin and myosin, and (3) intermediate filaments. Microtubules and microfilaments are the same in all cells; however, the protein composition of intermediate filament varies according to cell type. The intermediate filament of epithelial cells contains keratin. Mesenchymal cells contain vimentin, and neural cells contain neurofilament proteins. In acute cell injury, cytoskeleton becomes disorganized or partially degraded, which contributes to the blebbing of the cell membrane. Aggregation of intermediate filaments and dispersion of microfilaments may adversely affect the maintenance of cell shape and the movement of organelles. The cytoskeleton may also form cytoplasmic aggregates, such as Mallory hyalin in liver cells seen in chronic alcoholism.

The **cell membrane** is a semipermeable complex structure that separates the inside of the cell from the environment. The unit membrane is composed of a lipid bilayer with protein and carbohydrates inserted into it. The lipids of the cell membrane are susceptible to injury, especially by the free radicals that produce lipid peroxidation and alter lipid-protein interactions. The membrane functions depend on energy supply and the Na^+/K^+-ATPase. Cell injury is associated with blebbing of the cell membrane or its invagination. These invaginations contain Na^+ and H_2O and are known as **hypoxic vacuoles.**

During the reversible phase of cell injury, nuclear changes are subtle and include clumping of the DNA histone complexes (chromatin) or loosening of the interchromatinic substance and blebbing of the nuclear membrane. The nucleolus may show condensation of the fibrous and particulate components into distinct zones or some disorganization and fragmentation. All of these changes are

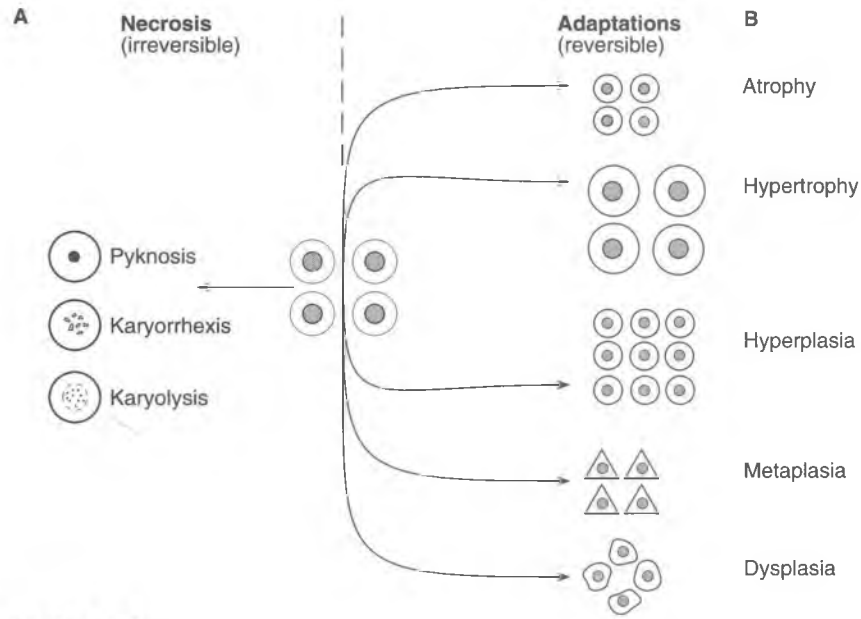


Figure 1-2.
A: In necrosis, nuclear changes in cell death include pyknosis, karyorrhexis, and karyolysis. Pyknosis is characterized by condensation of chromatin, karyorrhexis by segmentation of the nucleus, and karyolysis by enzymatic lysis of the chromatin. *B:* Adaptations of cells to chronic stress or injury include atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia.

reversible. Cell injury adversely affects DNA, RNA, and nuclear protein metabolism and inhibits the transcription and translation.

Adaptations

Cells can adapt to prolonged stress or repeated injuries by increasing and decreasing their functions. Functional changes usually cause structural changes that can be recognized on gross (naked eye) or microscopic examination of organs or microscopic examination of cells and tissues (Fig. 1-2).

Atrophy is a decrease in the size of an organ or individual cells. Atrophy of organs or tissues may result from either decreased numbers of cells or cell size. It may be physiologic, as in the reduction of the uterus following hormone withdrawal, or pathologic, as in muscle atrophy following denervation or ischemia. Aging often contributes to atrophy. In the so-called brown atrophy of the heart typical of aging, the heart is small and dark brown because the atrophic cardiac myocytes contain increased amounts of lipofuscin—the brown, lipid-rich pigment of aging. Atrophy should be distinguished from **hypoplasia,** a developmental disorder in which the organs fail to reach their normal size.

Hypertrophy is the opposite of atrophy and results from enlargement of individual cells (rather than increased number of cells) or of the entire organ. Increased functional demand posed on the heart by

high blood pressure typically causes left ventricular hypertrophy. Weight lifting causes hypertrophy of skeletal muscle. Hypertrophic muscle cells are large and have enlarged nuclei. Their cytoplasm contains an increase in the number of contractile fibers. Hypertrophy is reversible; if a weight lifter stops training, the muscles decrease in size.

Hyperplasia is an enlargement of an organ or tissue due to an increased number of cells. This is usually due to increased cellular proliferation. Although presumably decreased cell death can also result in a total increase in the numbers of cells, this appears to be a less frequent cause of hyperplasia. Hyperplasia can be physiologic or pathologic. Enlargement of breasts due to proliferation of cells in the lobules in pregnancy is an example of physiologic hyperplasia. Hyperplasia of the prostate, a common disease of aging, is an example of pathologic hyperplasia. Physiologic hyperplasia reverts to normal when the stimulus, usually a hormone, is removed. Pathologic hyperplasia is usually less responsive to ablation therapy.

Combined hypertrophy and hyperplasia occurs often because cellular hypertrophy almost always precedes cellular division in all tissues composed of cells capable of dividing. Thus, hypertrophy precedes hyperplasia at the cellular level. At the organ level, enlargement can result from hyperplasia, with accumulation of increased numbers of cells. Enlargement of the kidney after unilateral nephrectomy results first in the enlargement of tubular cells (hypertrophy), but later these cells also divide, increasing the number of kidney cells (hyperplasia).

Metaplasia is an adaptive response that results in the change of one adult (differentiated) cell type to another. Examples include the change of columnar epithelium to squamous epithelium **(squamous metaplasia)** and fibroblasts evolving into bone **(osseous metaplasia).** Occasionally, metaplasia can progress to dysplasia or neoplasia, as occurs in the bronchial epithelium of smokers. In most instances, however, metaplasia is a reversible, not a preneoplastic, process.

Dysplasia is a change in cell and tissue morphology related to altered cellular differentiation, usually in response to a chronic injurious stimulus. The best example is the dysplasia of bronchial epithelium induced by cigarette smoke. Initially, dysplasia-like metaplasia may be reversible if the stimulus that caused it is removed. The proliferation of cells may be autonomous and progress to neoplasia. Characteristically, the nuclei of these cells are enlarged disproportionately to the cytoplasm, reflecting discordant differentiation and a nuclear-cytoplasmic disproportion.

Intracellular Storage

The substances that accumulate in cells can be classified as endogenous or exogenous (Table 1-1). Materials that have their own color are called *pigments.*

Metabolic disturbances caused by cell injury may result in accumulation of metabolites (such as glycogen or lipid). For example, in glycogen storage diseases such as von Gierke (type I) glycogeno-

TABLE 1-1.
Materials Stored Inside Cells

Substance	Example
Glycogen	Glycogenesis
Mucopolysaccharide	Mucopolysaccharidosis
Lipid	Fatty liver
Hemosiderin*	Hemochromatosis
Bilirubin*	Jaundice
Melanin*	Sun tanning
Carbon particles	Anthracosis
Lipofuscin*	Aging

**Indicates pigments.*

sis, glycogen accumulates in the cytoplasm of liver and kidney cells. The best example of fatty change is fatty liver induced by alcohol. The four most important reasons for **alcohol-induced fatty liver** are (1) increased uptake or mobilization from peripheral fat stores; (2) increased lipogenesis (i.e., synthesis of triglycerides from other metabolites); (3) decreased breakdown of fatty acids by oxidation; and (4) decreased export of fat in the form of lipoproteins due to reduced synthesis of apoprotein (Fig. 1-3).

Iron is stored in the cells of the fixed macrophage system of the spleen, liver, and bone marrow in the form of **hemosiderin,** which represents aggregates of iron and iron-binding protein, **ferritin.** Increased amounts of hemosiderin are found in **hereditary hemochromatosis,** a genetic disease in which the absorption of iron in the intestine cannot be regulated. **Secondary hemochromatosis** results from iron overload, the result of repeated transfusions such as occurs in patients with hemolytic anemia.

IRREVERSIBLE CELL INJURY

Irreversible injury occurs when the cell cannot respond adequately to injury; typically, it is a function of concentration or duration of adverse exogenous stimulation. Irreversible cell injury results in cell death.There are two general types of **cell death:** (1) accidental, called *necrosis*, and (2) programmed, called *apoptosis.*

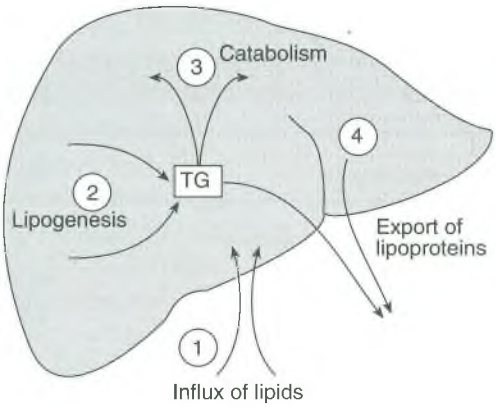


Figure 1-3.
Fatty liver induced by alcohol is caused by (1) increased influx of fat from peripheral stores; (2) increased lipogenesis and storage of fat in the form of triglycerides (TG); (3) reduced catabolism of TG; and (4) reduced export of lipids from the liver in the form of lipoproteins.

Necrosis is the term applied to the degradative processes that take place within the cell after a cell that has been irreversibly injured passes the point of no return. Morphologic changes in dying cells include cytoplasmic changes similar to those seen in reversible cell injury, albeit more pronounced, and nuclear changes, which are only found in irreversibly damaged cells. Rupture of the cell membrane is also a sign of irreversible cell injury. There are three types of nuclear changes: pyknosis, karyolysis, and karyorrhexis (see Fig. 1-2).

Apoptosis, or "active" dying, involves gene activation and enzyme action. Apoptosis occurs normally during development, but it also can be induced by viruses, drugs, or other means. It is marked by nuclear condensation, fragmentation and extrusion of nuclear debris, and condensation of the cytoplasm into acidophilic bodies, which are usually phagocytosed by adjacent cells that are normally nonphagocytic or tissue macrophages. In contrast to necrosis, apoptosis does not induce a significant inflammatory reaction. Isolated DNA from apoptotic cells exhibits a so-called laddering pattern typical of DNA segmentation into nucleosomes of approximately equal size. The differences between apoptosis and necrosis are given in Table 1-2.

Apoptotic cells are found during the formation of digits in developing fetal limbs. Cortisone treatment produces apoptosis in the thymus. Round acidophilic or Councilman-like bodies are apoptotic hepatocytes found in viral hepatitis.

Pathogenesis of Irreversible Cell Injury

Irreversible lethal cell injury can be induced by many means, such as hypoxia and anoxia, ischemia, activated oxygen radicals, toxins, or ionizing radiation.

Anoxia refers to deprivation of O_2. Ischemia, the main cause of anoxia, also includes deprivation of nutrients supplied to tissues by blood and waste accumulation. Lack of O_2 depletes ATP in the cells and stimulates glycolysis to compensate for ATP loss. Lactate accu-

TABLE 1-2.
Comparison of Apoptosis and Necrosis

Apoptosis	Necrosis
Metabolic changes	
Energy dependent	Energy independent
Gene activation	Inhibition of all cell functions
Protein synthesis	
Enzyme activity	
Cytoplasmic changes	
Cell membrane blebbing	Cell membrane rupture
Cell fragmentation	Cell dissolution
Nuclear changes	
Pyknosis, karyorrhexis, karyolysis	Nucleus fragmentation
Nuclear expulsion from cytoplasm	
DNA changes	
Fragmentation into nucleosomes ("ladder by electrophoresis")	Random lysis
Outcome	
Phagocytosis by non-professional phagocytes and macrophages	Phagocytosis by segmented neutrophils (acute inflammation and macrophages)

mulates as electron transport fails and the cell shifts to anaerobic metabolism. A drop of intracellular pH is initially protective, but it becomes harmful because it causes structural changes such as cross-linkage of proteins and aggregation of nuclear chromatin. RNA and protein synthesis slows and then stops as energy stores are depleted. The cell membrane becomes more permeable as the function of Na^+/K^+-ATPase diminishes, necessary for the extrusion of Na^+ and retention of K^+ by the cell. Water accumulates in the invaginations of the plasma membranes ("hypoxic vacuoles"). Cytoskeletal elements such as actin and tubulin are disrupted, contributing to outside blebbing of plasma membrane. Cytoplasmic vacuoles and vesicles derived from the endoplasmic reticulum and other elements of the cytocavitary network appear. Ribosomes disaggregate, which accounts for the loss of cytoplasmic basophilia. Finally, lysosomal membranes are disrupted with release of acid hydrolysis and

breakdown of cytoplasmic substances. Once the plasma membrane is ruptured, disintegration follows quite rapidly.

Ca^{2+} appears to play a central role in irreversible injury. It enters the cytoplasm from the extracellular fluid as well as from intracellular storage sites in the mitochondria and the endoplasmic reticulum. Ca^{2+} activates many enzymes (e.g., phospholipases and proteases), which contribute to cytoplasmic changes in anoxia.

Cell injury by O_2 radicals occurs in cells exposed to high concentrations of O_2, in reperfused infarcts, during radiation, and in many forms of inflammation. O_2 radicals are generated during the metabolic reduction of the four electrons bearing O_2 to H_2O. These intermediate O_2 species include superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\bullet$). All are unstable and potentially toxic. Activated O_2 species mediate cell killing during reperfusion injury and radiation-induced cell injury. They are formed inside injured cells but also by leukocytes and macrophages attracted to the site of cell injury.

O_2 radicals act on many key cellular components. They may damage DNA, inhibit RNA synthesis, or disrupt cell organelles by interacting with lipids in the membranes. Lipid peroxidation leads to formation of additional free radicals and autocatalytic amplification of the injury begun by the O_2 radicals.

Normal cells use several mechanisms to neutralize O_2 radicals. The most important of these are catalase, superoxide dismutase, and glutathione peroxidase.

Cell killing by viruses occurs two ways: direct killing by infection, producing a **cytopathic effect,** and a secondary **immune-mediated** cell killing of virus-infected cells. In the direct cytotoxic reaction, usually the virus enters the cell membrane, producing a pore that leads to fatal fluid and ion shifts. In the immune response, the viruses induce neoantigens, which are recognized by the cellular immune system. Infected cells are killed by immune cells such as T-lymphocytes or natural killer cells.

MORPHOLOGY OF NECROSIS

Several forms of necrosis can be recognized by gross examination (Fig. 1-4).

Coagulation necrosis results from ischemia and resembles cooked meat or a boiled egg. The tissue becomes homogeneous, pale, and rigid. The histologic appearance of increased cytoplasmic eosinophilia, loss of details such as cross striations in muscle, and loss of nuclei is often characteristic. Coagulation necrosis may be caused by ischemia of parenchymal organs and is typically seen in a

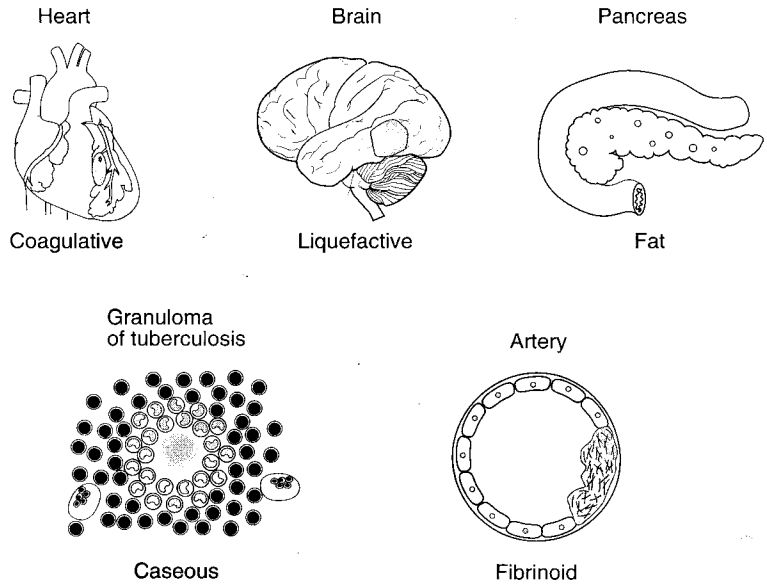


Figure 1-4.
Forms of necrosis.

myocardial infarct caused by coronary artery obstruction. A second example is renal cortical necrosis caused by mercury poisoning.

Liquefactive necrosis is seen in brain infarcts as a result of enzymatic breakdown and thermal dissolution of tissue components. The central zone of the necrotic area becomes liquid and usually is lost during processing for histologic examination. Liquefactive necrosis is also found in localized suppurative inflammation (abscess) in which the tissue is liquefied by the action of lytic enzymes released from leukocytes.

Fat necrosis is caused by enzymatic action of lipase on fat. Typically, it is found in association with acute pancreatitis, but sometimes it is also found in areas of traumatic injury to fat. The action of lipases leads to cleavage of triglycerides into glycerol and free fatty acids, which react with calcium, forming calcium soaps. This process, called *saponification*, leads to the formation of whitish specks in the necrotic tissue. Histologically, these areas stain a faint blue and show relatively little inflammation.

Caseous necrosis is a form of necrosis typically found in tuberculosis and some fungal diseases. Its name is derived from the cheesy appearance of the necrotic tissue, which resembles the curds that develop during the production of cheeses. Histologically, the necrotic area consists of granular amorphous material. The outlines of necrotic cells are not discernible as they are in coagulative necrosis. In tuberculosis, the areas of caseous necrosis are usually in the center of granulomas and composed of epithelioid macrophages, giant cells, and lymphocytes.

Fibrinoid necrosis is usually a histologic change seen in small blood vessels affected by autoimmune diseases such as polyarteritis

nodosa or by malignant hypertension. The walls of the vessels contain foci of homogeneous or granular eosinophilic material rich in fibrin.

Outcome of Necrosis

Dead cells can cause permanent defects or they can be replaced by regeneration in organs that can regenerate. For example, lost cells in the heart are replaced by fibroblasts, which produce collagenous scar tissue.

Calcium salts may be deposited to mark areas of previous cell injury. Like grave markers, the flecks of chalk show where the solubility was affected by the pH of the local inflammatory process, producing deposits called **dystrophic** calcification. When excessive calcium is circulated by mobilization of calcium from bone and similar elements, it again may exceed the solubility product and be deposited in tissues throughout the body. This usually is associated with hyperparathyroidism and is referred to as **metastatic** calcification.

Chapter 2

Inflammation and Repair

Inflammation is a natural defense response of multicellular organisms reacting to an injury or irritation. It can be caused by living pathogens such as bacteria and viruses, chemicals or physical agents, or immune mechanisms. Inflammation of short duration is called **acute** and that of longer duration is **chronic.** Although the inflammation has a primarily protective role and in most instances heals by spontaneous **resolution,** inflammation can also persist ad infinitum or cause harm and tissue destruction. Tissue damage can be repaired to some extent, depending on the site of injury. **Regeneration** is found in some tissues; in other areas, the repair entails replacement of normal cells with fibrous tissue **(scarring).**

CLINICAL SIGNS OF INFLAMMATION

Inflammation produces **localized** symptoms such as swelling, redness, warmth, pain, and loss of function, which are known as the classic signs of inflammation. It also causes **systemic** symptoms such as malaise, weakness, and fever. These symptoms are attributed to the action of cytokines released from inflammatory cells, destruction of tissue by bacteria or enzymes released from inflammatory cells, and various mediators of inflammation such as arachidonic acid derivatives or complement proteins. Fever is mediated by interleukin 1 (IL-1) and tumor necrosis factor–alpha (TNF-α) acting on the hypothalamic thermoregulatory centers. These substances release prostaglandin, which acts on the "central thermostat" in the hypothalamus, setting it higher and thus allowing the body to overheat. Aspirin, which inhibits the synthesis of prostaglandins, can reduce fever.

Laboratory findings indicative of inflammation are leukocytosis and a high erythrocyte sedimentation rate (ESR). *Leukocytosis* refers to

an increased number of leukocytes (more than the normal level) in blood. In bacterial infections, most of the white blood cells are neutrophils (neutrophilia). Viral infections are typically accompanied by lymphocytosis.

ESR is measured by allowing the blood drawn into a calibrated tube to deposit a sediment over a period of 2 hours. Under normal conditions, the proteins of the plasma do not allow efficient separation of red blood cells from the plasma. The blood of an ill patient forms sediments fast because the plasma contains some proteins in higher concentrations than normal and others in reduced amounts. For example, acute inflammation is associated with reduced levels of albumin in blood. Proteins that appear in higher concentrations in inflammation are called *acute phase reactants.* This group of proteins includes proteins such as C-reactive protein, ceruloplasmin, haptoglobin, and fibrinogen.

PATHOGENESIS OF INFLAMMATION

Mediators of Inflammation

Mediators of inflammation can be classified as plasma derived or cell derived. Plasma-derived mediators circulate in blood in an inactive form and are activated by the injury or various stimuli that initiate the inflammatory process. The most important **plasma-derived** mediators are

- Clotting factors, such as Hageman factor, thrombin, fibrinogen, fibrin split products
- Anticoagulants and fibrinolytic agents, such as plasmin
- Complement proteins
- Kinins, such as bradykinin

Cell-derived mediators of inflammation include the following:

- **Biogenic amines,** such as histamine and serotonin, are released from mast cells and platelets.
- **Arachidonic acid derivatives,** such as prostaglandins and leukotrienes, are derived from lipids in the plasma membrane of many inflammatory and tissue cells.
- **Cytokines,** such as interleukins, are derived from macrophages and lymphocytes.
- **Platelet-activating factor** is a lipid-derived substance released from a variety of cells. It activates platelets, as implied by its name, and has many other functions.
- **Nitric oxide** is released from endothelial cells and macrophages.

Cellular Response

The cells involved in acute inflammation are **polymorphonuclear leukocytes** (PMNs), platelets, and endothelial cells. Chronic inflammation is mediated by lymphocytes, macrophages, and plasma cells. Mast cells and eosinophils participate in allergic reactions. PMNs account for approximately 70% of all white blood cells (WBCs). They have a segmented nucleus, which consists of two to five parts, and a cytoplasm that contains granules. These granules stain neutrally with standard dyes; thus, the PMNs are also called *neutrophils.* The granules are of two kinds: *primary granules,* which contain enzymes such as myeloperoxidase, acid hydrolases, and cationic proteins; and *secondary granules,* which contain collagenase, lactoferrin, and alkaline phosphatase. Phospholipase A_2 is found in both types of granules.

PMNs are mobile cells that can migrate effectively toward chemotactic stimuli. They can actively phagocytize and kill bacteria with the oxygen radicals generated by the myeloperoxidase. In the presence of halides such as chloride or iodine ions, myeloperoxidase also generates hypochlorous acid, which is extremely bactericidal. PMNs are relatively short lived (2 to 4 days); when they die they form pus, a viscous yellow fluid composed of dead and dying PMNs and tissue debris.

Eosinophils account for 2% to 4% of all WBCs. They have a bilobed nucleus and a well-developed cytoplasm rich in granules that stain pink with eosin. Crystals are seen in the granules by electron microscopy. Eosinophils are less mobile than PMNs and have a limited capacity for phagocytosis. Eosinophils participate in inflammation evoked by parasites and in allergic reactions.

Mast cells are tissue derivatives of basophils, which form 1% of all WBCs. They have a bean-shaped nucleus and a well-developed cytoplasm, which contains numerous basophilic granules. These granules are rich in histamine and heparin. Mast cells typically mediate type I hypersensitivity reactions (e.g., hay fever, asthma, or atopic dermatitis).

Lymphocytes account for 20% to 30% of all WBCs. They have a round nucleus and very little cytoplasm. Lymphocytes are present in blood in two main forms: as B cells and T cells. B cells differentiate into immunoglobulin-secreting plasma cells, whereas T cells participate in cell-mediated hypersensitivity reactions. Lymphocytes are less motile than PMNs and do not phagocytize particulate material, although they can take up soluble antigens.

Plasma cells are derived from lymphocytes. These cells have a round nucleus eccentrically located in the cytoplasm, which is slightly basophilic. The basophilia reflects the abundance of ribosomes on the rough endoplasmic reticulum, the site of synthesis of immunoglobulins.

Macrophages are derived from circulating monocytes, which account for 5% to 10% of all WBCs. Macrophages are motile and actively

phagocytic. They also secrete numerous mediators of inflammation such as interleukins, interferons, and TNF. Macrophages also form granulomas in chronic inflammation. In granulomas, macrophages transform into epithelioid cells and multinucleated giant cells.

Acute Inflammation

Acute inflammation begins with vascular changes involving arterioles, capillaries, and venules. After transient constriction of arterioles, dilatation ensues. It persists, causing active hyperemia of inflamed tissue. This is followed by a decrease in the circulation (**stasis**) due to increased permeability of capillaries and venules and consequent increased viscosity of blood. Swelling of endothelial cells reduces the caliber of venules, further contributing to stasis. Stasis leads to *rouleaux* formation, whereby the red blood cells form columns or aggregates. Simultaneously, *margination* of leukocytes occurs along vessel walls. The mediators of inflammation released from the endothelial cells, platelets, and inflammatory cells modify the surface of leukocytes as well the endothelial cells, which are activated. In this process, the leukocyte and endothelial cells are stimulated to express adhesive molecules on their surface. The interaction of adhesion molecules and receptors, known as **selectins** and **integrins,** leads to an adherence of leukocytes to endothelial cells. Chemotactic factors from outside the blood vessels act as chemoattractants and stimulate the PMNs to transmigrate from the vessel toward the site of infection. Margination of PMNs, their adhesion to the endothelium, emigration through the vessel wall, and active movement toward the chemotactic stimulus are shown in Figure 2-1.

The neutrophils take up bacteria through a process called **phagocytosis,** which includes the numbered steps shown in Figure 2-2, described as follows:

- **Opsonization:** Coating of bacteria with IgG and complement (C3b) so they can be taken up by neutrophils. Uncoated bacteria may be phagocytized, but less efficiently.
- **Recognition and attachment:** Leukocytes have receptors on plasma membrane specific for Fc fragment of IgG and C3b, enabling them to selectively recognize coated bacteria and attach to them (opsonized bacteria).
- **Ingestion:** This is an energy-dependent process during which pseudopods and invaginations of plasma membrane surround bacteria, enclosing them in a phagocytic vacuole.
- **Degranulation:** Formation of phagolysosomes by fusion of phagocytic vacuole with lysosomes.
- **Bacterial killing:** This involves an oxygen-dependent mechanism, which generates oxygen radicals and nitric oxide, and an oxygen-independent mechanism, which is mediated by lysosomal hydrolases and cationic proteins (defensins).
- **Digestion:** Bacteria are digested by lysosomal enzymes.

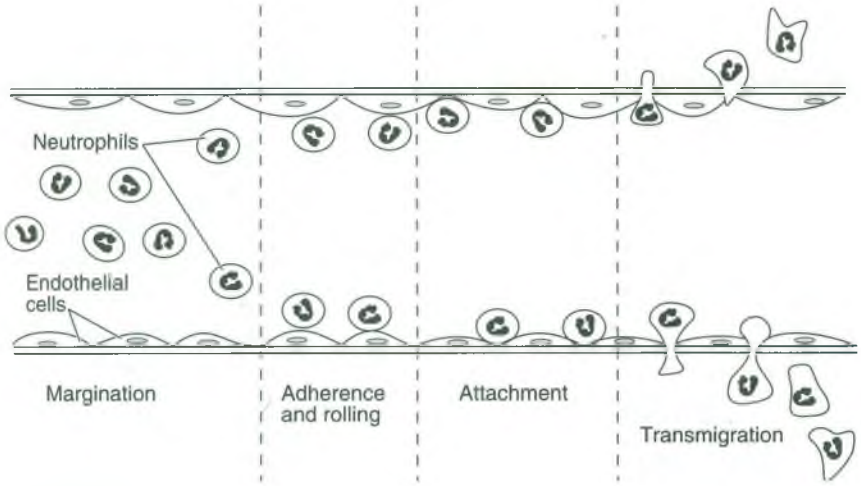


Figure 2-1.
Emigration of neutrophils from blood vessels in inflammation. Margination of leukocytes is followed by a selectin-mediated adherence to endothelial cells and rolling of neutrophils until they are firmly attached to endothelial cells mediated by integrins. Transmigration through the vessel wall occurs in response to chemotactic factors released from the tissue invaded by the pathogen.

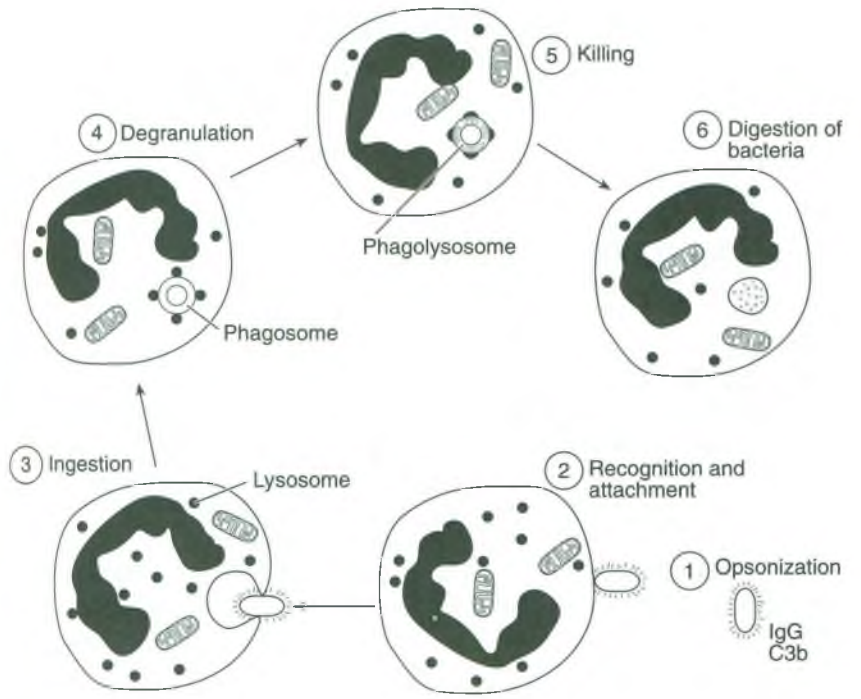


Figure 2-2.
Phagocytosis of bacteria in acute inflammation. (IgG, immunoglobulin G.)

Chronic Inflammation

Chronic inflammation may evolve from unresolved and persistent acute inflammation. Furthermore, in some cases, the pathogen evokes an immune response that perpetuates the inflammation. In either case, the short-lived PMNs are replaced by macrophages, lymphocytes, and plasma cells. Macrophages play a critical role because they can phagocytize the pathogens and the cellular detritus, and they are also capable of secreting numerous biologically active substances that modulate the reaction of other cells. Histologically, chronic inflammation can occur in two basic forms: (1) as a nonspecific interstitial infiltrate of lymphocytes, plasma cells, and macrophages; or (2) as a granuloma. Most chronic inflammation occurs as nonspecific infiltrates.

Granulomas are microscopic aggregates of macrophages and lymphocytes. Macrophages form intercellular contact and, because of their epithelial-like appearance, are called *epithelioid cells.* Some epithelioid cells fuse into multinucleated giant cells. Lymphocytes can be intermixed with macrophages or form peripheral rings around them. In some granulomas, such as tuberculosis or fungal diseases, the central part undergoes caseous necrosis. In contrast to these **caseating granulomas,** granulomas of sarcoidosis do not show any necrosis and are called **noncaseating granulomas.** Granulomas elicited by particulate foreign bodies, usually phagocytized into the cytoplasmic vacuoles of multinucleated giant cells, are called **foreign body granulomas.** Granulomas of syphilis show central coagulation necrosis surrounded by lymphocytes, macrophages, giant cells, and plasma cells. These granulomas are called **gummas** (Fig. 2-3).

MORPHOLOGY OF INFLAMMATION

Macroscopic and microscopic features of inflammation depend on the pathogen, severity and duration of injury, and anatomic site of inflammation. Depending on the nature of the exudate (i.e., the material that oozes out from the blood vessels during inflammation), several inflammatory reactions are recognized.

- **Serous inflammation** is characterized by a clear watery exudate resembling normal serum. The best examples of serous inflammation are blisters caused by burns or pleuritis that accompanies viral or tuberculous pneumonia.
- **Fibrinous inflammation** is characterized by a thick exudate rich in fibrin. Fibrinous pericarditis can be caused by rheumatic fever or tuberculosis. The surfaces of the epicardium and pericardium are covered with layers of sticky, yellow-white, stringy fibrin formed through polymerization of extravasated *fibrinogen.* Fibrinogen is one of the largest molecules of plasma, and its appear-

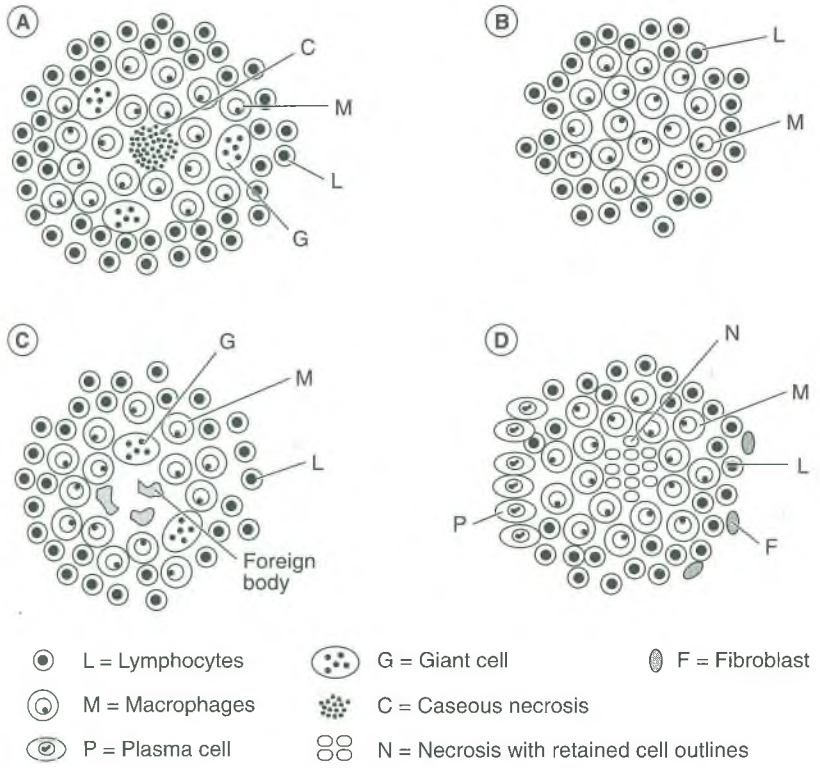


Figure 2-3.
Granulomas. *A:* Caseating granuloma. *B:* Noncaseating granulomas. *C:* Foreign body granuloma. *D:* Gumma.

ance in extravascular spaces is typically a sign of severe vascular injury that allows the passage of relatively large molecules.

- **Purulent inflammation** is characterized by an exudation of pus (i.e., numerous neutrophils disintegrate, giving the exudate a viscous yellow appearance). Purulent or suppurative inflammation is typically evoked by pyogenic bacteria. It may be combined with fibrinous inflammation (fibrinopurulent inflammation). Localized purulent inflammation is called an **abscess.**
- In **pseudomembranous inflammation,** exudation of fibrin and pus onto the mucosal surfaces leads to the formation of layers that appear as membranes. Because this exudate can be removed and is not a real membrane, it is called a *pseudomembrane.*
- **Hemorrhagic inflammation** is characterized by bleeding, which usually occurs in severe infections and in destruction of blood vessel walls. It may be combined with fibrinous inflammation (fibrinohemorrhagic inflammation).

Healing and Repair

The outcome of inflammation depends on the type of inflammatory reaction, its duration and extent, and the tissue or organ involved.

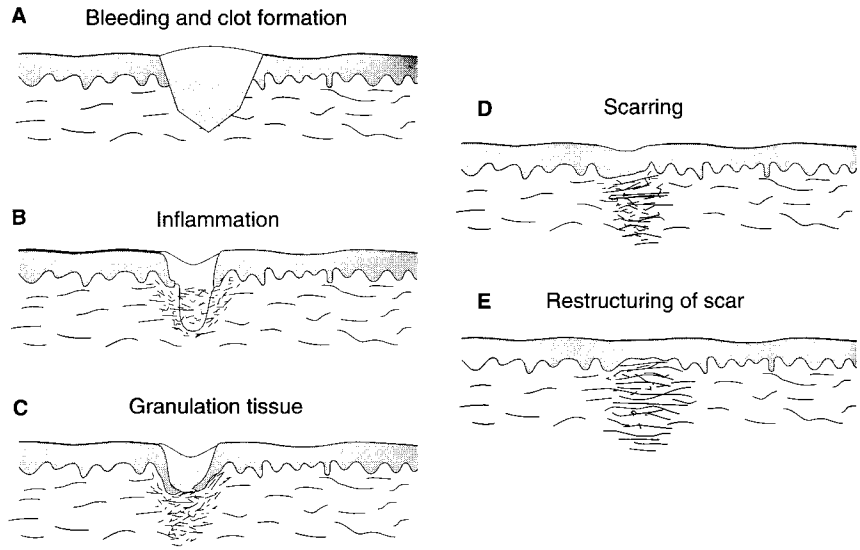


Figure 2-4.
Wound healing occurs in several phases. *A:* Bleeding and clot formation. *B:* Inflammation. *C:* Granulation tissue formation. *D:* Scarring. *E:* Restructuring of the scar.

In many respects, the outcome of inflammation resembles healing of wounds. A clean surgical incision heals promptly **(healing by primary intention),** whereas large irregular wounds caused by trauma take longer to heal and do not heal as readily **(healing by secondary intention).**

Healing by primary intention occurs throughout several stages (Fig. 2-4):

- **Bleeding and clot formation in the wound:** Blood oozes from the damaged blood vessel into the interstitial spaces. A fibrin clot fills the tissue defect and serves as a scaffold for the invading cells.
- **Inflammation:** The inflammatory cells from the blood phagocytize the tissue debris and prepare the soil for the ingrowth of blood vessels.
- **Granulation tissue formation:** The inflammatory cells, especially the macrophages, secrete substances that promote the ingrowth of blood vessel–forming cells (*angioblasts*) and fibroblasts. In the early stages of wound healing, the fibroblasts acquire contractile properties and are known as *myofibroblasts.* These cells mediate the first contracture of the wound, which results in close apposition of wound margins. Granulation tissue, which is rich in blood vessels, brings in additional macrophages and these in turn stimulate additional proliferation of fibroblasts and angioblasts (*angiogenesis*).
- **Scarring:** As the healing progresses, the granulation tissue fibroblasts become the most dominant cells. These cells synthesize collagen, which accounts for the transformation of the granulation tissue into a collagenous scar.

- **Restructuring of the scar:** As the healing progresses, the scar tissue is reorganized and acquires tensile strength and elasticity.

The healing of wounds depends on many factors such as the nutritional status of the host, the age of the host, and the vascularization and blood perfusion of the tissue. Factors that inhibit wound healing include infections and deficiencies of nutrition, vitamin C, and zinc. Corticosteroids also delay healing. Separation of wound margins is called wound **dehiscence.** Excessive scar formation is called **keloid. Contractures** are deformities caused by excessive contraction of scar tissue.

Regeneration

Regeneration is a form of healing in which the tissue defect is replaced by identical cells. Regeneration can occur only in organs composed of cells that can divide. Myocardial or striated muscle cells and neurons are **permanent** (postmitotic) cells and, accordingly, the injury of the brain, striated muscle, and myocardium cannot be repaired by regeneration. Instead, the defects in these organs are repaired by scarring in wounds. On the other hand, organs composed of **labile** (mitotic) cells, such as the skin or intestinal mucosa, can readily regenerate. Organs composed of **stable** (facultative mitotic) cells, such as liver or kidney, also can regenerate. Notice that mitotic cells form pools in which a certain number of cells are constantly in mitosis, acting as stem cells for all other cells. These cell populations are sensitive to cytotoxic drugs and radiation. Postmitotic permanent cells are not capable of entering the mitotic cycle and are also quite resistant to irradiation.

Chapter 3

Immunopathology

The body's immune defenses against biological organisms are mounted by interrelated but distinctly different responses referred to as *natural immunity* and *acquired immunity*. **Natural immunity** is mediated by various mechanisms:

- **Mechanical factors,** such as unbroken skin or mucous membranes, beating of cilia, and intestinal peristalsis, which prevent microbes from gaining access to the host, or elimination of noxious substances via coughing, sneezing, vomiting, or diarrhea
- **Humoral factors,** such as lysozyme in various body fluids, gastric and vaginal acidity, and complement and interferon
- **Inflammatory cells,** such as neutrophils and macrophages, which phagocytize and kill microorganisms, and mast cells and basophils, which produce mediators of inflammation
- **Natural killer (NK) cells,** which destroy virus and tumor-infected cells

Natural immunity requires no priming or sensitization and is not enhanced by previous exposure to the inciting agent. Also, it does not discriminate between various types of injurious agents—it lacks specificity.

Acquired immunity is mediated by several sets of cells that undergo a complex interaction when stimulated by foreign materials or microbes, collectively called **antigens.** The primary components of this defense system are lymphocytes and plasma cells, which respond to each antigen in a specific manner without cross-reacting with others. It has diversity: It is able to respond to almost any antigen it may encounter. After an encounter with an antigen, it develops memory; on re-exposure to the same antigen, it mounts fast to a specific immune response. Finally, this immune system is able to recruit or amplify other defense systems. By releasing bioactive substances, cytokines, its cells can activate other cells such as neutrophils and macrophages. It can also activate plasma proteins such as complement or kinins, classified as part of the natural immunity.

CELLS OF THE IMMUNE SYSTEM

Antigen introduced into the body is taken up by macrophages or other antigen-presenting cells, such as dendritic cells in lymph nodes or Langerhans' cells in the epidermis, and is passed to lymphocytes. These lymphocytes are classified as thymus-primed T-lymphocytes or bone marrow–derived B-lymphocytes. NK cells do not participate in specific immune reactions.

T-lymphocytes are responsible for cell-mediated immunity. Early during fetal life, T-cell precursors migrate from the bone marrow to the thymus, where they acquire their functional and phenotypic characteristics. T-lymphocytes reside in the thymus, paracortical regions of lymph nodes, and periarteriolar sheaths of the spleen. In the circulating blood, T cells account for 60% to 70% of all lymphocytes. Each T-lymphocyte has a unique antigen-specific receptor (T-cell receptor, or TCR). In approximately 95% of cells, the receptor consists of a disulfide-linked heterodimer composed of α or β polypeptide chains. Approximately 5% of cells have TCRs composed of γ and δ polypeptide chains. Each of the polypeptide chains has a variable antigen-binding region and a constant region. TCR diversity is due to somatic rearrangement of the genes that code for the α, β, γ, or δ chains. The TCRs are noncovalently linked to a cluster of polypeptides, the cluster designation (CD3) molecular complex, which is responsible for the transduction of signals and activation of the lymphocyte after antigen binding. Many other CD complexes are expressed on the surface of T-lymphocytes. Of these, CD4 and CD8 are most important because they allow lymphocytes to be sorted into two main subsets: $CD4^+$ helper/inducer cells and $CD8^+$ cytotoxic/suppressor cells.

$CD4^+$ cells regulate the functions of essentially all other cells participating in the immune response, including other T cells, B cells, macrophages, and NK cells. There are two functionally different subpopulations of $CD4^+$ cells: T-helper 1 (T_H1) and T-helper 2 (T_H2) cells. **T_H1** cells synthesize and secrete interleukin 2 (IL-2), and interferon-gamma (IN-γ), which facilitate macrophage-dependent immune responses such as delayed-type hypersensitivity and the production of opsonizing antibodies. **T_H2** cells synthesize and secrete IL-4 and -5, which aid in the synthesis of other antibodies. **$CD8^+$** cells are cytotoxic, but also may secrete cytokines, which suppress the immune response.

It should be noted that $CD4^+$ cells recognize antigens presented to them by antigen-presenting cells only in the context of class II major histocompatibility (MHC) antigens, whereas $CD8^+$ cells recognize antigens in the context of class I MCH.

B-lymphocytes account for 10% to 20% of lymphocytes in the peripheral blood. In addition, they are found in the follicles of

lymph nodes; the white pulp of the spleen, tonsils, bone marrow; and the mucosa-associated lymphoid system of the gastrointestinal and respiratory tracts.

B-lymphocytes express immunoglobulin M (IgM) on their surface, which serves as an antigen receptor. B-lymphocytes express several CD surface molecules, which change according to the maturation stage of each lymphocyte. Thus, B-lymphocytes can be classified as mature or immature. The function of different CDs is not known in all cases, but in some cases it is known. Complement receptor (CD2) also serves as a receptor for the **Epstein-Barr virus,** which accounts for the selective entry of this virus into B cells. On antigenic stimulation, B-lymphocytes become plasma cells, which secrete immunoglobulins.

Immunoglobulins belong to five classes: IgM, IgG, IgA, IgE, and IgD. IgM is the first to be secreted on antigenic stimulation. It is a pentamer of high molecular weight and thus the largest immunoglobulin. A second stimulus with the same antigen produces an IgG response. IgG is the most abundant immunoglobulin in blood. It is also the only antigen able to cross the placenta. IgA is a dimer, most abundantly found in secretions such as intestinal fluids or milk. IgE is secreted by plasma cells in various tissues and is usually attached to the surface of mast cells. IgD is of little significance.

All immunoglobulins have the same structure and are composed of two light chains and two heavy chains. The antigen-binding end of each immunoglobulin molecule is called the *Fab* end, and the other end is the *Fc* end. Fc receptors are found on neutrophils and macrophages.

Macrophages are part of the mononuclear phagocyte system, which includes many other cells such as Kupffer cells in the liver, Langerhans cells of the skin, microglia cells of the brain, and dendritic cells in the lymph nodes. Blood monocytes are considered precursors of some tissue mononuclear phagocytes. They play a significant role in inflammation and natural immunity and an equally important role in acquired immunity. Macrophages have numerous and diverse functions. In the context of acquired immunity, macrophages are essential for processing and presentation of antigens to T-lymphocytes. They also produce cytokines, which act on other cells of the immune system.

NK cells account for 10% to 15% of peripheral blood lymphocytes, which do not express surface immunoglobulins or have T-cell receptors. NK cells express two surface receptors, CD16 and CD56, and secrete IN-γ. CD16 is an Fc receptor for IgG, which allows it to lyse IgG-coated target cells and thus participate in the so-called antibody-dependent cytotoxic reaction. NK cells can destroy tumor cells, virally infected cells, and even some normal cells without previous sensitization.

TABLE 3-1.
Hypersensitivity Reactions

Type of Reaction	Antibody	Effector Cells	Examples of Diseases
Type I			
Anaphylactic	IgE	Mast cells	Eczema, hay fever, and asthma; systemic anaphylactic shock
Type II			
Complement-mediated cytotoxicity or membranolytic	IgG or IgM	No cells	Goodpasture syndrome; autoimmune hemolytic anemia; transfusion reactions; erythroblastosis fetalis
Antibody-dependent cell-mediated cytotoxicity		NK cells	Drug hypersensitivity reactions
Receptor binding with blockade or stimulation		No cells	Graves disease; myasthenia gravis
Type III			
Immune complex	IgG or IgM	Neutrophils and macrophages	Systemic lupus erythematosus; serum sickness; polyarteritis nodosa
Circulating			
Locally formed			
Type IV			
Cell-mediated (delayed type) hypersensitivity	No antibody	T-lymphocytes and macrophages (granulomas)	Contact dermatitis; sarcoidosis; tuberculosis

HYPERSENSITIVITY REACTIONS

Type I Hypersensitivity

Type I hypersensitivity **(anaphylaxis)** reactions occur within minutes after an antigen combines with antibodies coating mast cells in individuals previously sensitized to that antigen. **Systemic reactions** produce anaphylactic shock and may lead to death. **Local reactions** are characterized by cutaneous swellings and nasal, conjunctival, or both kinds of discharge and irritation, which leads to itching, sneezing, or coughing (Table 3-1 and Fig. 3-1).

Type I reactions are mediated by IgE antibodies attached to mast cells. When the antigen binds to the IgE-coated mast cells, they degranulate. The mast cell granules contain a variety of substances, known as **primary mediators.** The most important among

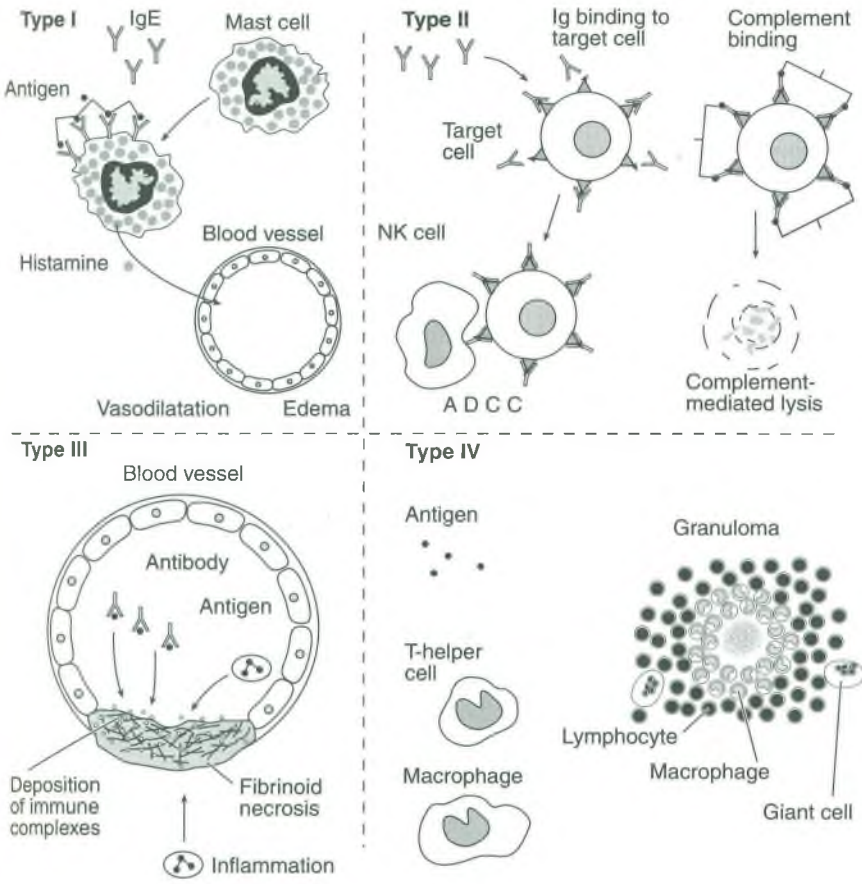


Figure 3-1.
Hypersensitivity reactions. (IgE, immunoglobulin E; NK, natural killer.)

these is histamine, which causes vasodilation and increased vascular permeability. Other components of granules are eosinophil chemotactic factor and enzymes such as chymase and heparin. **Secondary mediators** are synthesized from cell membrane lipids and include platelet-activating factor, leukotrienes, and prostaglandins. Mast cells also produce cytokines such as tumor necrosis factor–alpha (TNF-α), IL-1, IL-3, and IL-6. Leukotrienes cause smooth muscle contraction, especially in bronchi (bronchospasm), increase vasodilatation and permeability, and amplify inflammation. Systemic anaphylaxis can be induced in sensitized persons by the administration of heterologous proteins (e.g., antitetanus or anti–snake venom serum) or drugs (e.g., penicillin). Local anaphylactic reaction follows inhalation or ingestion of allergens (e.g., pollen, house dust, and animal dander). Urticaria, angioedema, allergic rhinitis (hay fever), and asthma are examples of localized anaphylaxis. Similar mast cell degranulation can also be caused by exposure to physical agents such as cold and heat; mediators of inflammation such as C3a, C5a, and IL-8; and some drugs such as codeine and morphine.

Type II Hypersensitivity

Type II hypersensitivity is mediated by antibodies directed toward antigens on cells or tissue components such as basement membranes. The antigens may be endogenous or exogenous. Endogenous antigens are formed from altered or damaged normal cell components, which become autoantigenic due to some structural changes induced by chemicals or viruses or for unknown reasons. For example, in Goodpasture syndrome, the globular portion of collagen type IV of the glomerular basement membrane becomes autoantigenic, eliciting production of membranolytic antibodies. Exogenous antigens such as blood group A erythrocytes transfused into group B persons are attacked by anti-A antibodies, and a hemolytic transfusion reaction occurs. Drugs absorbed into red blood cells can also act as hapten antigens and evoke a hemolytic reaction. Antibodies reacting with antigens on the surface of the attacked cells form antigen-antibody complexes that activate complement. Activation of the complement cascade leads to the formation of cytotoxic complement fragments and complexes, the best known of which is the membrane attack complex (see Table 3-1 and Fig. 3-1).

Complement-dependent cell lysis occurs in transfusion reactions, erythroblastosis fetalis, autoimmune hemolytic anemia, agranulocytosis, or thrombocytopenia. Lytic damage of the glomerular basement membrane occurs, for example, in Goodpasture syndrome. Antibody-coated cells and especially parasites and tumor cells can be destroyed without fixing complement. This **antibody-dependent cell-mediated cytotoxic reaction** is mediated by NK cells.

In certain human diseases caused by type II hypersensitivity, there is no cell destruction or tissue injury. Instead, there is **antibody-mediated cellular dysfunction.** Antibodies directed against cell surface receptors can alter cell function either by stimulation or inhibition. Antibodies directed against acetylcholine receptors of muscle cells at the neuromuscular junctions interfere with the transmission of nerve impulses and cause muscular weakness in myasthenia gravis. **Graves disease** is caused by antibodies to thyroid-stimulating hormone receptor, which binds to the surface of thyroid cells, stimulating thyroid hormone production and causing hyperthyroidism.

Type III Hypersensitivity

Type III hypersensitivity **(immune complex mediated)** is mediated by antigen-antibody complexes that produce tissue damage by activating a number of mediators, especially the complement system. Antigens may be **exogenous,** including foreign proteins, viruses, and bacteria, or **endogenous,** such as cell or tissue components (see Table 3-1 and Fig. 3-1).

Type III hypersensitivity has three phases: (1) the formation of the immune complexes; (2) deposition of the complexes in tissues; and (3) initiation of an inflammatory reaction. Immune complexes are typically deposited in the wall of blood vessels (e.g., arteries in

polyarteritis nodosa) or basement membranes (e.g., basement membrane of glomeruli or the epidermal-dermal junction in systemic lupus erythematosus [SLE]). By light microscopy in hematoxylin and eosin–stained sections, these deposits appear as a red amorphous material, referred to as *fibrinoid necrosis*. Immunofluorescence microscopy reveals that this material contains fibrin, immunoglobulins, and complement. The **Arthus reaction** is an example of a localized disease induced by this mechanism. Arthus reactions are induced experimentally by immunizing an animal and then injecting the same antigen intracutaneously. The antigen diffuses from the tissue into the wall of the blood vessel, combining with the antibody from circulation inside the vessel wall. The antigen-antibody complexes formed in the vessel wall elicit a local inflammation (vasculitis). **Polyarteritis nodosa** is a clinical equivalent of the experimental Arthus phenomenon. **Serum sickness, poststreptococcal glomerulonephritis, and SLE** are other important diseases produced by type III hypersensitivity reactions (see Table 3-1 and Fig. 3-1).

Type IV Hypersensitivity

Type IV hypersensitivity (cell mediated) is initiated by specifically sensitized T-helper lymphocytes, which are recruited to the sites of injury by macrophages and other lymphocytes. In other reactions marked by granuloma formation, the effector cells are macrophages. Typically, such granulomatous reactions begin when naive $CD4^+$ cells exposed to certain antigens differentiate into T_H1 cells capable of secreting cytokines such as IFN-γ, IL-2, and TNF-α. IFN-γ activates macrophages and transforms them into epithelioid cells or multinucleated giant cells. IL-2 amplifies the reaction by promoting the growth and differentiation of T-lymphocytes that secreted it (autocrine) and also other T-lymphocytes (paracrine). TNF-α acts on blood vessels, promoting the emigration of lymphocytes and macrophages from the circulation to the extravascular sites. All of these events lead to the formation of an aggregate of cells known as a *granuloma*. Classic examples of granulomatous type IV hypersensitivity include **sarcoidosis, tuberculosis,** or **tuberculin** reaction induced by injecting intradermally a protein antigen or tubercle bacilli (see Table 3-1 and Fig. 3-1).

TRANSPLANTATION IMMUNOLOGY

The rejection of transplanted organs is a complex process that involves both cell-mediated and humoral immunity. **T-cell–mediated reactions** are characterized by activation of $CD8^+$ cytotoxic lymphocytes and $CD4^+$ T-lymphocytes that respond to foreign antigens presented in the context of class I and II MHC. These events are triggered when recip-

ient lymphocytes contact donor HLA antigens. The $CD4^+$-helper lymphocytes recognize class II MHC molecules and are activated. Concomitantly, precursors of $CD8^+$ cytotoxic lymphocytes, having receptors for class I MHC molecules on their surface, differentiate into mature cytotoxic lymphocytes. $CD8^+$ lymphocytes lyse the grafted tissue, directly destroying the graft. $CD4^+$ lymphocytes secrete cytokines, the most important being IL-2 and IFN-γ. IL-2 acts on the $CD4^+$ lymphocytes, amplifying the reaction and stimulating the lymphocytes to secrete other interleukins, which, together with IL-2, activate B-lymphocytes and stimulate antibody production from newly formed plasma cells. IFN-γ acts on macrophages and grafted cells, stimulating them to express more MHC antigens, and thus rendering them more susceptible to the action of cytotoxic T-lymphocytes.

Graft Rejection

Graft rejection, as illustrated in the rejection of transplanted kidneys, can be classified as hyperacute, acute, and chronic.

Hyperacute rejection occurs when preformed antibodies against the donor are present in the recipient's circulation, such as in a recipient who has already rejected a kidney transplant or received prior blood transfusions from donors. This reaction may occur in multiparous women who have been sensitized to sperm or fetal antigens and have anti-HLA antibodies against grafts from their husbands or children. The rejection occurs immediately, that is, during the transplantation procedure. Antibodies rapidly deposit in the graft's vascular endothelium, fix complement, and cause endothelial cell injury. The kidney becomes cyanotic and mottled. Histologically, there are neutrophils in arterioles, glomerular capillaries, and peritubular capillaries, due to antigen-antibody complex and complement deposition. Thrombosis ensues, leading to cortical infarction.

Acute rejection may occur within days of the transplantation or months to years later, typically after immunosuppression treatment is terminated or the patient does not respond to it. Acute cellular rejection is characterized by interstitial infiltrates of mononuclear cells, primarily lymphocytes, causing tubular destruction. **Vasculitis** evidenced as infiltrates of lymphocytes in the subendothelial layers of the arteries is an ominous finding and carries a poor prognosis, because such necrotizing vasculitis with infiltration by neutrophils and the deposition of immunoglobulins, complement, and fibrin may cause thrombosis and lead to cortical infarction.

Chronic rejection is recognized by progressive loss of renal functions and elevation of creatinine levels over a period of 4 to 6 months. Histologically, there is intimal fibrosis primarily in the cortical arteries, leading to ischemia. There is also a mononuclear infiltrate in the interstitium. Progressive destruction of tubules occurs, in part, due to ischemia caused by narrowing of blood vessels and, in part, because of direct cytotoxic effect of lymphocytes on tubule cells.

Graft-Versus-Host Reaction

Graft-versus-host (GVH) reaction occurs when T cells transfused into an immunosuppressed host act against the host tissues. This could typically occur during blood transfusion into an irradiated host. Hematopoietic cells harvested from the bone marrow or as circulating stem cells also are transplanted as a treatment for aplastic anemia and immunodeficiency conditions. Leukemic patients irradiated with high doses and given hematopoietic stem cell transplants also can develop GVH reaction. Transplants of solid organs, especially the liver, also contain T cells, which can cause GVH reaction. In all these situations, the donor T-lymphocytes recognize the recipient's HLA antigens and react against them.

Acute GVH disease occurs within days or weeks of transplantation with allogenic bone marrow. The ensuing clinical manifestations include severe immunosuppression, predisposing to infection, cutaneous rash, and destruction of bile ducts, which leads to jaundice and intestinal mucosal ulcers, which leads to bloody diarrhea. **Chronic GVH disease** may evolve following attacks of an acute GVH form or insidiously some time after the grafting. Chronic GVH disease has the same features as the acute form, but the lesions are much more severe (e.g., the skin lesions show scaling and atrophy resembling systemic sclerosis). Esophageal strictures may be present, and recurrent infections are common. The GVH response can also be seen after grafts of solid organs such as the liver, which contains lymphocytes or their precursors.

AUTOIMMUNE DISEASES

Autoimmune diseases are based on immune reactions of endogenous antigens' reactions to foreign antigens that share antigenic properties with the host or reactions for which no cause can be identified. The autoantibodies can be directed to a single organ or tissue or to multiple organs or tissues. The most important autoimmune diseases are listed in Table 3-2.

Systemic Lupus Erythematosus

SLE is a **multisystemic autoimmune disease**. Its pathogenesis is not fully understood, but it appears to include the interaction of genetic, environmental, and hormonal factors, which activate helper T cells and B cells to produce a broad spectrum of autoantibodies. These antibodies react either directly with tissue antigens or form circulating antigen-antibody complexes, which deposit in blood vessels, activating complement. Complement activation results in the formation

TABLE 3-2.
Important Autoimmune Diseases

Primary Organs or Cells	Disease	Dominant Antigens That Induce Antibodies
Multiple organs (e.g., kidney, joints, skin)	Systemic lupus erythematosus	DNA, RNA, histones, ribonucleoproteins
Joints	Rheumatoid arthritis	Immunoglobulin
Salivary and lacrimal glands	Sjögren disease	Ribonucleoprotein
Lung, kidney, and upper respiratory tract	Wegener granulomatosis	Neutrophils
Skin	Bullous pemphigoid	Epidermal basement membrane
	Pemphigus vulgaris	Epidermal cells
Blood cells	Autoimmune hemolytic anemia	Erythrocytes
	Autoimmune thrombocytopenia	Platelets
Gastric mucosa	Atrophic gastritis	Parietal cells or intrinsic factor
Liver	Primary biliary cirrhosis	Mitochondria
	Autoimmune hepatitis	DNA, RNA, histones
Kidney	Membranous nephropathy	Numerous
	Goodpasture syndrome	Collagen type IV
Endocrine organs	Graves disease	Thyroid-stimulating hormone receptor
	Hashimoto disease	Thyroglobulin
	Addison disease	Adrenal cells
Central nervous system	Multiple sclerosis	Unknown
Muscle	Myasthenia gravis	Acetylcholine receptor
	Polymyositis	Muscle cells

of fragments and complexes that can damage tissue on their own. They also act as chemoattractants for neutrophils, which actively destroy cells and tissue components (Fig. 3-2).

Among the manifestations of SLE, kidney disease is the most important cause of disability. Immunologically mediated **glomerulonephritis** presents with proteinuria and hematuria and may progress to renal failure. Histologically, several patterns can be recognized: mesangial, focal proliferative, and diffuse proliferative or membranous glomerulonephritis. In most instances, glomerulonephritis responds well to corticosteroid or immunosuppressive therapy.

Skin lesions are common, but less life-threatening. The lesions occur on sun-exposed areas, most typically as an erythematous rash over the nose and cheeks **("butterfly rash").** Raised erythematous

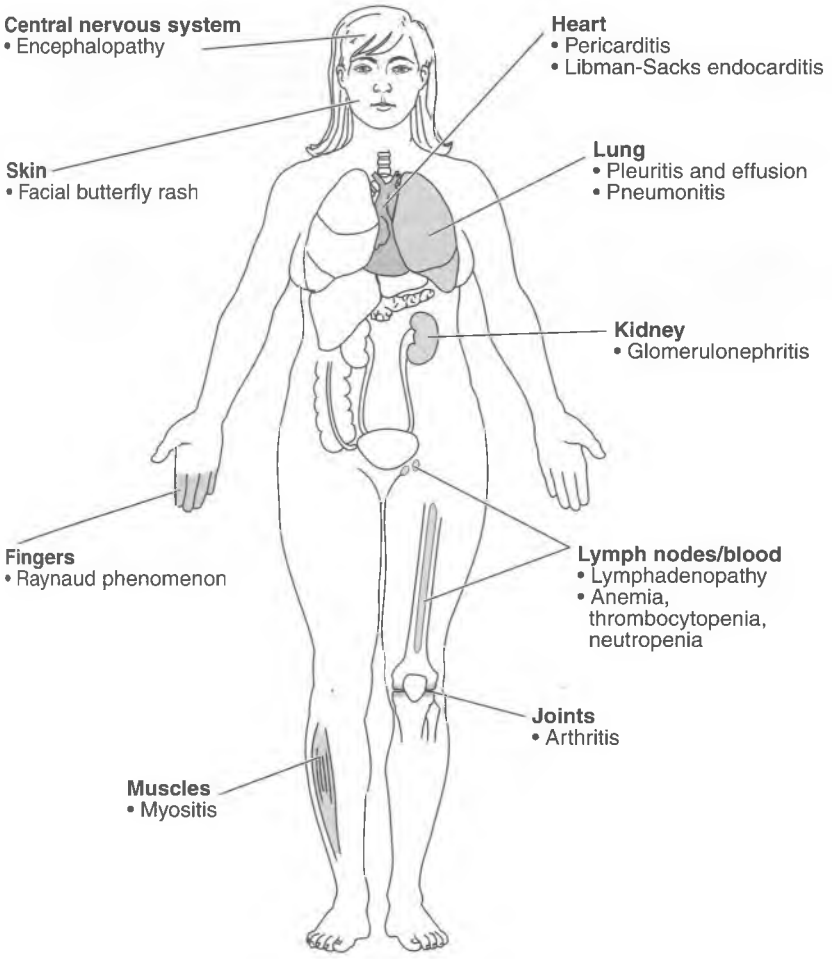


Figure 3-2.
Manifestations of systemic lupus erythematosus.

papules are found in **discoid lupus,** a variant disease limited to skin. Granular deposits of IgG and IgM complement accompanied by dermal inflammation along the epidermal-dermal basement membrane can be demonstrated by immunofluorescence microscopy.

Involvement of **joints** is also common. Although the joints are painful and swollen and histologically show signs of acute inflammation, major functional impairment or joint deformity rarely occurs. Other manifestations are less common and occur unpredictably and at a variable rate. For example, **heart** involvement (Libman-Sacks endocarditis and pericarditis) occurs in approximately 50% of cases and central nervous system (CNS) involvement in approximately 20% of cases.

A vast array of autoantibodies, particularly antinuclear antibodies (ANAs), have been identified and are listed in Table 3-3. Antibodies to double-stranded DNA (ssDNA) and particularly to Smith (Sm) antigen are virtually diagnostic for SLE.

TABLE 3-3.

Antibodies Used in the Diagnosis of Autoimmune Diseases

Antigens Eliciting Antibodies	Disease (% Positive)				
	Systemic Lupus Erythematosus	Systemic Sclerosis	CREST Syndrome	Sjögren Syndrome	Dermatomyositis/ Polymyositis
Nucleus (ANA)	95	80	80	65	50
Double-stranded DNA	50*				
Histones	60				
Smith antigen (Sm)	25*				
Ribonucleoproteins					
SS-A (Ro)	40			80*	
SS-B (La)	10			75*	
DNA topoisomerase I		50*	15		
Centromere		25	90		
Histidyl-tRNA synthetase					25

**Indicates high diagnostic value.*

ANA, antinuclear antibodies; CREST, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia.

Source: Modified from Cotran RS, et al. Robbins Pathologic Basis of Disease (5th ed). Philadelphia: Saunders, 1994;201.

Other Autoimmune Diseases

Sjögren syndrome is characterized by dry eyes and mouth (**keratoconjunctivitis sicca** and **xerostomia**). In the primary form, the disease is limited to the eyes and mouth. In the secondary form, which is more common, it is associated with other autoimmune diseases such as rheumatoid arthritis, SLE, and polymyositis.

Histologically, periductal and perivascular lymphocytic infiltrates are noted in the salivary and lacrimal glands. Most of the lymphocytes are $CD4^+$ helper T cells with a few B cells and plasma cells. Clinically, approximately 90% of patients are women between 40 and 60 years of age. They complain of dryness of the mouth and eyes and may show signs of enlargement of the salivary glands or lacrimal glands, lymph nodes, or both. Diagnosis is confirmed by serologic findings indicative of an autoimmune disorder. Approximately 90% of patients have antibodies directed against ribonucleoprotein antigens SS-A (Ro) and SS-B (La) (see Table 3-3).

Systemic sclerosis (scleroderma) is a disease of unknown etiology, characterized by excessive fibrosis of the skin and many internal organs and accompanied by changes in the microvasculature. It is thought to be immune mediated because the involved organs often

contain infiltrates of $CD4^+$ lymphocytes. Most patients have autoantibodies (see Table 3-3).

Two forms of the disease are recognized clinically: **diffuse scleroderma,** in which initial skin manifestations occur early in the disease, accompanied by symptoms referring to internal organs; and **localized scleroderma,** which has localized skin involvement initially and spreads to the viscera much later. The systemic form presents with skin lesions and a variety of lesions of the internal organs. Lesions of the kidney, gastrointestinal tract, and lung are found in 50% to 60% of patients. Most patients also have joint disease similar to rheumatoid arthritis but less debilitating. Pulmonary fibrosis and sclerosing esophagitis may be present. Myocarditis and pericarditis are found in approximately 30% of patients. The localized form of the disease is known as CREST syndrome, which stands for **c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia.

Systemic sclerosis affects mostly women in the 50- to 60-year-old age group. Skin atrophy and Raynaud phenomenon are often the presenting signs, often followed by esophageal dysmotility. Abdominal pain, dyspnea, signs referable to the kidney (e.g., mild proteinuria), and hypertension may be present. Serologic test results such as ANA are usually positive. Antibodies to DNA topoisomerase I and centromere are found almost exclusively in patients with systemic sclerosis and are diagnostic of this disease.

Dermatomyositis presents as an autoimmune skin and muscle disease. Either girls and young women or adults of both sexes are affected. In girls, it appears as a scaling rash, described as lilac or heliotrope discoloration on the eyelids accompanied by periorbital edema. Muscle weakness initially affects proximal limb muscles. Fine movements of fingers and toes are affected later. In adults, dermatomyositis is often a paraneoplastic syndrome; resection of the malignant tumor may alleviate the symptoms.

Polymyositis is clinically similar to dermatomyositis, but it does not involve the skin. Myofibers are directly injured by $CD8^+$ T-lymphocytes. It is a disease of adults and, like dermatomyositis of girls and young women, it usually responds well to corticosteroid treatment.

The diagnosis of all forms of inflammatory myositis is based on clinical signs, electromyography results, and elevations of muscle-related enzyme levels such as creatine kinase in serum and muscle biopsy. Approximately 50% of all patients have ANA. Autoantibodies to histidyl-tRNA synthetase (anti-Jo-1) are typical of inflammatory myopathies but are found only in 25% of patients.

Mixed connective tissue disease is characterized by concomitant clinical features of SLE, polymyositis, and systemic sclerosis. Clinical findings include fever, leukopenia, anemia, arthritis, swelling of the hands, Raynaud phenomenon, and abnormal esophageal motility. Whether mixed connective tissue disease is a distinct disease or a different manifestation of SLE and systemic sclerosis is debatable. Despite the obvious similarities, it is considered by some authorities

to be distinct from other autoimmune diseases because of the paucity of kidney disease and its excellent response to corticosteroids.

IMMUNODEFICIENCY DISEASES

Primary Immunodeficiencies

Primary immunodeficiency diseases are genetically determined and can arise from disorders of natural or acquired immunity. Symptoms appear in children between the ages of 6 months and 2 years and present as increased susceptibility to recurring infections. These diseases can be classified as follows:

- Predominantly antibody defects (B-cell deficiencies)
- Cell-mediated immunity defects (T-cell deficiencies)
- Combined immunodeficiencies (B- and T-cell deficiencies)
- Complement deficiencies
- Defects of phagocytic function

X-linked agammaglobulinemia of Bruton is one of the most common primary immunodeficiencies. It is found exclusively in male subjects and is characterized by an almost total absence of serum immunoglobulins and the virtual absence of B-lymphocytes in the blood. Histologically, lymph nodes and spleen have no germinal centers, and no plasma cells are seen in tissues. T-lymphocyte populations are normal. Clinical symptoms appear 6 to 12 months after birth, when the maternal immunoglobulins decline in the infant's blood. Recurrent bacterial infections such as conjunctivitis, pharyngitis, and bronchitis are typical. Most viral infections are handled normally, with a few exceptions. For example, echovirus may cause fetal encephalitis, and immunizations with live poliomyelitis vaccine may result in paralysis. If the children survive, they tend to develop autoimmune diseases in later life.

Isolated IgA deficiency is common in the United States and especially among whites, who are affected at a rate of 1:700. It is characterized by very low levels of circulating and secretory IgA, reflecting abnormal differentiation of IgA-secreting B-lymphocytes. Although IgA-positive B cells appear in normal numbers, these cells express an immature phenotype, evidenced by the presence of IgD and IgM on their surface. The deficiency may not be clinically apparent, or it may present with recurrent infections of the respiratory, gastrointestinal, and urogenital systems. Isolated IgA deficiency occurs also in an acquired nonfamilial form, which is often associated with toxoplasmosis, measles, or other viruses.

Patients deficient in IgA predispose to respiratory allergies and autoimmune diseases such as SLE and rheumatoid arthritis. Approximately 40% have antibodies to IgA. Transfusion of normal blood

containing IgA into such persons may promote a severe transfusion reaction and generalized anaphylaxis.

Common variable immunodeficiency is a relatively common, congenital, or acquired defect of both B and T cells. It affects both genders equally and presents clinically either in childhood and adolescence or adulthood. Thus, common variable immunodeficiency is not a single disease but represents a group of disorders, all of which are characterized by hypogammaglobulinemia, most often affecting all classes of antibody and sometimes only IgG. These patients have normal numbers of lymphocytes in the blood, which cannot differentiate into plasma cells. Some patients have increased numbers of suppressor T-lymphocytes, which inhibit antibody production. Histologically, the B-cell regions in lymphoid tissue appear hypercellular. Clinically, recurrent **bacterial infections** are common, and patients also suffer from **viral diseases** (e.g., viral enteritis, herpes zoster) and cannot combat parasitic infection (e.g., *Giardia lamblia*). These patients are at risk of developing autoimmune diseases and lymphoid malignancies.

DiGeorge syndrome results from the developmental failure of the third and fourth pharyngeal pouches, the primordia of the thymus, and parathyroid glands. Because the thymus never develops or is hypoplastic, a deficiency of T-lymphocytes and cell-mediated immunity ensues. In addition, tetany results from aplasia of parathyroid glands. Histologically, the thymic-dependent regions of the lymphoid organs are depleted. B-cell dependent regions are normal, as are serum immunoglobulin levels. Clinically, these patients are susceptible to viral and fungal infections. Thymic transplantation can restore cell-mediated immunity.

Severe combined immunodeficiency diseases are a group of disorders characterized by T- and B-lymphocyte deficiencies. The diseases occur in X-linked and autosomal recessive forms. Approximately 40% of those with autosomal recessive patterns lack adenosine deaminase, an enzyme involved in the degradation of purine nucleotides. Deficiency of adenosine deaminase leads to accumulation of deoxyadenosine and its derivatives, which are toxic to immature lymphocytes, particularly T cells. Autosomal recessive inheritance is also responsible for creating defects in T-cell activation. A significant number of X-linked forms produce mutations in a protein that is part of the receptor for cytokines, such as IL-2, IL-4, and IL-7. Without this protein, cytokine receptors do not function, and lymphocyte development is impaired. Histologically, in all forms of severe combined immunodeficiency diseases, the thymus is small and lymphoid cells are depleted. In all cases, peripheral lymphoid tissues are hypoplastic and depleted of T cells, B cells, or both. Immunoglobulins are absent. Clinically, infants suffer from recurrent bacterial, viral, fungal, and protozoal infections; unless a successful bone marrow transplantation is performed, these children die in early childhood.

Immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich syndrome) is an X-linked recessive disease characterized by depletion of circulating T-lymphocytes and those in the thymic-

dependent portion of lymphoid tissue. The thymus appears normal in the initial stages. Immunoglobulin levels are variable. IgM may be low, but IgG is normal. IgA and IgE may be elevated. Clinically, patients show increased susceptibility to recurrent infections, thrombocytopenia, and eczema and are prone to lymphoid malignancies.

Genetic deficiencies of the complement system adversely affect immune reactions and could result in immunodeficiency, which may present in various forms depending on which of the factors is deficient. Specific gene mutations of each of C1-Cq complement proteins or their inhibitors have been described. Deficiency of C3, for example, results in recurrent bacterial infections. Patients with complement disorders are at risk of developing SLE. Deficiency of C1 esterase inhibitor results in angioedema.

Defects of phagocytic function affect the body's ability to combat infection and mount an acute inflammatory response. This typically occurs in **chronic granulomatous disease, Job syndrome,** and several other rare congenital disorders.

Secondary (Acquired) Immunodeficiency Disease

Acquired immunodeficiency disease can result from viral infection, as in acquired immunodeficiency syndrome (AIDS), or after radiation therapy. Corticosteroids and cytotoxic drugs typically used for treatment of autoimmune diseases or cancer also may induce immunodeficiency.

AIDS is presently the most significant of the secondary immunodeficiency diseases. It is due to infection with **human immunodeficiency virus (HIV).** It is characterized by severe immunosuppression and associated with infections by opportunistic organisms, secondary neoplasms, neurologic manifestations, and nephropathy (Fig. 3-3). The three major routes of transmission are sexual contact, parenteral inoculation, and passage of the virus from infected mothers to newborns. Epidemiologically, five groups have been designated at risk:

- **Intravenous drug users**
- **Homosexual or bisexual men**
- **Hemophiliacs,** particularly those receiving large amounts of concentrated factor VIII before 1985 and long-term recipients of blood or blood components
- **Heterosexuals in contact with members of other high-risk groups**
- **Children of HIV-infected mothers**

Globally, heterosexual transmission is the most common means of HIV transmission. In the United States, this mode of transmission is beginning to surpass all others.

The HIV virus targets $CD4^+$ T-lymphocytes, monocytes, macrophages, and follicular dendritic cells. After lengthy incubations, the $CD4^+$ lymphocytes are lysed, leading to profound immunosuppression. Monocytes and macrophages are more resistant to lysis and are thought to act as safe havens for viral replication and storage and as transporters of the virus, particularly to the brain.

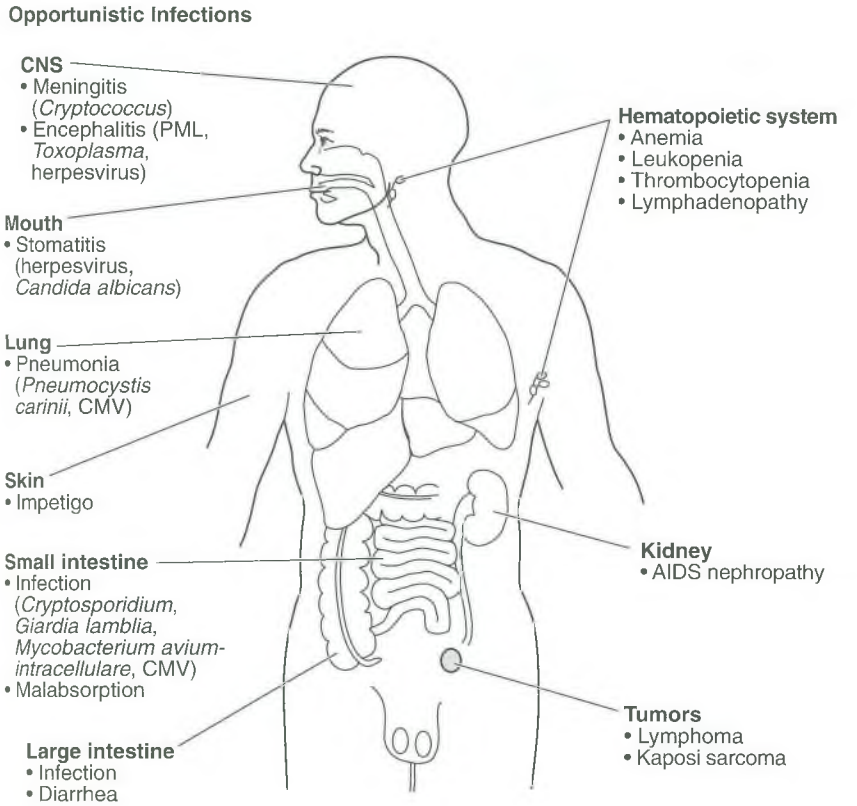


Figure 3-3.
Manifestations of acquired immunodeficiency syndrome. (CNS, central nervous system; PML, progressive multifocal leukoencephalopathy; CMV, cytomegalovirus; AIDS, acquired immunodeficiency virus.)

The natural history of the disease can be divided into three phases. The **early acute phase** is when viral replication, viremia, and viral seeding of lymphoid tissues occur. It is characterized clinically by mild, nonspecific symptoms such as sore throat and fever. The **middle chronic phase** is represented by smoldering, low-level virus replication in lymphoid tissue for up to several years. Patients are asymptomatic or develop generalized lymphadenopathy. The **final crisis phase** is represented by marked viral replication, suppression of immunity, and clinical disease, including secondary neoplasms and opportunistic infections. Major clinical aspects of AIDS are shown in Figure 3-3.

AIDS-defining **opportunistic infections** include *Pneumocystis carinii* pneumonia, toxoplasmosis, cryptococcosis of the CNS, and mycobacteriosis; viral (herpes simplex virus and cytomegalovirus) and fungal infections (*Candida, Aspergillus*) are also common. Several malignant tumors occur at a high rate such as Kaposi sarcoma, lymphomas (most notably primary lymphoma of the brain), and invasive cancer of the uterine cervix. The disease can be monitored clinically and by counting the $CD4^+$ cells in blood. A $CD4^+$ count >500 suggests a lower probability of progression; a count <200, or a rapidly decreasing count is typical of terminal, usually fatal stages of the disease. Presently, AIDS remains an incurable disease. For unknown reasons,

a small number of HIV-infected persons do not develop AIDS, most likely because they have inborn immunity to HIV.

AMYLOIDOSIS

Amyloidosis is a group of diseases characterized by the deposition of pathologic proteinaceous substances known as *amyloid.* Amyloid is defined morphologically and biophysically as fibrillar material, which, by x-ray crystallography, has a β-pleated configuration. Ultrastructurally, amyloid is composed of beaded, nonbranching fibrils 7 to 10 nm long; in histologic sections, all show green birefringence when stained with Congo red dye and examined under polarized light. Amyloid deposits can be systemic or localized (Table 3-4). Systemic amyloidosis is further classified as **primary amyloidosis,** when it is associated with monoclonal B-cell proliferations as with multiple myeloma, or **secondary amyloidosis** when it is associated with chronic inflammatory processes. **Localized amyloid** deposits are seen with Alzheimer disease, medullary carcinomas of the thyroid, and in the islets of Langerhans with type II diabetes mellitus.

In **systemic amyloidosis**, organs infiltrated with amyloid are enlarged and appear waxy and firm. Iodine painted on the surface generates a yellow that is transformed to blue-violet after exposure to sulfuric acid. Localized infiltrates of amyloid usually do not produce grossly visible changes. Histologically, all amyloid appears as amorphous, eosinophilic, and extracellular hyaline. Amyloid stains with Congo red dye. When examined under polarized light, the red changes to apple green.

Clinically, **systemic primary amyloidosis** and **amyloidosis secondary to chronic inflammation** are the most important forms. The disease is systemic, but most often it involves the kidneys, liver, spleen, lymph nodes, adrenals, and thyroid. Renal amyloidosis is characterized by deposits in the glomeruli and, to a lesser extent, in interstitial tissue, arteries, and arterioles. It presents with a nephrotic syndrome, which may progress to renal failure. In the liver, the amyloid deposits in the spaces of Disse encroach on adjacent tissues, compressing liver cells and causing liver failure. In the heart, deposits of amyloid in the subendocardium and between muscle fibers in the myocardium may cause heart failure. Adrenal amyloidosis may cause adrenal cortical insufficiency (Addison disease). Amyloidosis is incurable.

TABLE 3-4.
Classifications of Amyloidosis

Biochemical Type	Precursor Protein	Clinical Form
AL	Immunoglobulin γ light chain	Multiple myeloma–associated (primary amyloidosis)
AA	Serum amyloid–associated protein	Secondary, reactive (systemic)
AF	Transthyretin	Heredofamilial (familial amyloid polyneuropathy)
AE		Local, endocrine-related amyloid
	Calcitonin	Thyroid (medullary carcinoma)
	Amylin	Islets of Langerhans (diabetes)
AS	Atrial natriuretic polypeptide	Heart
	Transthyretin	Heart (amyloidosis of older age)
AH	β_2-Microglobulin	Chronic hemodialysis-related amyloid
$A\beta_2$	Amyloid precursor protein in the brain	Alzheimer disease

Chapter 4

Neoplasia

Neoplasia is a disorder of cell biology that results in **cell proliferation**. It is characterized by excessive formation of tumors or masses normally not found in the body. Growth occurs in an autonomous, disorganized, and seemingly purposeless manner and differs from the growth of normal cells.

For clinical purposes, tumors are classified as benign or malignant. **Benign** tumors have a limited growth capacity and do not invade adjacent tissues or cause death. **Malignant** tumors grow invasively, tend to disseminate, and may cause death. The most important differences between benign and malignant tumors are listed in Table 4-1.

Neoplasms must be distinguished from other abnormal tissue masses. **Hamartoma** is composed of cells or tissues normally present in an organ but arranged abnormally (e.g., a nevus is a skin mass of pigment cells). **Choristoma** is composed of normal cells found in an abnormal location (e.g., heterotopic pancreatic tissue in the stomach is a choristoma).

CLASSIFICATION AND NOMENCLATURE OF TUMORS

Tumors are best classified on the basis of clinical, anatomic, and histologic data. The most widely used method is a modified histogenetic classification in which the tumors are grouped according to their tissue of origin (Table 4-2). Each category comprises benign and malignant tumors.

Mesenchymal or connective tissue tumors are named for their cell of origin. Tumors derived from fibroblasts are called *fibromas;* those derived from fat cells are called *lipomas.* Malignant tumors composed of the same cells are called *sarcomas;* a prefix is then added to denote the histologic appearance or the origin of each tumor (e.g., *fibro*sarcoma or *lipo*sarcoma).

TABLE 4-1.
Features of Benign and Malignant Tumors

Feature	Benign Tumors	Malignant Tumors
Gross	Round	Irregular
	Encapsulated	Invasive
	Homogenous on cross section	Mottled, hemorrhagic with areas of necrosis
	No metastases	Metastases present in advanced cases
Histologic	Compression of adjacent normal tissue	Infiltrative growth
	Blood vessels scarce	Blood vessels abundant
Cellular	Well differentiated	Poorly differentiated
	Resembles cell of origin	Pleomorphism, anaplasia
	Mitoses rare	Mitoses numerous and atypical
	Nuclei regular	Nuclei irregular, hyperchromatic
	Nucleoli inconspicuous	Nucleoli enlarged
Genetic	DNA, normal amount	DNA increased
	Chromosomes normal	Chromosomes abnormal

Benign **epithelial tumors** are called *adenomas* if they originate from glandular tissue; if they originate from epithelium, they are called *epitheliomas*. Often the benign tumors originating from the skin or mucosal surfaces are called *papillomas* or *polyps*. Malignant epithelial tumors are called *carcinomas*. Tumors of specialized cells or organs are named for their cell of origin, such as renal cell carcinoma or hepatocellular carcinoma. Malignant tumors of glia cells are called *gliomas*. Malignant tumors of lymphoid cells are called *lymphomas*. The nature of some tumors remains elusive and therefore such tumors are named for their discoverer (e.g., Hodgkin disease, Ewing sarcoma).

GRADING AND STAGING OF TUMORS

Once a tumor is determined to be malignant, the most important features used to predict prognosis are the histologic grade and the stage or extent of the tumor. **Grading** is based on microscopic examination by a pathologist, who takes into account the appearance of the cells and the presence of cytologic and histologic features of anaplasia. Thus tumors can be classified as low-grade, intermediate, and high-grade malignancies. Histologic grading of

TABLE 4-2.
Classification of Tumors with Examples of Important Entities

Tissue or Cell of Origin	Benign	Malignant
Epithelium		
Squamous	Squamous cell papilloma	Squamous cell carcinoma
Transitional	Transitional cell papilloma	Transitional cell carcinoma
Glandular	Adenoma	Adenocarcinoma
Liver cell	Hepatocellular adenoma	Hepatocellular carcinoma
Mesenchyme		
Fibroblast	Fibroma	Fibrosarcoma
Fat cell	Lipoma	Liposarcoma
Smooth muscle cell	Leiomyoma	Leiomyosarcoma
Striated muscle cell	Rhabdomyoma	Rhabdomyosarcoma
Blood vessel endothelium	Hemangioma	Hemangiosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Hematopoietic and lymphoid		
Lymphocyte	—	Lymphoma
White blood cell precursors	—	Leukemia
Red blood cell precursors	—	Polycythemia vera
Nervous system		
Glia cells	—	Glioma
Neuroblast	Ganglioma	Neuroblastoma
Meninges	Meningioma	Malignant meningioma
Melanocyte	—	Melanoma
Germ cell	—	Seminoma/dysgerminoma
	Teratoma	Teratocarcinoma

tumors has prognostic significance, and, overall, low-grade tumors have a better prognosis than high-grade malignancies.

Staging of tumors is based on clinical and pathologic assessment of the extent of tumor spread. The most widely used is the tumor, nodes, and metastasis (TNM) system in which the size and local invasion of the primary tumor, involvement of regional and distant lymph nodes, and presence or absence of metastases to organs other than the primary site are assessed. Tumor stage is usually a more important prognostic finding than the grade of the tumor, but in most cases grading and staging are combined to predict prognosis and response of the tumor to treatment.

GROWTH OF TUMORS

Tumor cells form progressively growing masses. The most important reasons for such uncontrolled growth are as follows:

- **Tumor cells are "immortal."** If explanted in vitro, tumor cells grow continuously; when they reach the margins of the plastic dish, they grow over each other. In contrast, normal cells show "contact inhibition" and stop growing. Tumor cells then can be replated into other dish and grown for an indefinite number of generations. Normal cells, however, have a limited life span and can be grown in vitro only for a limited number of generations: Most human cells die after 50 passages.
- **Tumor cells need fewer nutrients than normal cells.** Tumor cells have a simplified metabolism and can survive with fewer nutrients and less oxygen than normal cells. They are more adaptable and can generate energy for their own needs more efficiently than normal cells. Tumor cells rely more on anaerobic metabolism than normal cells and tolerate anoxia better. On the other hand, tumors are very efficient at competing for normal nutrients and actually act as parasites, draining energy from the body.
- **Tumors can induce angiogenesis** (i.e., new blood formation) and thus assure their own blood supply.
- **Tumor cells are often invasive** and can grow toward the sources of energy, whereas normal cells are static and passively depend on energy supply.
- **Tumor cells are motile and less cohesive than normal cells.** Tumor cells can dissociate from each other more easily than normal cells. Thus, they can be entirely surrounded by interstitial fluid containing nutrients. In culture, they are less substrate dependent and can grow in suspension or in soft agar, where normal cells cannot survive.

Metastasis

The spread of tumor cells from their place of origin to another site that is anatomically distinct from it is called *metastasis.* Metastasis is the most reliable sign of **malignancy** of a tumor.

Metastasis is a stepwise process that begins with the appearance of a clone of invasive cells and permeation of tumor by new blood vessels. Local invasion is signaled by the breakdown of the basal lamina beneath the normal epithelium in which the tumor arises. This is mediated by enzymes (e.g., collagenases or proteases) and is followed by extension of cells, processes through the digested matrix, and migration of tumor cells. Thus, the tumor may invade adjacent structures such as nerves, which may account for pain associated with particular tumors. Tumor cells entering the lymphatics or

blood vessels are carried away from the main tumor mass. Most of these cells die, but some survive and attach to the wall of the vessels. Because of their invasive properties, these cells invade through the vessel wall and form a new colony. For the colony to survive, it must induce its blood supply (neovascularization), which allows it to grow and form metastatic nodules.

Three main routes of metastasis are recognized: **hematogenous, lymphatic,** and **direct seeding of body cavities.** Thin-walled lymphatic vessels and blood capillaries are easily invaded by tumor cells, which accounts for spreading by both the hematogenous and lymphatic routes. Thicker-walled vessels such as arteries are relatively resistant to tumor invasion. Cartilage seems resistant to tumor invasion, most likely due to its relatively avascular nature.

Certain tumors appear to spread preferentially either by the lymphatics or the bloodstream, but there are no universal rules. Sarcomas of bones and soft tissues are more likely to invade blood vessels and metastasize hematogenously to the lungs. Carcinomas arising in organs that have a rich lymphatic drainage (e.g., breast, intestine) metastasize through the lymphatics. Liver and kidney tumors metastasize through blood vessels because these organs have a much more abundant blood supply than lymphatic flow. Ovarian carcinomas metastasize by seeding the peritoneal cavity.

ETIOLOGY OF CANCER

Clinical, epidemiologic, and experimental studies performed during the past 100 years have shown that cancer can be caused by chemicals, physical agents such as x-rays or ultraviolet (UV) light, and biological factors such as viruses and oncogenes. The most important chemical carcinogens known to cause cancer in humans are listed in Table 4-3. Unquestionably, polycyclic hydrocarbons in cigarette smoke are the most harmful cancer-causing substance in our environment.

The most important physical carcinogens are irradiation or UV light. These agents may cause DNA damage, which, even if repaired, may result in mutations that ultimately lead to cancer. The most common **radiation-induced cancers** are leukemia and lymphoma and thyroid carcinomas. **UV light** induces **skin cancers** such as basal cell carcinoma, squamous cell carcinoma, and melanomas. Fair-skinned individuals are at greater risk than those with pigmented skin. Individuals who have xeroderma pigmentosum, an inborn error of DNA repair, are extremely sensitive to sunlight and are prone to develop UV-induced skin cancer at an early age.

Asbestos, an insulation material derived from fibrous silicates in the soil, is another well-known human physical carcinogen. Prolonged exposure to asbestos particles in the air causes mesotheliomas

TABLE 4-3.
Human Environmental Carcinogens

Source/Carcinogen	Tumor
Tobacco (polycyclic hydrocarbon)	Lung, bladder, esophageal, and many other cancers
Aniline dyes (aromatic amines)	Bladder cancer
Arsenic	Skin and lung cancers
Chromium	Lung cancer
Nickel	Nose and lung cancers
Uranium	Lung cancer

of the pleura and lung cancer. In lung cancer, asbestos is apparently a cocarcinogen with cigarette smoking. The mechanism of fiber carcinogenesis is unknown.

Viruses are potentially important causes of human or animal cancer. Viruses were initially identified as a transmissible cause of cancer in animals such as Rous sarcoma and virus Shope papilloma. **Human papilloma virus** is now a recognized major contributor to the development of cervical cancer; hepatitis B and C viruses contribute to human liver cancer development. **Epstein-Barr virus** is linked to Burkitt lymphoma and nasopharyngeal carcinoma. Although it is clear that viral nucleic acid is necessary in the carcinogenic process, it is not entirely established how it transforms cells. At the present time, human T-cell lymphoma leukemia virus I is the only definitely proven human viral carcinogen.

Both DNA and RNA viruses can induce neoplastic transformation. The viral genome can become integrated into the cellular DNA either directly or by the process of reverse transcription. The virus may provide the cell with the transforming gene sequence **(oncogene)** directly or induce the expression of preexisting cellular gene **(proto-oncogene).** Viruses also may act in concert with chemicals or be activated by chemicals to induce tumors by a mechanism termed *cocarcinogenicity.*

Human Oncogenes

After the discovery of viral oncogenes, it became apparent that normal human cells have equivalent genes that also contain the tumorigenic DNA sequences. These genes, called **oncogenes,** are active during growth and differentiation of cells. They encode proteins that act as growth factors, growth factor receptors, or signal transducers. Inappropriate activation or dysregulation of proto-oncogenes may lead to their transformation into oncogenes. Cellular oncogenes may become activated by carcinogenic adducts, mutation, unregulated amplifica-

tion, or by translocation to another site on the chromosome. These gene translocations are usually associated with chromosomal changes that can be seen by chromosome analysis (karyotyping) of tumor cells.

The best known human chromosomal change associated with malignancy is the so-called **Philadelphia chromosome,** chromosome 21 with shortened long arms, part of which was translocated to chromosome 9. This results in the formation of a hybrid c-*abl-bcr* gene, which plays a pathogenetic role in chronic myelogenous leukemia. In Burkitt lymphoma, the translocation of the c-*myc* gene to the vicinity of the immunoglobulin heavy chain gene leads to amplification of this proto-oncogene. Specific chromosomal changes have been identified in many other human neoplasms.

Human Tumor-Suppressor Genes

Normal human genomes contain numerous regulatory genes. Genes that inhibit the formation of tumors are known as *tumor-suppressor genes.* Loss of these genes or their inactivation could lead to tumor formation. The best known tumor-suppressor gene is the retinoblastoma gene (**Rb-1**) located on chromosome 13. The deletion of Rb-1 on both chromosomes leads to formation of eye and bone tumors (retinoblastoma and osteosarcoma). Many other tumor-suppressor genes have been identified, such as **NF-1** (deleted in neurofibromatosis) and **WT-1** (deleted in Wilms tumor).

Genetic predisposition to cancer plays an important role in the pathogenesis of many human tumors. Genetic changes may make the affected person more susceptible to carcinogens, as in **xeroderma pigmentosum.** Hereditary chromosomal breakage syndromes, such as Bloom syndrome and Fanconi syndrome, characterized by increased fragility of chromosomes, also predispose to cancer. In other instances, internal control of neoplastic proliferation is lost in the familial form of retinoblastoma. The most important hereditary diseases predisposed to cause cancer are listed in Table 4-4.

TUMOR IMMUNOLOGY

Tumor cells, often recognized by the host's immune system as foreign, may evoke a variety of immune reactions, which may to some extent retard or inhibit tumor growth. These reactions involve T cells, B cells, natural killer cells, and macrophages or neutrophils. In most cases, the body's defense most likely may eliminate early nascent tumors, but it cannot prevent the tumor from expanding or metastasizing. Immunosuppressed individuals also appear more prone to develop neoplasms. For example, lymphomas and Kaposi sarcoma are common complications of acquired immunodeficiency

TABLE 4-4.
Hereditary Cancer Syndromes

Tumor	Organ
Retinoblastoma	Eye
Neurofibromatosis	Peripheral nerves
Familial adenomatous polyposis coli	Large intestine
Wilms tumor	Kidney
Multiple endocrine neoplasia syndromes	Thyroid, parathyroid, adrenal islets of Langerhans
Xeroderma pigmentosum	Skin
Breast cancer*	Breast

**Only approximately 10% of women with breast cancer have a hereditary predisposition related to the* BRCA1 *gene.*

syndrome, and immune diseases such as Sjögren disease are associated with a higher incidence of lymphoma, both suggesting that the immune system plays an important role in controlling tumor growth.

EFFECTS OF TUMORS ON THE HOST

Tumors may produce local and systemic symptoms. Local symptoms depend on the location of the tumor and may include the following symptoms:

- **Compression,** due to the mass effect of the tumor. For example, lung tumors may cause a cough resulting from the irritation of bronchi. Compression of vital centers in the brain causes death.
- **Obstruction** of the lumen of a hollow organ, such as the intestine or bronchus. Obstruction of the colon leads to constipation.
- **Bleeding,** due to erosion of blood vessels. For example, hematuria is an early sign of renal cancer.
- **Systemic symptoms** include a variety of nonspecific findings such as nausea, vomiting, weight loss, fatigue, or fever. Tumors also may induce a variety of **paraneoplastic syndromes,** which are mediated by hormones, immune mechanisms, cytokines, and various mediators of inflammation produced by the tumor or by the body in response to the tumor. These paraneoplastic syndromes are clinical manifestations of tumors and are unrelated to the local effects of the tumor or the presence of metas-

TABLE 4-5.
Paraneoplastic Syndromes

Type of Syndrome	Mediators	Typical Tumor
Hormonal		
Cushing syndrome	Adrenocorticotropic hormone	Small cell carcinoma of lung
Syndrome of inappropriate antidiuretic hormone secretion	Antidiuretic hormone	Small cell carcinoma of lung
Hypercalcemia	Parathyroid-like polypeptide	Squamous cell carcinoma of lung
Neurologic		
Myasthenia gravis	Antibodies to acetylcholine receptor	Thymoma
Eaton-Lambert myasthenic syndrome	Antibodies to chloride channel at neuromuscular junction	Small cell carcinoma of lung
Hematologic		
Thrombosis	Tissue thromboplastin	Adenocarcinoma of pancreas and gastrointestinal system
Polycythemia	Erythropoietin	Renal cell carcinoma
Dermatologic		
Acanthosis nigricans	—	Gastric carcinoma
Dermatomyositis	Antibodies	Carcinoma of the gastrointestinal tract

tasis. Inappropriate or unexpected hormonal activity of a tumor may cause endocrine syndromes such as **Cushing syndrome,** which results from adrenocorticotropic hormone production by a lung tumor. **Hypercalcemia** is particularly frequent and may be found in up to 10% of cancer patients. Hypercalcemia is particularly common in patients with breast cancer or squamous cell carcinoma of the lung, which can secrete a parathormone-like peptide. The most important paraneoplastic syndromes are listed in Table 4-5.

EPIDEMIOLOGY AND DIAGNOSIS OF CANCER

The **epidemiology** of cancer has given invaluable clues about environmental carcinogens. Epidemiologic studies have shown that lung cancer is linked to cigarette smoking, mesothelioma to asbestos, liver cancer to hepatitis B virus infection, and melanoma to sunlight exposure.

TABLE 4-6.
Tumor Markers Used in Clinical Practice

Marker	Tumor
Alpha fetoprotein	Hepatocellular cancer
	Germ cell tumor of ovary and testis
Carcinoembryonic antigen	Adenocarcinoma of gastrointestinal tract
Prostate-specific antigen	Carcinoma of prostate
Human chorionic gonadotropin	Germ cell tumor
	Choriocarcinoma

Cancer accounts for approximately 25% of all deaths. The most common cancer in men is **carcinoma of the prostate** (40%) and in women is **carcinoma of the breast** (30%). The most deadly type of cancer is carcinoma of the lungs, which accounts for 30% of cancer deaths.

Cancer epidemiology has revealed important geographic differences in the incidence of cancer. For example, carcinoma of the stomach is common in Japan but less common in the United States. Colon carcinoma is most common in the United States and Western Europe and less common in Africa and Asia. Liver cancer is common in Africa and Asia.

The incidence of cancer has changed over the past 100 years. Gastric cancer was common in the United States at the turn of the century, but since then its incidence has decreased. The incidence of carcinoma of the cervix has decreased due to widespread use of Papanicolaou smears for early detection of preneoplastic changes. The incidence of lung carcinoma in women has increased dramatically due to smoking.

In most instances, the **diagnosis of cancer** is based on a standard clinical workup that includes a history and complete physical examination. Ancillary studies include radiography, laboratory tests, and, if a tumor mass is identified, a biopsy. This can be performed with a fine needle **(fine-needle aspiration biopsy)** or surgically **(incisional biopsy).** Cytology is also used for screening **(vaginal exfoliative cytology).** Several biochemical tests based on measurement of so-called tumor markers have been introduced into clinical practice. The most widely used laboratory tests in the diagnosis of cancer are listed in Table 4-6. Cancer has few absolutely diagnostic clinical or laboratory features, and cytology and histology remain the only definitive diagnostic methods.

Chapter 5

Genetic and Developmental Disorders

Many human diseases have a genetic basis, and even those that have exogenous causes are critically influenced by the genetic constitution of the affected person. This discussion is limited to diseases that are inherited or can be traced to defined genetic defects or developmental disturbances operating during the prenatal life in utero.

The cause of most **developmental disorders,** more than 75% of those recognized at birth or in later life, remains unknown. The remaining malformations can be traced to hereditary traits, genetic mutations, and various exogenous factors. The best known teratogens are drugs such as antiepileptic drugs (e.g., hydantoin) and the anticoagulant warfarin. Thalidomide, a sleeping pill removed from the market because of its teratogenicity but reintroduced for cancer therapy, can cause abnormalities of arms and legs (phocomelia). Alcohol, if taken in large amounts during early pregnancy, may cause **fetal alcohol syndrome,** characterized by growth retardation, distinct facial features, and mental retardation. **Rubella,** a well-known teratogenic virus, causes a typical triad including microcephaly, microphthalmia, and cardiac defects. Exposure in utero to x-rays and gamma rays may cause malformations, as attested to by an increased incidence of birth defects after the atomic bomb explosion in Japan in 1945 and the meltdown of the Chernobyl atomic power station in Ukraine during the 1980s. Severe developmental malformations are incompatible with normal life, and most affected fetuses are aborted during the early stages of pregnancy. Those that are born represent only a small fraction of those conceived.

Genetic disorders can be classified for practical clinical purposes into two groups: (1) those linked to **chromosomal abnormalities** (known also as *karyotypic* or *cytogenetic* abnormalities); and (2) those in whom the genetic defect cannot be demonstrated on chromosomal analysis, but it can be documented by analyzing the genealogy of the family tree or by biochemical and molecular biological testing. These abnormalities are known as **single gene defects** and are classified as new mutations or hereditary disorders that are inherited as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive traits.

TABLE 5-1.
Glossary of Common Cytogenetic Terms

Term	Definition
Aneuploid	Change in chromosomal number due to a loss or addition of chromosomes (e.g., 45,X; 47,XXY)
Deletion	Loss of a part of a chromosome
Diploid	46 chromosomes (i.e., normal karyotype [2n]); two haploid sets
Haploid	One-half set (23 chromosomes), normally found only in mature sperm and oocytes
Inversion	Rearrangements of parts of the chromosome after two breaks during cell division Both breaks on one side of the centromere lead to paracentric inversion; breaks in both arms produce a pericentric inversion
Isochromosome	Abnormal chromosome formed through a transverse rather than longitudinal division of the centromere during cell division
Monosomy	Lack of one of the paired chromosomes
Mosaicism	Condition in which two or more chromosomally different cell lines are present in tissues of the same person
Nondisjunction	Failure of paired chromosomes to disjoin at anaphase during cell division, typically causing numeric chromosomal abnormalities
Polyploidy	More than two haploid sets of chromosomes (i.e., [3n] 69 is triploidy, [4n] 92 is tetraploidy)
Ring chromosomes	Abnormal circular chromosomes formed after at least two chromosomal breaks, followed by annealing of fragments
Tetraploidy	Four copies of haploid set (92,XXXX or 92,XXYY)
Triploidy	Three copies of a haploid set (69,XXX; 69,XXY; or 69,XYY) Triploidy is not viable and results in spontaneous abortion or premature delivery of a nonviable infant with multiple malformations
Translocation	Transfer of a fragment of one chromosome to another It can be of two types: Reciprocal translocation is when the exchange of material between two chromosomes does not alter the shape or length of two chromosomes involved. It can be detected only by chromosome banding. Robertsonian translocation involves the acrocentric chromosomes, parts of which are transferred to another chromosome. It is evidenced as shortening of the donor and elongation of the recipient chromosome.
Trisomy	Addition of an extra chromosome to the normal pair (e.g., 47,XXX)

CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities are divided into two groups: those affecting 1 of the 22 autosomes (numbered 1 to 22), and those affecting the sex chromosomes (X and Y). The chromosomal abnormalities can be further classified as numeric or structural. The most important terms of clinical cytogenetics are listed in Table 5-1.

TABLE 5-2.
Most Important Chromosomal (Cytogenetic) Syndromes

Syndrome	Most Common Karyotype	Incidence	Main Features
Klinefelter	47,XXY	1:850 males	Eunuchoid tall male, infertility, testicular atrophy
Turner	45,X	1:1,000 females	Short female with web neck, infertility, streak gonads
Down	47,XX,* 21+	1:600	Typical facial features, mental retardation
Patau	47,XY,* 18+	1:3,000	Multiple malformations, usually lethal in infancy
Edwards	47,XX,* 18+	1:5,000	Multiple malformations, usually lethal in infancy

**Autosomal trisomies occur at the same rate in female and male subjects and thus the karyotype could be either female (XX) or male (XY).*

Numerical abnormalities are deviations from the normal diploid number of chromosomes (46,XX or 46,XY). These include **aneuploidy** (any number of chromosomes above or below the normal number of 46) and **triploidy** (three sets of normal haploid complements; i.e., $3 \times 23 = 69$). Each human chromosome occurs in duplicate, except for the X and Y chromosomes, which are paired to each other, and if one of these chromosomes is lost, a **monosomy** develops. All autosomal monosomies are lethal. Children born with monosomy of X chromosome (45,X) have Turner syndrome. Embryos that have 45,Y die early in pregnancy. Additional chromosomes in excess of the normal two in the pair are called *trisomy* if there are three chromosomes, *tetrasomy* if there are four chromosomes, and so on. The most common numerical chromosomal abnormalities are listed in Table 5-2.

Structural chromosomal abnormalities include deletions or translocations of parts of the chromatids and formation of abnormal chromosomes known as *ring chromosomes*, or *isochromosomes*. Structural chromosomal anomalies are of less clinical significance than numerical abnormalities. Abnormal chromosomes are occasionally found in normal people. In the clinical setting, abnormal chromosomes are most often found in Turner syndrome patients. Deletion of the short arm of chromosome 5 (46,XX-5p) results in the so-called **cri du chat syndrome,** a rare condition that has a high mortality in infancy.

Sex Chromosome Abnormalities

Turner syndrome, complete or partial monosomy of chromosome X, is characterized by hypogonadism and a variety of other somatic abnormalities that occur at a variable rate. Chromosomal

TABLE 5-3.
Features of Turner Syndrome and Klinefelter Syndrome

Feature	Turner Syndrome	Klinefelter Syndrome
Incidence	1:1,000 females	1:850 males
Karyotype	45,X (60%) 46,X,i(X); 46,X,r(X) 46,XX-; 46,XXp-; mosaicism	47,XXY (80%) 48,XXXY; 49,XXXY; mosaicism
Body	Short Broad chest Web neck	Tall Gynecomastia Eunuchoid
Extremities	Cubitus valgus Peripheral lymphedema at birth	Long arms and legs
Genital organs	Streak ovary; no oocytes Hypoplastic uterus No pubic hair	Testicular atrophy Aspermatogenesis Small penis No pubic hair
Fertility	Infertile	Infertile

analysis shows that approximately 50% of patients have a 45,X karyotype, whereas the remaining 50% have one normal and one abnormal X chromosome, such as an isochromosome X or a ring chromosome X. Because of this chromosomal defect, the ovaries do not develop normally but transform into a connective tissue band ("streak gonads") that does not respond to gonadotrophic stimulation and is incapable of producing estrogens. These patients never develop secondary sex characteristics, do not enter puberty, never menstruate, and are infertile. Other somatic features of Turner syndrome include short stature, web neck **(pterygium coli),** coarctation of the aorta, and broad chest with widely spaced nipples. Hormonal substitution therapy may be used to stimulate the development of secondary sex characteristics, but it cannot restore fertility.

Klinefelter syndrome in most cases is related to a 47,XXY karyotype, although some patients may have more than two X chromosomes. Phenotypically male, these patients are tall, have small testes and penises, and never achieve sexual maturity. Testes show no spermatogenesis and, accordingly, these patients are infertile. Hormonal findings include elevated follicle-stimulating hormone and estrogen levels, which account for eunuchoid body proportions, lack of male type of body hair, and gynecomastia. The main features of Turner and Klinefelter syndromes are listed in Table 5-3.

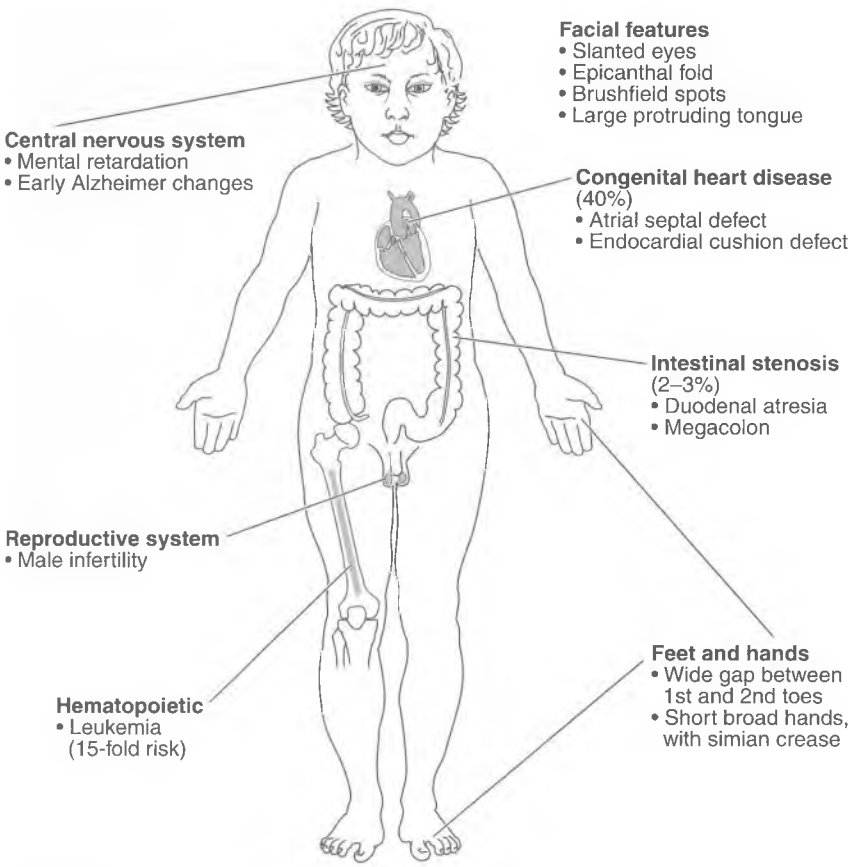


Figure 5-1.
Down syndrome.

Autosomal Chromosomal Abnormalities

Loss of autosomes (i.e., monosomy) of any of the autosomes is incompatible with normal life, and such fetuses are aborted spontaneously. On the other hand, trisomies may adversely affect development, but such infants may be born alive and may even survive. The most important in this group, trisomy, involves chromosome 21 (Down syndrome).

Down syndrome is characterized by a typical constellation of signs and symptoms, which include mental deficiency, characteristic facial features, and abnormal extremities with clinodactyly and a simian crease on the palms (Fig. 5-1). Facial features include a low bridged nose with everted nares and effaced philtrum, closely set eyes that are slanted and show palpebral epicanthus, and macroglossia. Approximately 40% of cases have congenital heart disease, and many are at risk of developing acute leukemia, which occurs 10 to 20 times more than in the general population. Immunologic disturbances predispose these children to repeated infections and autoimmune disorders. With quality care, however, Down syndrome patients

may live an almost normal life span. Almost all of those who die after puberty show neuropathologic signs of Alzheimer disease, which apparently develops at an accelerated rate in these individuals.

Most patients with Down syndrome (95%) have 47 chromosomes (47,XX +21 or 47,XY +21). The third chromosome, 21, in most instances can be traced to abnormal meiotic division during the maturation of the maternal germ cells in the ovary. Because these meiotic abnormalities occur more often in older women, the incidence of Down syndrome is increased in women who become pregnant after the age of 35 years. Because of this increased incidence of Down syndrome, prenatal diagnosis is offered routinely to all pregnant women over the age of 35 years. In a small number of cases (5%), Down syndrome is related to a robertsonian translocation of the long arm of chromosome 21 to another chromosome. Such translocation may be already present in the otherwise normal mother of these Down patients, and it can be transmitted to patients' offspring. Accordingly, the translocation form of Down syndrome can be hereditary.

SINGLE GENE DEFECTS

All human genes located on autosomes occur in duplicates known as *alleles*, which are classified as either dominant or recessive. A person with two dominant or two recessive genes is called a **homozygote,** whereas those who have one dominant and one recessive allele are called **heterozygotes.** Some genes located on the X chromosome are not present on the Y chromosome, which is much shorter. Thus, some X-linked recessive genes, which are not expressed in heterozygote female subjects, could act unopposed by another allele in male subjects and are expressed in male subjects who have only one copy of that gene. According to the laws of mendelian genetics, the diseases inherited to abnormal alleles are classified as autosomal dominant or recessive and sex-linked autosomal or recessive, depending on the location of the abnormal allele and whether it is dominant or recessive and present as unicate or in duplicate. Thousands of genetic disorders grouped into these main categories have been identified, but only the most important examples are discussed here. Sex-linked dominant diseases are rare and are not mentioned either.

Autosomal Dominant Disorders

Autosomal dominant disorders are transmitted by a single gene that is dominant in relationship to its allele. The gene is expressed fully in heterozygotes and because it has a 50% chance of being found in one of the gametes, it is transmitted to 50% of the sons or daughters

TABLE 5-4.
Examples of Autosomal Dominant Disorders

Organ System Affected	Disorder	Incidence
Nervous	Huntington disease	1:15,000
	Neurofibromatosis type I	1:3,500
Urinary	Polycystic kidney disease (adult type)	1:1,000
Gastrointestinal	Familial adenomatous polyposis coli	1:10,000
Blood	Hereditary elliptocytosis	1:2,500
	Hereditary spherocytosis	1:5,000
	von Willebrand disease	1:8,000
Connective tissue and bone	Marfan syndrome	1:10,000
	Achondroplasia	1:5,000
	Osteogenesis imperfecta (types I–IV)	1:10,000
	Ehlers-Danlos syndrome (types I–IV)	1:5,000
Metabolic	Familial hypercholesterolemia	1:500
	Acute intermittent porphyria	1:15,000

of an affected person. The trait is evident in every generation. The most common autosomal dominant diseases are listed in Table 5-4.

Marfan syndrome is a multisystemic disease caused by a mutation in the gene that encodes an intercellular protein called fibrillin. Fibrillin acts as a glue, and without it the connective tissues of many organs are loosely structured. People affected by Marfan syndrome are typically tall, suffer from loose joints that are prone to luxations, have cardiovascular symptoms related to loosely structured mitral and tricuspid valves (floppy valve syndrome) and aneurysmal dilatation of the aorta, and have eye disorders such as cataracts, luxation of lens, and detachment of the retina.

Osteogenesis imperfecta includes several variants, all of which are related to a defect in the genes encoding collagen type I. Mutation of this gene affects many organs because collagen type I is the major structural protein of the human body, and it is found in essentially all tissues. Affected persons have friable bones prone to fractures. The most severe form of osteogenesis imperfecta is lethal in utero, whereas the milder form presents with only minor skeletal deformities and blue sclerae.

Ehlers-Danlos syndrome (EDS) includes several diseases characterized by hyperelasticity of skin, hypermobility of joints, and fragility of blood vessels resulting in frequent bleeding. The disease is genetically heterogeneous, and 10 clinical subtypes are recognized. It may be caused by mutations of genes encoding one of the collagens or related enzymes and connective tissue components. For example, the gene for collagen type III is mutated in EDS IV, and the gene for col-

lagen type I is mutated in EDS VII. Gene encoding lysyl oxidase is mutated in EDS IX, and the gene for fibronectin is mutated in EDS X.

Achondroplasia is a defect of endochondral ossification, which is essential for normal growth of long bones. The disease is linked to the mutation of the gene encoding the receptor for the fibroblast growth factor. Affected persons are dwarfed because they have short limbs. The head and body, which are formed mostly by intramembranous ossification, are disproportionately large in comparison with the arms and legs.

Hereditary spherocytosis is a hemolytic anemia due to an intracorpuscular defect of red blood cells (RBCs). It is caused by a mutation of the gene for spectrin, a structural cytoskeletal protein of RBCs. Because of a deficiency of spectrin, the RBCs assume a rounded shape and are less pliable. These abnormal RBCs are destroyed at an increased rate during their passage through the spleen, which results in **chronic hemolytic anemia.**

Adult polycystic kidney disease is related to a gene on chromosome 16 whose function is not fully understood. The genetic defect leads to progressive changes in renal tubules, which undergo cystic dilatation and become afunctional. Renal failure develops in the third or fourth decade of life.

Huntington disease is related to an expanded CAG trinucleotide repeat on chromosome 4, encoding a gene whose function is not known. The disease presents at midlife as progressive dementia associated with chorea (involuntary movements) and affective outbursts.

Familial hypercholesterolemia is related to mutation of the gene that encodes the cell surface receptor for the low-density lipoprotein. Because low-density lipoprotein cannot be removed efficiently from the circulation, hyperlipidemia results, leading to accelerated atherosclerosis and deposition of cholesterol in tissues. Cholesterol-laden macrophages form small yellow subcutaneous nodules known as *xanthomas.*

Autosomal Recessive Disorders

Autosomal recessive disorders are clinically evident only if both alleles are present (i.e., the person is a homozygote). By definition, both parents must be asymptomatic carriers of the abnormal allele. Numerous diseases are classified as autosomal recessive disorders, and many of the genes causing them have been identified. The most important among these diseases are listed in Table 5-5.

Cystic fibrosis is the most common lethal autosomal recessive disorder of humans, affecting 1 in 2,500 newborn white babies. The disease was traced to the mutation of a gene on chromosome 7, which encodes the cystic fibrosis transmembrane conductance regulator. The cystic fibrosis transmembrane conductance regulator controls the transport of chloride across the cell membrane and is essential for facilitating cellular secretion. Cystic fibrosis affects most notably the pancreas and bronchial glands and the gastrointestinal system. Viscous secretions accumulate in the lumen of these organs,

TABLE 5-5.
Examples of Autosomal Recessive Disorders

Organ System Affected	Disorder	Incidence
Nervous	Neurogenic muscular atrophy	1:20,000
	Friedreich ataxia	1:10,000
	Metachromatic leukodystrophy	1:100,000
Blood	Sickle cell anemia	1:1,000
	Thalassemia	1:5,000
Skeletal	Ehlers-Danlos syndrome (types VI and X)	1:20,000
Endocrine	Congenital adrenal hyperplasia	1:10,000
Metabolic	Cystic fibrosis	1:2,500
	Phenylketonuria	1:5,000
	Lysosomal storage diseases	1:10,000
	α_1-Antitrypsin deficiency	1:7,000
	Wilson disease	1:50,000
	Hereditary hemochromatosis	1:3,000
	Glycogen storage diseases	1:50,000

blocking the flow of mucus and enzymes (Fig. 5-2). Cystic dilatation of pancreatic ducts distended with inspissated mucus leads to pancreatic fibrosis, which impairs pancreatic function and causes malabsorption of nutrients. **Bronchial obstruction with mucus** leads to bronchiectasis and recurrent bouts of pneumonia, evolving into chronic abscesses. **Deficiency of digestive enzymes** in the intestines and the obstruction of bile ducts leads to malabsorption and nutritional disturbances. Male patients are infertile because of the partial agenesis of the epididymis.

Cystic fibrosis may present early in life and even at the time of birth. In these neonates, it may cause complete obstruction of the intestine by viscid meconium. Hyperperistalsis of intestines may lead to intestinal rupture **(meconium peritonitis)** or intestinal paralysis **(meconium ileus).** Cystic fibrosis is an incurable disease, and most patients die in their third decade, usually due to pulmonary infections.

Lysosomal storage diseases result from storage of intermediate metabolites or undegraded products of metabolism in the lysosomes. These diseases are related to mutations of genes that encode enzymes critical in the intermediate metabolism of lipids, carbohydrates, and proteins. For example, **Tay-Sachs disease** is a deficiency of the α-subunit of hexosaminidase, which results in the accumulation of ganglioside GM_2 in neurons and retinal cells, with subsequent mental deterioration and blindness. **Gaucher disease** is a sulfatidosis caused by a deficiency of glucocerebrosidase. Three clinicopathologic subtypes are recognized; however, type I accounts for

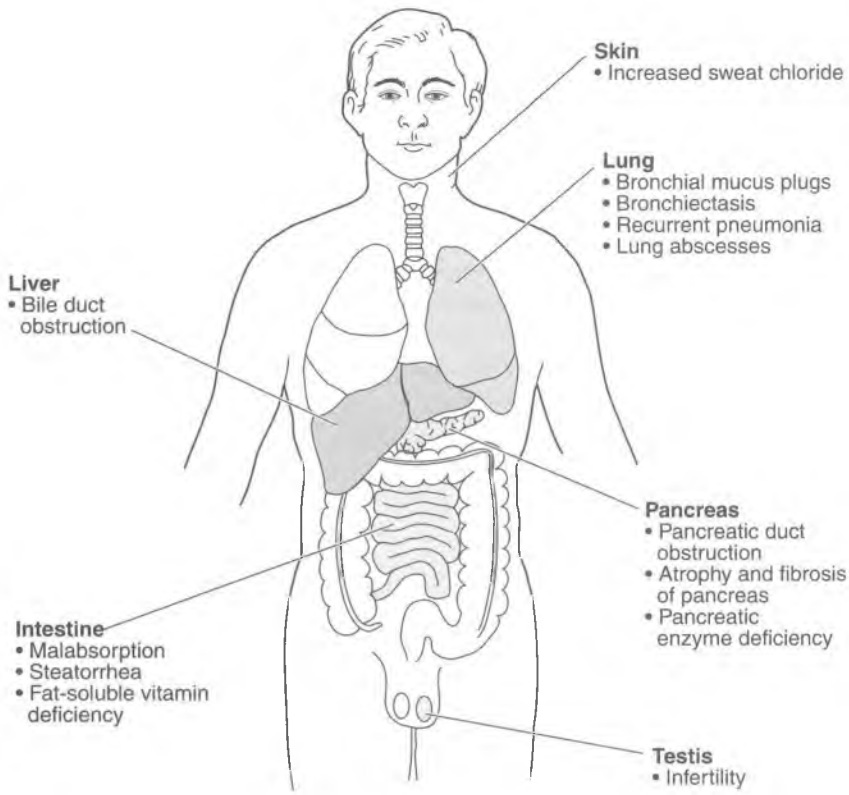


Figure 5-2.
Main lesions in cystic fibrosis.

99% of all cases. The enzyme defect causes accumulation of glucosylceramide in macrophages and fixed phagocytic cells of the spleen and the liver. **Mucopolysaccharidoses** are a group of diseases, each of which is related to a deficiency of a particular enzyme that results in the accumulation of mucopolysaccharides in lysosomes and consequent development of skeletal and cardiovascular neurologic abnormalities. The most important examples of lysosomal storage diseases are given in Table 5-6.

Disorders of intermediate metabolism of carbohydrates, lipids, and amino acids are often caused by single gene mutations. During the course of these diseases, metabolic by-products or unmetabolized substrates accumulate in the cytosol. There are at least 12 distinct forms of **glycogenoses,** each of which is based on a deficiency of a specific enzyme in the intermediate metabolism of carbohydrates. Glycogen accumulates most often in the liver or muscles, heart, and, to a lesser extent, in other organs. The most important of these is glycogenesis type I (von Gierke disease), a deficiency of glucose-6-phosphatase, which leads to accumulation of glycogen in the liver and the kidneys and high mortality in infancy. Glycogen accumulates in the hyaloplasm of all forms of glycogenesis except in glycogenosis type II (**Pompe disease** or acid maltase deficiency), which is characterized by lysosomal accumulation.

TABLE 5-6.
Lysosomal Storage Diseases

Disease	Enzyme Deficiency	Stored Substance
Sphingolipidoses		
Tay-Sachs disease	Hexosaminidase α-subunit	GM_2 ganglioside
Sandhoff disease	Hexosaminidase β-subunit	GM_2 ganglioside and globoside
Sulfatidoses		
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Mucopolysaccharidoses		
Hurler syndrome	α-L-Iduronidase	Dermatan and heparan sulfate
Hunter syndrome	Iduronate sulfatase	Dermatan sulfate
Lipidoses		
Wolman disease	Acid lipase	Triglycerides and cholesterol
Carbohydrate storage diseases		
Pompe disease	α-1,4 Glucosidase	Glycogen
Mannosidosis	α-Mannosidase	Mannose-rich oligosaccharides

Disorders of amino acid metabolism are best illustrated by diseases caused by defects in the metabolism of phenylalanine and tyrosine (Fig. 5-3). Several diseases in this group can be traced to mutations of genes encoding specific enzymes. **Phenylketonuria** is a systemic disorder caused by a deficiency of phenylalanine hydroxylase, resulting in an accumulation of phenylketones in the body. Unless treated with a diet deficient in phenylalanine, progressive deterioration of mental functions evolves early in childhood. **Albinism** is a defect in the synthesis of melanin. **Tyrosinemia** is a severe metabolic disturbance presenting as acute liver disease in childhood or as chronic renal disease and cirrhosis with neurologic disturbances. **Alkaptonuria** is characterized by deposits of homogentisic acid in connective tissue and cartilage, which causes degenerative joint disease.

X-Linked Recessive Disorders

X-linked recessive disorders are related to mutations of recessive X chromosome–linked genes, which are not found on the Y chromosome. Accordingly, such genes are expressed only in male subjects, even though they are inherited from the mother. The daughters who inherit the same defective gene from the mother are not affected, although they are asymptomatic carriers and can transmit the disease to their own male offspring. The most important diseases inherited as X-linked recessive traits are listed in Table 5-7.

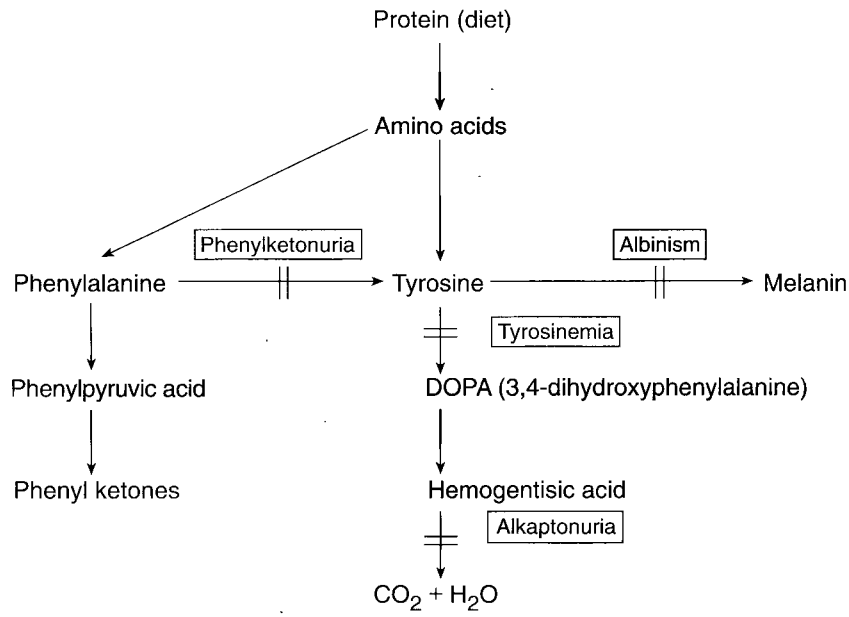


Figure 5-3.
Metabolic diseases caused by abnormal metabolism of phenylalanine and tyrosine, including phenylketonuria, albinism, tyrosinemia, and alkaptonuria.

Duchenne muscular dystrophy is caused by a mutation or partial deletion of a large gene that encodes a structural protein called **dystrophin.** Without dystrophin the muscle cells degenerate, and most affected patients die by the age of 20 years due to respiratory insufficiency caused by changes in the diaphragm and thoracic muscles. **Hemophilias A and B** are severe bleeding disorders caused by a defect in the gene encoding the coagulation factors VIII and IX, respectively. **Fragile X syndrome** is a form of mental deficiency related to a fragile site on the X chromosome, which contains abnormally amplified repeats of CGG nucleotide triplets. Patients have enlarged testicles. A similar form of mental deficiency linked to fragile X chromosome syndrome also occurs in women, but at a lower rate.

Multifactorial Inheritance

In contrast to single gene disorders, which are inherited according to the laws of mendelian genetics, most human diseases that have a hereditary base are mediated by more than one gene and thus are polygenic. Such polygenic diseases evolve at a different rate in different individuals and may be influenced by age, sex, race, and social and environmental factors. These multifactorial diseases that reflect the balance between nature and nurture include some of the most prevalent human diseases, the most important of which are listed in Table 5-8.

TABLE 5-7.
Examples of X-Linked Recessive Disorders

Organ System Affected	Disorder	Incidence
Nervous	Fragile X syndrome	1:2,000
Blood	Hemophilia A	1:10,000
	Hemophilia B	1:50,000
	Glucose-6-phosphate dehydrogenase deficiency	1:400
Immune	X-linked agammaglobulinemia	1:10,000
	X-linked severe combined immunodeficiency	1:100,000
Musculoskeletal	Duchenne muscular dystrophy	1:3,500
	Becker muscular dystrophy	1:6,000
Endocrine	Adrenoleukodystrophy	1:100,000

TABLE 5-8.
Examples of Diseases Based on Multifactorial Inheritance

Neonates and Infants	Adults
Anencephaly	Atherosclerosis
Spina bifida	Non–insulin-dependent diabetes mellitus
Cleft lip or palate	Gout
Congenital heart disease	Schizophrenia
Pyloric stenosis	Psoriasis

NEONATAL DISEASES

Diseases of the neonatal period reflect various disturbances of prenatal development, infections acquired transplacentally or during delivery, or diseases acquired immediately after birth. All of these diseases are more common in infants born to older mothers or women who were sick during pregnancy. Infants born before term (i.e., before 38 to 40 weeks of pregnancy) are more prone to infections and other diseases than infants born at term.

Premature infants weigh less than normal infants, which at 40 weeks should range from 2,700 to 4,000 g. All major organs of such premature infants are functionally immature. Most clinical features

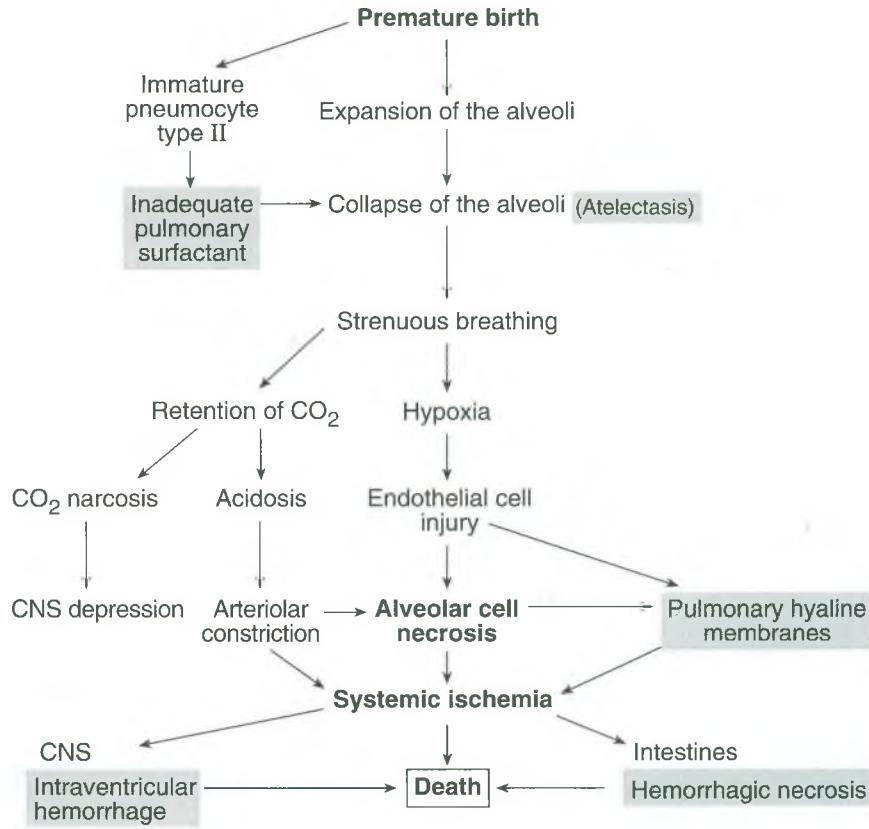


Figure 5-4.
Pathogenesis of respiratory distress of premature infants. (CNS, central nervous system.)

result, however, from the immaturity of the lungs, which cannot maintain normal respiration (Fig. 5-4). Type II pneumocytes of such infants do not secrete the adult type of pulmonary alveolar surfactant and therefore their alveoli cannot remain open. **Atelectasis of the alveoli** is typically associated with exudation of fibrin into the alveolar sacs and respiratory bronchioli and the development of so-called hyaline membranes. **Respiratory distress syndrome** of the newborn resulting from pulmonary immaturity requires treatment, and without ventilatory assistance, such infants do not survive. The most serious complications include intraventricular hemorrhage and hemorrhagic intestinal necrosis, both of which are associated with high mortality. Infants who recover tend to develop chronic lung lesions known as **pulmonary dysplasia.** This form of lung disease is especially common in very small premature babies (<1,500 g at birth) and those maintained on positive pressure respirators. The lungs in these infants show signs of interstitial fibrosis, atelectasis, and various forms of metaplasia of the lining epithelium. These changes impede oxygen uptake and gas exchanges. Nevertheless, most infants have a good chance for complete recovery.

Birth Injury

Birth injury is relatively common, although most infants injured during delivery recover and have only minimal residual pathology. The most common injury is **cephalhematoma,** or bleeding beneath the periosteum of calvarial bones, which heals without any consequences. Intracranial hemorrhages are a complication of forceps delivery of prolonged birth through a very narrow birth canal. Peripheral nerve injuries or **avulsions,** which most often involve the brachial plexus, are rare but may result in permanent paralysis of the extremities.

Chapter 6

Circulatory Disturbances

Circulatory disturbances include the following disorders:

- Disorders of extracellular fluid distribution in the body (e.g., edema)
- Disorders of blood flow (e.g., hyperemia)
- Bleeding disorders (e.g., hemorrhage)
- Thrombosis, embolism, infarction, and shock

EDEMA

Edema is excessive accumulation of fluid in the interstitial spaces or body cavities. The edema fluid may be classified as an exudate or a transudate. **Exudate** develops during inflammation and has a high specific gravity (>1.20). It contains proteins in high concentration and inflammatory cells, which impart a turbid appearance. **Transudate** has low specific gravity (<1.15), contains little protein, and has few or no inflammatory cells, making it translucent. Pathogenetically, edema can be classified as caused by

- **Increased hydrostatic pressure.** Blood pressure forces the fluid from the blood vessels into the interstitial spaces (Fig. 6-1). This type of edema typically occurs in the lower extremities of patients who have **congestive heart failure.** In such cases, central venous pressure is increased, impeding the return of the venous blood from the periphery into the lungs and right ventricle. Increased venous pressure causes stasis of blood in the venules and capillaries, and the increased intracapillary pressure forces the fluid into the interstitial spaces. Pulmonary edema develops through a similar mechanism in left-sided heart failure, which leads to increased pressure in the pulmonary veins and transudation of fluid into the alveoli from pulmonary capillaries.

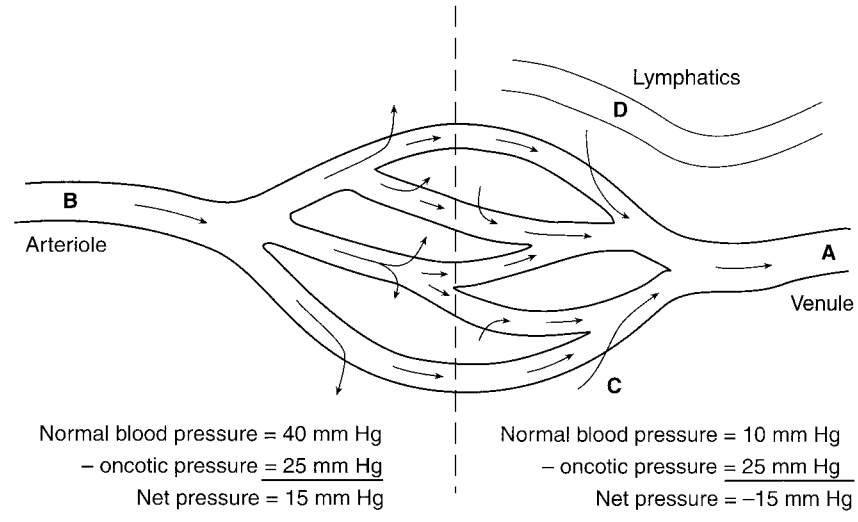


Figure 6-1.
Pathogenesis of edema. *A:* Increased hydrostatic pressure. *B:* Decreased oncotic pressure. *C:* Increased permeability of the vessel wall. *D:* Lymphatic obstruction.

- **Decreased osmotic pressure,** as in **end-stage liver disease** (cirrhosis) or **nephrotic syndrome.** Osmotic pressure of the plasma, which keeps the fluid from leaking into the interstitial spaces, is primarily a function of albumin. Albumin is produced by the liver, and if the liver is damaged, hypoalbuminemia develops. In **nephrotic syndrome,** a kidney disease characterized by proteinuria due to increased permeability of the glomerular basement membranes, hypoalbuminemia develops because of excessive loss of albumin in urine. In either case, hypoalbuminemia is accompanied by decreased plasma osmotic pressure, which allows the fluid to leak into the interstitial spaces.
- **Increased vascular permeability,** as in **inflammation, septic shock, or anaphylactic shock.** Inflammatory cells secrete numerous cytokines and generate arachidonic acid derivatives, which may increase the permeability of the blood vessel wall. Endotoxin produced by bacteria has the same effect. In anaphylactic shock, a form of hypersensitivity reaction type I, the reaction of antigen with IgE attached to mast cells causes a massive release of histamine, causing vasodilatation and increased permeability of the blood vessels.
- **Obstruction of lymphatics** by **tumors, fibrous tissue, or parasites.** Lymphatics are the main drainage route for the interstitial fluid and, if obstructed, edema may ensue distally to the obstruction. Breast cancer obstructing the lymph flow in the axilla causes edema of the arm. Similar events account for the edema of the arm due to fibrosis of the lymphatics caused by radiation. Lymphatic obstruction in the groin by parasites such as filaria causes marked edema of the legs known as *elephantiasis.*

In many cases, edema has more than one cause. For example, the accumulation of fluid in the abdominal cavity of patients who

TABLE 6-1.
Forms of Edema

Type of Edema	Body Site	Common Cause
Anasarca	Entire body	Hypoalbuminemia of cirrhosis or nephrotic syndrome
Ascites	Peritoneal cavity	Cirrhosis
Brain edema	Brain	Brain trauma, tumors, inflammation
Hydropericardium	Pericardial cavity	Viral pericarditis
Hydrothorax	Pleural cavity	Heart failure, pneumonia
Lymphedema	Extremities	Obstruction of lymphatics by tumor, parasite, or fibrosis
Postural edema	Extremities	Heart failure
Pulmonary edema	Lung	Left-sided heart failure, adult respiratory distress syndrome

have cirrhosis of the liver is due in part to hypoalbuminemia and in part to increased portal pressure caused by fibrous tissue in the liver, impeding the normal flow of blood through the liver. In chronic heart failure, hypoperfusion of kidneys leads to retention of sodium, which is accompanied by retention of fluid in the expanded extracellular spaces. Hypoperfusion of the kidneys also triggers a release of renin, which leads to a release of aldosterone, further promoting sodium retention. Edema can be localized or generalized. The basic forms of edema are listed in Table 6-1.

DISORDERS OF BLOOD FLOW

Normal blood flow depends on the efficiency of the central pump, the heart, and the capacity of the vascular system. Failure of the heart or occlusion of the blood vessels that impedes the blood supply to a body part results in **ischemia.** Marked accumulation of blood in the blood vessels is called *hyperemia.* Hyperemia is classified as active or passive. **Active hyperemia** occurs on dilatation of the precapillary sphincters (arterioles) as in working muscle or at a site of inflammation. **Passive hyperemia (congestion)** occurs due to stasis of blood in capillaries and venules, as in heart failure or obstruction of venous flow by thrombosis. Chronic passive congestion of the liver (known as **nutmeg liver** because of its resemblance to a cross-sectioned nutmeg) is a painful enlargement of the liver typically found in patients who have chronic right-sided heart failure. It is often accompanied by congestive splenomegaly and **chronic**

TABLE 6-2.
Clinically Important Forms of Hemorrhage

Skin and mucosal hemorrhages
- Petechia: capillary or venular hemorrhage, <1 mm in diameter
- Ecchymosis: same as petechia but >1 cm in diameter
- Purpura: generalized microvascular hemorrhages due to vascular defects or platelet disorders
- Hematoma: accumulation of blood in subcutaneous tissue

Gastrointestinal hemorrhages
- Hematemesis: vomited blood
- Hematochezia: blood in feces
- Melena: coffee ground type of material in feces derived from upper gastrointestinal bleeding in which the blood has been exposed to hydrochloric acid

Bleeding into body cavities
- Hemothorax, hemoperitoneum, hematopericardium

Respiratory tract bleeding
- Epistaxis: nose bleed
- Hemoptysis: expectorated blood

Gynecologic bleeding disorders
- Menorrhagia: excessive menstrual bleeding
- Metrorrhagia: bleeding unrelated to menstrual period
- Spotting: a few drops of blood in the vaginal contents

stasis dermatitis of the lower extremities. Chronic passive congestion of the lungs in left-sided heart failure is accompanied by intra-alveolar hemorrhages. The extravasated red blood cells (RBCs) are hemolyzed and taken up by alveolar macrophages. These macrophages contain brown hemosiderin granules and are known as **heart failure cells,** which can often be seen in the sputum. Chronic passive congestion of the lungs also leads to alveolar fibrosis, known as **brown induration of the lungs.**

Hemorrhage

Hemorrhage is marked by an outflow of blood from the vascular spaces into the interstitial tissue spaces, body cavities, or outside the body. Hemorrhages can be classified on the basis of their anatomic location as cardiac, arterial, capillary, or venous. On the basis of the pathogenesis, hemorrhages can be due to vascular wall injury (e.g., trauma or vitamin C deficiency) or coagulation defects involving platelets or plasma coagulation factors (e.g., hemophilia or thrombocytopenia). Clinically important terms used for various forms of hemorrhages are listed in Table 6-2.

THROMBOSIS

Thrombus, or **clot,** is the solid aggregate of blood formed during coagulation. Thrombus is essential for hemostasis and is normally formed to prevent excessive bleeding. Thrombosis is considered to be pathologic

- If the thrombus forms under inappropriate circumstances (e.g., in intact blood vessels, as in varicose veins of the legs)
- If a large thrombus forms over some pathologically altered blood vessel, as in an atherosclerotic aorta
- If the thrombosis occurs in an uncontrollable manner, as in disseminated intravascular coagulation (DIC)

Causes of Thrombosis

The three most important causes of thrombosis, known as the **Virchow triad,** are changes in the vessel wall, blood flow, and composition of blood.

Changes in the vessel wall can be found in the veins or arteries. Endocardial changes of the cardiac chambers and valves should also be included in this category. Venous diseases that predispose to thrombosis are thrombophlebitis (inflammation of veins), chemicals used to induce obliteration of veins (sclerotherapy), or trauma injury resulting from catheters. Arterial thrombi occur most often over ulcerated atherosclerotic lesions. Various forms of vasculitis predispose to thrombosis. In polyarteritis nodosa, thrombi are in the arteries. **Buerger disease** (thromboangiitis obliterans) is characterized by formation of thrombi in both arteries and veins of extremities. Mural thrombi in the left ventricle are seen overlying myocardial infarcts. Bacterial endocarditis can cause thrombi on cardiac valves. Valvular vegetations of marantic endocarditis also represent thrombi, which, in contrast to bacterial endocarditis, do not contain bacteria (nonbacterial endocarditis).

Changes in blood flow that predispose to thrombosis are all characterized by stasis or increased turbulence of the bloodstream. This typically occurs in varicose veins, aneurysm of the aorta, and systemic or pulmonary veins in congestive heart failure. **Changes in blood composition** that predispose to thrombosis are often associated with hyperviscosity of the blood, as in polycythemia or Waldenström macroglobulinemia. Sickle cell anemia leads to formation of thrombi because the abnormal RBCs tend to form clumps in small blood vessels. Pregnancy and oral contraceptives increase the coagulability of the blood.

Formation and Fate of Thrombi

Thrombi typically form on internal surfaces of the blood vessels or the heart. Under normal circumstances, the intact endothelium

secretes prostacyclin and other substances that prevent coagulation. Injured endothelium secretes thromboxane and procoagulants, which have the opposite effect and could initiate the clotting sequence by activating platelets or the coagulation cascade in the plasma. Severe damage of the endothelium resulting in a loss of endothelial cells exposes the plasma to connective tissue, which can activate the extrinsic coagulation pathway. Blood that leaks from a damaged vessel coagulates when in contact with the perivascular tissue due to the action of tissue thromboplastin.

The first step in the formation of intravascular thrombi is **platelet aggregation.** Aggregated platelets release coagulants, which activate the coagulation cascade and form the fibrin thrombus. Fibrin, which represents strands of polymerized fibrinogen, forms a mesh that includes the platelets, RBCs, and white blood cells. Although fibrin is colorless, the RBCs trapped in the mesh color the thrombus red. The thrombus grows by attracting more fibrin, which forms layers alternating with layers of RBCs (lines of Zahn). The thrombus is attached to the vessel wall on one end, and on the other ("tail") end, it floats freely in the blood. Turbulence caused by the moving trail of the thrombus promotes coagulation of the blood until the entire blood vessel becomes occluded and the blood flow stops.

The fate of the thrombus depends on its location, size, and how firmly it is attached to the vessel wall (Fig. 6-2). A small thrombus can be lysed through the action of fibrinolytic enzymes in the blood such as plasmin. Loosely attached thrombus or parts thereof can be carried away as a **thromboembolus.** Ingrowth of granulation tissue into the thrombus from the vessel wall leads to **organization** of the thrombus. Such a thrombus ultimately can be **recanalized,** and the blood flow can be re-established through the previously occluded blood vessel.

Infarction

Occlusion of the blood vessel by particulate material, most often by thrombi, causes ischemia and anoxic necrosis of the tissue distal to the occlusion. This area of ischemic necrosis is called **infarct,** and the process leading to it is called an **infarction.** Most infarcts are caused by arterial thrombi or thromboemboli, but in some instances they can also be due to obstruction of venous outflow. Infarcts can also occur without occlusion of a vessel, typically when the perfusion of an organ is inadequate due to heart failure or shock. Such infarcts, known as **watershed infarcts,** typically occur in the brain when the border zone between the perfusion territory of the basal artery and carotid artery is not reached by blood in hypotensive episodes after myocardial infarction.

Infarcts of organs such as the heart, kidney, or spleen, which occur due to an occlusion of terminal arteries in their parenchyma, are typically **pale.** On the other hand, infarcts of organs that have dual circulation, such as the liver or the lungs, are **red.** In the lungs, the occlusion of a branch of the pulmonary artery causes necrosis in

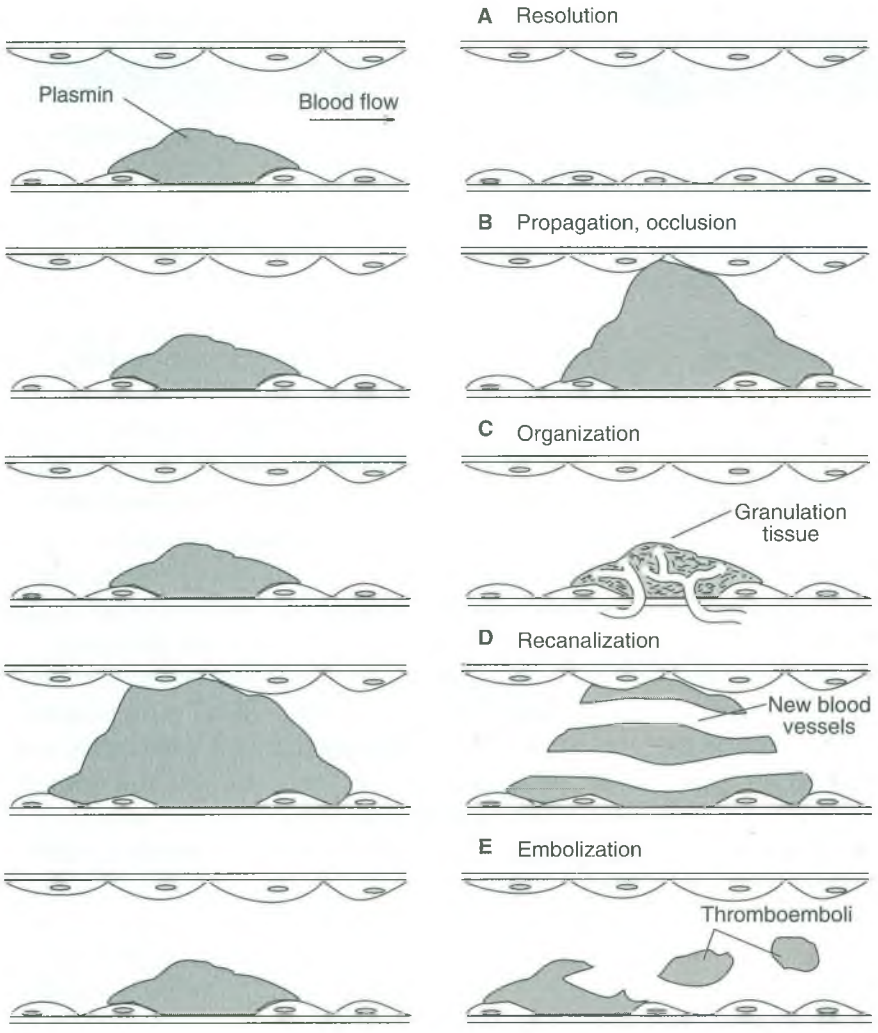


Figure 6-2.
The formation and fate of the thrombus. *A:* Resolution through the actions of fibrinolytic enzymes (plasmin). *B:* Propagation (i.e., growth) of the thrombus may result in occlusion of vessels. *C:* Organization of the thrombus through the ingrowth of granulation tissue. *D:* The thrombus is recanalized and blood flow re-established. *E:* The thrombus gives rise to emboli.

the anatomic site supplied by venous blood from this vessel. However, because the same segment receives arterial blood from the bronchial artery, the area is perfused by arterial blood from this source. Blood entering the necrotic area seeps out from the damaged vessels and enters the alveoli, giving the infarcted area a red color. The same is true for infarcts of the liver. Infarcts of the small intestine are also red because of the extensive anastomosing of intestinal arteries.

Venous infarcts are also red because ischemia occurs typically due to obstruction of the outflow, which prevents the inflow of oxygenated blood into the affected area. Stagnant venous blood ulti-

Substance	Source	Clinical Example
Thrombus	Leg veins	Pulmonary embolism from venous thrombi
Fat droplets	Bone marrow	Brain or lung emboli after bone fracture
Air	Air	Injection of air into the vein
Amniotic fluid	Uterus	Postpartum disseminated intravascular coagulation due to amniotic fluid entry into veins
Cholesterol	Aorta	Postsurgical peripheral arterial occlusion with cholesterol crystals

mately seeps out from the damaged blood vessels into the tissue, col oring the vessels red.

Infarcts can occur in any organ. Clinically, the most importa infarcts are those affecting the heart, brain, kidneys, and lung Heart and brain infarcts can be lethal. Because the brain and hea consist of postmitotic permanent cells, necrotic cells cannot *regenerated, and thus these organs remain permanently dama Myocardial infarct heals by scarring. Brain infarct transforms in fluid-filled pseudocyst.*

Embolism

Embolism or obstruction of blood flow can be due to an impaction of the blood vessel lumen by solid, liquid, or gaseous material carried by the blood. The main forms of embolism are listed in Table 6-3.

Thromboemboli are the most common form of particulate material that can be carried by blood from one site to another. Those that travel by venous blood are called **venous,** and those that travel through arteries are called **arterial.** Most thromboemboli originate in the deep leg veins and are carried by venous circulation to the lungs. In the lungs, these emboli can occlude the main pulmonary artery and its principal branches **(saddle embolus)** and cause instantaneous death. Smaller thromboemboli occlude minor pulmonary artery branches and cause pulmonary infarcts. Thromboemboli that cross from the right side of the heart through a foramen ovale or interventricular septal defect to the left side and into the arterial circulation are called **paradoxical emboli.** Arterial thromboemboli originate in the left ventricle, on the valves of the left side of the heart, or in the aorta and the major arteries. The most common source of arterial thromboemboli are thrombi overlying atherosclerotic lesions of the aorta. Arterial thromboemboli can cause infarcts in any organs or extremities.

Fat embolism is typically a complication of a fracture of the long bones, wherein the medullary fat enters into the venous circulation. Fat droplets are carried to the lungs and cause pulmonary difficulties. These droplets can be filtered through the lung circulation into the systemic arterial blood flow and reach various organs. The most important consequences of this event are **multiple petechial hemorrhages** in the brain caused by the occlusion of small cerebral blood vessels by fat. **Air embolism** can occur if large amounts of atmospheric air enter the veins, such as during an unintentional tear of a major vein during thoracic surgery. Air can be injected into the venous blood by injection and is typically used for euthanasia of dogs by veterinarians. During **decompression** of deep sea divers returning to the sea surface after diving, the nitrogen normally present in the blood can form bubbles that may occlude small blood vessels. **Caisson disease,** a decompression disease in people working under high pressure and returning to atmospheric pressure, typically causes pain and even ischemic microinfarcts in the bones (bends).

Amniotic fluid embolism occurs when the amniotic fluid enters venous circulation from the pregnant uterus during the delivery. The amniotic fluid contains fetal squames, vernix caseosa, and several substances, all of which can act as tissue thromboplastin and initiate a fatal DIC.

Atheromatous emboli are cholesterol crystals that detach from ulcerated atheromatous plaques in the aorta or major blood vessels during various procedures such as radiologically guided endarterectomy or cardiovascular surgery. Showers of cholesterol emboli may completely occlude the branches of renal arteries or other organs and cause infarcts.

SHOCK

Shock is a form of generalized vascular collapse characterized by a marked underfilling of vessels with blood (i.e., a disparity between the volume of circulating blood and the vascular space it occupies). Shock may be caused by heart failure **(cardiogenic shock),** blood loss **(hypovolemic shock),** or loss of peripheral vascular tonus **(vasogenic or hypotonic shock).** Whatever the cause of shock, the circulatory collapse leads to hypoperfusion of tissues and the ensuing hypoxia results in multiple organ failure. Foci of necrosis develop in all major organs. Lung edema with formation of hyaline membranes, known as *adult respiratory distress syndrome;* renal tubular necrosis; and centrolobular necrosis of the liver develop at a predictable rate. **Adult respiratory distress syndrome** has high mortality. Many patients also develop **brain edema** with compression of vital centers, which may

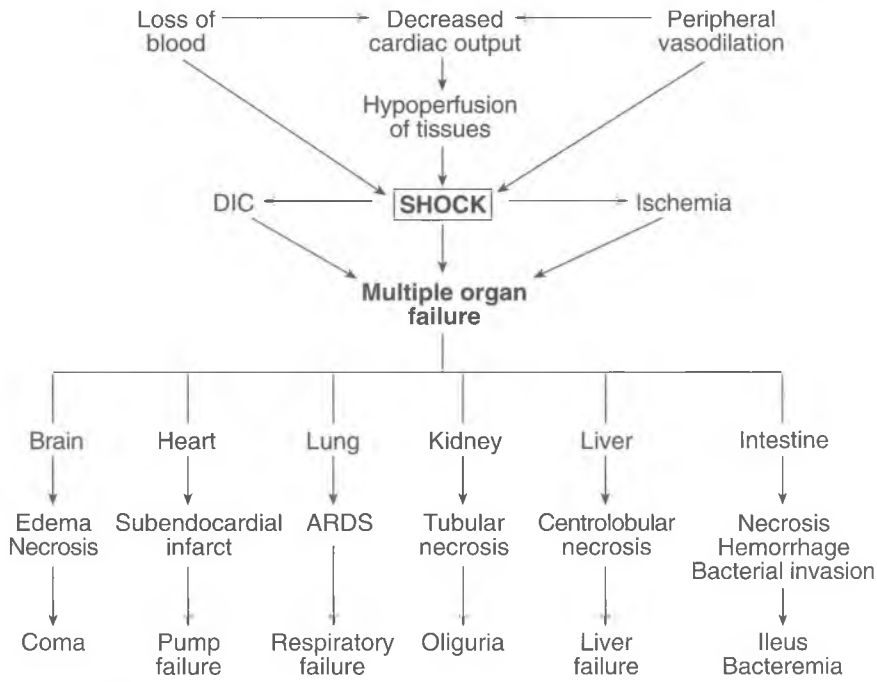


Figure 6-3.
Pathogenesis of shock. (DIC, disseminated intravascular coagulation; ARDS, adult respiratory distress syndrome.)

cause death. Hypoperfusion of the brain causes watershed infarcts and zonal necrosis of deep cortex (laminar necrosis). Most patients also develop microvascular thrombi typical of the syndrome of DIC. Consumption of platelets and coagulation factors during DIC leads to hemorrhage, which is often fatal. The pathogenesis of clinicopathologic features of shock is shown in Figure 6-3.

Chapter 7

Cardiovascular System

The most important cardiovascular diseases discussed here are

- Atherosclerosis
- Ischemic heart disease
- Hypertensive heart disease and pulmonary hypertensive disease (cor pulmonale)
- Valvular diseases
- Rheumatic fever
- Congenital heart diseases

In some instances, these diseases may be related. For example, calcific aortic valve stenosis may impair coronary artery filling, leading to ischemic heart disease. Hypertensive heart disease may evolve to ischemic heart disease because hypertension is a risk factor for atherosclerosis.

ATHEROSCLEROSIS

Atherosclerosis is a multifactorial disease of large and medium-sized arteries that is characterized by accumulation of lipids, fibrosis, and calcification of the arterial walls. It is one of the most prevalent diseases in developed countries, and it accounts directly or indirectly for approximately 50% of all deaths.

The **etiology** of atherosclerosis is complex and not fully understood. Well-documented risk factors include:

- **Age.** Atherosclerosis is a disease of older age and is rarely found in people under the age of 40.
- **Sex.** Men are more often affected than women but only until women reach menopause, when gender differences become negligible.
- **Heredity.** Metabolic diseases inherited as mendelian traits (e.g., familial hypercholesterolemia) or polygenic diseases (e.g., diabetes) account for some of the familial cases of atherosclerosis, but in many families with known predisposition to atherosclerosis, the genetic factors are less obvious.

- **Diet.** A Western diet rich in lipids plays an important role in the pathogenesis of atherosclerosis and explains in part the geographic differences in the prevalence of the disease. A high-fat diet causes hyperlipidemia. High levels of low-density lipoprotein and cholesterol are poor prognostic findings. Obesity itself is a risk factor.
- **Hypertension.** High blood pressure plays an important role in the pathogenesis of early vascular lesions of atherosclerosis, but it also accelerates the course of the disease.

The **pathogenesis** of atherosclerosis has been studied clinically and in experimental animals. According to the most prevalent theory, dubbed the *response-to-injury theory*, the crucial initiating event that ultimately leads to the formation of typical atherosclerotic lesions is the injury to the endothelial cells. The injured endothelial cells lose their barrier capacity, allowing the influx of various substances from the plasma into the vessel wall. Loss of antithrombogenic functions of endothelial cells is accompanied by attachment of platelets to the luminal surface. Growth factors such as platelet-derived growth factor or fibroblast growth factor released from the platelets stimulate the proliferation of smooth muscle cells, which grow into the intima of the artery and become lipid laden. At the same time, macrophages enter the vessel wall and take up the lipid, transforming it into foam cells. The lipid released from dead and dying smooth muscle cells and macrophages becomes oxidized and broken down. Cholesterol crystals and a mixture of cell debris, altered collagen, and other intercellular matrix molecules form a softened area in the vessel wall, known as **atheroma.**

Tissue damage heals by scarring, but it also elicits a lymphocytic response. Lymphocytes are a major source of growth factors and mediators that act on macrophages, smooth muscle cells, and fibroblasts, perpetuating the pathologic process that ultimately destroys all layers of the blood vessel. The fibrotic scar tissue and lipid-rich atheromas attract calcium salts and, accordingly, most advanced atheromatous lesions are heavily calcified.

In accordance with the pathogenetic data, **pathologic changes** of atherosclerosis can be classified as follows:

- **Early precursor lesions,** such as **fatty streaks** and **intimal thickening**
- **Atheromatous plaques,** representing fully developed atheromas surrounded by fibrous scars and calcifications
- **Complications of atherosclerosis,** including intimal ulcerations, often covered with thrombi and infiltrated with blood. Weakening of the arterial wall may cause aneurysms (i.e., bulging of the thinned vessel wall).

Clinical manifestations of atherosclerosis depend on the extent of the lesions, their location, and the presence or absence of complications. Atherosclerosis is most often generalized, involving all major arteries. It may be localized, however, and involve only the following areas:

- Heart vessels (coronary atherosclerosis)
- Aorta and its major branches

- Peripheral arteries of the extremities
- Cerebral arteries

In all of these clinical forms of atherosclerosis, most symptoms develop due to ischemia caused by the **progressive narrowing** or the **complete occlusion** of the arterial lumen by the atherosclerotic plaques. Rupture of atherosclerotic plaques is often accompanied by formation of thrombi, which develop suddenly and typically cause acute infarction in the area supplied by the affected artery. Other clinical manifestations of atherosclerosis are less common but not less important and include

- Arterial emboli originating from the mural thrombi overlying ruptured and ulcerated atheromas or aneurysms
- Cholesterol emboli originating from ruptured atheromas
- Atherosclerotic aneurysms that dilate progressively or rupture

ISCHEMIC HEART DISEASE

The term *ischemic heart disease* includes a spectrum of circulatory disorders stemming from an imbalance between myocardial oxygen supply and demand. Most often it is due to inadequate blood supply, which not only causes myocardial hypoxia or anoxia but also reduces the availability of nutrients and impedes the removal of metabolic degradation products. The most common cause of ischemic heart disease is **coronary atherosclerosis.**

Based on the rate of development of the atherosclerotic coronary stenosis, its extent, and the manner in which the myocardium responds, four distinct clinical syndromes are recognized: angina pectoris, myocardial infarct, chronic ischemic heart disease, and sudden cardiac death.

Angina Pectoris

Angina pectoris is characterized by intermittent attacks of substernal or precordial chest discomfort and pain caused by transient myocardial ischemia that is not sufficient to cause necrosis of heart cells. The three forms of angina are stable (typical), Prinzmetal (variant), and unstable (crescendo).

Stable angina, also called *typical angina,* is the most common form typically associated with increased oxygen demand due to exercise or strenuous activity, such as walking up stairs or running. Coronary perfusion is hampered by atherosclerotic stenosis of the coronary artery or on occasion by vasospasm. On electrocardiogram (ECG), it is recognized by a **depression of the ST seg-**

TABLE 7-1.
Complications of Myocardial Infarcts

Complication	Time Period	Pathogenesis
Early		
Sudden death	Any time	Ventricular fibrillation, asystole, heart block
Arrhythmias	First few days	Lesion of conduction system
Cardiac failure	Any time	Necrosis of myocardium
Pericarditis	2–4 days	Transmural infarct extending to epicardium
Cardiac tamponade	5–7 days	Rupture of necrotic myocardium
Mitral incompetence	5–7 days	Papillary muscle necrosis or rupture
Late		
Mural thrombosis	1–2 weeks or longer	Release of thromboplastin from necrotic endocardium
Emboli	Weeks or months	Mural thrombosis
Ventricular aneurysm	1–2 months or longer	Bulging of ventricle at the site of collagenous scar
Dressler syndrome	Weeks to months	Autoimmune pericarditis

ment. Symptoms can be relieved by rest and vasodilators such as nitroglycerin.

Prinzmetal or variant angina occurs at rest and is thought to be related to coronary spasm. Affected persons may have significant atherosclerosis, but the attacks are generally not related to physical exertion, hypertension, or increased heart rate. Vasospasms can be seen in some cases during angiography. ECG shows ST elevation. Symptoms are relieved by vasodilators such as nitroglycerin or calcium channel blockers.

Unstable angina (crescendo angina) begins as typical angina, but with time the episodes of pain become more common, tend to occur at rest, and last longer. These patients have advanced coronary atherosclerosis, and in most cases ischemia is precipitated by fissuring of atherosclerotic plaques with superimposed thrombosis or vasospasm. Microscopic platelet thrombi are thought to form in these sites and precipitate spasm or formation of fibrin thrombi. Histologic signs of focal myocardial necrosis and fibrosis are found in the heart at autopsy. Aspirin may prevent the progression of vascular occlusion, because it prevents platelet aggregation.

Myocardial Infarction

Myocardial infarction is the most important form of ischemic heart disease and is the leading cause of death in the United States. There are two types of myocardial infarctions: transmural and subendocardial (Table 7-1).

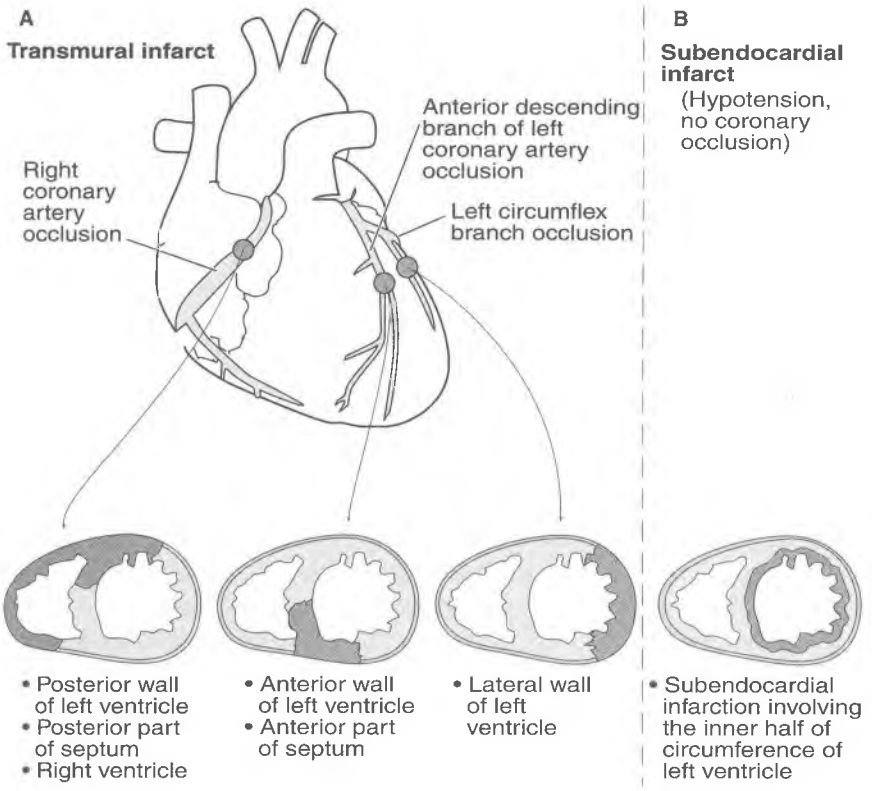


Figure 7-1.
Myocardial infarcts. *A:* Transmural infarcts are found in defined anatomic areas corresponding to parts of the heart supplied by each of the three major arteries. *B:* Subendocardial infarct is circumferential and does not correspond to a defined anatomic region perfused by any given artery.

Transmural infarcts are the most common form of myocardial infarction and are characterized by coagulation necrosis that involves from more than half to the full thickness of the ventricular wall, anatomically corresponding to the supply area of a single coronary artery (Fig. 7-1). These infarcts are generally caused by an occlusion of one of the major coronary arteries by a thrombus forming at the site of a ruptured atherosclerotic plaque. Because occlusive thrombi form within a short period after the rupture of the plaque, cardiac failure develops rapidly, and many patients die or develop signs of cardiogenic shock. Minor infarcts may cause less obvious symptoms, and some even remain unnoticed.

Subendocardial infarct is characterized by widespread foci of necrosis, limited to the inner third of the ventricular wall and not to the perfusion zone of a single coronary artery. These infarcts are precipitated by hypoperfusion of the myocardium, which typically occurs due to heart failure, hemorrhage, or peripheral blood pooling in shock.

Because the subendocardial portions of the heart are the last to receive the blood from the coronary arteries, these areas become ischemic first when the blood perfusion pressure decreases. However, most patients have severe atherosclerosis, which has already contributed to a marginal blood supply of the myocardium, and thus the hypotensive episode represents only the ultimate event, the proverbial straw that broke the camel's back.

Approximately 50% of transmural infarcts are found in the distribution of the left anterior descending branch of the left coronary artery, which supplies the anterior wall of the left ventricle near the apex and the anterior two-thirds of the interventricular septum (see Fig. 7-1). Approximately 30% are found in the distribution of the right coronary artery, which supplies the posterior wall of the left ventricle, the posterior one-third of the interventricular septum, and, on some occasions, the posterior right ventricular wall. The left circumflex coronary artery is occluded in approximately 15% to 20% of cases, causing infarctions in the lateral wall of the left ventricle. The right ventricle is rarely infarcted (1% to 3%). Atrial infarction can be found in 5% to 10% of cases, often in association with large posterior left ventricular infarcts.

Pathology varies, and the changes depend on the time that has elapsed between occlusion and death. On gross examination of the heart, the early changes of myocardial ischemia cannot be recognized with confidence, although some infarcts appear as distinctly pale areas 12 to 24 hours after the occlusion of the coronary. Necrotic fibers can be recognized histologically during that period. At 24 to 30 hours, the infarcted area is infiltrated with neutrophils, which persist for 1 to 3 days and are replaced with macrophages. During this inflammatory phase, the myocardium appears yellow and softer than normal. The influx of macrophages is followed by resorption of necrotic muscle cells and formation of granulation tissue. Granulation tissue is replaced by fibroblasts, which contribute to final healing by scarring, usually within 6 weeks of coronary occlusion. Myocardial scars are composed of collagen and appear as white patches.

Clinical diagnosis of myocardial infarction is based on the following factors:

- **Symptoms,** such as severe substernal or precordial pain that may radiate to the left shoulder, arm, or jaw. In addition, there may be sweating, vomiting, nausea, or dyspnea; symptoms of cardiogenic shock are present in severe cases.
- **ECG changes,** manifested by early elevation of the ST segment, inversion of the T wave, and new Q waves.
- **Biochemical laboratory data,** which include serum enzymes such as creatine kinase, aspartate aminotransferase, and lactate dehydrogenase, and new markers for myocardial infarct are proteins such as troponin, myoglobin, or myosin, which are released into serum from damaged cardiac myocytes.

Chronic Ischemic Heart Disease

Chronic ischemic heart disease is found in patients with severe atherosclerosis. It may present as gradually progressive myocardial ischemia or as a series of repeated infarcts, resulting in myocardial fibrosis. The patients are often but not always elderly and usually have a history of angina or previous myocardial infarctions.

HYPERTENSIVE HEART DISEASE

Hypertensive heart disease, the second most common cause of heart disease, is characterized by cardiac hypertrophy caused by an increased demand imposed on the heart by systemic hypertension (>140/90 mm Hg). Because the diagnosis is circumstantial, other causes of left ventricular hypertrophy such as valvular disease or hypertrophic cardiomyopathy must be excluded.

Systemic hypertension induces pressure overload in the left ventricle, resulting in concentric hypertrophy of the ventricular wall. This increases the ratio of the wall thickness to the radius of the ventricular chamber and the weight of the heart. In addition, the increased thickness of the wall imparts stiffness to the wall and impairs ventricular filling during diastole. Microscopically, there is enlargement of myocytes, accompanied by interstitial fibrosis.

Clinical features depend on the severity of the hypertension. Patients may die of unrelated causes, develop ischemic heart disease because of the potentiating effects of hypertension on coronary atherosclerosis, or suffer progressive renal damage, cerebral vascular disease, or congestive heart failure. All patients with hypertrophic heart are at danger from sudden cardiac death.

Cor Pulmonale

Right-sided hypertensive heart disease or cor pulmonale is right ventricular enlargement resulting from pulmonary hypertension caused by diseases of the lung, pulmonary vessels, disorders affecting chest movement, or conditions causing arteriolar constriction. Back pressure from the failing left ventricle also causes cor pulmonale.

Acute cor pulmonale refers to dilatation of the right ventricle following massive pulmonary embolism. **Chronic cor pulmonale** is right ventricular hypertrophy with late stage dilatation. Conditions predisposing to the development of cor pulmonale are listed in Table 7-2.

TABLE 7-2.
Causes of Chronic Cor Pulmonale

Site of Lesion	Disease
Pulmonary vasculature	Pulmonary thromboemboli
	Primary pulmonary hypertension
	Pulmonary arteritis (e.g., Wegener granulomatosis, Churg-Strauss syndrome)
Pulmonary parenchyma	Pulmonary fibrosis
	Chronic obstructive pulmonary disease
	Cystic fibrosis
Chest wall	Kyphoscoliosis
	Obesity (pickwickian syndrome)
	Muscle weakness (e.g., myasthenia gravis, myotonic dystrophy)

VALVULAR HEART DISEASE

Valvular diseases can be classified as developmental, inflammatory, and degenerative. They may affect the valves of one, more than one, or all four cardiac ostia. The valve cusps may be damaged, distorted, or completely destroyed. The connective tissue annulus, papillary muscles, chordae tendineae, or all three may also be affected. Diseases of heart valves cause valvular **insufficiency,** which allows reversal of blood flow or **stenosis,** which impedes forward flow of blood. These changes are associated with adaptive changes in the heart, which tries to compensate for the hemodynamic problems caused by the altered valve. The most common adaptive change is hypertrophy and dilatation of ventricles, which, if uncorrected, predisposes the heart to failure.

Endocarditis

Endocarditis may be infective or sterile. **Infective endocarditis** is a consequence of colonization of heart valves, endocardium, or both by microorganisms. Infection with highly virulent microbes causing massive destruction of valves or acute heart failure is classified as **acute endocarditis,** in contrast to protracted, less destructive infection with less virulent bacteria, which is known as **subacute endocarditis.** *Staphylococcus aureus* is the most common cause of the acute

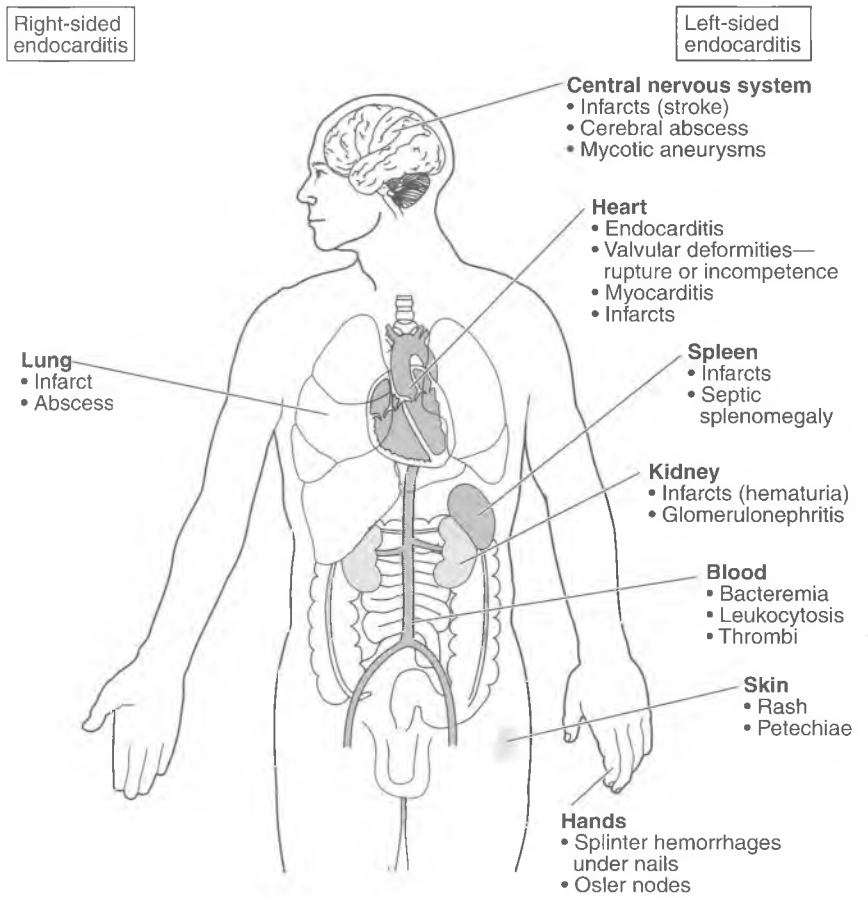


Figure 7-2.
Clinical symptoms and complications of infective endocarditis.

form, and *Streptococcus viridans* is the most common cause of subacute endocarditis. Other bacteria and fungi are less commonly involved.

In most cases, **pathology** is restricted to the mitral and aortic valves; however, in intravenous drug abusers, right-sided valves are also involved. The most common conditions that predispose to infectious endocarditis include congenital heart disease, rheumatic fever, and degenerative calcific aortic stenosis. The valves are covered with verrucous vegetations (excrescences), which are most prominent along the lines of closure. Excrescences are composed of fibrin, inflammatory cells, and bacteria. Bacteria also destroy valves and can cause rupture of chordae tendineae. Valvular deformities result.

Clinical features include fever and leukocytosis, which usually are associated with bacteremia and positive blood culture results. Heart murmurs are typically heard. Destruction of valves may cause cardiac insufficiency. Detachment of vegetations results in sepsis and septic emboli, which cause infarcts and abscesses in many organs (Fig. 7-2).

Nonbacterial thrombotic endocarditis (marantic endocarditis) is characterized by the deposition of small, sterile, fibrin thrombi on previously normal valves. It is thought to be due to activation of blood coagulation by underlying debilitating diseases such as cancer

and is closely related to disseminated intravascular coagulation. The main disease usually overshadows symptoms attributable to endocardial lesions, which are usually noticed only at autopsy. Fibrin deposits such as this can become infected, whereon the nonbacterial endocarditis becomes bacterial.

Endocarditis (Libman-Sacks disease) of systemic lupus erythematosus (SLE) usually presents with small, sterile, fibrinous vegetations on the ventricular surface of the mitral and tricuspid valves.

Degenerative Valvular Disease

Calcific aortic valve stenosis is an age-related degeneration. The calcified valves are rigid and nodular, and the orifice is stenosed. Calcification of congenital bicuspid valves is yet another form of valvular calcification and deformity. Rheumatic fever can also cause valvular calcification, but it is rare today.

Mitral valve prolapse (floppy valve) is an idiopathic condition in which one or both mitral leaflets balloon back into the left atrium during systole. It is found in 5% to 10% of all adults in the United States and is diagnosed as a midsystolic "click" in young persons who are otherwise asymptomatic. Histologically, the fibrous layer of the valve is thinned, and there is thickening of the spongiosus layer with myxomatous changes of leaflets and chordae.

Carcinoid Heart Disease

Carcinoid heart disease is a term describing the changes in the heart caused by bioactive substances released into the circulation from carcinoid tumors that have metastasized to the liver. Serotonin, kallikrein, bradykinin, neuropeptides, and other products of carcinoid tumor are normally metabolized in the liver. However, if the intestinal carcinoid tumors have metastasized to the liver, its secretory products are not neutralized in the liver and reach the right side of the heart unmodified. In the right side of the heart, these substances cause fibrous intimal thickenings of the endocardium of the right ventricle or tricuspid and pulmonary valves. The bioactive products are inactivated in the lungs; thus, left-sided heart lesions are not observed.

Prosthetic Valves

Prosthetic valves used to replace damaged valves are made either of metal and plastic or are animal tissues (e.g., pig heart valves). The most frequent complications with the use of these valves include thromboembolism, partial dehiscence, infective endocarditis, and structural deterioration or dysfunction due to ingrowth of fibrous

connective tissue, which may interfere with the function of the valves. These valves may damage circulating blood cells and cause mechanical intravascular hemolysis.

RHEUMATIC HEART DISEASE

Rheumatic Fever

Rheumatic fever is a systemic disease thought to be caused by an **abnormal immune response to streptococci.** It most often affects children between the ages of 5 and 15 years. The diagnosis is made using clinical and laboratory findings known as **Jones criteria.** These criteria are divided into major and minor manifestations. Major criteria include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum of the skin. Minor criteria include fever, elevated erythrocyte sedimentation rate, leukocytosis, ECG changes, and a history of a previous episode of rheumatic fever.

Diagnosis is made based on evidence of a preceding group A streptococcal (β-hemolytic) infection and either two major manifestations or one major and two minor manifestations of the Jones criteria.

The pathogenesis of rheumatic fever is not clear, although all patients have antistreptococcal antibodies. It is not known whether the tissue lesions are directly caused by such antibodies or some other mechanism. Typical histologic lesions consist of central fibrinoid necrosis surrounded by lymphocytes, macrophages, and histiocytes, which form so-called Aschoff bodies. Aschoff bodies destroy normal tissues but heal, leaving behind foci of fibrosis.

Rheumatic heart disease is a **pancarditis**, which means that it may present with endocarditis, myocarditis, or pericarditis. Verrucous endocarditis is most often on the mitral and aortic valves. Valvular deformities are common and involve both the leaflets and chordae tendineae. Deformed valves are prone to calcification or infections. Myocarditis can involve any part of the heart and cause myocardial or conductive system cell destruction. There is also serofibrinous pericarditis, but it is usually mild.

Clinical features vary. Endocardial lesions cause murmurs and valvular insufficiency. Myocarditis can cause arrhythmias such as atrial fibrillation or cardiac failure. Pericarditis presents with a typical friction murmur. In chronic stages of the disease, symptoms pertaining to mitral or aortic valve stenosis or insufficiency predominate. Mitral valve lesions lead to dilatation of the left atrium, pulmonary congestion, and right ventricular hypertrophy. Stenotic aortic valve lesions impede outflow of blood from the left ventricle. Aortic insufficiency causes regurgitation of blood from the aorta into the left ventricle, which is usually hypertrophic and dilated.

TABLE 7-3.

Most Common Congenital Heart Diseases Observed Clinically

Disease	Percent Occurrence
Acyanotic	
Ventricular septal defect	30
Atrial septal defect	5
Pulmonary stenosis	10
Aortic stenosis	10
Persistent patent ductus arteriosus	10
Coarctation of the aorta	5
Early cyanotic	
Tetralogy of Fallot	10
Transportation of great vessels	5

Source: Modified from Moller JH, Anderson RC. 1,000 consecutive children with a cardiac malformation with 26- to 37-year follow-up. Am J Cardiol 1992;70:661.

CONGENITAL HEART DISEASE

Abnormalities of the heart, great vessels, or both, represent the most common type of heart disease among infants and children. The reported incidence of congenital heart disease is 6 to 8 per 1,000 live births. In most cases, the cause of congenital heart disease is unknown. Chromosomal defects and viral infections during pregnancy account for a few cases.

Although there are more than 50 different malformations, eight conditions listed in Table 7-3 account for 85% to 90% of clinically diagnosed cases. These diseases can be clinically classified into two groups: those that present with cyanosis early after birth, and those that are acyanotic until the heart begins to fail.

The most common clinically diagnosed congenital heart disease is **ventricular septal defect.** The defect allows the shunting of blood from left to right—hence, the disease is initially acyanotic. As the overburdened pulmonary circulation and right ventricle adapt over time, pulmonary hypertension develops, reversing the flow of the blood through the defect. Right-to-left shunting results in late cyanosis (Fig. 7-3).

Tetralogy of Fallot is the most common cyanotic heart disease. It comprises a ventricular septal defect, dextroposition of the aorta, stenosis of the pulmonary artery, and right ventricular hypertrophy (Fig. 7-4). **Patent ductus arteriosus** and **coarctation of the aorta** are the most important anomalies of the major blood vessels. All of these diseases can be treated surgically.

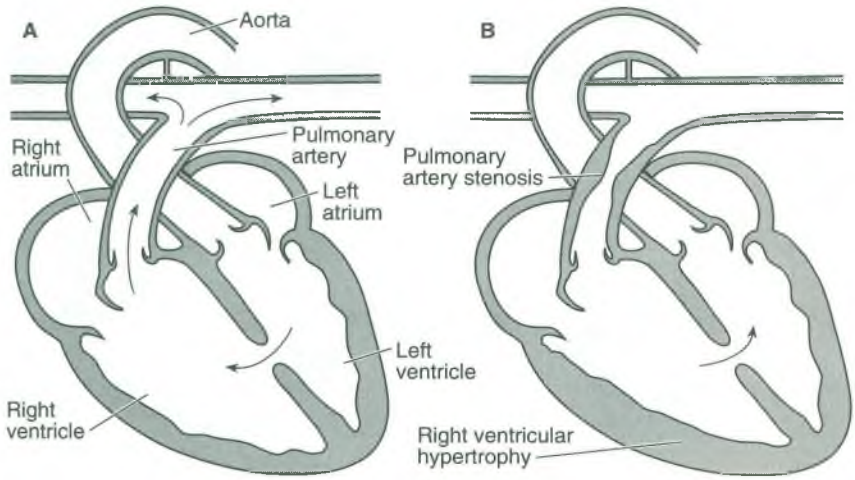


Figure 7-3.
A: Ventricular septal defect. In early stages, there is left-to-right shunting.
B: Shunt reverses itself due to pulmonary hypertension.

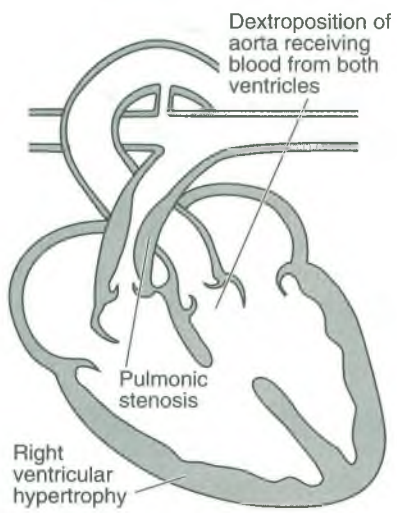


Figure 7-4.
Tetralogy of Fallot includes ventricular septal defect, dextroposition of the aorta, stenosis of pulmonary artery, and right ventricular hypertrophy.

MYOCARDIAL DISEASES

The term *cardiomyopathy* is used to denote that which encompasses a heterogeneous group of primary myocardial diseases that cannot be related to coronary atherosclerosis, hypertension, valvular disease, infections, or congenital heart disease. On the other hand, the term *myocarditis* is used for inflammatory myocardial diseases related to identifiable pathogens or autoimmune mechanisms.

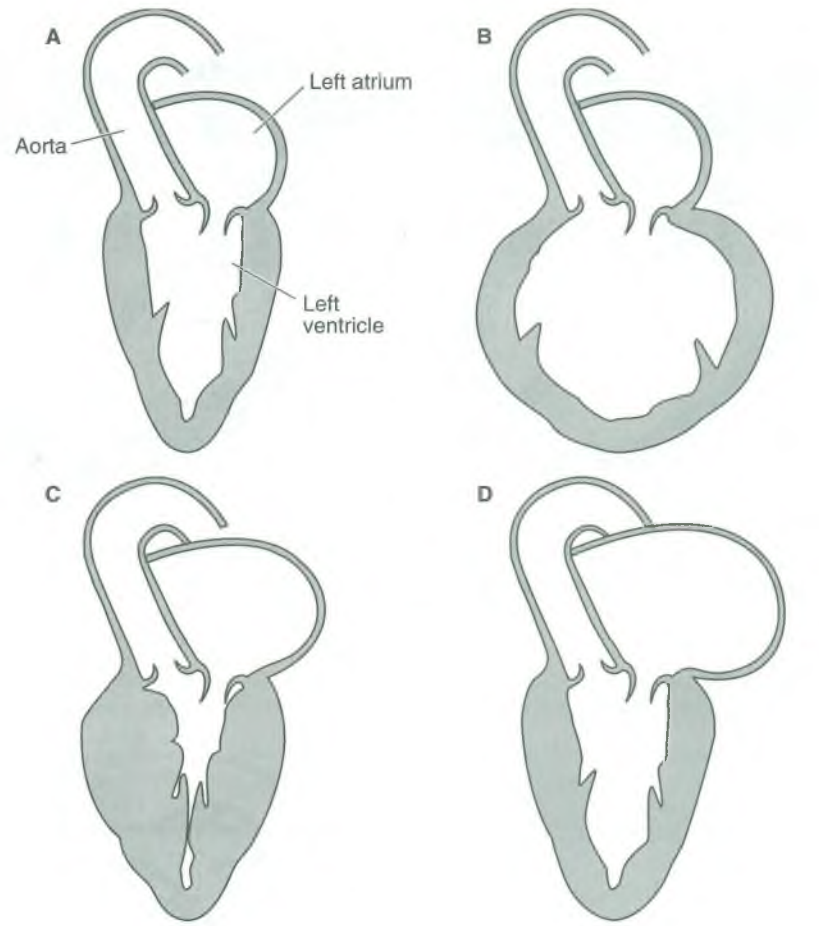


Figure 7-5.
Cardiomyopathies. *A:* Normal heart. *B:* Dilated cardiomyopathy. *C:* Hypertrophic cardiomyopathy. *D:* Restrictive cardiomyopathy.

Cardiomyopathies

Cardiomyopathies are classified on the basis of clinical and pathologic features into three groups: dilated, hypertrophic, and restrictive (Fig. 7-5).

Dilated cardiomyopathy is a systolic disorder characterized by the gradual development of cardiac failure due to hypertrophy and dilatation of all four chambers of the heart. Mural thrombi may be present in the ventricles. In most cases, the cause of dilated cardiomyopathy is not known. A minority can be related to hemochromatosis, sarcoidosis, alcohol, and drugs such as doxorubicin. It is assumed that many cases represent the end stage of viral myocarditis, in which the causative pathogen can no longer be seen.

Hypertrophic cardiomyopathy is a diastolic disorder caused by massive idiopathic myocardial hypertrophy. In approximately 50% of cases, it is familial and caused by a mutation of the gene for the heavy chain of myosin. Friedreich ataxia and other genetic diseases may cause similar changes. Classically, there is a disproportionate thickening of the

TABLE 7-4.
Important Causes of Myocarditis

- Infections
  - Viruses (e.g., coxsackievirus, enteric cytopathic human orphan virus, influenza)
  - Rickettsia
  - Bacteria (e.g., *Corynebacterium diphtheriae, Borrelia recurrentis*)
  - Protozoa (e.g., *Trypanosoma cruzi, Toxoplasma gondii*)
- Immune-mediated reactions
  - Autoimmune diseases (e.g., systemic lupus erythematosus, scleroderma)
  - Drug hypersensitivity (e.g., penicillin, sulfonamides)
  - Transplant rejection
  - Sarcoidosis
- Unknown
  - Giant cell myocarditis

ventricular septum compared with the left ventricular free wall (asymmetric septal hypertrophy). The left ventricular outflow track can be narrowed during systole when the septum is markedly thickened at the level of the mitral valve. The accelerated blood flow through the region of obstruction pulls the anterior leaflet of the mitral valve toward the septum, leading to mitral regurgitation. The course of hypertrophic cardiomyopathy is variable. Sudden death is the most feared complication, particularly in young men with a family history.

Restrictive cardiomyopathy, the rarest form of cardiomyopathy, is a defect of diastolic relaxation that impedes left ventricular filling, but does not affect ventricular contraction. The ventricles are normal to slightly enlarged, the cavities are not dilated, and the myocardium is firm. Both atria are usually dilated. Restrictive cardiomyopathy is a feature of amyloidosis in radiation fibrosis and rare diseases such as endomyocardial fibrosis or Löffler endomyocarditis. There is interstitial myocardial fibrosis that prevents dilatation of the ventricles.

Cardiomyopathies are incurable diseases for which heart transplantation is the only treatment.

Myocarditis

Myocarditis, an inflammation of heart muscle, is classified as infectious, autoimmune, or idiopathic (Table 7-4). Most cases are of presumptive **viral origin**, but the virus may be difficult to demonstrate in the heart. Myocarditis may be encountered in typhus, Lyme disease, and Chagas disease. Diphtheria toxin carried from the throat

by blood can damage cardiac myocytes and cause inflammation. Myocarditis may occur in the course of systemic autoimmune diseases such as SLE or systemic sclerosis. Myocarditis caused by drug hypersensitivity or sarcoidosis is also thought to be immune mediated. All heart transplants contain infiltrates of host's lymphocytes. Giant cell myocarditis is a distinct histologic disease of unknown origin. All forms of myocarditis are potentially lethal, and many patients ultimately must receive heart transplantation.

NEOPLASMS

Neoplasms of the heart are rare. The most common primary tumor of the heart in adults is the myxoma, which, in approximately 90% of cases, is located in the atria. However, it can be found in all four chambers. The major clinical manifestation of this neoplasm is due to a "ball-valve" obstruction of the mitral orifice and arterial embolization to distant sites.

Rhabdomyoma is the most common heart tumor in infants and children, although it is also considered a hamartoma. It forms nodular masses in the myocardium. Metastases to the heart are rare; the most common are from carcinomas of the lung and breast, melanomas, or leukemias and lymphomas.

DISEASES OF THE PERICARDIUM

Pericardial lesions are common complications of other heart diseases or systemic diseases, but occasionally the pericardium is the only site of the disease in the body.

Acute pericarditis is characterized by filling of the pericardial cavity by an inflammatory exudate. It may be caused by viruses, pyogenic bacteria, *Mycobacterium tuberculosis,* and fungi and other parasites. Immune-mediated noninfectious pericarditis may be encountered in rheumatic fever, SLE, and scleroderma. Finally, pericarditis is a complication of myocardial infarction, uremia, heart surgery, trauma, and radiation.

Constrictive pericarditis is characterized by dense fibrous connective tissue that encases the heart, restricting diastolic expansion. It is often idiopathic, but occasionally a history of suppurative or caseous pericarditis is noted. In such cases, the pericardial sac is obliterated; consequently, there is no hypertrophy and dilatation. Rather, the cardiac output is reduced. Constrictive pericarditis is treated by pericardiectomy (i.e., surgical removal of the fibrous tissue).

TABLE 7-5.
Classification of Hypertension

Primary (essential), 90%
Secondary, 10%
Renal diseases
Adrenal cortical hypersecretion
Pheochromocytoma
Vascular diseases (coarctation of aorta, polyarteritis)
Psychogenic

DISEASES OF THE ARTERIES

The most important disease of the arteries is atherosclerosis, which was previously described. Significant numbers of adults have hypertension, which also affects the arteries. All other vascular diseases are rare and only inflammatory diseases (arteritis) are discussed here.

Hypertension

Arterial hypertension is empirically defined as sustained elevation of **diastolic pressure >90 mm Hg, systolic pressure >140 mm Hg**, or both pressures are elevated. Hypertension is an age-related disease, and by the age of 65 years approximately 40% of all whites and 50% of blacks in the United States have elevated blood pressure. Most (90%) have primary or idiopathic hypertension, which is of unknown etiology. Secondary hypertension (i.e., related to an identifiable cause) accounts for <10% of all cases (Table 7-5).

The pathogenesis of hypertension is complex. Because normal blood pressure is a product of cardiac output and peripheral resistance, all conditions that permanently increase the cardiac output or peripheral resistance lead to hypertension.

Pathologically, the most prominent changes caused by hypertension are in arterioles and arteries and, as stated previously, hypertension also causes hypertrophy of the left ventricle. The changes depend on the duration of the disease and how rapidly it has developed. Slowly evolving hypertension **(benign hypertension)** is characterized by hyalinization of arterioles. **Malignant hypertension** of sudden onset, associated with sustained diastolic pressure >110 mm Hg, causes fibrinoid necrosis and con-

centric proliferation of smooth muscle cells in arterioles with marked narrowing of their lumen. Whatever the type of hypertension, arteries show intimal fibrosis and accelerated atherosclerosis. Hypertension is also a major risk factor for the formation of so-called **dissecting aneurysms** of the aorta. In this condition, the blood penetrates through a small tear in the intima and, by separating the layers of the aorta, forms a barrel-like space in the vessel wall, which fills with blood. Dissecting aneurysms are associated with high mortality due to exsanguination.

The **clinical features** of hypertension are highly variable. Because hypertension accelerates atherosclerosis, many symptoms are similar to those caused by atherosclerosis. The heart is enlarged, typically showing left ventricular hypertrophy. Such hearts are prone to failure. **Cerebrovascular changes** may be associated with nonspecific symptoms such as headache and vertigo, which may progress to a more advanced form of disease (hypertensive encephalopathy), marked by blurring of the eyesight due to papilledema and even loss of consciousness. Hypertensive hemorrhages into the basal ganglia, pons, or cerebellum are found in severe untreated hypertension and are clinically recognized as stroke. **Eye changes** are common in prolonged untreated hypertension and are recognized on ophthalmologic examination by their typical retinal vascular changes.

Renal changes are seen in the arteries, arterioles, and glomeruli and result in decreased glomerular filtration rate and retention of fluids and sodium. Hypoperfusion of the kidneys may also increase the production of renin, which aggravates the hypertension by stimulating the production of aldosterone in the zona glomerulosa of the adrenals.

Vasculitis

Vasculitis is a term used to describe several inflammatory diseases of the blood vessels and includes several clinicopathologic entities, the majority of which have an **immune origin**. The inflammation may involve the aorta, large and medium-sized arteries, arterioles, capillaries, or venules and veins. Although several types of blood vessels are involved, in many cases the predominant anatomic site of inflammation is used as the primary criterion for the classification of vasculitides (Table 7-6).

Polyarteritis nodosa involves medium- and small-sized arteries that show fibrinoid necrosis and acute transmural inflammation, leading to the formation of microaneurysms. It is considered to be a clinical equivalent of an Arthus phenomenon (i.e., type III hypersensitivity immune complex reaction). In a significant number of cases, the immune complexes contain hepatitis B viral surface antigen. The disease predominantly affects young adults and is characterized by a progressive course. It may affect any of the major organs, but in an unpredictable manner. Histologically, the vascular changes vary, and it is typical to find acute and chronic lesions in the same organ.

TABLE 7-6.
Forms of Vasculitis

Disease	Vessel Involved	Site	Age (yrs)
Polyarteritis nodosa	Medium-sized and small arteries	Unpredictable	20–50
Wegener granulomatosis	Medium-sized and small arteries	Upper respiratory, lung, kidney	40–60
Microscopic polyangiitis	Arterioles, capillaries, venules	Skin or any internal organ	Any
Temporal arteritis	Elastic arteries	Temporal and other cranial	60–90
Kawasaki disease	Small and medium-sized arteries	Skin, oral mucosa, coronaries	5–15
Thromboangiitis obliterans (Buerger disease)	Medium-sized and small arteries and veins	—	30–60

Wegener granulomatosis is a necrotizing vasculitis involving three sites: upper respiratory tract, lungs, and kidneys. It is considered to be an autoimmune disease, but its pathogenesis remains obscure. Antineutrophil cytoplasmic antibodies of C type (C-ANCA) are found in the blood of most patients. The disease has a relentlessly progressive course, and most patients die within 2 years of onset, due to renal failure or lung disease. Fortunately, the disease responds well to cytotoxic therapy with cyclophosphamide.

Microscopic polyangiitis, also known as *hypersensitivity vasculitis,* involves arterioles, capillaries, and venules. In many cases, it represents an allergic reaction to drugs or infectious agents, but often no obvious cause can be determined. Skin, lungs, and kidneys are most often involved, but other organs can be affected as well. Histologically, the walls of small vessels are infiltrated with neutrophils (leukocytoclastic vasculitis) that disrupt the vessel wall, causing perivascular hemorrhage. Immune complexes may be found in these lesions in early stages of the disease, but are not seen later. Antineutrophilic cytoplasmic antibody of P type (P-ANCA) is found in approximately 70% of cases. In general, the disease has a limited course and good prognosis unless widespread, in which case it may produce permanent lesions of vital organs such as the brain.

Temporal arteritis is a granulomatous disease of unknown origin involving segments of the temporal artery. Granulomas contain giant cells, hence the synonym *giant cell arteritis.* Because it may involve other cranial arteries, it is also known as *cranial arteritis.* Typically, nevertheless, it is most often found in temporal arteries of older people, more often in women than men. Approximately 1% of all people who are 80 years of age have this disease. The involved segments of the artery show nodular thickening and marked narrowing of the lumen. This causes changes in the soft tissues, but also may cause eye problems and cerebral ischemia.

Takayasu arteritis is a granulomatous disease of unknown origin involving the aorta and its main branches. It has a predilection for women who are younger than 40 years of age. Most often the disease is most pronounced on the aortic arch, leading to ischemia of upper extremities. Hence the synonym *pulseless disease.* Involvement of the lower aorta and its branches may result in intermittent claudication and ischemic necrosis of lower extremities. Coronary artery involvement causes cardiac ischemia. Aortic aneurysms are yet another complication. The course of the disease is variable.

Kawasaki disease (mucocutaneous lymph node syndrome) is a multisystemic disease of unknown etiology, affecting infants and small children. It presents with high fever, rash, oral and conjunctival lesions, and lymphadenopathy. Acute vasculitis involving medium and small coronary arteries has a usually self-limited course.

Thromboangiitis obliterans (Buerger disease) is an inflammatory disease of medium-sized vessels of the lower extremities. Arteries and adjacent veins become occluded by thrombi. It is almost always found in young men who smoke tobacco. Vaso-occlusive attacks usually begin with cramping pain in the legs, corresponding to episodes of ischemia. Repeated attacks may result in gangrene. The disease may subside if the patient stops smoking.

ANEURYSMS

Aneurysms are abnormal dilatations of blood vessels. They affect mostly large elastic vessels such as the aorta and its major branches. Aneurysms are classified by shape as fusiform, cylindrical, saccular, or dissecting; however, etiologic classification is more useful (Table 7-7).

Atherosclerotic Aneurysms

Atherosclerotic aneurysms are the most common form of aneurysm. They occur most frequently in the **abdominal aorta** above the iliac bifurcation and below the origin of the renal arteries. They may be fusiform, cylindrical, or saccular. The iliac, femoral, and popliteal vessels are also frequently involved. Ulceration of the endothelium and complicated atherosclerosis lead to mural thrombosis. Rupture is frequent due to dissection behind the clot and perforation of the weakened wall. Embolization from the mural thrombus or atherosclerotic plaque is another common complication.

TABLE 7-7.
Etiologic Classification of Aneurysms

Type	Common Location
Congenital defect	
Berry aneurysm	Circle of Willis
Marfan syndrome	Aorta
Degenerative or mechanical dissection	
Atherosclerosis	Aorta
Cystic medial necrosis	Aorta
Dissecting	Aorta
Traumatic	Aorta
Autoimmune	
Takayasu disease	Aorta
Kawasaki disease	Coronaries
Polyarteritis nodosa	Medium-sized arteries
Other	
Infectious (mycotic)	Small arteries
Syphilitic	Aorta

Syphilitic Aneurysms

Syphilitic aneurysms, usually found in the ascending aorta and arch in the thorax, were the most common forms of aneurysms in the early to mid-twentieth century, but are rare today. Syphilis produces a vasculitis in the vasa vasorum, with endothelial proliferation obliterating the lumen and a perivascular infiltration of plasma cells and lymphocytes. Elastic tissue fragments, and the media is weakened. A characteristic atherosclerotic plaque produces a flaking appearance not unlike the peeling bark of a sycamore tree (tree bark lesion).

Dissecting Aneurysms

Dissecting aneurysms are a complication of hypertension, atherosclerosis, or so-called cystic medial necrosis, which is a degenerative change with deposition of mucopolysaccharides in the media of the aorta. Marfan syndrome is yet another predisposing condition. Dissection usually occurs adjacent to an atherosclerotic plaque and can extend proximally, distally, or both. The dissection may on occasion reenter the aortic lumen, producing a double-barreled aorta. Rupture is usually rapidly fatal, with rupture into the pericardium producing cardiac tamponade.

Mycotic Aneurysms

Mycotic aneurysms are related to bacterial infection and cause a localized weakening of the arterial wall. Typically, they occur after an occlusion of a small artery by a septic thromboembolus and are a common complication of bacterial endocarditis.

Berry Aneurysms

Berry aneurysms are congenital small saccular aneurysms of the arteries at the base of the brain. They arise at weakened points of the media at branching points in the circle of Willis. Berry aneurysms are an important cause of intracranial hemorrhage.

DISEASES OF VEINS

Venous diseases are less incapacitating than arterial diseases. The most important are **dilatations** of veins (varicosities) and **venous thrombosis. Varicose veins** are seen most frequently in the lower extremities, particularly the calves. They develop due to chronic stagnation of blood in people who stand for long periods (e.g., sales personnel) or those who have heart failure and poor circulation. **Esophageal varices** are seen in individuals with portal hypertension, most often caused by cirrhosis of the liver. **Varicosities of hemorrhoidal veins** (piles or hemorrhoids) may be seen above the junction of the rectal mucosa within the squamous epithelium (internal) or beneath the anal squamous epithelium and epidermis (external). Dilated veins are prone to thrombosis **(phlebothrombosis),** and stasis may also predispose to infection. More commonly, the vein wall becomes inflamed first, leading to a secondary clot formation **(thrombophlebitis).** This can produce life-threatening pulmonary emboli.

TUMORS OF BLOOD VESSELS

Tumors of blood vessels are common and in most cases benign. **Hemangiomas** are usually classified by histologic type as capillary, venous, or mixed. **Juvenile hemangiomas** or strawberry hemangiomas are found on the skin of newborns. **Cavernous hemangiomas** are lesions composed of larger blood vessels and may be found in the liver and spleen. They may be discussed under thrombosis and fibrosis. **Glomus tumors** (glomangiomas) are painful tumors of fin-

gers, composed of branching vascular spaces surrounded by smooth muscle cells, which resemble the temperature-sensing glomus body. Malignant tumors of blood vessels are rare, and include **angiosarcomas, hemangiopericytomas, and Kaposi sarcoma.** Kaposi sarcoma was once consider a rare tumor, but its incidence has increased with the acquired immunodeficiency syndrome epidemic.

Chapter 8

Respiratory System

The major diseases of the lungs can be classified as follows:

- Developmental
- Mechanical
- Circulatory
- Obstructive
- Restrictive
- Inflammatory
- Neoplastic

In addition to the major intrinsic diseases of the respiratory system, the lungs are intimately related to the cardiovascular system. Consequently, vascular diseases of the lungs often result from heart pathology, such as congestive heart failure or valvular disease, or vascular disease such as deep vein thrombosis promoting pulmonary emboli. Finally, the lungs, like the liver, are preferred targets for tumor metastasis.

DEVELOPMENTAL DISORDERS

Hypoplasia is a rare congenital anomaly of the lung. The lung is smaller than normal due to decreased numbers of acini. It may be solitary or accompanied by hypoplasia of the bronchi and pulmonary vessels.

A **tracheoesophageal fistula** is a developmental defect in which the trachea is connected with the middle of the esophagus. Food enters the lungs through the fistula, causing aspiration pneumonia.

Bronchogenic cysts are outpouchings derived from bronchi. They are lined by bronchial epithelium and filled with mucus. These cysts may communicate with bronchi from which they arose or be entirely separated from them. Complications include inflammation and abscess formation, rupture into bronchi resulting in hemoptysis, or rupture into the pleural cavity leading to pneumothorax or interstitial emphysema.

Bronchopulmonary sequestration is a term used to describe lobes or portions of lung tissue that are isolated from the airway sys-

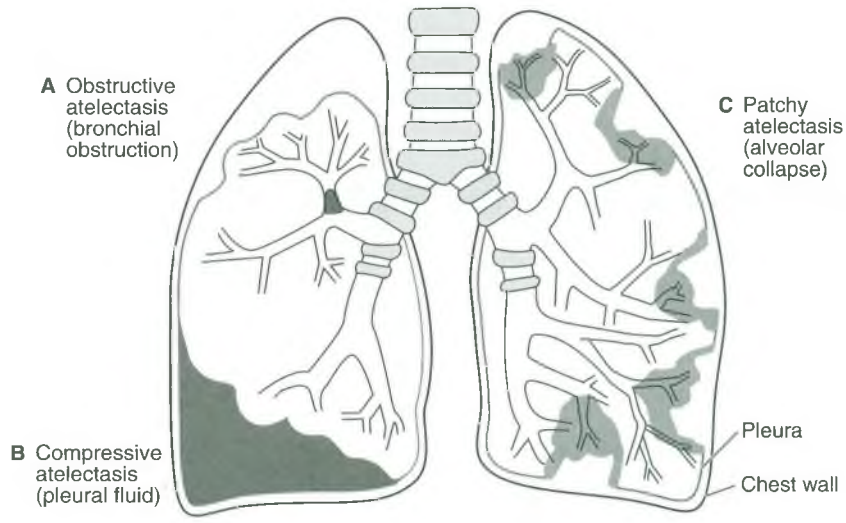


Figure 8-1.
Atelectasis. *A:* Obstructive atelectasis. *B:* Compressive atelectasis. *C:* Patchy atelectasis.

tem. Their blood supply is direct from the aorta or its branches. **Intralobar** sequestrations are located in the lung, whereas **extralobar** sequestrations can be found anywhere in the thorax, including the mediastinum. These lesions usually present as pulmonary masses resembling neoplasms.

MECHANICAL OBSTRUCTION

Atelectasis represents airless lung parenchyma due to incomplete expansion of the lungs or collapse of previously inflated lungs. Atelectasis of premature infants is a result of incomplete expansion of lungs due to inadequate pulmonary surfactant production. There are three main forms of atelectasis in adults (Fig. 8-1):

- **Obstructive atelectasis** results from complete obstruction of an airway, with subsequent resorption of air from that lung segment. Blood flow remains normal. Bronchi can be obstructed by tumors, foreign bodies, excess secretions and spasm of bronchi (e.g., as in asthma), or inflammatory exudates in airways (e.g., as in bronchitis or bronchiolitis).
- **Compressive atelectasis** results from the external compression of the lungs with pleural fluid (e.g., such as transudate or exudate), air (e.g., as in pneumothorax), or solid tissue (e.g., pleural tumors). Ascites or tumors in the peritoneal cavity may elevate the diaphragm and cause atelectasis of the lower lobes. Lung com-

pression by pleural transudate due to heart failure is the most common cause of hydrothorax and can be recognized by radiography, which shows a typical shift of the mediastinum to the other side.

- **Patchy atelectasis** is a consequence of incomplete expansion and focal collapse of alveoli in the lungs of premature infants. It is related to pulmonary immaturity and the inability of fetal surfactant to keep the alveoli open.

CIRCULATORY DISORDERS

Pulmonary Edema

Pulmonary edema represents the most common feature of left-sided heart failure. At autopsy, the lungs are heavy and wet. Frothy fluid oozes from the cut surface. Histologically, there is accumulation of proteinaceous fluid in the alveoli. Because of congestion, the capillaries are dilated and some blood oozes into the alveoli. In long-standing cases, macrophages bearing hemosiderin pigment (heart failure cells) are seen in the alveoli, which have thickened septa (brown induration).

Adult Respiratory Distress Syndrome

Adult respiratory distress syndrome (ARDS) is a syndrome characterized by **rapid onset of respiratory insufficiency**, marked by severe dyspnea, cyanosis, and hypoxia refractory to oxygen therapy. It results from a variety of underlying conditions that can be classified into two groups: **direct alveolar cell injury** caused by pulmonary infections, inhalation of irritant gases, and aspiration of gastric contents or foreign material; **capillary damage** caused by systemic diseases such as sepsis or shock, or by metabolic diseases that cause diffuse capillary damage. All cases of ARDS show severe edema. The edema fluid is rich in fibrin, which is deposited along the damaged alveolar lining in the form of hyaline membranes. ARDS has high mortality. Pulmonary fibrosis is found in those who survive. The most important causes of ARDS are listed in Table 8-1.

Pulmonary Embolism

Occlusion of the pulmonary artery or its branches by emboli (≤95% are from thrombi in the deep veins of the legs) occurs in several forms:

- **Massive occlusion** of the pulmonary artery (saddle embolism) is usually lethal.

TABLE 8-1.
Common Causes of Adult Respiratory Distress Syndrome

- Shock
  - Septic
  - Hypovolemic
  - Traumatic
  - Cardiac
- Aspiration or inhalation
  - Gastric contents
  - Drowning
  - Smoke and fumes
- Drugs and toxins
  - Heroin overdose
  - Cytotoxic and anticancer drugs
  - Paraquat
- Metabolic disorders
  - Acute pancreatitis
  - Renal failure
  - Diabetic ketoacidosis

- **Small pulmonary solitary emboli** may cause infarcts and hemoptysis. Many of these are asymptomatic.
- **Repeated "showers" of multiple small emboli** occlude branches of pulmonary artery and cause pulmonary hypertension.

The diagnosis of pulmonary embolism is difficult. Infarcts are seen by chest radiography only 12 to 36 hours postocclusion. Elevation of lactate dehydrogenase in serum is seen with large pulmonary embolisms. Ventilation-perfusion scans are of value but complex to perform. Pulmonary angiography is the definitive procedure for establishing a diagnosis. Nonfatal acute emboli can resolve via fibrinolysis. Multiple unresolved pulmonary embolism can lead to pulmonary hypertension or chronic cor pulmonale.

Pulmonary Hypertension

Pulmonary hypertension can be **primary** (idiopathic) or **secondary** to chronic obstructive pulmonary disease (e.g., emphysema) or interstitial lung diseases. In addition, recurrent pulmonary emboli, congenital heart diseases with left-to-right shunts, left-sided heart failure, mitral stenosis, or insufficiency may cause pulmonary congestion and hypertension. In all of these diseases, pulmonary arteri-

oles and small arteries show medial hypertrophy and intimal fibrosis. The extent of vessel wall thickening and luminal narrowing can be graded from I to VI in histology sections.

The primary form of pulmonary hypertension is typically found in women aged 20 to 40 years, whereas the secondary form occurs in older people. The clinical presentation is dyspnea, fatigue, and, to a lesser degree, angina-like chest pain. With time, the dyspnea becomes more severe. Cor pulmonale with cyanosis, pulmonary thrombosis, and bouts of pneumonia are common in advanced cases. Treatment is with vasodilators and antithrombotic drugs, but it is most often unsuccessful.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) refers to a group of diseases caused by recurrent airflow obstruction. The most important among these diseases are emphysema and chronic bronchitis. Patients with COPD exhibit increased pulmonary resistance and limited maximal expiratory air flow rates during forced expiration. This can be caused by narrowing of airways, seen in chronic bronchitis, or loss of elastic recoil, seen in emphysema.

Emphysema

Emphysema is characterized by abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, with destruction of their walls but without fibrosis. The most severe form is found in male smokers in the fifth to eighth decades. Emphysema may complicate chronic bronchitis. In a familial form, emphysema has been linked to a hereditary deficiency of α_1-antitrypsin.

Pathologically, there are four types of emphysema (Fig. 8-2):

- **Centrilobular emphysema** involves the respiratory bronchioles, sparing the distal alveoli. It is most common in the upper lobes, and is most often associated with smoking. Inflammation is observed around bronchi and bronchioles, and abundant black pigment is noted in their walls.
- **Panlobular emphysema** involves the entire acinus including the respiratory bronchiole, alveolar duct, and alveoli. It occurs in the lower lobes on the anterior margins of the lungs and is most severe at the bases. Emphysema caused by α_1-antitrypsin deficiency presents in this form.
- **Paraseptal emphysema** spares the proximal portion of the acinus and is predominant in the distal part of the respiratory unit. It is located next to the pleura and at the lobule margins. In

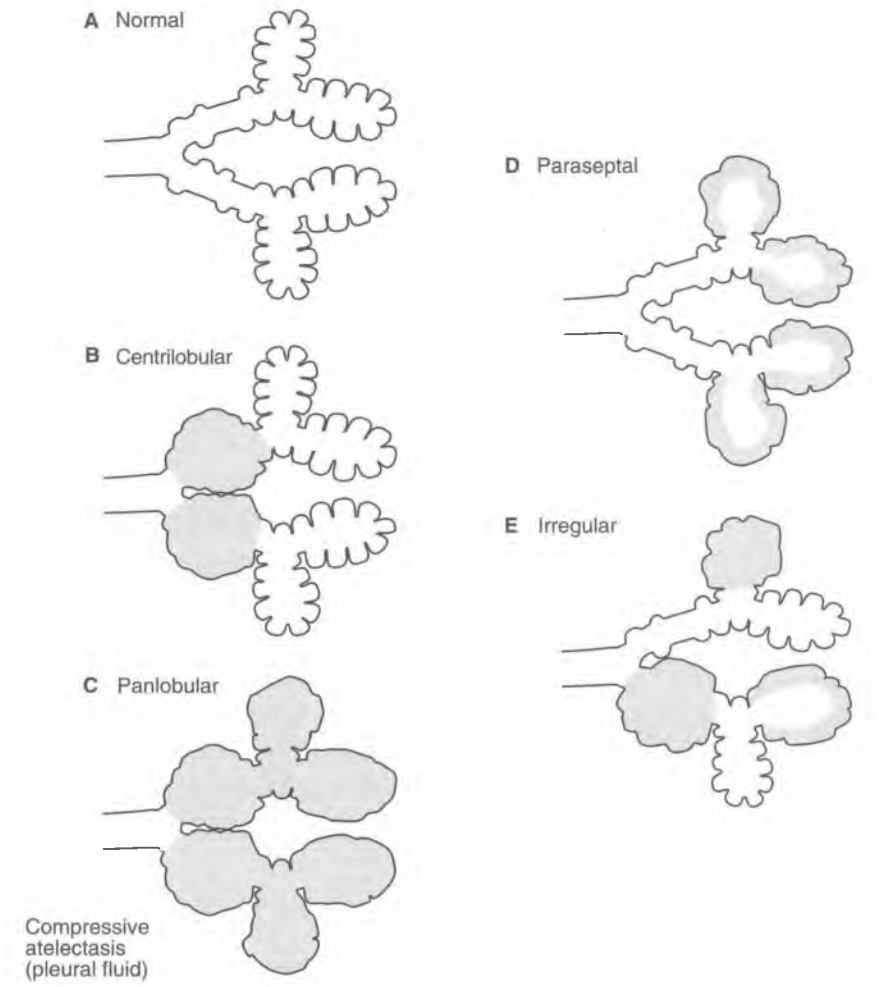


Figure 8-2.
Emphysema. *A:* Normal acinus. *B:* Centrilobular emphysema. *C:* Panlobular emphysema. *D:* Paraseptal emphysema. *E:* Irregular emphysema.

addition, it is found adjacent to regions of fibrosis or scarring. It may be responsible for some cases of spontaneous pneumothorax in young adults.

- **Irregular emphysema** is associated with irregular involvement of the acinus and is the most common form of emphysema. It is most often associated with scarring caused by other lung diseases. It is often limited to small parts of the lung and is thus asymptomatic.

Clinical symptoms of emphysema appear only if more than one-third of each lung has been destroyed. Dyspnea, which develops insidiously, is usually mild and is the first and most consistent sign. More variable signs include wheezing and coughing. Weight loss is common and may be severe. The patients are often barrel-chested but appear well oxygenated. The pulmonary function test results are not diagnostic—the most consistent finding is prolonged forced expiration.

Chronic Bronchitis

Chronic bronchitis is defined clinically as a disease marked by persistent cough, with sputum production during at least 3 months and over a period of at least 2 consecutive years. Smoking, industrial fumes, and smog are the most important pathogenic factors. Cigarette smoking is by far the most prevalent cause. Chronic irritation by fumes and particles in tobacco smoke and superimposed infections cause hypersecretion of mucus throughout the tracheobronchial tree. Histologically, there is hypertrophy of mucus-secreting glands in the trachea and bronchi, which increases the ratio of the gland layer to the thickness of the wall (Reid index). In addition, there is bronchiolar narrowing due to goblet cell metaplasia and mucus plugging. Inflammation and fibrosis of the bronchial wall can extend into the alveoli and cause destruction or fibrosis of the lung parenchyma.

Clinically, the disease is characterized by **persistent cough** and **large amounts of sputum.** Long-standing complications include chronic dyspnea, loss of respiratory reserve, and diminution of respiratory functions resulting in hypercapnia, hypoxemia, and cyanosis. Cor pulmonale and right-sided heart failure are common. Over time, pulmonary infections become more common and more resistant to treatment. Dilatation of bronchi **(bronchiectasis)** or impaction of bronchioli with mucus and organizing inflammation **(bronchiolitis obliterans)** are common complications.

Emphysema and chronic bronchitis in most instances are related to cigarette smoking. As such, these two diseases share many clinical features. Patients who predominantly have emphysema are usually short of breath but well oxygenated ("pink puffers"), whereas those with chronic bronchitis are coughing continuously and cyanotic ("blue bloaters") (Table 8-2).

Bronchiectasis

Bronchiectasis is abnormal, irreversible dilatation of the bronchi and bronchioles in the presence of chronic infection and suppuration. It is a common **complication of chronic bronchitis,** but it can also result from bronchial obstruction caused by tumors and foreign bodies or necrotizing pneumonia. Diffuse bronchiectasis may be a complication of asthma or cystic fibrosis. It usually affects the lower lobes of the lungs bilaterally and is most severe in distal bronchi and bronchioles. Histologically, the dilated bronchi and bronchioli contain mucopurulent exudate, and their walls show chronic inflammation and peribronchial fibrosis. Clinically, bronchiectasis is characterized by **severe, persistent cough,** which becomes paroxysmal; dyspnea and fever; and copious foul-smelling sputum, often tinged with blood. Respiratory failure and cor pulmonale are the most important complications. Hematogenous spread of bacteria from the bronchiectasis may result in **sepsis and abscesses** in other organs. Amyloidosis is a less common complication.

TABLE 8-2.

Comparison of Patients with Chronic Obstructive Pulmonary Disease: Predominant Emphysema Versus Predominant Chronic Bronchitis

Features	Predominantly Emphysema	Predominantly Chronic Bronchitis
Appearance	"Pink puffer"	"Blue bloater"
Age	55–80 years	45–60 years
Symptoms		
Dyspnea	Mild, slowly progressive	Early onset, exacerbated during infection
Sputum production	Scant, mucus	Copious, purulent
Chest	Barrel-shaped, thin	Barrel-shaped
Weight loss	Prominent	Not evident
Findings		
Auscultation	No abnormal sounds	Rhonchi ("noisy chest")
Radiology	Hyperlucent lungs	Prominent bronchial tree and peribronchial fibrosis
	Small heart	Large heart
Bacterial culture results	Negative	Positive sputum

BRONCHIAL ASTHMA

Bronchial asthma is a disease marked by episodic airway narrowing caused by a hyperreactive response of the tracheobronchial tree to a variety of stimuli. There are two types of asthma:

- **Extrinsic asthma** is a type of allergy or hypersensitivity (atopic) reaction to specific allergens or environmental chemicals.
- **Intrinsic asthma** is induced by nonimmune mechanisms such as infections (especially respiratory viral infections), sensitivity to aspirin, or exercise.

Atopic (allergic) asthma triggered by **environmental antigens** (e.g., dusts, pollens, animal dander) is more common. It is a form of type I hypersensitivity reaction in which there is an immediate response followed by a late phase reaction. In the immediate response, the antigen reacts with IgE-coated mast cells, which release mediators such as histamine. Concomitantly, there is stimulation of subepithelial vagal receptors causing bronchial constriction. Collectively, these events generate a clinical picture that is characterized by bronchoconstriction, edema, mucus secretion, facial flushing, and occasionally even systemic symptoms such as hypotension in the late phase reaction, which occurs several hours later. The initial mast cell–mediated injury is amplified by neutrophils, eosinophils, and macrophages recruited to the bronchial

mucosa. It is mediated by substances such as leukotrienes, cytokines, and other substances released from these inflammatory cells. The nature of the allergen can be detected by skin tests. Serum IgE levels are elevated, and there is also eosinophilia.

Intrinsic nonatopic asthma is initiated most frequently by **respiratory viral infections** (e.g., rhinovirus, parainfluenza virus). It is thought to result from virally induced inflammation of the respiratory tract mucosa, which in turn reduces the threshold of the subepithelial vagal receptors to irritants. The attacks of bronchospasm can be induced by a variety of nonspecific stimuli such as cold, excessive emotional stress, or drugs. Serum levels of IgE are normal.

The principal lesions of asthma are found in the bronchi, which typically are full of mucus and inflamed. Histologically, the mucus contains shed epithelial cells, Curschmann spirals, eosinophils, and eosinophil granules in the form of Charcot-Leyden crystals. Other characteristic changes include thickening of bronchial subepithelial basement membrane, inflammatory infiltrates rich in eosinophils, edema of the bronchial walls, and hypertrophy of submucosal glands and muscles of the bronchial walls.

Clinically, asthma is characterized as **episodic attacks of coughing** producing a large amount of mucus. Complications include emphysema, chronic bronchitis, bronchiectasis, and pneumonia. Cor pulmonale with resulting heart failure can also occur. Autopsy findings in patients who die in status asthmaticus show overinflated lungs and occlusion of bronchi and bronchioles with thick mucus plugs.

OCCUPATIONAL LUNG DISEASES

Occupational lung diseases or **pneumoconioses** include diseases of the lung that result from inhalation of mineral dust, minute organic particles, and chemical fumes and vapors (Table 8-3).

The development of pneumoconiosis depends on several factors such as the amount of dust in ambient air, duration of exposure, and effectiveness of the patient's clearance mechanism. In addition, the size and shape of the particles play an important role. Particles of 1 to 5 μm are most dangerous because they can enter the bronchioles and air sacs and remain in their walls. Smaller particles are usually more soluble in respiratory fluids and therefore can reach toxic levels more rapidly. Larger particles promote fibrosis. Some particles such as quartz generate and react with free radicals or stimulate inflammatory cells to release mediators. The effect of agents such as asbestos is enhanced when combined with other irritants (e.g., smoking).

TABLE 8-3.
Occupational Lung Diseases (Pneumoconioses)

Disease	Noxious Inhalant	Profession at Risk
Caused by inorganic materials		
Coal workers' pneumoconiosis	Coal dust	Coal miners
Silicosis	Silica crystals	Sandblasters, miners, stonecutters
Asbestosis	Amphibole asbestos (crocidolite, amosite)	Miners, insulation workers, shipyard workers
Berylliosis	Beryllium	Aerospace and ceramic industries
Caused by organic dusts		
Farmer's lung	Moldy hay	Farming
Bagassosis	Moldy cane sugar	Paper industry
Bird-breeder's lung	Avian proteins	Farming
Caused by fumes		
Chronic bronchitis	Sulfur dioxide, ammonia	Chemical industry

Coal Workers' Pneumoconioses

Coal workers' pneumoconioses (CWP) occurs in several forms:

- **Asymptomatic anthracosis,** in which coal dust pigment accumulates with no cellular reaction
- **Simple CWP,** characterized by nodules of carbon-laden macrophages with minimal to no respiratory compromise
- **Complicated CWP or progressive massive fibrosis,** which develops over a long time and leads to pulmonary dysfunction

Clinically, most patients have only mild symptoms, but progressive massive fibrosis can be complicated by pulmonary hypertension and cor pulmonale. The incidence of tuberculosis, chronic bronchitis, and emphysema, even without cigarette smoking, is increased. Concurrence of CWP and rheumatoid arthritis is marked by the appearance of pulmonary nodules **(Caplan syndrome).** The lung nodules show fibrinoid necrosis. Confluent nodules may form cavitary lesions, resembling tuberculosis.

Silicosis

Silicosis is caused by the **inhalation of crystalline silicon dioxide** (silica). The initial lesions, localized in the upper lung lobes, consist of nodules of macrophages filled with silica crystals. Silica activates macrophages to release mediators that amplify tissue destruction and stimulate fibrosis. Typical nodules composed of concentric layers of collagen are formed. The nodules contain birefringent silica

crystals visible under polarized light. Coalescence of nodules leads to massive pulmonary fibrosis. Tuberculosis is yet another complication. Clinical features vary. Pulmonary function is generally normal or may be moderately compromised unless progressive massive fibrosis ensues. In progressive massive fibrosis, the lungs are compromised considerably, the patients are dyspneic, and the condition can progress on its own, even without additional exposure.

Asbestosis

Asbestosis results from the **inhalation of asbestos,** particularly the straight amphibole fibers. The curvilinear serpentine fibers, the most common form of asbestos such as chrysotiles, are also fibrogenic but less dangerous. Amphiboles can align themselves in the airstream, which carries them into deeper portions of lung. Fibers are taken up by macrophages, or they penetrate epithelial cells and arrive in the pulmonary interstitium where they induce fibrosis. Diffuse interstitial fibrosis is most prominent in the lower lung lobes. It commences around respiratory bronchioles and alveolar ducts and ultimately reaches the alveolar sacs. Subpleural fibrosis and hyaline pleural plaques are also common.

Microscopically, diffuse interstitial fibrosis predominates. The presence of golden brown, fusiform, beaded rods that consist of asbestos fibers coated with iron-containing protein (**asbestos bodies**) are of diagnostic significance.

Clinically, **dyspnea** is the most common symptom. It occurs 10 to 20 years after initial exposure and is progressive. Cough with sputum production intensifies as the disease progresses, but the disease may remain static for a long time. Cor pulmonale and congestive heart failure are found in advanced cases. Asbestosis is a risk factor for bronchogenic carcinoma, mesothelioma, and laryngeal carcinoma. Concomitant cigarette smoking increases the risk of bronchogenic carcinoma approximately 50 times.

INTERSTITIAL DISEASES OF UNCERTAIN ETIOLOGY

The lung can be affected by a number of diseases of which the etiology remains uncertain. In some cases, the clinical and pathologic findings suggest an immune pathogenesis, as in sarcoidosis and hypersensitivity pneumonitis. In other cases, the cause is obscure and the diseases are named descriptively, such as usual interstitial pneumonitis, desquamative interstitial pneumonitis, and pulmonary alveolar proteinosis.

Sarcoidosis

Sarcoidosis is an idiopathic disease thought to represent a type IV (cell-mediated) hypersensitivity reaction. It is characterized by the formation of **noncaseous granulomas** in the lungs, lymph nodes, spleen, liver, bone marrow, skin, eyes, and, to a lesser degree, other organs. Hilar lymphadenopathy, which is bilateral, or lung lesions are observed on chest radiography in the majority of cases. Histologically, the noncaseating granulomas are composed of epithelioid cells surrounded by a rim of lymphocytes. Laminated concretions containing calcium (Schaumann bodies) and stellate inclusions in giant cells (asteroid bodies) may be found but are not diagnostic of sarcoidosis.

Sarcoidosis is more common in women than in men. There is a much higher prevalence in African-Americans than in whites, and it is virtually nonexistent in Chinese and Southeast Asians. Clinically, it may be asymptomatic and only found as a bilateral hilar adenopathy on chest radiography, or it may present as peripheral lymphadenopathy, splenomegaly, or hepatomegaly. Lung disease causes shortness of breath, cough, chest pain, and hemoptysis. In addition, fever, fatigue, weight loss, anorexia, and night sweats are frequently reported. The vast majority of patients recover without any residues; a lesser number develop permanent loss of some pulmonary function, and there is approximately a 10% mortality. The majority of deaths result from progressive pulmonary fibrosis and cor pulmonale.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis occurs as an adverse reaction to **organic dust particles** in sensitized persons. The best known forms of hypersensitivity pneumonitis are farmer's lung, pigeon breeder's lung, air-conditioner lung, and byssinosis of textile workers. The lungs show signs of immune complex (type III) or cell-mediated (type IV) hypersensitivity reaction. Histologically, there is infiltration of alveolar septa with lymphocytes and macrophages or granuloma formation. Ultimately, pulmonary fibrosis develops.

Wegener Granulomatosis

Wegener granulomatosis is a disease presumably of immune origin that presents with a triad that includes upper and lower respiratory tract involvement and kidney disease. The lung shows arteritis, granulomas, and widespread necrosis.

Usual Interstitial Pneumonitis

Usual interstitial pneumonitis is also known as idiopathic pulmonary fibrosis **(Hamman-Rich syndrome),** or chronic interstitial pneumoni-

TABLE 8-4.
Factors Predisposing to Pneumonia

Mechanism	Cause	Feature
Airway obstruction	Tumor, foreign body	Accumulation of mucus
Cough reflex suppression	Brain injury, coma, anesthesia, alcoholism	Inadequate clearance of bacteria, aspiration of gastric contents
Ciliary activity suppression	Smoking, viral infection, Kartagener syndrome	Inadequate clearance, repeat infection typical
Phagocytic cell dysfunction	Alcohol, smoking	Predisposes to lobar pneumonia
Immunosuppression	Human immunodeficiency virus, cytotoxic drugs, lymphoma	Mixed flora (bacteria, virus, fungus)
Fluid in alveoli	Heart failure, shock, adult respiratory distress syndrome	Bacterial superinfection

tis. It is a condition characterized by diffuse interstitial inflammation and fibrosis. It is histologically similar to the pneumoconioses and other conditions causing interstitial fibrosis, except that it is not related to an identifiable cause. Most likely, it represents the end stage of many lung diseases in which pneumocyte type I injury is followed by pneumocyte type II hyperplasia, pulmonary edema, fibrin-rich hyaline membranes, and infiltration of alveolar septa with mononuclear inflammatory cells. The fibrin ultimately undergoes organization, giving way to fibrosis, which obliterates the alveoli and contributes to marked thickening of the alveolar septa. Ultimately, the lung is composed of fibrous tissue separating spaces lined by cuboidal or columnar epithelium **(honeycomb lung).** Hypoxemia and cyanosis are common in advanced cases. Pulmonary hypertension and cor pulmonale develop, and ultimately cardiac failure ensues.

PULMONARY INFECTIONS

Pulmonary infections **(pneumonia)** can be classified according to their etiology as bacterial, viral, and fungal. Pneumonia can be acute or chronic. Clinically, pneumonia is classified as **community acquired** or **hospital acquired** (nosocomial). Many factors that reduce pulmonary resistance to infection predispose to pneumonia (Table 8-4).

Histologically, pneumonias can be classified as **alveolar**, if the inflammation is marked by intra-alveolar exudation, or **interstitial**, if

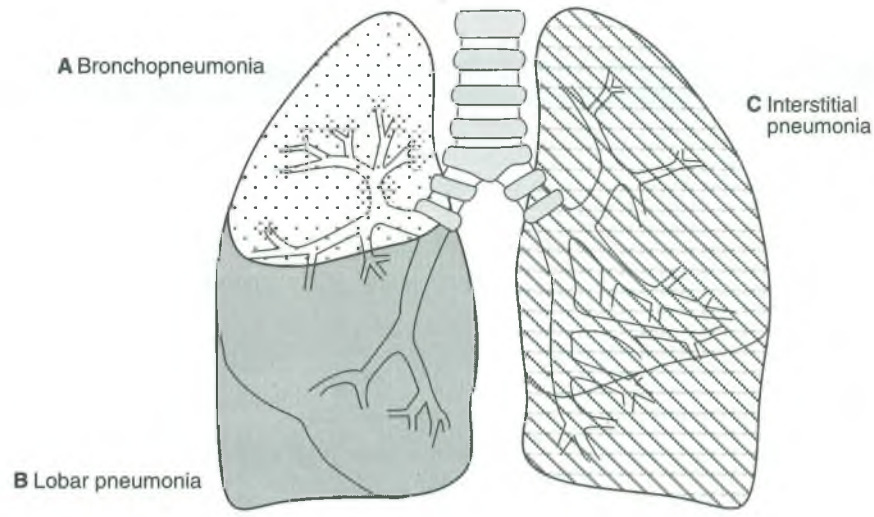


Figure 8-3.
Main forms of pneumonia. *A:* Bronchopneumonia. *B:* Lobar pneumonia. *C:* Interstitial pneumonia.

the inflammation is predominantly in the alveolar septa. Depending on the extent, pneumonia can be **lobar** if it involves the entire lobe, or **lobular** if limited to respiratory units surrounding individual bronchial branches. Lobular pneumonia is also called bronchopneumonia (Fig. 8-3). The most common causes of pneumonia are listed in Table 8-5.

Bronchopneumonia

Bronchopneumonia **(lobular pneumonia)** is characterized by a patchy distribution of consolidated areas in the lung parenchyma around bronchi and bronchioli. It is caused by **bacteria** and is most frequently found in infants, elderly or debilitated persons, or those with chronic heart or lung disease or cancer. Often, it is a complication of aspiration or pre-existent bacterial bronchitis. Histologically, bronchi, bronchioles, and adjacent alveoli contain a purulent exudate composed predominantly of neutrophils. Complications include spread into a lobar pneumonia, formation of abscesses or pleuritis, and formation of empyema. Fibrosis is a complication of long-standing or recurrent infections. Bacteremia and metastatic abscesses are found in severe or terminal cases.

Lobar Pneumonia

Lobar pneumonia is characterized by massive intra-alveolar exudation of neutrophils leading to consolidation of an entire lobe or the entire lung. The vast majority of cases are caused by *Streptococcus pneu-*

TABLE 8-5.
Most Common Causes of Pneumonia

Type	Etiology	Feature
Acute		
Bronchopneumonia	Bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae*)	Peribronchial intra-alveolar exudate associated with bronchitis (neutrophils)
Lobar pneumonia	Bacteria (*S. pneumoniae* most common)	Diffuse intra-alveolar exudate (neutrophils)
Interstitial pneumonia	Mycoplasma pneumoniae Viruses (influenza, respiratory syncytial virus, adenovirus) *Chlamydia psittaci* *Coxiella burnetii* (Q fever)	Diffuse interstitial infiltrates (lymphocytes and macrophages) Hyaline membranes
Chronic		
Recurrent/persistent	Bacteria (*Staphylococcus, Streptococcus, Pseudomonas*)	Peribronchial intra-alveolar exudate (neutrophils)
Granulomatous pneumonia	*Mycobacterium tuberculosis* Fungi (*Histoplasma capsulatum, Aspergillus, Cryptococcus, Candida albicans*)	Caseating granuloma, fibrosis, cavitation Necrotizing granuloma, fibrosis, cavitation
Lobar pneumonia	*Pneumocystis carinii*	Intra-alveolar proteinaceous material

moniae. Less common causes are *Klebsiella pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* and some gram-negative organisms such as *Pseudomonas aeruginosa* and *Proteus vulgaris.* The extent of the lesion depends on the virulence of the organism and the host's ability or inability to respond. **Immunocompromised persons** such as those suffering from acquired immunodeficiency syndrome (AIDS) and those afflicted by cancer or alcoholism are most susceptible.

Infections follow inhalation or aspiration of pathogens into the tracheobronchial tree and alveoli, where they spread from one alveolus to another via the pores of Kohn. Classically, four stages are recognized: (1) **congestion,** in which the lungs are heavy and wet due to hyperemia, alveolar fluid, neutrophils, and large numbers of bacteria; (2) **red hepatization,** in which the alveoli contain large numbers of red blood cells and a fibrinopurulent exudate; (3) **gray hepatization,** characterized by lysis of red blood cells and persistence of the fibrinopurulent exudate; and (4) **resolution,** the stage in which the exudate dissolves and is either reabsorbed or expectorated, upon which the lungs return to normal.

With antibiotic treatment, the four stages may be modified considerably and are rarely seen in a pure form today. Pleuritis, which is almost always present, usually resolves in parallel with the resolution of pneumonia, but if healing does not occur, fibrous adhesions between the visceral and parietal pleura remain.

Clinical features include cough, malaise, fever, and pleuritic pain and friction rubs due to pleuritis. A rusty, brown purulent sputum is typical. Complications are similar to those of bronchopneumonia. Mortality is high.

Interstitial Pneumonia

Interstitial pneumonitis is historically also called *primary atypical pneumonia* because it does not show the typical features of bacterial pneumonia. On radiography, the lungs show a reticular pattern of infiltration and no signs of patchy consolidation. It is caused by the viruses *Mycoplasma pneumoniae* or *Chlamydia psittaci* or rickettsiae such as *Coxiella burnetii.* It is characterized predominantly by interstitial inflammation, which may be bilateral or unilateral and often involves the whole lobe. Histologically, the lesions are characterized by a mononuclear inflammatory cell infiltrate in the alveolar septa. The alveoli may contain proteinaceous edematous fluid or hyaline membranes in response to alveolar cell damage. When the disease subsides, the alveoli are restored to normal.

The **clinical presentation varies** depending on the extent of infection, but in most instances the disease is mild. Cough is the most common symptom, but often fever, headache, muscle aches, and leg pain may be the only signs. Elevated cold agglutinins are found in those cases caused by *Mycoplasma.* Complications are rare and include superimposed bacterial pneumonia. Higher mortality can be expected in the elderly, especially during epidemics of influenza that occur almost every winter.

Pneumocystis carinii, a widespread **opportunist fungus,** may cause severe pneumonia in immunosuppressed persons and is the major cause of death in AIDS patients. The pneumonia is diffuse or patchy. The alveoli are filled with foamy material composed of proliferating organisms, proteinaceous material, and cellular debris. The interstitium may contain mononuclear cell infiltrates. Concomitant infections with bacteria, viruses, particularly cytomegalovirus, and fungi are frequently observed in AIDS patients. Diagnosis is based on identifying the organisms in bronchoalveolar lavage fluid, sputum, or transbronchial biopsy specimens stained with silver, Giemsa stain, or toluidine blue.

Lung Abscesses

Lung abscesses are destructive cavitary lesions filled with pus. They are generally caused by bacteria such as *S. aureus.* A variety of gram-negative organisms and anaerobic organisms generally found in the oral cavity can be frequently isolated from these lesions. The organisms are introduced by the following:

- **Aspiration of infected material** (e.g., aspiration of gastric contents after a binge of drinking alcohol, in comatose patients, or after surgery)
- **Massive pneumonia** caused by pus-forming bacteria such as *S. aureus*
- **Septic emboli** from thrombophlebitis or bacterial endocarditis of the tricuspid valve in drug addicts
- **Necrotic lung cancer** that undergoes necrosis and is secondarily infected
- **Spread of infection from adjacent organs** (e.g., esophagopulmonary fistula)

The abscesses may be solitary if caused by aspiration, or multiple and scattered in cases of septic emboli. On gross examination, they appear as softened areas in consolidated lung parenchyma or cavities filled with pus. Chronic abscesses have a fibrous capsule in all cases. The exudate consists predominantly of neutrophils.

The **clinical presentation** is characterized by cough and fever. Copious amounts of foul-smelling purulent or blood-stained sputum are found if the abscess drains into the bronchi. Chest pain and weight loss are also common. In chronic cases, clubbing of fingers and toes may be found. Diagnosis is confirmed by chest radiography, but occasionally bronchoscopy is needed to distinguish an abscess from necrotic cancer or tuberculosis and fungal lesions, such as aspergilloma. Complications include extension of the infection into the pleural cavity, hemorrhage, and the development of brain abscesses or meningitis due to septic emboli. Amyloidosis is a rare complication.

Pulmonary Tuberculosis

Pulmonary tuberculosis remains the major cause of morbidity and mortality, and every year approximately 70,000 new cases are registered in the United States. Typically, primary infection presents as the **Ghon complex.** It consists of a focus of lung infection, which appears as a consolidation of subpleural lung parenchyma and enlarged bronchi or as mediastinal lymph nodes draining the lymph from the lung lesion. In the majority of these cases, patients are asymptomatic, and the lesions heal spontaneously by fibrosis and calcification. **Secondary pulmonary tuberculosis** occurs due to reactivation of infection from microorganisms remaining in the lungs from the primary infection. This reactivation is more damaging than the primary disease. Most frequently, it presents as a consolidation within the lung apices; however, the hilus and regional lymph nodes can also be involved. The lesion can evolve into a large cavitating mass, or the mycobacteria can disseminate

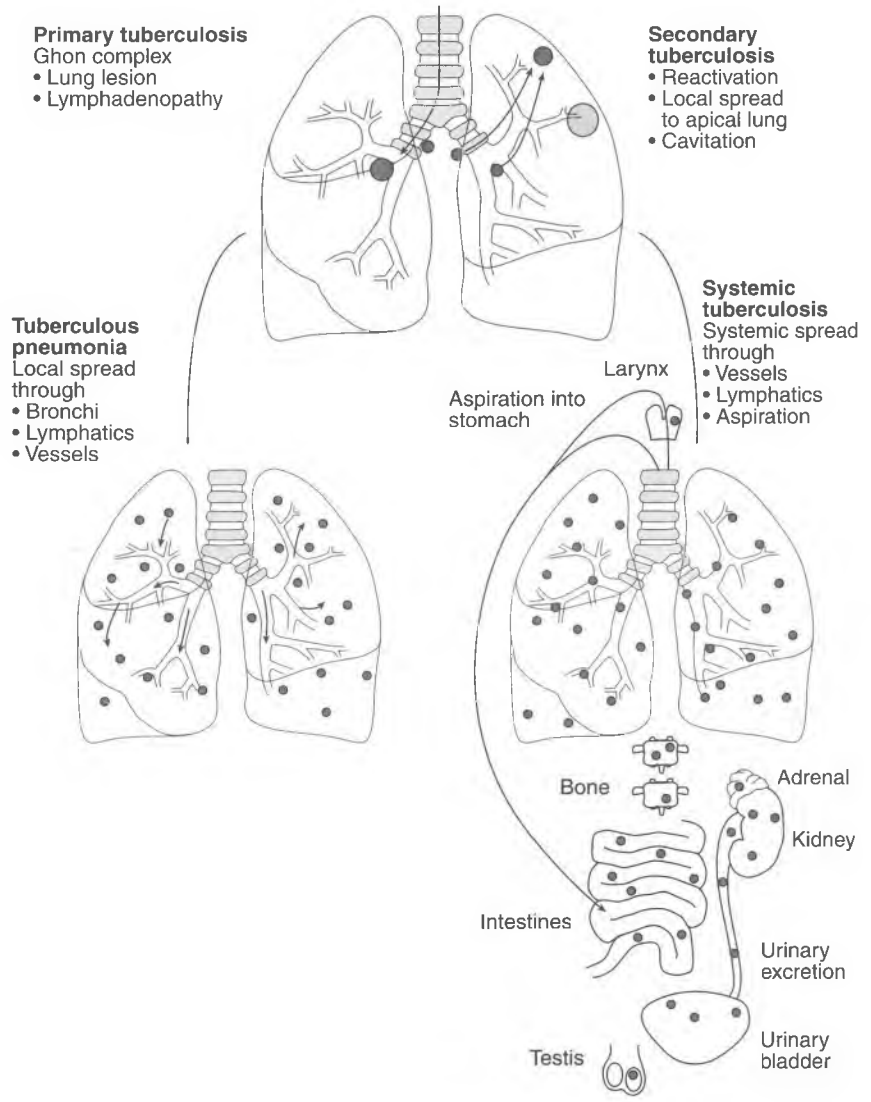


Figure 8-4.
Tuberculosis of the lung. Primary tuberculosis presents as the Ghon complex, consisting of a lung lesion and localized lymphadenopathy. Secondary tuberculosis represents reactivation of residual bacilli in the scarred Ghon complex, which usually spreads to the apical part of the lungs where the lesions may undergo cavitation. Massive local spread through the bronchi or pulmonary lymphatics and blood vessels leads to tuberculous pneumonia. Systemic dissemination leads to the spread of tuberculosis to other organs.

in the form of miliary tuberculosis throughout the lungs and to other organs. Tuberculous bronchopneumonia generally occurs in highly sensitized individuals (Fig. 8-4). All pulmonary lesions are histologically composed of caseating granulomas. Chronic lesions show fibrosis and calcification.

LUNG CARCINOMA

Carcinoma of the lung is one of the most common malignancies, vying for the leading position with prostate cancer in men and with breast cancer in women. It is the most frequent fatal malignancy. Typically, it occurs between the ages of 40 and 70 and has a peak incidence in the fifth and sixth decades. Approximately 90% to 95% of primary tumors in the lungs are **bronchogenic carcinomas.** The etiology of lung cancer has not been fully elucidated, but a strong positive epidemiologic link between tobacco smoking and lung cancer has been firmly established. Approximately 80% of lung cancers occur in smokers, who have a 50 to 60 times risk of developing lung cancer. There are also positive links with exposure to radiation, uranium, asbestos, and other industrial hazards. Those exposed to **asbestos** have a fivefold increased risk of developing lung cancer, the most frequent malignancy in asbestos workers. Genetic factors may play a pathogenetic role, but the significance of these factors is unclear.

Lung carcinomas can be classified as central or peripheral. **Central** carcinomas arising from major bronchi account for the majority of cases. **Peripheral** tumors originating from bronchioli (e.g., bronchioloalveolar carcinoma or peripheral adenocarcinoma) and those of the pleura and mesotheliomas are less common.

Histologically, four major histologic categories of bronchogenic carcinoma are recognized: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma.

Squamous cell carcinoma is most commonly found in men and women who **smoke**. It originates in the larger, central bronchi and spreads locally. Histologically, well-differentiated neoplasms produce keratin and cells form intercellular bridges, which are less prominent in less-differentiated tumors.

Adenocarcinoma is the most common type of lung cancer in **nonsmokers.** It is usually in peripheral locations and is sometimes associated with scars. Histologically, the well-differentiated neoplasms form glands composed of mucin-secreting cells. Adenocarcinomas spreading along the alveolar septa are called bronchioloalveolar carcinomas.

Small cell carcinoma is also linked to **smoking.** It is a highly malignant tumor composed of small cells that have round nuclei, which resemble lymphocytes, or spindle-shaped nuclei called oat cells. Because of rapid growth, tumors contain large areas of necrosis. Neurosecretory granules are found in the cytoplasm by electron microscopy. These neoplasms are associated with several paraneoplastic syndromes, and are the most common lung cancer associated with ectopic hormone production. Some of the more common hormones include antidiuretic hormone and adrenocorticotropin hormone. Small cell carcinoma is generally found at the hilus or central in the lung, and it is the most aggressive of lung tumors. It **metastasizes widely** and is thus not amenable to surgical excision. Chemotherapy may prolong life, but is rarely if ever curative.

TABLE 8-6.
Lung Tumors

Histologic Type	Frequency (%)	Location	Epidemiology	Special Features
Squamous cell carcinoma	25–40	Central, in the hilus	Associated with smoking	Grows rapidly and early metastases to local lymph nodes
Adenocarcinoma	25–40	Peripheral or central	Most common in nonsmokers	May be associated with scars
Bronchoalveolar carcinoma	5	Peripheral, in parenchyma	Equal gender distribution	Adenocarcinoma of terminal bronchioles spreading to alveoli
Small cell carcinoma	20–25	Central, in the hilus	Associated with cigarette smoking	Highly aggressive but responds to chemotherapy; 50% die in first year; paraneoplastic syndromes common
Large cell carcinoma	10–15	Central, in the hilus; may be peripheral	Associated with smoking, but not always	Cells undifferentiated squamous cell or adenocarcinoma
Mesothelioma	1–3	Pleural	Exposure to asbestos	50% die in first year
Carcinoid	1–2	Central, less often peripheral	Unrelated to smoking	90% survival

Large cell carcinoma is composed of large, polygonal cells with vesicular nuclei. Some variants include giant cells, clear cells, or spindle cells. It is an anaplastic carcinoma that probably represents undifferentiated squamous cell carcinomas or adenocarcinomas.

Carcinoid is a low-grade malignant tumor composed of neuroendocrine cells. It has an excellent prognosis if diagnosed early and resected before it has spread to distant sites.

Mesothelioma is a malignant tumor of the pleura. It is a highly malignant tumor, and most patients die within 2 years of diagnosis.

The salient features of common lung tumors are summarized in Table 8-6.

Clinical features may vary, but most bronchogenic carcinomas present with cough, weight loss, chest pain, and dyspnea, in descending order. The tumors metastasize by lymphatic and hematogenous routes. Metastases are widespread and in many instances occur early in the course of disease. In some instances, metastatic lesions are the initial presentation. Besides local lymph nodes, metastases are most often found in the liver, brain, and bone. For reasons that are obscure, the adrenal glands contain metastases in more than 50% of the cases.

Systemic effects include the paraneoplastic syndromes such as Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion, and hypercalcemia. Neoplasms in the apices in the superior pulmonary sulcus tend to invade neural structures around the trachea and cervical sympathetic plexuses. These tumors, called **Pancoast tumors,** present with pain in the distribution of the ulnar nerve and enophthalmos, ptosis, miosis, and anhidrosis **(Horner syndrome).**

Diagnosis of lung cancer can be made by radiography, cytologic examination of sputum, bronchial washings or brushings, and cytologic examination of fine-needle aspirates. The overall 5-year survival rate is approximately 10%.

Metastatic Tumors

Metastatic tumors are the most common malignancy in the lung. They arise from a variety of sources via both lymphatics and hematogenous routes. They are usually recognized as multiple discrete nodules scattered throughout all lobes. Some, however, confine themselves to peribronchiolar and perivascular tissue spaces. This may be a reflection of lymphatic rather than hematogenous spread. **Carcinomas,** including those arising in breast, colon, stomach, kidneys, ovaries, and uterus; **sarcomas,** including leiomyosarcomas and osteosarcomas; and **malignant melanomas** all metastasize to the lungs. Finally, esophageal carcinomas and mediastinal lymphomas may be found in the lungs as a result of contiguous growth.

Malignant Mesotheliomas

Malignant mesotheliomas are uncommon, but an increased incidence has been observed in individuals with heavy **asbestos exposure.** There does not appear to be an increase in the incidence of mesotheliomas in asbestos workers who smoke, contrasted to the risk with bronchogenic carcinomas. These neoplasms arise from either the visceral or parietal pleura and spread widely in the pleural space. They often invade thoracic structures and are associated with marked pleural effusion.

Histologically, tumors are often biphasic and composed of two cell types: spindle-shaped cells and cuboidal epithelial lining cells. Special stains, immunohistochemistry, or electron microscopy are often necessary to differentiate neoplasms from adenocarcinomas.

Clinical presentation includes chest pain, dyspnea, and recurrent pleural effusion. The lung is invaded directly, and there is often metastatic spread to hilar lymph nodes and other distant organs, including the liver. Fifty percent of all patients die within 12 months of diagnosis, and few survive more than 2 years.

Mesotheliomas are not unique to the pleura but may arise in the peritoneum, pericardium, or tunica vaginalis testis.

TABLE 8-7.
Pleural Diseases

Disease	Pathology (Material Filling the Pleural Space)	Most Common Cause
Hydrothorax	Transudate	Heart failure Viral infection
Pleuritis	Exudate	Infection
Empyema	Pus	Infection with pyogenic bacteria
Pneumothorax	Air	Trauma
Fibrothorax	Fibrosis	Chronic infection
Mesothelioma	Neoplasia	Asbestosis

DISEASES OF THE PLEURA

Pleura envelops the lungs and is typically involved by most diseases that affect the lungs. Infections **(pleuritis)** are typically found in association with pneumonia. **Pneumoconioses** such as asbestosis typically cause pleural fibrosis and pleural plaques. **Lung tumors** often spread to the pleura. The pleura is often involved by metastatic tumors, which are much more common than primary mesotheliomas of the pleura.

Pneumothorax is defined as air or gas in the pleural cavity. It can be spontaneous, traumatic, or therapeutic. Spontaneous pneumothorax can be a complication of any lung disease that ruptures alveoli. It is most commonly associated with emphysema, asthma, and tuberculosis. Traumatic pneumothorax is caused by a perforating chest injury, which may or may not penetrate the lung. Once the wound seals, resorption of the air in the pleural space is slow. **Spontaneous idiopathic pneumothorax** is a clinically important condition that occurs in young people. It results from rupture of small, peripheral subpleural blebs and subsides spontaneously. Recurrent attacks are common and disabling. Pneumothorax causes compression, collapse, and atelectasis of the lung and may produce respiratory distress.

Other important pleural diseases are listed in Table 8-7.

Chapter 9

Hematopoietic and Lymphoid System

The pathology of the hematopoietic and lymphoid system is presented under three major headings:

- **Disorders of red blood cells** (RBCs), which include anemias and polycythemias
- **Bleeding disorders**
- **Disorders of white blood cells** (WBCs), which include leukemias, lymphomas, multiple myeloma, and related disorders

ANEMIAS

Anemia is a reduction of the circulating RBC mass below normal limits as determined by the age and gender of the patient. Anemias can be classified according to their etiology (e.g., iron deficiency), morphology of RBCs (e.g., microcytic hypochromic), or pathogenesis (e.g., increased loss and rate of destruction or impaired red cell production) (Table 9-1 and Fig. 9-1).

Certain clinical signs and symptoms are common to all anemias irrespective of their etiology. Skin and mucosae are typically pale. A variety of functional symptoms may be present, most of which reflect a decreased supply of oxygen to vital organs (Fig. 9-2). Specific anemias have unique features. For example, jaundice is a feature of hemolytic anemia. In iron deficiency anemia, the nails are brittle, and there is atrophic glossitis. Megaloblastic anemia is associated with atrophic gastritis and neurologic symptoms. Splenomegaly is a feature of hereditary spherocytosis and autoimmune hemolytic anemias.

Anemias Due to Blood Loss

Acute blood loss (hemorrhage) results in hypovolemia, which evokes a shift of interstitial water to the vascular compartment, leading to hemo-

TABLE 9-1.
Pathogenetic Classification of Anemias

Pathogenetic Mechanism	Example
Blood loss	
Acute	Wound, rupture of aorta
Chronic	Peptic ulcer, cancer of gastrointestinal system, menstrual bleeding
Increased blood cell destruction	
Intrinsic red blood cell defect	Hereditary spherocytosis, sickle-cell disease, thalassemia
Extrinsic causes	Autoimmune hemolytic anemia, mechanical red blood cell injury, malaria
Impaired hematopoiesis	Iron deficiency, vitamin B_{12} deficiency, aplastic anemia

dilution and a decrease of the hematocrit level. The peripheral blood morphology remains unchanged. Erythropoietin production, stimulated by the reduced oxygen tension, leads to bone marrow hyperplasia and a release in completely mature RBCs (reticulocytes) into the circulation. The RBC count peaks approximately 7 days after massive hemorrhage. In well-nourished persons, blood loss is compensated easily.

Chronic blood loss leads to anemia when the blood loss exceeds the bone marrow's ability to replace the lost RBCs. In men, the most common cause is hemorrhage from the gastrointestinal tract (e.g., peptic ulcer, carcinoma of the colon). In women, the blood loss is most often related to uterine bleeding (e.g., heavy menstrual bleeding).

Hemolytic Anemias

Hemolytic anemias are characterized by destruction of RBCs and a release of hemoglobin from destroyed cells.

Hemolysis can be classified as intravascular or extravascular. **Extravascular hemolysis,** which occurs inside the fixed macrophage cells of the liver, spleen, bone marrow, and lymph nodes, is more common. **Intravascular hemolysis,** as the name implies, occurs inside blood vessels. In both forms of hemolysis, hemoglobin is released from the RBC, and its porphyrin part is transformed into bilirubin, which accounts for the jaundice in these patients. Bilirubin is excreted in bile. The iron from hemoglobin is stored as hemosiderin. In intravascular hemolysis, free hemoglobin is bound to haptoglobin, a transport protein that helps remove hemoglobin from circulation. During this process, the concentration is reduced

in the blood. Excess free hemoglobin **(hemoglobinemia)** is filtered in the kidney and appears in the urine **(hemoglobinuria).** In extravascular hemolysis, there is no hemoglobinemia or hemoglobinuria. Instead, there is usually splenomegaly and hepatomegaly.

Hemolytic anemias can be classified as hereditary or acquired. Hereditary causes that usually produce changes in the reticulocyte morphology are classified as **intrinsic,** whereas the acquired forms of anemia have **extrinsic** causes, such as toxins and antibodies, or infectious agents, such as malaria.

Inherited Intracorpuscular Abnormalities of Red Blood Cells

Hereditary spherocytosis is an autosomal dominant condition, most frequently found in people of Northern European extraction. It is caused by a defect in the cytoskeleton of RBCs, which leads to membrane instability. Spectrin deficiency is the most common cause. Because of this defect, cells are spheroidal (rather than concave), less deformable, and subject to sequestration and phagocytosis in the spleen. In blood smears, the cells appear round, abnormally small, and lack central pallor. **Clinically,** this disease is characterized by anemia, splenomegaly, and jaundice. Diagnosis is based on family history and the presence of spherocytes in the peripheral blood. These spherocytes show increased osmotic fragility. Splenectomy is usually beneficial.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a sex-linked inherited enzyme deficiency characterized by abnormalities of the hexose monophosphate shunt or glutathione metabolism, essential for inactivating oxidants. Although there are many variants, two forms of the disease, designated G6PD A and G6PD Mediterranean, are the most common causes of significant hemolysis. Approximately 10% of African-Americans have G6PD A. The Mediterranean form, which is more severe because of lower levels of G6PD, is most often found in populations of the Middle East. The hemolytic crises are triggered in older RBCs by certain drugs, such as primaquine, sulfonamides, and nitrofurans, or in some instances by infections. **Clinically,** acute intravascular hemolysis with jaundice, hemoglobinemia, and hemoglobinuria occurs within 2 to 3 days after the triggering event. The disease has a self-limited course because only older RBCs are affected.

Sickle cell anemia is an inherited hemoglobinopathy characterized by a structurally abnormal hemoglobin (HbS). The condition is characterized by chronic hemolytic anemia and episodic sickling of cells in small blood vessels, which may become occluded.

Hemoglobin is a tetramer of four globin chains divided into two α and two β pairs. Clinically significant sickle cell anemia occurs as a result of a point mutation in the β-globin chain. The mutation substitutes a valine for glutamic acid in the sixth position. In heterozygotes (~8% of African-Americans), approximately 40% of the hemoglobin is HbS, whereas in homozygotes, 100% of the hemoglobin is HbS. When HbS is deoxygenated, it aggregates and polymerizes, leading to distortion of RBCs. Initially, with oxygenation, the RBCs resume their normal shape; however, with repeated bouts of sickling, membrane damage occurs so

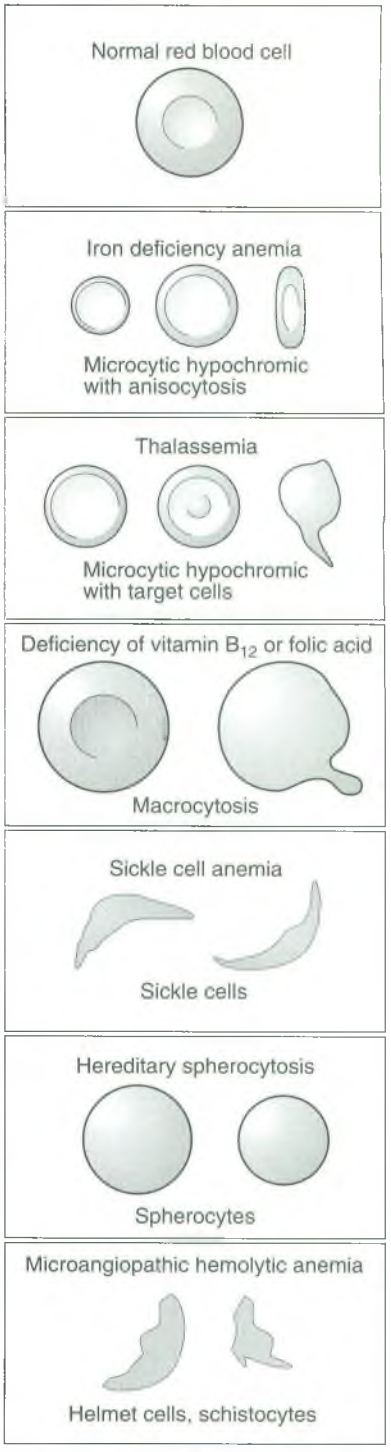


Figure 9-1.
Morphology of red blood cells in some forms of anemia.

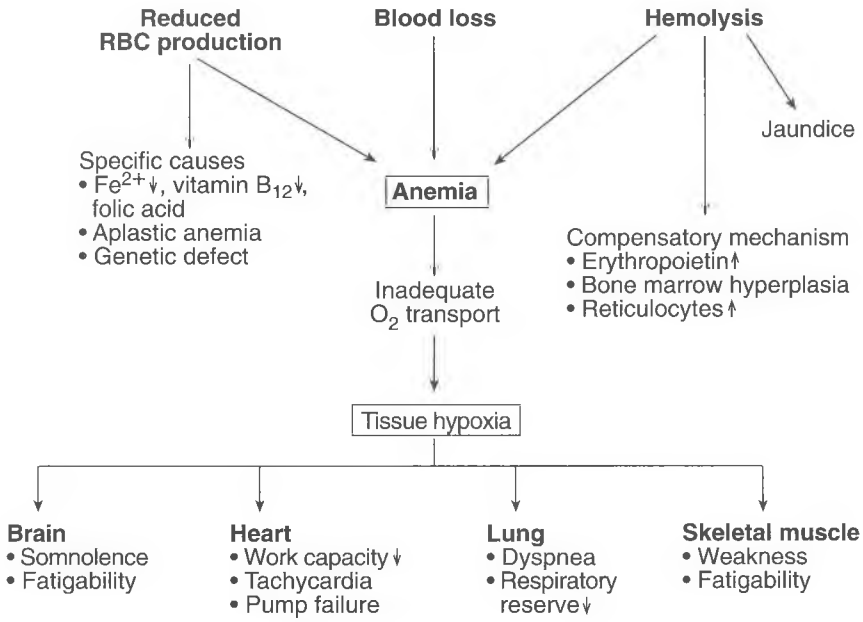


Figure 9-2.
Pathology and symptoms and signs of anemia. (RBC, red blood cell.)

that the sickle-shaped RBCs remain in circulation. In addition, sickled cells lose potassium and water and gain calcium, which leads to increased density and increased hemoglobin concentration. Irreversibly sickled cells hemolyze inside the blood vessels. More often, they are sequestered in the spleen and hemolyzed intracellularly. Microvascular occlusions with sickled cells also occur, leading to thrombosis.

In addition to the classic signs and symptoms of anemia, there is bone marrow hyperplasia, which may lead to bone resorption and even formation of reactive new bone. Extramedullary hematopoiesis is common in the liver and spleen. Histologically, there is congestion of splenic red pulp, with thrombosis and infarction leading to scarring **(autosplenectomy).** Infarctions are also seen in the bones, brain, kidney, liver, and retina (Fig. 9-3).

Diagnosis is made on the basis of clinical data and finding sickle cells in peripheral blood smears and hemoglobin electrophoresis, which is used to demonstrate the abnormal hemoglobin.

Clinical features result from ischemic changes caused by sickling. Cerebral ischemia has most serious consequences, but bone infarcts, skin ulcerations, and other pathologic findings contribute to the debilitating effects of this disease.

Sickle cell anemia has high mortality, and many patients die of overwhelming infections within the first 3 years of life, but some may live until the fourth or fifth decades.

Hemolysis Caused by Extrinsic Factors

Hemolysis of structurally normal RBCs may be mediated by antibodies, mechanical injury, infections such as malaria or bartonellosis, or toxins

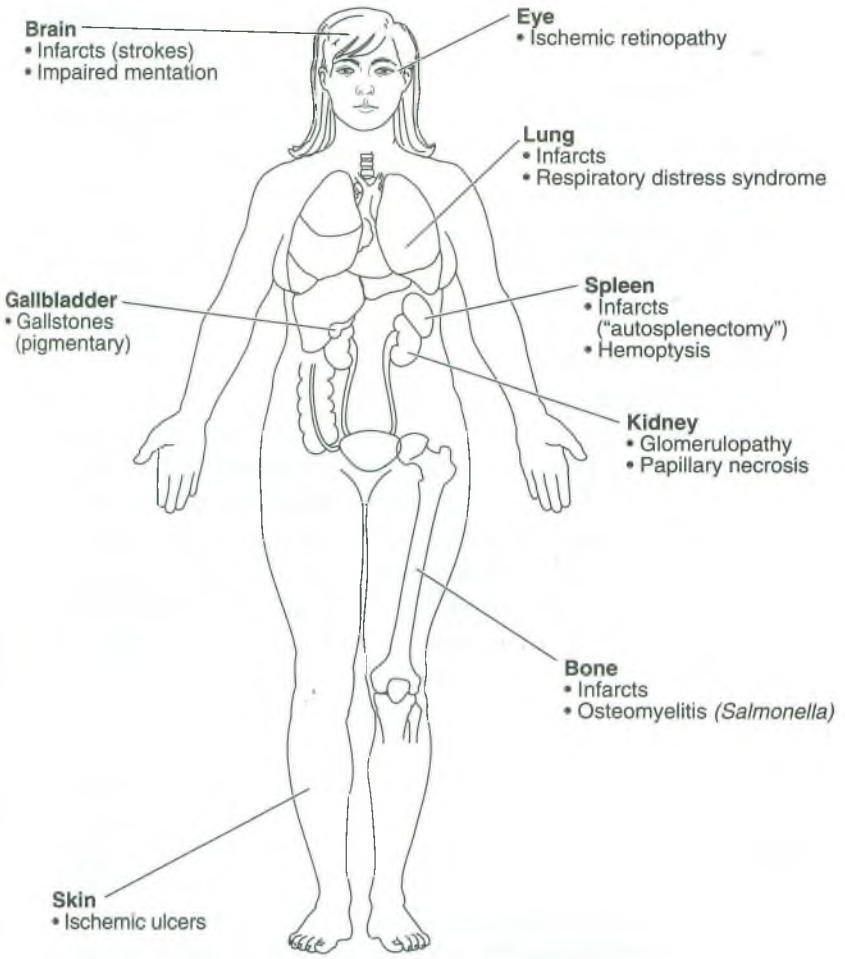


Figure 9-3.
Pathology and symptoms and signs of sickle cell anemia.

such as lead. The antibody-mediated hemolytic anemias are divided into three groups in accordance with the nature of the antibody involved (Coombs antiglobulin test) and the temperature at which the antibodies are most active.

Warm antibody type hemolytic anemia is the most common form of immune hemolytic anemia. It occurs in an idiopathic form, but it also may be seen secondary to neoplastic diseases such as lymphomas and leukemias; drugs such as penicillin, phenacetin, and α-methyldopa; and autoimmune disorders, especially systemic lupus erythematosus. The antibodies are IgG, usually do not fix complement, and are active at 37°C. There is no intravascular hemolysis. Rather, antibody-coated cells are attached to the Fc receptor of monocytes and splenic macrophages, whereupon they become spheroidal. The spherocytes are then sequestered in the spleen, resulting in moderate-to-severe splenomegaly.

Cold agglutinin type immune hemolytic anemias are caused by IgM antibodies that bind to red cells most avidly at 0° to 4°C. They occur **acutely** during recovery from acute mycoplasma infections

and infectious mononucleosis. The condition is self-limiting and rarely produces marked hemolysis. A **chronic form** occurs idiopathically or in conjunction with certain lymphoproliferative disorders. These IgM antibodies are usually monoclonal. Hemolysis occurs typically in vessels of the distal parts of extremities because the lower temperature promotes agglutination of antibody-coated RBCs and fixing of complement. Although the antibodies are released from the RBC and return to the central body parts when a temperature of 37°C is reached, C3, and especially C3b, remain bound to many cells, leaving them susceptible to phagocytosis by macrophages in the liver and spleen. Besides the signs of hemolysis, which are usually evident, the agglutination of RBCs in peripheral vessels can also lead to microvascular occlusion, resulting in Raynaud phenomenon.

Cold hemolysin hemolytic anemias are caused by IgG antibodies that bind to red cells, fix complement at a low temperature, and cause hemolysis when the temperature is elevated to 30°C. The autoantibodies are directed against P blood group antigens and associated with cold hemolysis. This results in **paroxysmal cold hemoglobinuria,** which is characterized by acute intermittent massive hemolysis, often with hemoglobinuria in patients exposed to cold. Hemolysis of this type may be a complication of viral diseases such as measles and mumps.

Transfusion reactions and erythroblastosis fetalis are hemolytic disorders caused by antibodies reacting with blood group antigens.

Traumatic hemolytic anemia can be induced in a variety of mechanical devices such as the extracorporeal circulation machine. Clinically important hemolysis is observed in patients who have heart valve prostheses. **Microangiopathic hemolytic anemias** observed in thrombotic thrombocytopenic purpura, disseminated intravascular coagulation (DIC), hemolytic uremic syndrome, or malignant hypertension are also characterized by intravascular hemolysis, which occurs when RBCs pass through microvasculature (arterioles and capillaries) partially occluded by thrombi. The RBCs either rupture or assume various abnormal shapes (e.g., burr cells, helmet cells, schistocytes), which makes them more susceptible to hemolysis.

Impaired Red Cell Production

These anemias are produced by conditions that either interfere with the proliferation or differentiation of stem cells or in which there is a deficiency of essential ingredients such as vitamin B_{12} or iron.

Aplastic Anemia

Aplastic anemia is a term used for **bone marrow failure** caused by a destruction or suppression of multipotent myeloid stem cells. This entails cessation or markedly diminished production and release of mature descendants of all three major hematopoietic lines (RBCs, granulocytes, and thrombocytes).

Aplastic anemia may be either inherited (Fanconi anemia), which is rare, or acquired. The acquired form is usually without an obvious cause (i.e., idiopathic). In addition, however, aplastic anemia may be caused by drugs and chemicals such as alkylating agents, antimetabolites, chloramphenicol, and organic arsenicals; physical agents such as radiation; and viral infections such as hepatitis virus C, cytomegalovirus, Epstein-Barr virus, and varicella zoster virus.

Aplastic anemia typically shows **bone marrow changes.** The marrow is hypocellular and composed of fibrous stroma or contains a few lymphocytes and plasma cells, which populate the empty marrow spaces. Few or no erythroid cells, myeloid cells, or megakaryocytes are observed.

Clinically, aplastic anemia may occur at any age and in either gender. Signs and symptoms vary, depending on what cell lines are most affected. For example, infections are prevalent if leukocytes are depleted first **(agranulocytosis)** and excessive bleeding is observed with **thrombocytopenia.** Pallor and weakness are associated with decreased RBC counts. The remaining red cells are normocytic and normochromic, and there is no reticulocytosis, indicating that erythropoiesis is suppressed. Diagnosis of aplastic anemia is based on examining the peripheral blood, which shows low RBC, WBC, and platelet counts, and bone marrow, which shows depletion of all hematopoietic cell precursors.

Myelophthisic Anemia

Myelophthisic anemia results from the replacement of hematopoietic cells in the bone marrow by other cells. Most often, it is caused by metastatic carcinoma or leukemia. Pancytopenia may even result from focal replacement of the bone marrow. It has been postulated that tumor cells disrupt the hematopoietic microenvironment or secrete cytokines that inhibit hematopoiesis.

Megaloblastic Anemia

Megaloblastic (pernicious) anemia develops due to a deficiency of either vitamin B_{12} or folate. It may result from inadequate intake in the diet, abnormal absorption, increased requirement, or drugs that interfere with the use of these essential nutrients (Table 9-2).

Malabsorption of vitamin B_{12} is most often related to atrophic gastritis, an immunologic disease characterized by a loss of gastric parietal cells, which secrete intrinsic factor. Without intrinsic factor, vitamin B_{12} cannot be absorbed in the small intestine.

Folic acid deficiency results from inadequate intake or impaired absorption. Dietary deficiency is encountered in alcoholics, the very old, or the indigent poor. Diseases of the small intestine (e.g., sprue, lymphoma, Crohn disease) interfere with the absorption of both vitamin B_{12} and folate.

Lack of vitamin B_{12} and folic acid affects DNA synthesis, but the synthesis of RNA and proteins is unaffected. Thus, cytoplasm of RBC

TABLE 9-2.
Causes of Megaloblastic Anemia

Pathogenetic Mechanism	Vitamin B_{12}	Folic Acid
Inadequate intake	Rare; only in strict vegetarians	Alcoholism, malnutrition
Impaired absorption	Atrophic gastritis, total gastrectomy, Crohn disease, resection of terminal ileum	Sprue, disease of the small intestine
Intraluminal consumption in the small intestine	Bacterial overgrowth (blind loop syndromes), *Diphyllobothrium latum*	
Increased demand		Pregnancy, neoplastic states
Drugs	Para-aminosalicylic acid	Methotrexate, hydantoins

precursors expands without concomitant nuclear changes. Instead of normoblasts, the normal RBC precursors, the bone marrow contains megaloblasts. The peripheral blood contains fewer RBCs, which are larger than normal (macrocytic). Precursors of neutrophils and megakaryocytes are also larger than normal, and the neutrophils are hypersegmented. Premature destruction of granulocytes and platelet precursors leads to leukopenia and thrombocytopenia.

In addition to megaloblastic macrocytic anemia and atrophic gastritis, patients also have **atrophic glossitis.** The spinal cord shows **myelin degeneration** of the dorsal and lateral tracts, which causes paresthesias in fingers and toes. The loss of proprioception, sense of vibration, and sense of position affects walking and other movements. Untreated cases develop ataxia. Brain changes may cause somnolence, altered sense of smell and taste, and even affect mentation. These patients are at increased risk of gastric cancer and cardiac failure due to hypoxia. Folate deficiency produces identical hematologic findings, but without atrophic gastritis and spinal cord and cerebral changes. Megaloblastic anemia responds well to treatment with vitamin B_{12} or folate.

Thalassemia Syndromes

The thalassemia syndromes are characterized by a lack of or decreased synthesis of either the α or β chains of hemoglobin A, which has two α

and two β chains ($\alpha_2\beta_2$). β-Thalassemia is characterized by reduced (β^+ category) or absent (β^- category) synthesis of the β-globin chain in the presence of normal α-chain synthesis. α-Thalassemia is a defect of α-globin chain synthesis. The defect in globin chain synthesis impedes hemoglobin synthesis as well as erythropoiesis in general. RBCs containing the defective hemoglobin hemolyze at an accelerated rate. Morphologically, all thalassemias are classified as microcytic hypochromic with anisocytosis. Abnormal hemoglobin often precipitates, which results in the formation of target cells.

Several clinical syndromes are recognized. **Thalassemia major,** a severe form of β-thalassemia, is found in patients who are homozygous for the β-globin gene mutation. The incidence is highest in Mediterranean countries and parts of Africa and Southeast Asia. In the United States, immigrants from these regions have the highest incidence. **Thalassemia intermedia** is a less severe form found in heterozygotes, whereas **thalassemia minor** is usually asymptomatic.

The **α-thalassemias** are also a heterogenous group, but the terminology differs from the terms used for β-thalassemias. Because the normal genotype has four α genes, the severity of the various clinical syndromes varies, depending on how many (one, two, three, or all four) genes are affected. In general, however, the hemolytic anemia and ineffective erythropoiesis is less severe than that in β-thalassemias, except in the most severe form **(hydrops fetalis),** which is incompatible with life. Pathologic changes in thalassemia patients depend on the severity of the disease. In all cases, the bone marrow is hyperplastic, which may cause thinning of the bony cortex or reactive new bone formation. Splenomegaly and hepatomegaly result from erythrophagocytosis and extramedullary hematopoiesis. Hemosiderin accumulates in the spleen and liver, and secondary hemochromatosis may result from numerous transfusions, which these patients typically receive.

Iron Deficiency Anemia

Iron deficiency anemia is the most common form of anemia in the United States. Iron is an essential mineral, important for the synthesis of hemoglobin, myoglobin, and respiratory enzymes. The vast majority, however, is used in hemoglobin. Iron is stored in many organs, in particular in the parenchymal cells of the liver and in macrophages in the spleen, bone marrow, and skeletal muscles. It is stored as **ferritin,** a protein-iron complex that aggregates into granules of **hemosiderin.** A small amount of ferritin is found in the circulation; generally, it is a good indicator of whether iron storage pools are adequate. Iron is transported by **transferrin,** a glycoprotein that binds iron and normally is approximately one-third iron saturated. The saturation of transferrin is measured clinically as total iron-binding capacity (TIBC).

Iron is absorbed in the duodenum and to a lesser degree in the stomach, ileum, and colon. Dietary iron comes from heme sources such as hemoglobin, myoglobin, and other animal proteins and nonheme sources. Approximately 25% of heme iron and 1% to 2%

TABLE 9-3.
Causes of Iron Deficiency Anemia

Cause	Disease or Condition
Increased demand	Infancy and childhood Pregnancy
Inadequate intake	Dietary deficiency
Impaired absorption	Sprue Diarrhea Gastrectomy
Increased loss	Gastrointestinal bleeding Heavy menstrual bleeding Aspirin intake

of nonheme iron is absorbed. Iron balance is maintained through limiting absorption.

Iron deficiency results from inadequate intake, impaired absorption, increased demand, or chronic blood loss. Dietary deficiency is common in the elderly and poor. Impaired absorption is observed in sprue, chronic diarrhea, or after gastrectomy. Increased iron requirements are found in growing children and pregnant women. Iron deficiency due to excessive loss is seen in women with heavy menstrual bleeding, patients who have peptic ulcers, cancer of the gastrointestinal tract, or other diseases causing chronic bleeding (Table 9-3).

The pathologic and laboratory findings are typical. The bone marrow is characterized by an increased number of normoblasts and little stainable iron. The peripheral blood contains microcytic, hypochromic red cells, with marked anisocytosis. Serum iron and ferritin levels are low, TIBC is increased, and transferrin saturation calculated as iron/TIBC is <15% (normal, 30%). This form of anemia responds well to oral iron.

POLYCYTHEMIA

Polycythemia **(erythrocytosis)** refers to an increased concentration of RBCs in circulation. It can be *relative,* due to hemoconcentration caused by loss of plasma, or *absolute,* when the total RBC volume is increased. Absolute polycythemia may be *primary,* due to clonal neoplastic proliferation of myeloid stem cells (polycythemia rubra vera), or *secondary,* due to increased levels of erythropoietin (Table 9-4).

TABLE 9-4.
Forms of Polycythemia*

Type	Disease	Cause	Feature
Relative	Spurious polycythemia	Hemoconcentration	Normal red cell volume
Absolute			
Primary	Polycythemia rubra vera	Neoplasia	Epo decreased or normal
Secondary	Reactive polycythemia	Heart disease	Epo increased (regulated)
	Lung disease		
	High altitude		
	Tumors		Epo increased (unregulated)
	Renal cystic disease		

**Total red cell volume can be measured by ^{51}Cr uptake.*
Epo, erythropoietin in circulating blood.

Polycythemia rubra vera is a neoplastic disease considered to be one of the myelodysplastic syndromes. After an initial proliferative phase that lasts 2 to 6 years, the disease may stabilize for 4 to 6 years, finally transforming into leukemia or myelofibrosis. **Secondary polycythemia** evolves in response to hypoxia, as in high altitudes or in patients with chronic heart or lung disease. Alternatively, erythropoietin may be produced in an unregulated manner from renal tumors or renal tissue compressed by renal cysts in polycystic kidney disease.

Bleeding Disorders

Bleeding disorders (hemorrhagic diatheses) can be caused by abnormalities of vessel walls, platelets, or clotting factors.

Bleeding Disorders Caused by Abnormalities of Vessel Walls

Bleeding disorders resulting from abnormalities of vessel walls **(vascular purpura)** have many causes. **Infectious causes** include meningococcemia (Waterhouse-Friderichsen syndrome), measles, and rickettsioses. All forms of endotoxemia or septic shock may present with purpura. They usually damage vessel walls directly or through the initiation of DIC. **Structural defects** in the vascular wall are the underlying cause of bleeding in scurvy, the Ehlers-Danlos syndromes, and to some extent in the elderly whose tissues, including the blood vessels, undergo age-related atrophy. Corticosteroid treatment or Cushing syndrome also cause vessel wall weakening. **Hypersensitivity diseases** such as hypersensitivity vasculitis or **Henoch-Schönlein purpura** are characterized by deposits of immune complexes in the walls of small

TABLE 9-5.
Causes of Thrombocytopenia

Pathogenesis	Disease
Decreased platelet production	
Stem cell deficiency	Aplastic anemia
Myelophthisis	Leukemia, cancer metastasis to bones
Drug-induced suppression	Cytotoxic drugs
Infection	Human immunodeficiency virus infection, measles
Decreased platelet survival	
Immune mediated	Idiopathic thrombocytopenic purpura, systemic lupus erythematosus
Drugs	Heparin, quinidine
Microangiopathic/mechanical	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
Accelerated platelet removal	
Splenic pooling	Hypersplenism

vessels. Petechial bleeding occurs in the skin, gastrointestinal tract, kidney, and in many other organs.

Clinically, vascular purpura presents with petechiae or purpura of the skin and mucous membranes. There may be gastrointestinal bleeding, epistaxis, or menorrhagia. Larger hemorrhages in joints, muscles, and subperiosteum of bones are less common. The platelet counts, bleeding times, and coagulation times are all normal.

Bleeding Disorders Related to Thrombocytopenia

Thrombocytopenia is an important cause of generalized bleeding. Normally, the blood contains 150,000 to 300,000 platelets per μl. Thrombocytopenia is defined when counts decrease below 100,000/μl; however, clinical evidence of **post-traumatic bleeding** does not occur until the counts are in the range of 20,000 to 50,000/μl. **Spontaneous bleeding** does not occur until platelet counts decrease <20,000/μl.

The major causes of thrombocytopenia are grouped in three major categories: decreased platelet production, decreased platelet survival, and increased platelet sequestration (Table 9-5). These disturbances occur in many systemic diseases, but in some cases thrombocytopenia is the only abnormality.

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are destroyed by antiplatelet antibodies. It occurs in two forms:

- **Acute ITP** is a self-limited bleeding disorder of children. It usually occurs after an infection and has a self-limited course.

- **Chronic ITP** affects adults, usually women in the 20- to 40-year age group. The target antigens of ITP appear to be two glycoproteins found on the surface of platelets IIb/IIIa and Ib. Platelets opsonized by autoantibodies are phagocytized by phagocytic cells in the spleen and liver.

Morphologically, the spleen is normal in size, but there is congestion of sinusoids and enlargement of follicles with prominent germinal centers. The bone marrow appears normal, but there are increased numbers of megakaryocytes, some of which are immature. Large platelets (megathrombocytes) are seen on peripheral blood smears due to accelerated thrombopoiesis.

Clinically, ITP occurs most often in adults, particularly women of child-bearing age. The disease may present as easy bruising, nosebleeds, or melena or a sudden appearance of widespread petechial hemorrhages. The diagnosis is made by documenting the thrombocytopenia in the presence of normal number of megakaryocytes in the bone marrow. The **bleeding time is prolonged**, but other clotting test results are normal. The diagnosis is made by excluding other causes of thrombocytopenia, especially infections and autoimmune diseases such as systemic lupus erythematosus, AIDS, viral infections, and drug reactions.

Thrombotic microangiopathies purpura, hemolytic uremic syndrome, and DIC are clinically distinct diseases, grouped under the heading of thrombotic microangiopathies because they have the same pathophysiology and similar pathologic changes. **Thrombotic microangiopathies purpura** is typically found in adult women who present in classical cases with a pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. **Hemolytic uremic syndrome** affects children and presents as hemolytic anemia with renal failure but no neurologic symptoms. **DIC** is an acute systemic manifestation of sepsis, shock, or terminal cancer and other major diseases (Table 9-6) characterized by the formation of fibrin thrombi in microcirculation and the consumption of fibrin and other coagulation factors (consumptive coagulopathy). It is caused by an entry of procoagulants, such as tissue thromboplastin or endotoxin, into the circulation. Depletion of coagulation factors from blood leads to hemorrhage. The symptoms of DIC are partially due to thrombosis (ischemia) and partially due to hemorrhage.

Bleeding disorders due to defective platelet function may be inherited or acquired. Congenital diseases may be due to defects in platelet adhesion **(Bernard-Soulier syndrome),** platelet aggregation **(thrombasthenia),** or disorders of platelet secretory function. Acquired platelet dysfunction may be related to ingestion of aspirin and nonsteroidal anti-inflammatory drugs. Aspirin inhibits cyclooxygenase, which suppresses the synthesis of thromboxane A_2, a potent aggregator of platelets. Abnormalities in platelet function have also been found in chronic renal failure and some metabolic disorders.

Bleeding Disorders Due to Abnormalities in Clotting Factors

Clotting factor disorders are classified as **acquired** (liver disease, vitamin K deficiency, and DIC) and **inherited** (hemophilia A and hemo-

TABLE 9-6.
Common Causes of Disseminated Intravascular Coagulation

- Infections
  - Gram-negative sepsis
  - Meningococcemia
  - Rickettsial infections
- Massive tissue injury
  - Trauma
  - Burns
- Neoplasms
  - Carcinomas (pancreas, stomach, colon)
  - Acute promyelocytic leukemia
- Obstetric disorders
  - Toxemia of pregnancy
  - Abruptio placentae
  - Amniotic fluid embolism
- Miscellaneous conditions
  - Snakebite
  - Heat stroke
  - Vasculitis
  - Aortic aneurysm
  - Liver disease

philia B, von Willebrand disease, other coagulation-factor deficiencies). Except for disorders of factors VIII and IX, which are sex linked, all other bleeding disorders are inherited as autosomal recessive traits.

Hemophilia A (deficiency of factor VIII) is the most common hereditary bleeding disorder transmitted as an X-linked trait. Intramuscular hematomas and spontaneous bleeding are common in severe hemophilia, but even patients with mild disease experience prolonged bleeding after surgery or trauma and hemorrhage in joints **(hemarthrosis),** which can lead to crippling deformities. These patients have normal bleeding times, normal platelet counts, and prolonged activated partial thromboplastin times (aPTTs). Factor VIII is reduced in the blood. In severe hemophilia, the blood level of factor VIII is 1%; in moderate hemophilia, it is 2% to 5%; and in mild hemophilia, it is 5% to 30% of the normal concentration. For normal hemostasis, the concentration should be >30%. The treatment involves infusion of factor VIII.

Hemophilia B (Christmas disease or factor IX deficiency) is less common than hemophilia A, but it is clinically indistinguishable from it. As in hemophilia A, the bleeding time is normal, and the aPTT is prolonged. The final diagnosis of hemophilia A or B is made by demonstrating low levels of factor VIII or IX in the blood.

von Willebrand disease is one of the most common inherited bleeding disorders in humans. It is usually transmitted as an autosomal dominant disease, but may also occur in an autosomal reces-

TABLE 9-7.
Pathogenetic Classification of Bleeding Disorders

Pathogenetic Mechanism	Platelet Count	Bleeding Time	Activated Partial Thromboplastin Time	Prothrombin Time	Diseases
Intrinsic pathway defect	N	N	Prolonged	N	Hemophilia, von Willebrand disease, autoantibodies
Extrinsic pathway defect	N	N	N	Prolonged	Liver disease, vitamin K deficiency
Common pathway defect	N	N	Prolonged	Prolonged	Liver disease, vitamin K deficiency, disseminated intravascular coagulation (late)
Platelet defect	Decreased	Prolonged	N	N	Thrombocytopenia
Blood vessel defect	N, decreased	Prolonged	N	N	Vascular purpura

N, normal.

sive form, which is less common. There are three major types of this disease. In **types I and III,** patients have a reduced level of circulating vWF. In **type II,** patients have a qualitative defect in vWF. The deficiency of vWF is typically associated with a decreased concentration of plasma factor VIII. Clinically, the disease presents with spontaneous bleeding from mucous membranes, excessive bleeding from wounds, and menorrhagia. Laboratory findings include reflecting concomitant disturbances of prolonged bleeding time in the presence of a normal platelet counts, platelet function, and the coagulation pathway.

The diagnosis of bleeding disorders is based on laboratory studies, as shown in Table 9-7.

DISORDERS OF WHITE BLOOD CELLS

The reduction of circulating WBCs in circulation is called **leukopenia.** *Neutropenia* (agranulocytosis) refers to a deficiency of neutrophils; *lymphopenia* means a reduced number of lymphocytes. An increased number of leukocytes is called *leukocytosis,* and an increased number of lymphocytes is called *lymphocytosis.*

TABLE 9-8.
Causes of Leukocytosis

Type of Leukocytosis	Causes
Neutrophilic	Bacterial infection Tissue necrosis (e.g., infarct, trauma, burns) Metabolic disorder (e.g., gout)
Eosinophilic	Allergy (e.g., asthma, allergic skin diseases) Parasitic infection Drug reaction
Monocytic	Chronic infection (e.g., tuberculosis, malaria) Autoimmune diseases (e.g., systemic lupus erythematosus)
Lymphocytic	Viral infections Autoimmune diseases

Neutropenia

Neutropenia **(agranulocytosis)** is defined as a condition in which the total number of WBCs is reduced to <1,000/μl. Neutropenia can be *selective* (i.e., if only neutrophils are affected) or *generalized* (i.e., if part of total pancytopenia) as typically encountered in bone marrow failure **(aplastic anemia).** The cause of neutropenia may be inadequate formation or maturation of neutrophils in the bone marrow or accelerated removal of neutrophils from the circulation. In inadequate formation or maturation of neutrophils, the bone marrow is either hypocellular or replete with immature precursors of WBCs, which do not mature and do not enter the circulation. In such cases, neutropenia may be the first manifestation of leukemia. Neutropenia caused by accelerated removal of neutrophils is often immune mediated and is typically associated with splenomegaly.

Leukocytosis

Leukocytosis presents as an increase of leukocytes in the peripheral circulation. It is usually a reaction to stimuli that act on the bone marrow to increase WBC production or accelerate the release of WBCs into circulation. Depending on the predominant cell type in peripheral blood, leukocytosis may be classified as neutrophilic, eosinophilic, monocytic, or lymphocytic (Table 9-8). The circulating WBCs are usually mature, but in extreme forms when the WBC count exceeds 30,000 to 40,000/μl, many immature forms may be

seen. Such **leukemoid reactions** must be distinguished from leukemia (i.e., true neoplastic proliferation of WBC precursors). In contrast to leukemia, cells that do not express surface alkaline phosphatase, cells found in leukemoid reaction are alkaline phosphatase positive, like normal leukocytes.

Reactive Lymphadenitis

Enlargement of lymph nodes **(lymphadenopathy)** may be reactive or neoplastic. The reactive lymph node enlargement is most often caused by infections, which may be *systemic,* as in infectious mononucleosis or AIDS, or *localized,* as in neck lymphadenopathy or rubella infection. Localized infections typically cause lymphadenitis along the normal lymphatic drainage routes. Arm infection leads to enlargement of cubital and axillary lymph nodes, whereas leg infection causes enlargement of inguinal lymph nodes. Lymph node enlargement is also found in the area draining the lymph from a malignant tumor, in which case the lymph nodes may contain immune cells and macrophages or metastatic foci of tumor cells. Lymphadenopathy is a common feature of systemic autoimmune diseases such as systemic lupus erythematosus.

NEOPLASTIC DISEASES OF WHITE BLOOD CELLS

Neoplastic diseases of WBCs can be histogenetically classified as malignant proliferation of myeloid cells, lymphoid cells, and plasma cells.

Neoplastic proliferation of myeloid cells and their precursors occurs in the bone marrow and includes several myeloproliferative disorders. If the neoplastic cells enter the peripheral circulation, the disease is called **leukemia.** Neoplastic proliferation of lymphoid cells and their precursors can occur in the bone marrow and may be accompanied by leukemia. On the other hand, lymphoid cell neoplasms **(lymphoma)** may be limited to lymph nodes, the spleen, or the thymus. Lymphomas also may involve the mucosa-associated lymphoid system (MALT; **maltoma**) and internal organs that contain few lymphocytes under normal circumstances **(extranodal lymphoma).** Plasma cell neoplasms typically originate in the bone marrow **(multiple myeloma)** but may occur also as extramedullary lesions **(plasmacytoma).**

Myeloproliferative Disorders

Myeloproliferative disorders represent a group of diseases characterized by malignant transformation of myeloid stem cells in the bone marrow. The disorder may present affecting the granulocytic, erythroid, or megakaryocytic cell lines or all three of these lineages,

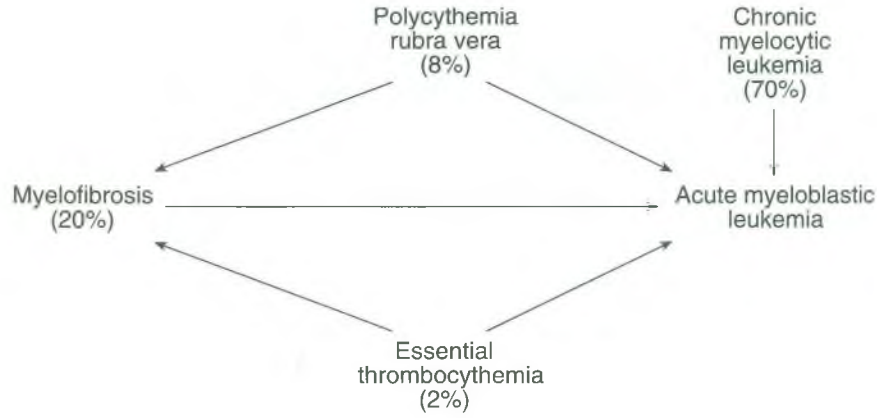


Figure 9-4.
Myeloproliferative disorders.

which originate from a common precursor. Proliferation of granulocytic precursors causes **CML** (discussed in the section on leukemia); proliferation of RBC precursors leads to **polycythemia rubra vera** (discussed in the section on RBC diseases); and the disturbance of maturation of megakaryocytes leads to essential thrombocythemia. Altered stem cells secrete growth factors that promote proliferation of fibroblasts causing **myelofibrosis.** Because the main defect underlying these four diseases resides in altered stem cells, it is not uncommon to see transformation of one disease into another (Fig. 9-4).

Myelofibrosis, also known as *agnogenic myeloid metaplasia,* is characterized by fibrosis of the bone marrow that replaces the normal hematopoietic elements. In response to stem cell loss from the bone marrow, the hematopoiesis is shifted to the spleen, liver, and other extramedullary sites. **Clinically,** the disease presents with anemia, leukopenia, and thrombocytopenia, which cause fatigue and a reduced resistance to infection and result in a bleeding tendency. Splenomegaly is common. Bone marrow aspiration usually yields a "dry tap." Myelofibrosis may progress to leukemia; overall, it has a poor prognosis.

Essential thrombocythemia is diagnosed when the platelet count is consistently >1 million platelets per μl. Because the platelets are often abnormal, the disease may present with recurrent thrombosis or a bleeding tendency, epistaxis, menorrhagia, or gastrointestinal bleeding. Peripheral blood smears show numerous, often enlarged, platelets, and the bone marrow contains an increased number of megakaryocytes, which are enlarged and have multisegmented nuclei. Platelets are sequestered by the spleen, which is initially enlarged, but then shrinks because the engulfed platelets damage the endothelial cells of the sinuses, causing splenic fibrosis and atrophy. This results in a loss of splenic function, and the reduced splenic clearance of platelets contributes to thrombocythemia.

Leukemia

Leukemia is a malignancy of WBC precursors, characterized by overcrowding of the bone marrow with neoplastic cells and an increase of WBCs in the peripheral blood. Leukemia can be classified into two major groups: **myeloblastic** and **lymphoblastic.** Depending on the rapidity of onset of the disease, these two main groups can be further classified as *acute* or *chronic.* On the basis of differentiation of neoplastic cells, acute myeloid leukemia is classified into seven subgroups and acute lymphoblastic leukemia into three groups. **Chronic myeloid leukemia** (CML) is not further classified. **Chronic lymphocytic leukemia** (CLL) has several subtypes. Nevertheless, because most of these subtypes (e.g., hairy cell leukemia, Sézary syndrome) are rare, the term *chronic lymphocytic leukemia* is used for the chronic B-cell lymphocytic leukemia, which accounts for 95% of all cases.

It is important to note that leukemias do not have a benign counterpart. In some cases, leukemia is preceded by one of the myeloproliferative disorders. In other cases, leukemia may be preceded by a **myelodysplastic syndrome,** a group of diseases characterized by ineffective hematopoiesis and pancytopenia. This group includes entities such as refractory anemia, refractory anemia with ringed sideroblasts, or refractory anemia with excess blasts and chronic myelomonocytic leukemia. Myelodysplastic syndromes occur in the elderly. Most patients are asymptomatic and are diagnosed accidentally. Over time, approximately 30% of these patients develop acute myeloid leukemia. Others may suffer from anemia and chronic infections or bleeding.

The **etiology** of leukemia is *not known,* but several factors may play a pathogenetic role. The genetic nature of leukemias is highlighted by the high concordance of childhood acute lymphoblastic leukemia in identical twins and a four times higher incidence of leukemia in siblings of an affected child. Down syndrome and chromosomal fragility syndromes such as Bloom syndrome and Fanconi syndrome are associated with a high incidence of leukemia.

Ionizing radiation induces leukemia, as evidenced by the high incidence of leukemia in survivors of the atomic bomb blasts and workers inadequately protected from radiation. Drugs and chemicals, such as benzene, chloramphenicol, and cytotoxic drugs, are also known to induce leukemia. Only a few cases can be traced to these environmental carcinogens, and in most cases the cause of leukemia is unknown.

RNA retroviruses have been extensively studied in leukemic patients, but so far only one virus has been identified as the definitive cause of a rare form of leukemia known as adult T-cell leukemia/lymphoma. **Endogenous oncogenes** play an important role in some leukemias, and their activation is usually associated with chromosomal breaks, deletions, or translocation. Typical chromosomal changes are found in essentially all leukemias and even

preleukemic conditions (e.g., myelofibrosis and myelodysplastic syndromes). The best known of these is the translocation between the long arms of chromosomes 9 and 22 found in chronic myelocytic leukemia, known as the **Philadelphia chromosome.**

All leukemias share some common clinical and pathologic features. The bone marrow is typically hypercellular and contains an increased number of immature WBC precursors (blasts). Due to the replacement of the normal blood marrow, patients suffer from anemia, thrombocytopenia, and leukopenia. This results in fatigue and other signs of tissue hypoxia, a bleeding tendency, and increased susceptibility to infections. The spleen and liver are enlarged. In lymphoid leukemia, lymph nodes are infiltrated with neoplastic cells and are also enlarged. Internal organs may be infiltrated, especially in advanced stages of the disease. Solid tumors composed of leukemic granulocytes, which are greenish yellow and thus called *chloromas*, are occasionally found in the skin, soft tissues, or internal organs. Death is usually due to overwhelming infection or uncontrollable bleeding.

Acute lymphoblastic leukemia (ALL) is diagnosed when the bone marrow is composed of 30% lymphoblasts. Malignant cells typically contain the enzyme terminal deoxynucleotidyl transferase (TdT), a marker of immature lymphoid cells. In approximately 70% of cases, cells are positive for CALLA, a common ALL antigen; 20% of cases have T-cell antigens; 9% are null cells; and only 1% are classified as B cells. Morphologically, these cells can be classified as L1, L2, and L3, which is important for treatment and prognosis.

ALL accounts for 20% of all leukemias, and it is the most common form of leukemia in children younger than 5 years of age. The disease **evolves rapidly** and is usually characterized by **lymphadenopathy.** Extranodal lymphoid infiltrates (e.g., in the brain or testes) are common. Remission can be induced with modern chemotherapy, and >50% of patients can be permanently cured. Children ages 1 to 9 years have a better prognosis than adults or infants younger than 1 year of age. Unfavorable findings are L2 morphology, T-cell markers, certain chromosomal changes, and a peripheral blood count >25,000/μl. For unknown reasons, African-American children have a worse prognosis than others.

Acute myelogenous leukemia (AML) is diagnosed when the bone marrow is composed of >30% myeloblasts. According to the French-American-British classification, based on a variety of cytochemical stains, AML is subdivided into several groups designated M1 through M7, but with a few notable exceptions, this classification has a limited prognostic value and guidelines for therapy. For example, M3 (promyelocytic) leukemia responds well to retinoic acid treatment.

AML accounts for 80% of cases of acute leukemia in adults. In most cases, the disease originates de novo, but in some instances it represents a *secondary* event related to chemotherapy of another malignancy, such as Hodgkin disease or solid cancer of internal organs. AML may also be the late outcome of myelodysplastic syndromes.

Chemotherapy may induce complete remission in most cases, but the disease recurs and only a few patients survive 5 years after diagnosis. Total body irradiation with bone marrow transplantation after the first chemotherapy-induced remission has a somewhat better prognosis.

CML is diagnosed when the bone marrow shows excessive proliferation of myeloid precursor cells, and the peripheral blood contains an increased number of myelocytic cells in various stages of maturation. The neoplastic cells of 90% of patients have the **Philadelphia chromosome.** This marker chromosome is present in the bone marrow precursors of all WBCs, erythroblasts, and megakaryocytes, indicating that the malignant transformation occurred in the common myeloid stem cell. Molecular biology shows that these cells express the hybrid *bcr-abl* gene. Most neoplastic cells in the peripheral blood are immature and lack alkaline phosphatase, the marker of normal neutrophils. Serum vitamin B_{12} is high because the tumor cells secrete the vitamin B_{12}–binding protein. There is usually anemia and thrombocytopenia, although in early stages of the disease, the platelet count can be elevated. Despite leukocytosis, infections are common.

CML is a disease of adult age, with a peak incidence at approximately age 60. Despite its name, the disease usually does not last more than 2 to 3 years. In typical instances, the disease has a triphasic course: After a slowly progressive initial stage, it enters an accelerated phase, and finally a blast crisis, resembling AML. In approximately 50% of cases, the blast phase occurs suddenly, without a transitional accelerated phase. The **prognosis is poor,** and even total body irradiation with bone marrow transplantation does not substantially prolong life, although it may prolong the symptom-free remission period. The 10% of patients who are Philadelphia chromosome negative have a worse prognosis than others.

Chronic lymphocytic leukemia is diagnosed when there are >15,000/μl lymphocytes in the peripheral blood and 40% of bone marrow cells are lymphocytes. Morphologically, the tumor cells resemble mature lymphocytes. These cells express the gene *bcl*-2, and in 95% cases they are identifiable as B-lymphocytes. Chronic lymphocytic leukemia is a disease of the elderly. The disease has a slowly progressive course, and most patients live 7 to 9 years after diagnosis. Ultimately, the disease may enter a blast crisis or the patient dies of repeated bouts of infection. Chemotherapy has no effect on the course of the disease, and it is usually not given until the disease enters the terminal blast phase.

LYMPHOMAS

Lymphomas are malignant tumors of lymphoid cells residing in the bone marrow, lymph nodes, spleen, thymus, or mucosa-associated lymphoid tissue, and less often other organs, which under normal

circumstances contain only minor lymphoid cell populations. Clinically and pathologically, lymphomas are divided into two major groups: **Hodgkin disease** and **non-Hodgkin lymphoma** (NHL). Each of these groups comprises several distinct clinicopathologic entities. Lymphomas account for 3% of all human malignancies: Two-thirds of these are NHLs, and one-third are Hodgkin lymphomas.

The etiology and pathogenesis of lymphomas are poorly understood, but in general this group of diseases shares many features with leukemias. The same oncogenes and tumor-suppressor genes implicated in the pathogenesis of leukemia are found in lymphomas. ALL and chronic lymphocytic leukemia are actually considered to be leukemic forms of lymphoblastic and chronic well-differentiated lymphocytic lymphoma, respectively. The best known gene is *bcl*-2, found in B-cell well-differentiated lymphoma. Environmental factors also play a possible pathogenetic role, as evidenced by a high incidence of lymphoma in sub-Saharan Africa. Lymphomas occur often in immunosuppressed persons and are a well-known complication of AIDS.

Non-Hodgkin Lymphomas

NHLs are neoplasms originating from B- or T-lymphocytes and their less-differentiated precursors. Numerous clinicopathologic entities have been recognized, but for practical purposes the National Institutes of Health Working Classification groups all of these subtypes of NHL into four categories: low-grade lymphoma, intermediate-grade lymphoma, high-grade lymphoma, and miscellaneous groups (Table 9-9). A classification called Revised European American lymphoma was proposed in 1994. It divides lymphomas into two groups: B-cell and T-cell derived. Presently, the Working Classification is used more frequently.

Low-grade lymphomas are composed of cells that resemble mature lymphocytes. The neoplastic cells may diffusely infiltrate the entire lymph node or form follicles. **Intermediate-grade** lymphomas may be diffuse or follicular, but cytologically these lesions are more anaplastic than well-differentiated lymphomas and often contain large cells or mixed population of cells. **High-grade** lymphomas are composed of anaplastic large cells or immature small lymphoid cells, which diffusely infiltrate the lymph nodes and often extend into the nonlymphoid tissues. The high-grade lymphoma group includes **lymphoblastic, immunoblastic, and Burkitt lymphomas.**

The **miscellaneous group** of lymphomas includes entities that are different from other NHLs. **Mycosis fungoides** is a low-grade T-cell lymphoma that typically involves the skin. It is closely related to the **Sézary syndrome**, characterized by the appearance of neoplastic T-lymphocytes in the peripheral blood. **Hairy cell leukemia** is a low-grade lymphoma leukemia in which the bone marrow and spleen are most often infiltrated by B cells that have cell surface projections and contain cytoplasmic tartrate-resistant acid phosphatase. Rare neoplasms of macrophages (histiocytes) are also included in this group.

TABLE 9-9.

Classification of Lymphomas According to the Working Formulation

Grade	Category	Percentage of Cases*
Low	Small lymphocytic	
	Follicular small cleaved cell	23
	Follicular mixed small cleaved and large cell	
Intermediate	Follicular large cell	
	Diffuse small cleaved cell	
	Diffuse mixed small and large cell	
	Diffuse large cell	20
High	Large cell immunoblastic	8
	Lymphoblastic	
	Small noncleaved cell (Burkitt)	
Miscellaneous	Composite; mycosis fungoides; histiocytic; extramedullary plasmacytoma; unclassified	

**Percentages are given only for the three most common lymphomas. The relative incidence of all others is <8%.*

Source: Adapted from Rosenberg SA, et al. The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute Sponsor Study Classification of Non-Hodgkin's Lymphomas: summary and description of a working formulation for clinical usage. Cancer 1982;49:2112–2135.

Clinical presentation of lymphoma varies, but in general the symptoms can be attributed to lymph node enlargement, infiltration of the bone marrow, or extranodal spread to tumors. Lymphomas affect the immune system and generally suppress the normal B- and T-cell functions. Thus, infections are common. The prognosis depends on the type of lymphoma. Well-differentiated lymphomas have an indolent course, but do not respond to chemotherapy. On the other hand, the rapidly proliferating cells of high-grade lymphomas respond well to chemotherapy, but these diseases tend to relapse.

Hodgkin Disease

Hodgkin disease is a form of lymphoma that occurs in four histologic forms (Table 9-10), all of which contain distinct giant cells known as *Reed-Sternberg cells*. Reed-Sternberg cells have a bilobed nucleus with nucleoli surrounded by a halo that gives them an owl-eyed appearance. The disease has a bimodal age distribution: a high peak in the 20- to 30-year age group and a smaller peak at approximately 60 years of age.

TABLE 9-10.
Hodgkin Disease Subtypes

Histologic Subtype	Percentage of Each Subtype	Prognosis
Lymphocyte predominant	6–8	Best
Nodular sclerosis	65	Good
Mixed cellularity	25	Good
Lymphocyte depleted	4–5	Worst

Nodular sclerosis is the most common form of Hodgkin disease, accounting for approximately 60% of all cases. Histologically, the lymph node shows broad bands of fibrosis. Typical Reed-Sternberg cells are rare; instead, there are numerous lacunar cells. This form has a tendency to involve the mediastinal lymphoid tissue. It affects male and female subjects equally and is almost exclusively found in young people. **Mixed cellularity** is the second most common form of Hodgkin disease, with a variety of cells including lymphocytes, eosinophils, plasma cells, macrophages, and numerous Reed-Sternberg cells. Mixed cellularity often presents with widespread lesions and often has systemic symptoms. The **lymphocyte predominance** subtype of Hodgkin disease is characterized by dense lymphocytic infiltrates and a paucity of Reed-Sternberg cells. It is typically found in male subjects, is limited to cervical or inguinal lymph nodes, and has an indolent course. The **lymphocyte-depleted** form of Hodgkin disease shows fibrosis and irregularly shaped Reed-Sternberg cells replacing the lymphocytes in the lymph node.

Clinically, Hodgkin disease presents with **lymph node enlargement.** The presence of systemic symptoms, such as sweat and fever, is found in some patients. These are designated as B group, in contrast to A group patients who do not have such symptoms. Neck lymph nodes are most often involved, and the disease tends to spread contiguously to adjacent lymph node clusters. In contrast to non-Hodgkin disease, the involvement of the Waldeyer ring, periaortic lymph nodes, and extranodal tissues is rare, and the leukemic form is only exceptionally found. The response to chemotherapy is excellent, and 75% of patients survive at least 5 years. The prognosis depends on the stage of the disease at the time of diagnosis and to a lesser degree on the subtype of Hodgkin disease. Lymphocyte predominance has the best prognosis, and the lymphocyte-depletion subtype the worst. The presence of systemic symptoms (B group) and advanced age also carry an unfavorable prognosis. If the disease relapses, salvage by chemotherapy can be achieved in 50% of cases.

PLASMA CELL NEOPLASMS

Monoclonal proliferation of plasma cells and plasmacytoid lymphocytes can result in several distinct clinicopathologic entities, the most important of which are multiple myeloma, Waldenström macroglobulinemia, monoclonal gammopathy of unknown significance (MNGUS), and solitary plasmacytoma. Common to all of these diseases is that they produce a monoclonal protein (M component) that can be detected as a peak by standard plasma electrophoresis or a distinct band by immunoelectrophoresis. The M component can be equivalent to normal plasma immunoglobulins or to the lambda or kappa chain of the immunoglobulin molecule. The light chain of the immunoglobulin molecule may be excreted in the urine as the Bence Jones protein.

Multiple Myeloma

Multiple myeloma is a neoplasm of well-differentiated plasma cells capable of secreting immunoglobulins. These neoplastic cells proliferate in the bone marrow, producing lytic bone lesions, which are typically accompanied by hypercalcemia. In 60% of cases, neoplastic plasma cells secrete IgG, in 20% cases IgA, whereas in the remaining cases, the tumor cells secrete IgD, IgE, or only the immunoglobulin light or heavy chain. The disease is associated with reduced concentration of normal immunoglobulins, which accounts for increased susceptibility to infections. Excess of light chain may be deposited in the tissues as amyloid of the AL type. Excretion of light chains in urine (Bence Jones proteinuria) and amyloid deposition in tissues damage the kidneys. Renal failure is the most common cause of death in these patients (Fig. 9-5).

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is a neoplasm of lymphoid cells that are at a stage in between a normal lymphocyte and an early plasma cell. These plasmacytoid lymphocytes secrete IgM (macroglobulin), which results in hyperviscosity of blood. In contrast to multiple myeloma, Waldenström macroglobulinemia does not produce punched-out lytic bone lesions, but infiltrates the bone in a more diffuse manner, as lymphoma.

Monoclonal Gammopathy of Unknown Significance

MNGUS is a term used for the condition in which a monoclonal peak (M component) is found in the plasma by electrophoresis in the absence

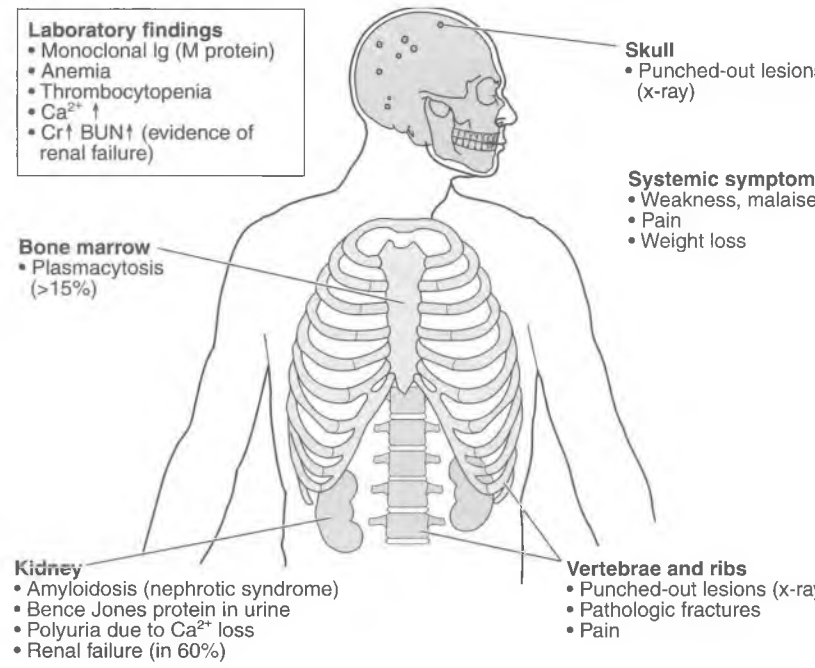


Figure 9-5.
Pathology and signs and symptoms of multiple myeloma. (Cr, creatinine; BUN, blood urea nitrogen.)

of bone marrow infiltrates typical of multiple myeloma. MNGUS is found in the elderly, and in most instances it produces no clinical symptoms. Approximately 20% of all people with MNGUS develop multiple myeloma, macroglobulinemia, lymphoma, or amyloidosis.

Solitary Plasmacytoma

Solitary plasmacytoma is a lesion histologically identical to the lesions of multiple myeloma, except that it is solitary and often located outside the bones. Solitary plasmacytoma of the bone may be the first manifestation of multiple myeloma, in which case additional bone marrow lesions develop over a period of several years. Extraosseous plasmacytomas can be resected. These curable lesions only exceptionally evolve into multiple myeloma.

HISTIOCYTOSES

Neoplastic proliferation of macrophages (histiocytes) may produce several clinicopathologic entities. **Langerhans cell histiocy-**

tosis is characterized by a proliferation of neoplastic cells that have the immunohistochemical and electron microscopic features of Langerhans cells normally found in the skin. In the solitary form, it is usually called **eosinophilic granuloma.** In the multifocal form, it produces **Hand-Schüller-Christian disease,** which is characterized by defects of the skull bones, diabetes insipidus, and exophthalmos. In infants and children younger than 3 years of age, disseminated Langerhans cell histiocytosis is known as **Letterer-Siwe disease.** It presents with lytic bone lesions, skin infiltrates, lymphadenopathy, and hepatosplenomegaly and is fatal unless treated aggressively with cytotoxic drugs.

PATHOLOGY OF THE THYMUS

The most important diseases of the thymus are agenesis, hyperplasia, and tumors. **Agenesis** of the thymus is associated with T-cell immunodeficiency. It is a feature of the DiGeorge and Nezelof syndromes. **Hyperplasia** of the thymus is found in some patients with myasthenia gravis. Primary tumors of the thymus are called **thymomas** if benign, or **thymic carcinomas** if malignant. Thymoma is more common. Thymic tumors are often associated with myasthenia gravis, especially in young women. Other thymic tumors include lymphomas, carcinoids, and mediastinal germ cell tumors.

PATHOLOGY OF THE SPLEEN

The most important diseases of the spleen are developmental abnormalities, reactive changes, and neoplasms. **Developmental** pathology of the spleen includes conditions such as asplenia, polysplenia, and heterotopic spleen formation. **Reactive** changes can be classified as those induced by chronic passive congestion, infection (splenitis), or accumulation of metabolites as in Gaucher disease. Pooling of blood cells in splenic sinusoids and their destruction is seen in various hemolytic anemias, ITP, or thrombotic microangiopathies purpura. The enlarged spleen is sensitive to pressure and may rupture. The enlargement of the spleen may be accompanied by suppression of bone marrow functions and result in anemia, leukopenia, and thrombocytopenia (hypersplenism syndrome). Splenomegaly is a common feature of vari-

TABLE 9-11.
Causes of Splenomegaly

Cause	Example
Infection	Sepsis, infectious mononucleosis, malaria
Congestion	Cirrhosis, right-sided heart failure
Neoplasia	Lymphoma, leukemia (chronic more often than acute)
Hemolytic anemias	Hereditary spherocytosis
Autoimmune diseases	Rheumatoid arthritis (Felty syndrome), systemic lupus erythematosus
Storage diseases	Gaucher disease

ous lymphomas and leukemias. For reasons that are not completely known, the spleen is a rare site for metastases from other sites. Important causes of splenomegaly are listed in Table 9-11.

Chapter 10

Gastrointestinal System

DISEASES OF THE MOUTH, TEETH, AND SALIVARY GLANDS

Diseases of the Mouth

Developmental disorders of the mouth result from incomplete fusion of the fetal primordia of the lips **(cleft lip)** or palate **(cleft palate).** Micrognathia (small mandible) or macroglossia (large tongue) may occur as isolated defects or as part of a systemic multiorgan disease.

Inflammation of the mouth is called **stomatitis,** of the lips **cheilitis,** and of the tongue **glossitis.** Viral infection of the lips, such as herpes simplex type I, presents with grouped vesicles that tend to ulcerate (cold sores). *Candida albicans* infection of the mouth (thrush) is typically found in debilitated sickly infants and small children. In adults, it is usually found in people suffering from diabetes, cancer, or acquired immunodeficiency syndrome (AIDS). Many systemic diseases present with oral lesions (Table 10-1).

Neoplasms of the mouth originate predominantly from the squamous epithelium, but can also originate from primordia of the teeth and small salivary glands. Squamous cell carcinoma is thus the most common form of cancer. It occurs most often on the lips and the floor of the mouth. It is causally related to tobacco smoking. Pipe smoking is associated with an increased incidence of lip cancer. The invasive squamous cell carcinoma is often preceded by a preinvasive carcinoma in situ, which presents as white or red induration of the mucosa called **leukoplakia** or **erythroplakia.** These clinical terms are also used for inflammatory oral plaques; a biopsy must be performed to determine whether such a lesion is benign or malignant.

Diseases of Teeth

Dental caries and periodontal disease are caused by a variety of bacteria, the most important of which is *Streptococcus mutans.* Bacteria attach to teeth and form calcified plaques (tartar). From the plaques, bacteria can dissolve the enamel and cause caries or colonize the periodontal pocket and cause periodontitis. **Dental caries** is

TABLE 10-1.
Oral Manifestations of Some Systemic Diseases

Disease	Manifestation
Infection	
Scarlet fever	Reddened tongue ("raspberry tongue") or white tongue with hyperemic papillae ("strawberry tongue")
Measles	Redness around Stensen duct (Koplik spot)
Acquired immunodeficiency syndrome	Hairy leukoplakia, thrush, ulcers
Autoimmune diseases	
Lichen planus	Lace-like white macules
Pemphigus vulgaris	Vesicles and bullae prone to ulceration
Erythema multiforme	Red macules and bullae
Sjögren syndrome	Xerostomia
Hematologic disorders	
Anemia	Pale mucosae
Leukemia	Bleeding from gingiva, fungal and bacterial infections

an enzymatic demineralization of enamel and leads to formation of a cavity in the tooth. Caries allows the entry of bacteria into the central canal, causing pulpitis, which in turn can lead to apical or periapical abscess formation and even osteomyelitis, although it does consist of granulation tissue (Fig. 10-1). Chronic inflammation at the site of the abscess is wrongly called *granuloma.* Healing of abscess tissues leaves a pseudocyst. Adequate saliva, high-roughage and low-carbohydrate diets, and fluoridation of the drinking water help to reduce the incidence of caries.

Periodontal disease is the primary cause of tooth loss in adults. Bacteria colonize the periodontal packet under the gingiva and cause periodontitis, which results in destruction of the periodontal ligaments and loosening and loss of teeth.

Tumors of teeth, called *adamantinoma* or *myeloblastoma,* originate from fetal remnants of the tooth primordium (enamel organ).

Diseases of the Salivary Glands

Sialadenitis, inflammation of salivary glands, may be caused by viruses, bacteria, or autoimmune disorders. The most common type of viral infection is **mumps,** which affects the major salivary glands, particularly the parotid gland. The pancreas and testes may also be

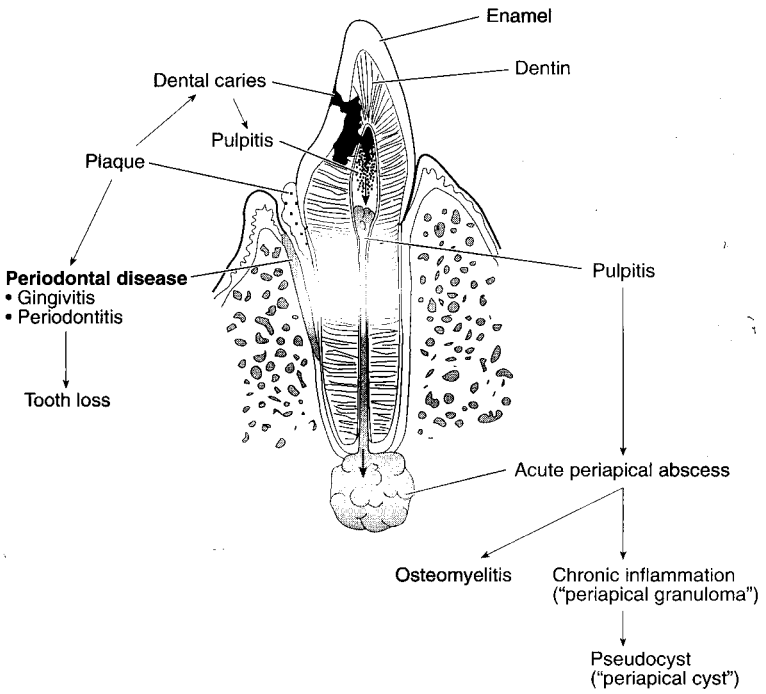


Figure 10-1.
Dental caries and periodontal disease.

involved. **Sjögren syndrome** is an autoimmune disease that affects salivary glands and mucus-secreting glands of the nasal mucosa, leading to xerostomia (dry mouth). The lacrimal glands are also involved, which leads to keratoconjunctivitis sicca (dry eyes). **Xerostomia** may be induced by drugs and also results from salivary gland atrophy secondary to irradiation. Occasionally, the main salivary duct is obstructed with stones (sialolithiasis).

Salivary gland neoplasms are uncommon and are most often found in the 40- to 60-year-old age group. The vast majority of these neoplasms arise in the parotid gland (70%), and most are benign. Of the approximately 15% of parotid gland tumors that are found, 40% of those found in the submandibular gland are malignant, and 50% of those found in the minor salivary glands are malignant. Histologically, these tumors occur in several forms, but the most common are pleomorphic adenomas.

Pleomorphic adenomas (mixed tumors) make up approximately 60% of tumors in the parotid gland and are less common in the other glands. Histologically, these neoplasms are encapsulated and composed of epithelial cells and myoepithelial cells arranged in a myxoid tissue that often has foci of cartilage. They recur if they are not completely excised, and a small percentage (5%) are malignant. Other less common tumors are mucoepidermoid carcinoma, acinic cell carcinoma, and papillary cystadenoma lymphomatosum (Warthin tumor).

DISEASES OF THE ESOPHAGUS

Non-Neoplastic Diseases

Diverticula of the esophagus are uncommon. Pulsion diverticula **(Zenker diverticula)** are outpouchings of the posterior pharynx above the cricopharyngeus muscle. They are most common in elderly men and are attributed to a weakened wall, which is pushed out by intraluminal pressure. **Traction diverticula** in the midportion of the esophagus result from the wall pulling out because of inflammatory processes such as tuberculosis.

Motor disorders of the esophagus result in **dysphagia,** a difficulty in swallowing, or **odynophagia** (pain on swallowing). Swallowing is a complex function that is heavily dependent on voluntary muscle action and innervation. Thus, dysphagia can result from cerebral vascular accidents, primary neurologic diseases, and diseases that affect skeletal muscles such as scleroderma, dermatomyositis, or myasthenia gravis.

The most important esophageal cause of dysphagia is functional spasm, known as **nutcracker esophagus,** which it resembles in barium swallow study results. **Achalasia (cardiospasm)** results from failure of the lower esophageal sphincter to relax, absence of peristalsis, and a high resting tone in the lower esophagus. The esophagus above the sphincter progressively dilates. Achalasia is most often idiopathic, but it may be caused by degeneration of the myenteric plexus as in Chagas disease (trypanosomiasis). Occasionally, swallowing is impeded by **strictures** and **esophageal webs.**

Hernia of the esophagus through the diaphragm is called **hiatus hernia.** There are two types: **sliding,** in which the cardiac portion of the esophagus is pulled into the chest, and **rolling** (paraesophageal), in which the junction of the stomach and esophagus remains in the abdominal cavity, but the stomach rolls up beside the esophagus in the chest. The sliding type is much more common, accounting for 80% to 90% of all cases. It is a common disease typically associated with regurgitation of the gastric contents into the esophagus.

Esophagitis may be caused by infections (e.g., viral or fungal), chemicals, or mechanical irritants such as a nasogastric tube. The most common cause of esophagitis is reflux of gastric juice due to the incompetence of lower esophageal sphincter or to hiatal hernia (reflux esophagitis). **Reflux esophagitis** may lead to glandular metaplasia of normal esophageal squamous epithelium **(Barrett esophagus).**

Esophageal bleeding usually occurs from tears in the mucus in the lower esophagus. Repeated vomiting may induce lacerations of the distal esophageal and proximal gastric mucosa associated with significant bleeding. Most frequently this is seen after heavy alcohol intake and is known as the **Mallory-Weiss syndrome. Esophageal varices,** which are dilated veins in the submucosa in the lower esophagus and at the esophagogastric junction, are a complication of portal hypertension caused by cirrhosis of the liver. Rupture of

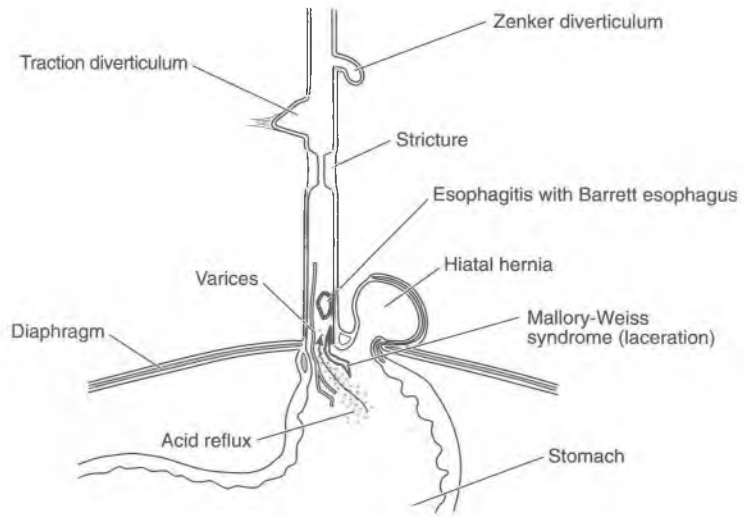


Figure 10-2.
Non-neoplastic esophageal diseases.

esophageal varices causes hematemesis or melena. It is one of the most common causes of death in cirrhosis.

The most important non-neoplastic diseases of the esophagus are presented in Figure 10-2.

Neoplasms of the Esophagus

Malignant tumors of the esophagus represent approximately 5% of all gastrointestinal malignancies, with an incidence of 10,000 to 11,000 per year. In the United States, esophageal cancer is strongly associated with **cigarette smoking** and **alcohol abuse.** It is more common in males (4:1) and is more common in blacks than whites. It is usually far advanced when detected. Histologically, most tumors are squamous cell carcinomas. In the lower third of the esophagus, almost one-half of tumors are adenocarcinomas, originating from glandular epithelium in the Barrett esophagus. Symptoms include pain and emaciation because the tumor interferes with eating. The tumor tends to infiltrate adjacent organs in the mediastinum before spreading. Few tumors are resectable, and the 5-year survival rate is 10% to 20%.

DISEASES OF THE STOMACH

Non-Neoplastic Disorders

Congenital disorders of the stomach are rare. Nevertheless, **congenital pyloric stenosis** is the most common indication for abdominal surgery in the first 6 months of life. It is predominantly a male disease

(4:1). The infant develops colic and projectile vomiting at approximately 2 to 3 weeks of age and can become significantly dehydrated. Incision of the hypertrophied pyloric sphincter is usually curative.

Gastritis, inflammation of the stomach, is extremely common. Two major forms are recognized: **erosive gastritis (acute gastritis),** which shows a spectrum of changes from mild hyperemia of the gastric mucosa to acute gastric ulceration, and **nonerosive gastritis (chronic atrophic gastritis).** Erosive gastritis may be caused by ingested chemicals or drugs such as aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Gastric erosions develop also in response to trauma, sepsis, burns **(Curling ulcer),** and brain trauma and swelling **(Cushing ulcer).** Because the mucosa and submucosa of the stomach are so richly supplied with blood, it appears that ischemia may be the common pathway linking these multiple causes. Anything that increases mucosal cell turnover, decreases mucus or prostaglandin production, and decreases the intramural pH undoubtedly contributes to acute gastritis, gastric erosion, and acute gastric ulceration.

Chronic nonerosive gastritis has multiple causes, but two of the more significant causes are autoantibodies and ***Helicobacter pylori.*** Autoimmune gastritis primarily involves the fundus. It is characterized by fundic gastric atrophy; antibodies to parietal cells, intrinsic factor, or both; and achlorhydria. The lack of intrinsic factor interferes with vitamin B_{12} absorption and leads to **pernicious anemia.** *H. pylori* infection primarily affects the pyloric antrum. Chronic gastritis is associated with an increased risk of gastric cancer.

Peptic ulcer disease is an extremely common multifactorial disorder. Ulcers can occur in the stomach or duodenum. There is a predilection for ulcers to be found in the first part of duodenum and the lesser curvature of the antral portion of the stomach. Acid and pepsin are necessary for chronic ulcer formation. *H. pylori* infection also plays a role. NSAIDs and aspirin may contribute to and exacerbate the disease.

Grossly, the chronic peptic ulcer has a characteristic appearance and regular outline as if it had been scooped or punched out, a smooth base, and a rolled up mucosal border in which the folds disappear right at the edge. Microscopically, the bottom of the ulcer has three layers consisting of necrotic tissue, inflammatory exudate, and a layer of granulation tissue. Ulcers bleed and perforate, and in the duodenum they may cause stenosis or obstruction. Gastric ulcers undergo malignant transformation in approximately 2% to 3% of cases. Duodenal ulcers never give rise to cancer.

Neoplasms of the Stomach

Tumors of the stomach are classified as *epithelial* and *nonepithelial.* Adenocarcinomas are the most common epithelial tumor. Lymphomas and sarcomas represent the nonepithelial tumors, which account for <10% of all neoplasms. Benign tumors are less common and include hyperplastic polyps, adenomatous polyps, and leiomyomas.

Gastric adenocarcinoma was once the most frequently seen malignancy in men in the United States, but its incidence has been steadily

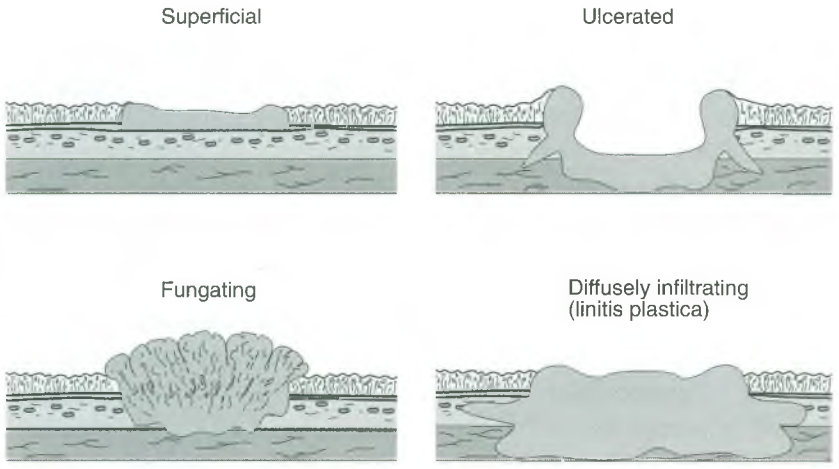


Figure 10-3.
Gastric cancer.

declining. It has a high incidence in Japan and Chile, most likely reflecting the prevalence of local carcinogens or diet (e.g., smoked fish).

On gross examination, four patterns of growth are recognized: superficial, ulcerating, fungating or polypoid, and diffusely infiltrating (linitis plastica) (Fig. 10-3). Histologically, gastric cancers are adenocarcinomas that may be further classified as being intestinal or diffuse. In linitis plastica, the stomach is usually infiltrated with mucus-filled round cells (signet ring cells). Only superficial carcinomas detected early in the course of the disease can be cured. Overall, the 5-year survival rate in the United States is 20%. In Japan, where yearly screening for gastric carcinomas is performed routinely, early diagnosis of gastric carcinoma has a 95% 10-year survival rate.

Gastric lymphomas originate in the mucosa-associated lymphoid tissue (MALT) or represent a spread of a systemic lymphoma to the gastrointestinal tract. Maltomas have a better prognosis than gastric adenocarcinomas. **Leiomyomas** and **leiomyosarcomas** of the stomach are rare tumors. The distinction between benign and malignant smooth muscle cell tumors is not easy to make, but in general the benign tumors are small, and those >6 to 7 cm are malignant.

DISEASES OF THE INTESTINES

Diverticula, Hernias, and Obstructions

Diverticula, or outpouchings of the intestinal wall, are most often found in the rectosigmoid portion of the large intestines of the elderly. Diverticula of the small intestine can be either congenital or

acquired, solitary or multiple. Acquired diverticula occur far less frequently than those of the large intestine and also occur less frequently than congenital diverticula. The most common congenital diverticulum, **Meckel diverticulum,** is a remnant of the omphalomesenteric (vitelline) duct, which is present in approximately 2% of the population. It occurs in the distal ileum, approximately 2 feet from its termination in the colon (50 to 60 cm). It is approximately 2 inches long (5 cm). Approximately 60% of patients are under 2 years of age **(mnemonic: 2, 2, 2, 2).** It often contains ectopic gastric epithelium or foci of pancreatic tissue. Symptoms due to inflammation resemble appendicitis, except that they localize on the left side. Perforation with peritonitis, obstruction, and intussusception of the small intestine may be related to inflamed or twisted Meckel diverticulum.

Herniation in the small intestine into the inguinal region of male subjects or the femoral canal in female subjects occurs often. Symptoms relate to the mass effect of the protruding intestinal loops or intestinal obstruction. Intestinal obstruction also can be caused by adhesions, volvulus, intussusception, and other causes such as impaction with meconium (meconium ileus) seen in infants with cystic fibrosis. Rupture of the obstructed intestines causes peritonitis.

Enteritis

Infectious diarrhea, inflammation of the intestines, may involve the entire gastrointestinal tract (gastroenteritis), or it may be localized to specific parts of the intestine (e.g., ileitis, appendicitis, colitis, proctitis). It is a major health problem in underdeveloped countries and a major cause of morbidity and mortality, especially among children. In the United States, diarrhea among children is usually caused by viruses (rotavirus or Norwalk virus). It is also a common complication of food poisoning caused by staphylococci or *Escherichia coli* enterotoxin. Bacterial enteritis can be toxin mediated or caused by bacterial invasion of the intestinal wall. Two most notable toxigenic organisms are ***Vibrio cholerae*** and toxigenic ***E. coli.*** *E. coli* causes the familiar travelers' diarrhea, which is characterized by mild inflammatory changes in the bowel mucosa. This type of diarrhea is short lived and responds to symptomatic therapy. **Cholera** produces severe (rice water) diarrhea with life-threatening dehydration, although the pathologic lesions are inconspicuous. The invasive organisms generally produce more obvious damage to the intestinal mucosa, including inflammation and ulceration. **Invasive organisms** include many species of *Salmonella,* invasive *E. coli, Yersinia, Campylobacter,* and *Shigella. Clostridium difficile* causes pseudomembranous colitis in patients taking broad-spectrum antibiotics, especially clindamycin or ampicillin. Tuberculous enteritis is rare in the United States and usually is caused by *Mycobacterium tuberculosis. Mycobacterium avium-intracellulare* infects the small intestine and is a cause of diarrhea in AIDS patients. **Amebiasis** is a disease of the tropics caused by *Entamoeba histolytica.* It causes deep flash-like

TABLE 10-2.
Comparison of Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Involvement		
Colon	Discontinuous, skip areas	Continuous diffuse
Rectum	Uncommon	Common
Terminal ileum	Common	Not involved
Macroscopic lesions		
Linear (aphthous) ulcers	Common	Uncommon
Cobblestone mucosa	Common	Uncommon
Intestinal wall	Thickened	Thin
Lumen	Narrow (strictures)	Dilated (megacolon)
Fistulae	Yes	No
Microscopic lesions		
Crypt abscess	May be present	Common
Extent of inflammation	Transmural	Mucosal
Granulomas	Yes (50%)	No
Ulceration	Deep	Shallow
Pseudopolyps	No	Yes

ulcers in the cecum, occasionally complicated by extension of the infection to the liver, where it forms amebic abscesses.

Appendicitis is an acute intestinal infection localized to the appendix. It may occur at any age, but is more common in children and teenagers. It is usually caused by obstruction of the lumen of the appendix by a foreign body, a fecalith, or lymph node enlargement. The appendix may rupture and cause peritonitis, which is initially localized (perityphlitic abscess), but may become widespread.

Inflammatory Bowel Disease

Inflammatory bowel disease is a term that encompasses two entities: Crohn disease and ulcerative colitis. These two diseases have many features in common but also differences (Table 10-2). **Crohn disease** is a granulomatous inflammatory disease of young adults, which occurs slightly more often in women. Jews are affected more often than non-Jews, and many patients have a familial history of inflammatory bowel disease (either Crohn disease or ulcerative colitis). The disease may involve the terminal ileum or colon, but in most cases both the ileum and colon are affected. The perianal region is often involved. Typically, there are "skip areas" between the affected segments. Pathologic findings in a typical case include linear ulceration of the mucosa, **transmural inflammation** with thickening and edema of all layers of the intestine. There is a tendency to form deep fissures, sinuses, and fistulas. **Extraintestinal**

manifestations include uveitis, arthritis, skin disease such as erythema nodosum and pyoderma gangrenosum, stones in the gallbladder and kidney, and sclerosing cholangitis. **Clinical features** are diarrhea, fever, pain, and weight loss when the distal ileum is affected. Anemia develops due to iron and vitamin B_{12} deficiency. Remissions and relapses occur, and in the most severe cases, the intestine must be resected. Crohn disease is associated with a slightly increased incidence of colon cancer.

Ulcerative colitis is an inflammatory disease of unknown origin that affects predominantly young adults, with a peak onset in the 20- to 30-year-old age group. Like Crohn disease, it is more common in Jews than other ethnic groups and whites more than other races. Family history is found in approximately 20% of cases. In contrast to Crohn disease, ulcerative colitis is limited to the colon and appendix; the small intestine is not involved. The disease typically begins in the rectum, spreading proximally. The ulcerations develop quickly, and there are no skip areas. Histologically, the initial lesions present as acute inflammation of the colonic crypts *(crypt abscess),* extending into lamina propria and resulting in ulcerations of the mucosa. Mucosal epithelium regenerates to some extent, but ulcerations persist, and the nonulcerated mucosa remains flattened and atrophic for prolonged periods. The inflammation is limited to the mucosa, and the deeper layers of the colon are not affected, as in Crohn disease. Fistulas do not form, but the weakened intestinal wall predisposes to dilatation. In severe cases, there is marked dilatation of the large intestine *(megacolon),* which may rupture and cause peritonitis.

The regeneration of the mucosa may lead to the formation of **pseudopolyps.** The epithelium, undergoing constant regeneration, may show atypia. Such **epithelial dysplasia** may give rise to **adenocarcinomas,** which occur in approximately 10% of all chronic incurable cases. Extraintestinal complications involving the eyes, joints, skin, and bile ducts are identical to those of Crohn disease. The clinical features of ulcerative colitis are similar to those in Crohn disease: In most patients, the disease has a chronic course with episodes of exacerbation after remissions. Current methods of treatment do not give satisfactory results. In severe cases and those with dysplasia or cancer, colectomy must be performed.

Malabsorption Syndrome

Malabsorption syndrome results from inadequate absorption of nutrients in the small intestine. It can be attributed to the following abnormalities:

- **Intraluminal digestion,** caused by deficiency of pancreatic enzymes (e.g., chronic pancreatitis) or bile (e.g., biliary obstruction)
- **Mucosal absorption,** caused by small intestinal disease such as celiac disease or Whipple disease

TABLE 10-3.
Causes of Malabsorption

Abnormal intraluminal digestion
Pancreatic insufficiency
Bile duct obstruction
Bacterial overgrowth
Abnormal mucosal absorption
Celiac sprue
Enteritis (*Giardia lamblia, Strongyloides stercoralis, Mycobacterium avium-intracellulare*)
Whipple disease
Crohn disease
Postmucosal obstruction
Lymphoma
Radiation enteritis
Amyloidosis

- **Postmucosal transport of nutrients,** as in intestinal lymphoma, which obstructs the lymphatics

In some instances, malabsorption syndrome is caused by more than one mechanism (Table 10-3). For example, Crohn disease of the terminal ileum impairs the recirculation of bile, adversely affecting intraluminal digestion of food. Nutrients cannot be absorbed adequately through the ulcerated mucosa. The thickened and inflamed wall of the ileum also impairs the postmucosal transport of nutrients.

Celiac disease, a disease of the small intestine, is characterized by villous atrophy induced by gliadin in the wheat protein **gluten.** The normal intestinal villi undergo atrophy and are shortened. The crypts show active mitoses and occupy two-thirds of the entire mucosa. Patients placed on a gluten-free diet recover in 80% of cases. The disease affects mostly children and young adults. Celiac disease is associated with an increased risk of intestinal lymphoma.

Whipple disease is a rare cause of malabsorption and affects mostly adult men. It is caused by the bacterium *Trophermyma whippleii,* which multiplies and lives inside the macrophages residing in the lamina propria of the small intestinal mucosa. Extraintestinal spread of the infection to lymph nodes is found in 30% of patients, who also may have arthritis and pleural or abdominal effusions. Other organs are involved less often. The diagnosis of Whipple disease is established by small intestinal biopsy. The disease responds well to treatment with antibiotics.

Circulatory Disorders

Atherosclerotic narrowing of intestinal arteries and their branches may cause ischemia, which typically occurs in the elderly and is most pronounced in the rectosigmoid and at the splenic flexure of the colon. **Ischemic colitis** is characterized by focal necrosis of the mucosa, followed by fibrosis of the lamina propria. It usually presents as indistinct abdominal pain and blood in the feces or as diarrhea. Larger infarcts may cause more pronounced fibrosis, which may narrow the intestinal lumen and mimic carcinoma.

Arterial infarcts caused by sudden occlusion of a major intestinal artery by thrombi or emboli are characterized by massive hemorrhagic necrosis of intestinal loops. This catastrophic event usually necessitates surgical resection of the intestinal loop and has a high mortality.

Venous infarcts of the intestines may also be caused by venous thrombosis. This is typically seen in hypercoagulable states such as Trousseau syndrome caused by abdominal cancer. **Hypotensive infarcts** due to hypoperfusion of the intestinal mucosa are found in shock caused by profuse bleeding or heart failure.

Bleeding from the intestines is called **hematochezia.** The most common cause of rectal bleeding is dilated and thrombosed veins of the hemorrhoidal plexus **(hemorrhoids).** It can be caused by cancer, diverticulosis, inflammatory bowel disease, and almost all infectious diseases involving the intestines.

Angiodysplasia, a vascular lesion of the right side of the colon composed of interanastomizing thin-walled mucosal vessels, is an important cause of bleeding in the elderly. The cause of this vascular lesion is not known.

Neoplasms of the Intestines

Tumors of the intestines can originate from the epithelium, mesenchymal tissues, and lymphoid cells and are classified as benign or malignant. They are common in the colon, but relatively rare in the small intestine and the appendix.

Benign tumors of the intestines are mostly of epithelial origin. They protrude into the ileum; thus they are called *polyps.* Like all other tumors of the intestines, they are located predominantly in the large intestine. **Polyps** are histologically classified into two major groups (Fig. 10-4 and Table 10-4):

- **Non-neoplastic polyps,** which include hyperplastic polyps, hamartomatous polyps, juvenile retention polyps, and lymphoid polyps
- **Neoplastic polyps,** which include tubular adenomas and villous adenomas

Hyperplastic polyps are the most common polyps in the colon. They appear like dewdrops on the mucosa and usually measure <5 mm. They are composed of hyperplastic epithelial cells that form glands

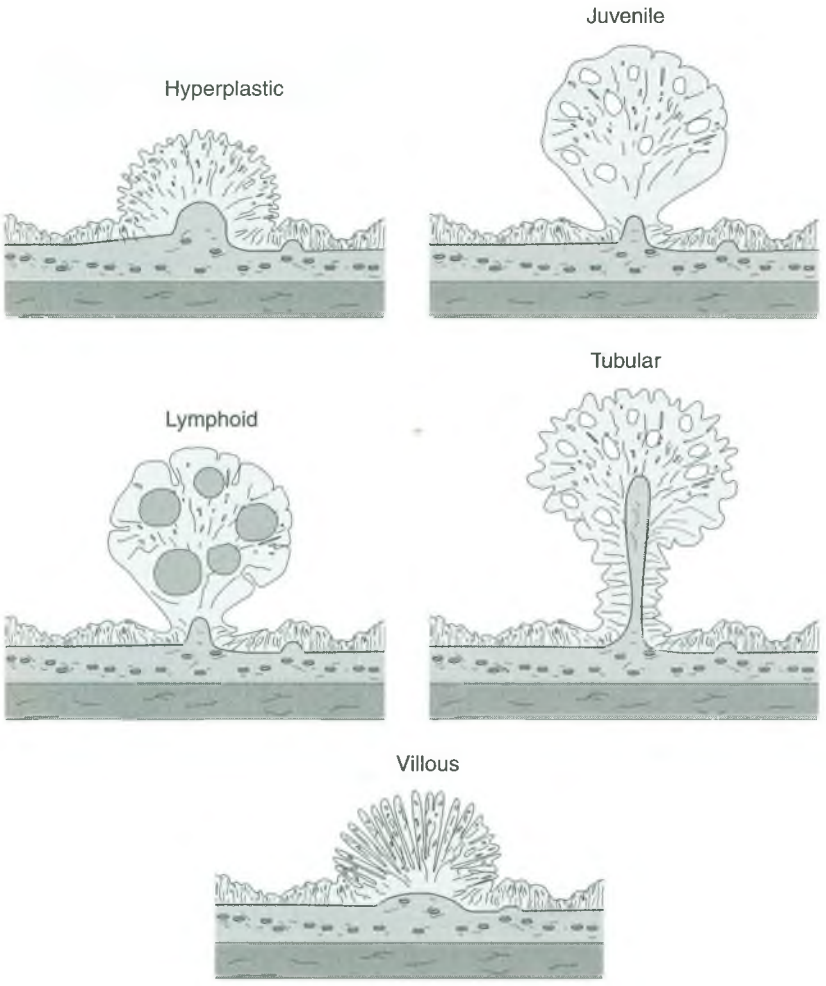


Figure 10-4.
Colonic polyps.

with serrated luminal contours. Hyperplastic polyps are usually asymptomatic and are discovered by chance during endoscopy.

Hamartomatous polyps composed of irregularly arranged glands and strands of smooth muscle are found in Peutz-Jeghers syndrome. **Juvenile retention polyps** are found in children and adolescents. **Lymphoid polyps** are composed of hyperplastic lymph nodes causing mucosal bulging. None of these polyps is considered to be preneoplastic, nor do they evolve into carcinoma.

Neoplastic polyps are classified as tubular or villous adenomas or tubulovillous adenomas. They may be solitary or multiple. Tubular adenomas account for 80% of all neoplastic polyps. The incidence of tubular adenomas increases with age; by age 60 years, at least 30% of all men and women have such tumors in their large intestine. Pure villous adenomas are also age-related tumors, but they occur less often. In patients afflicted with the **familial adenomatous polyposis coli syndrome,** an autosomal dominant tumor syndrome, the colon contains hundreds of neoplastic polyps.

TABLE 10-4.
Tumors of the Colon

- **Benign tumors**
  - Non-neoplastic polyps
    - Hyperplastic
    - Hamartomatous
    - Juvenile (retention)
    - Lymphoid
  - Neoplastic polyps
    - Tubular adenoma
    - Villous adenoma
    - Tubulovillous adenoma
  - Benign mesenchymal tumors
    - Lipoma
    - Neurinoma
- **Malignant tumors**
  - Adenocarcinoma
  - Carcinoid tumor
  - Lymphoma
  - Leiomyosarcoma
  - Gastrointestinal stromal tumors

Tubular adenomas are pedunculated tumors that have a rounded part (head) and an elongated stalk. Most of them are multiple and measure <2 cm in diameter. Histologically, they are composed of regular glands that have round or oval lumen and are lined with uniform cuboidal cells.

Villous adenomas are sessile broad-based lesions composed of finger-like villi. These villi are lined by uniform mucus-secreting, tall cylindrical cells with nuclei located at the base. **Tubulovillous adenomas** have the pedunculated appearance of tubular adenomas but are composed of both tubular glands and villi. Tubular adenomas give rise to cancer in 1% to 2% of cases, whereas the malignant transformation of villous adenomas occurs in approximately 50% of cases.

Carcinoma of the intestines is the second most lethal cancer in men and is ranked third after carcinomas of the breast and lung in women. Histologically, most of these tumors are classified as adenocarcinomas and occur most often in the colon; only 2% are found in the small intestine, and 1% are found in the appendix. The left part of the colon is more often involved than any other part. Approximately 50% of all cancers are located in the rectosigmoid and can be reached by the finger during rectal examination.

On gross examination, carcinomas of the cecum appear as flat, plate-like ulcerated lesions, whereas those of the left side of the colon assume a napkin ring–like appearance, narrowing the lumen of the intestine. Tumor cells invade the wall of the intestine, extending into the pericolic fat and mesenteric lymph nodes. Tumor cells

metastasize through the portal vein to the liver and also to other and distant organs. **Clinical findings** depend on the location of the tumor and the extent of its spread. Carcinoma of the colon tends to bleed, and **occult blood** found in the feces can be the first sign of this malignancy. Long-term bleeding could cause anemia. Carcinoma of the left side of the colon interferes with defecation and could cause obstruction. Feces passing through the narrowed lumen are thin like a pencil. The prognosis of colon cancer depends on the extent of its spread, as determined by using the modified Dukes classification. More than 90% of patients with a stage A lesion (confined to the mucosa) survive 5 years, whereas the survival rate is only 10% in those with stage D lesions. Early diagnosis is the only way of improving the cure rate of colon carcinoma patients. It is based on examination for occult blood, rectoscopy, or colonoscopy. Tumors also release the **carcinoembryonic antigen** into blood, which serves as a tumor marker. However, this test is not specific enough to be used for screenings for colon cancer. It is used most often for follow-up of colon cancer patients to determine the recurrence of tumors after colectomy.

Other tumors of the intestines are less common. The most important of these neoplasms are carcinoid tumors, lymphomas, smooth muscle cell tumors, and so-called gastrointestinal stromal tumors.

Carcinoid tumors are low-grade malignant tumors of neuroendocrine cells. These tumors can occur in any part of the gastrointestinal tract, but are most often located in the appendix and small intestine. They secrete serotonin and polypeptide hormones, which could increase the mobility of the intestines and cause colic or diarrhea. Bioactive substances from carcinoid tumors are carried by portal blood to the liver, where they are inactivated. Only after the carcinoids are metastasized to the liver do they secrete into the systemic circulation. Serotonin and other products secreted by these hepatic metastases reach the right side of the heart and produce endocardial and valvular changes typical of the carcinoid heart disease.

Chapter 11

Liver and Biliary System

HEPATIC FAILURE

The liver has an abundant reserve and a remarkable ability to regenerate. However, when 80% or more of the hepatic mass is destroyed or dysfunctional, liver failure becomes clinically apparent. The liver cells may be present, as in cirrhosis, but disruption of the blood supply and loss of normal hepatic architecture may render the cells dysfunctional. Hepatic failure manifests as an inability of the liver to excrete certain substances (e.g., bilirubin), an inability of the liver to detoxify certain substances (e.g., ammonia), or an inability to synthesize proteins (e.g., coagulation factors and albumin). Liver cells are released into blood enzymes such as alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase. Alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase combined with serum albumin, prothrombin, and bilirubin measurements are called **liver function tests.**

Jaundice becomes clinically evident when bilirubin increases to >3 mg/dl. Jaundice is a feature of acute and chronic liver failure, and it may be due to either conjugated or unconjugated hyperbilirubinemia.

Encephalopathy develops because liver cannot detoxify toxic metabolites such as ammonia and mercaptans and false neurotransmitters such as γ-aminobutyric acid. These substances act on the brain, cause coma, and may even kill the patient. Hepatic encephalopathy is characterized by irritability, a flapping tremor *(asterixis)*, a musty smell to the breath, and a progressive loss of mental functions and deepening coma. Although ammonia may not be entirely responsible for all neurologic symptoms and coma, its serum concentration is one of the most reliable indicators of hepatic encephalopathy.

Hepatorenal syndrome is a sudden renal failure with oliguria in patients with acute hepatic failure or chronic liver disease. Hypoperfusion of the kidney is probably responsible for renal failure, but its pathogenesis is not completely understood. Curiously, kidneys that have virtually ceased to put out urine can be transplanted and function well in the new recipient.

Coagulopathy is a constant feature of liver failure. The liver produces coagulation factors; thus it is not surprising that a bleeding tendency develops if the liver cannot function properly. In viral hepatitis, the activated prothrombin time may be the most reliable method of assessing the need to hospitalize the patient.

Hypoalbuminemia is invariably present in end-stage liver disease because the liver is the only source of albumin. Hypoalbuminemia may lead to edema and contributes to **ascites** formation in chronic liver failure.

Portal hypertension is a common feature of cirrhosis, which interferes with blood flow through the liver, raising the blood pressure in the portal system. Ascites, splenomegaly, and esophageal varices are typical signs of portal hypertension.

Endocrine abnormalities develop because the damaged liver has a reduced capacity to catabolize steroid hormones. Excess estrogen causes dermal **spider angiomas,** breast enlargement in men **(gynecomastia),** and **testicular atrophy.** The pubic hair may show a feminine distribution, and there may be loss of chest hair.

JAUNDICE

Bilirubin is derived from the heme portion (80%) of hemoglobin, and the remainder is derived from other hemoproteins (Fig. 11-1). The heme is separated from the iron and globin components in the mononuclear phagocytic system of the spleen and liver and released into the blood in the form of bilirubin, which is transported to the liver bound to albumin. In the sinusoids of the liver, it binds to a carrier protein on the surface of hepatocytes, which mediates its uptake. In the cytoplasm, it is acted on by the uridine diphosphoglucuronyl transferase (UDPGT) to form the water-soluble diglucuronide, which can be excreted in the bile. When bilirubin reaches the intestine, bacteria convert it to a mixture of water-soluble compounds known as *urobilinogen.* Bilirubin and bile salts are mostly excreted in feces, but some are reabsorbed and circulated in the blood (enterohepatic circulation of the bilirubin and bile salts).

Jaundice, or icterus, presents as yellow discoloration of skin, mucosae, and other tissues. It is caused by an accumulation of bilirubin in blood and tissues. Clinically, it becomes apparent when bilirubin levels in serum reach approximately 2 to 3 g/dl. Jaundice can be caused by

- **Overproduction of bilirubin** (hemolytic jaundice)
- **Abnormal hepatic processing of bilirubin** (hepatocellular jaundice)
- **Blocked excretion of bilirubin** (obstructive jaundice or cholestasis)

Biochemically, jaundice can be classified as predominantly **unconjugated** or predominantly **conjugated hyperbilirubinemia** (Table 11-1).

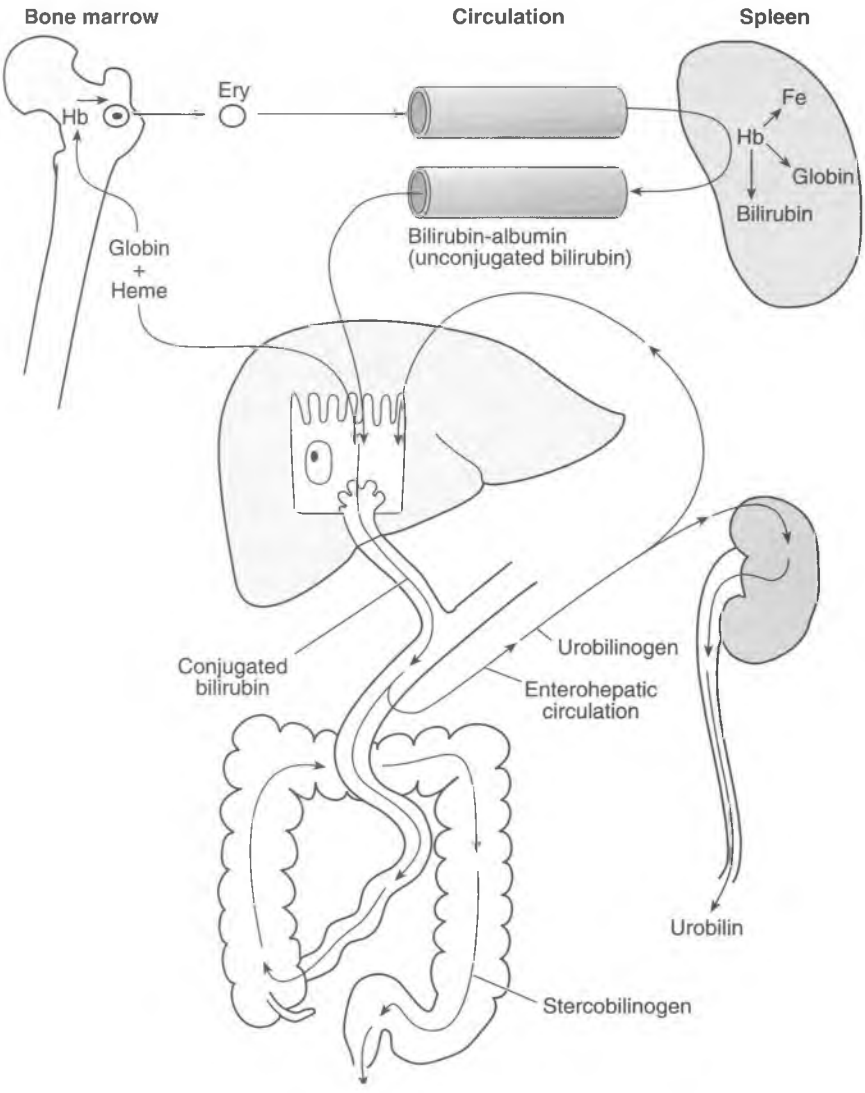


Figure 11-1.
Bilirubin metabolism and causes of jaundice.

In hemolytic jaundice, blood contains unconjugated bilirubin. In hepatocellular jaundice, blood contains a mixture in which conjugated predominates over unconjugated bilirubin. In obstructive jaundice most of the bilirubin in blood is in the conjugated form.

Hemolytic jaundice, a form of unconjugated hyperbilirubinemia, is caused by excessive breakdown of red blood cells (RBCs). It is usually mild because hemolysis usually does not produce indirect levels of bilirubin above approximately 2 to 3 mg/dl. In the newborn, with massive hemolytic anemia caused by maternofetal blood group incompatibility, the mechanisms for bilirubin uptake and conjugation in the liver are not fully functional, and serum levels of bilirubin can increase to >20 mg/dl. This is associated with passage

TABLE 11-1.
Classification of Jaundice

Predominantly unconjugated hyperbilirubinemia
Overproduction
Hemolytic anemia
Ineffective erythropoiesis (e.g., megaloblastic anemias)
Decreased hepatic uptake
Drugs (e.g., rifampin)
Decreased conjugation
Gilbert syndrome
Crigler-Najjar syndrome types I and II
Drugs (e.g., chloramphenicol)
Combination of overproduction and liver cell dysfunction
Neonatal jaundice
Predominantly conjugated hyperbilirubinemia
Impaired hepatic excretion
Dubin-Johnson syndrome
Rotor syndrome
Hepatitis (viral, drug-induced)
Primary biliary cirrhosis
Sepsis
Extrahepatic biliary obstruction
Gallstones
Tumors (carcinoma of bile ducts, head of pancreas)
Primary sclerosing cholangitis
Congenital biliary atresia

of bilirubin across the blood-brain barrier and deposition of bilirubin into basal ganglia of the brain **(kernicterus).** In adults, unconjugated bilirubin does not cross the blood-brain barrier. Because it is bound to albumin, it does not appear in urine.

Hepatocellular jaundice results from inadequate uptake, conjugation, or excretion of bilirubin. This typically occurs in hepatitis and various liver diseases marked by liver cell injury. Liver function test results are typically abnormal.

Incomplete or faulty conjugation of bilirubin in liver cells is a cause of jaundice in several inherited disorders. **Crigler-Najjar disease** is a congenital autosomal recessive disorder characterized by complete absence of UDPGT activity (type I) or its marked reduction (type II). Infants who have type I disease cannot create the enzyme following phenobarbital stimulation, whereas individuals with type II can. Type I disease is rapidly fatal due to bilirubin encephalopathy (kernicterus).

Gilbert syndrome is an autosomal dominant benign disorder with mild unconjugated hyperbilirubinemia due to a defect in bilirubin conjugation and no evidence of liver disease. Approximately 5% of the population has the disease, which is more common in male subjects.

Dubin-Johnson syndrome is a relatively benign disorder of intracellular transport, excretion, or transport and excretion of conjugated bilirubin. Patients show chronic or episodic jaundice, and their livers are black due to lysosomal accumulation of a black pigment. Blood contains increased amounts of conjugated bilirubin.

Rotor syndrome is also a familial form of mild conjugated hyperbilirubinemia. There is no pigment accumulation in the liver.

Neonatal jaundice develops in most premature and many full-term babies. During pregnancy, maternal liver metabolizes and excretes fetal bilirubin because the fetal liver cannot adequately take up, conjugate, and excrete bilirubin. The destruction of fetal RBCs immediately after birth, which occurs physiologically, overburdens the neonatal liver, resulting in unconjugated hyperbilirubinemia. Exposure to light can enhance conjugation of bilirubin in the newborn and is used to treat severely jaundiced babies.

Cholestatic jaundice occurs due to an obstruction of bile flow. Obstruction of the biliary system can occur at various levels. It is considered to be either intrahepatic or extrahepatic.

Intrahepatic obstruction can be caused by fibrosis, tumors, or destruction of intrahepatic bile ducts as in primary biliary cirrhosis. **Extrahepatic obstruction** may be caused by stones in the common bile duct, tumors, or fibrotic scars. Long-standing biliary obstruction induces periportal hepatic fibrosis, which may induce secondary biliary cirrhosis.

VIRAL HEPATITIS

Hepatitis usually results from infection with one of several of hepatotropic viruses (labeled hepatitis viruses A through E, known as HAV, HBV, HCV, HDV, and HEV). Other viruses such as Epstein-Barr virus and herpesvirus are less common causes. Yellow fever is an important viral cause of liver failure in the tropics, but is uncommon in the United States. It is important to note the following:

- In clinical practice, the term *viral hepatitis* comprises diseases caused by five viruses (HAV, HBV, HCV, HDV, and HEV), but new viruses are added to this list each year.
- All viral hepatitides have **four phases:** (1) incubation phase, which varies from 2 to 26 weeks; (2) preicteric phase, characterized by nonspecific symptoms; (3) icteric phase; and (4) recovery phase.

- **HAV and HEV** infections are acquired by the **oral** route, whereas other viruses (e.g., HBV, HCV, and HDV) are transmitted by **blood** or **body fluids** on close body contact such as sexual intercourse.
- HAV and HEV, in contrast with other viruses, do not cause chronic hepatitis or a carrier state.
- **Vaccines** have been developed for HAV and HBV.

Pathologic changes caused by hepatotropic viruses are remarkably similar. These changes include ballooning degeneration and focal apoptotic cell death of hepatocytes in the form of acidophilic bodies; lobular disarray; hyperplasia of Kupffer cells; and inflammatory cells, mostly lymphocytes and macrophages in portal tracts and the lobule. Regeneration of hepatocytes is common. Fibrosis is inconspicuous and is usually limited to the portal tract in protracted disease. Infection with HBV and HCV can cause chronic hepatitis characterized by fibrosis, widening of portal tracts, and formation of fibrous septa that extend into the lobules. Extensive fibrosis combined with massive distortion of the liver architecture and formation of hepatocellular nodules is called **cirrhosis.**

Hepatitis A

HAV is an RNA virus belonging to the small **picornavirus** class. It is spread by the fecal-oral route, and infections tend to occur in epidemic outbreaks, especially in underdeveloped countries, where it typically affects children. In the United States, the infection is usually subclinical as evidenced by the fact that 50% of 50-year-old adults have antibodies to HAV, although they have no recollection of an episode of hepatitis. The virus appears to be directly cytotoxic to liver cells. Most of the symptoms are nonspecific, such as malaise and fatigue. Jaundice is mild but associated with bilirubin in urine. Liver function test results are abnormal. There is a short incubation period (~3 weeks), and the disease is usually mild. Massive or submassive liver necrosis **(fulminant hepatitis)** is rare (1:1,000). Antibodies appear first as IgM and then within 4 to 6 weeks of infection, IgM is replaced by IgG, which lasts a lifetime. HAV does not cause chronic liver disease, and there are no HAV carriers.

Hepatitis B

HBV is a **DNA hepadnavirus.** The virus consists of a DNA core, a DNA polymerase protein and a related protein known as the *E antigen,* and a capsule that contains the surface (S) antigen. The transmission is usually by blood, intimate contact, or exchange of bodily fluids. HBV was formerly related to blood transfusion; routine screening has aided in its elimination as a transfusion-related pathogen. The incubation period is longer than hepatitis A and lasts approximately 2 to 3 months. In addition to acute self-limited hepatitis, HBV can cause fulminant liver failure (<1%) or chronic hepatitis

(5% to 10%). Approximately 0.1% to 1.0% of all blood donors worldwide are asymptomatic carriers. Chronic hepatitis can lead to cirrhosis, which may be complicated by hepatocellular carcinoma.

Hepatitis C

HCV is an **RNA flavivirus** and is transmitted by blood or body fluids during close contact such as sexual intercourse. In approximately 40% of cases, the mode of infection cannot be established. The infection usually causes mild hepatitis, which is often asymptomatic. Nevertheless, the virus may persist and more often than any other viral infection, it may cause chronic hepatitis, estimated to occur in 50% of infected persons. Cirrhosis develops in 50% of those with chronic hepatitis, some of whom also develop hepatocellular carcinoma.

Hepatitis D (Delta Agent)

HDV is a **replication defective RNA virus** that requires hepatitis B as a helper for replication in human liver cells. Infection may be a *coinfection* with HBV or superimposed on chronic HBV infections or asymptomatic HBV carriers. Coinfection seems to carry greater morbidity and mortality, whereas superinfection leads to a higher incidence and severity of chronic hepatitis. HDV is most prevalent in HBV-infected persons in Africa; for an unknown reason, it is not common in Japan and China. In the United States, HDV is relatively rare and restricted to HBV-infected drug addicts and hemophiliacs.

Hepatitis E

HEV is an **RNA virus** causing sporadic outbreaks of mild hepatitis in children similar to hepatitis A. It is known to occur worldwide and is endemic in India, Africa, and Mexico. Travelers to these areas may become infected by the oral route. HEV infection is not associated with chronic hepatitis or a carrier state.

BACTERIAL LIVER DISEASE

Bacteria may reach the liver through the bile ducts and cause ascending cholangitis or hematogenously and cause **liver abscesses.** Bacteria traveling through the portal vein originate in the intestines. Previously, liver abscess was an important complication of acute appendicitis. Today, it is a complication of inflammatory bowel disease. Hematogenous abscesses of arterial origin are a complication of systemic bacteremia.

PARASITIC AND PROTOZOAL LIVER DISEASES

Parasitic infections of the liver are more common in the tropics than in the United States. Important pathogens are *Schistosoma mansoni, Schistosoma japonicum, Echinococcus granulosus,* and *Opisthorchis sinensis. Entamoeba histolytica* is the most important protozoal pathogen.

TOXIC HEPATITIS

Toxic liver injury may be caused by a variety of exogenous substances or drugs. Some of these agents are *direct* hepatotoxins, meaning they act on the liver without further modification. Other agents are *indirect* hepatotoxins in that they require metabolic conversion to a toxic compound. *Predictable* hepatotoxins are those that cause liver cell injury in everyone in a dose-dependent manner. Acetaminophen is toxic if taken in large amounts. *Unpredictable* hepatotoxins cause liver cell injury in only sensitive individuals who may lack an essential enzyme or are allergic to that substance. Often the cause of an unpredictable hepatotoxic reaction is not known (*idiosyncratic reaction*). Many drugs belong to this group of hepatotoxins. The common toxic responses in the liver are inflammation and necrosis, indistinguishable from viral hepatitis. Some drugs cause cholestasis or steatosis (fatty liver).

ALCOHOLIC LIVER DISEASE

There are an estimated six million chronic alcoholics in the United States. Alcohol causes three forms of liver injury: fatty liver, alcoholic hepatitis, and cirrhosis.

Alcohol-induced fatty change occurs in anyone who drinks 80 to 90 g of alcohol per day. Fat accumulates in the liver due to an influx of free fatty acids mobilized from fat stores, excessive hepatic synthesis of triglyceride, failure of export in the form of lipoprotein, and decreased breakdown (metabolism). **Fatty liver** causes no clinical symptoms and is reversible.

Alcoholic hepatitis is an inflammation that develops in approximately 10% to 15% of chronic alcoholics. Alcohol is a zone 3 (pericentral) toxin, causing direct liver cell injury evidenced as either fatty change or ballooning degeneration and necrosis. The hepatocellular changes are associated with eosinophilic fibrillar cytoplas-

mic aggregates known as **alcoholic hyaline** or **Mallory bodies.** These bodies are composed of intermediate filaments (keratin). Damaged cells disintegrate, provoking an intralobular acute inflammation and fibrosis, which is most prominent around the centrilobular vein. The portal tracts may show chronic inflammation, which occasionally spills across the limiting plate.

Alcoholic hepatitis is usually diagnosed after a binge of heavy drinking. The patient typically presents with an acute onset of fever, malaise, and is usually very sick. Fever, leukocytosis, and jaundice may be present. Women are slightly more often affected than men.

Alcoholic cirrhosis is the end-stage liver disease that develops in approximately 20% of chronic alcohol abusers. Although there is a rough relationship between the dose of alcohol and duration of consumption and severe liver injury, the exact pathogenesis of alcoholic cirrhosis remains unknown. Factors that may play a role include gender, race, individual susceptibility, and type of alcohol consumed. The presence of other diseases such as diabetes mellitus, hemochromatosis, or chronic viral hepatitis may play a pathogenetic role.

Cirrhosis

Cirrhosis is a synonym for **end-stage chronic liver disease**. The architecture of the entire liver is altered, and the normal liver parenchyma is replaced by nodules composed of regenerating hepatocytes circumferentially surrounded by fibrous septa, which contain the blood vessels and bile ducts. Parenchymal changes alter the blood flow through the hepatic parenchyma and impede excretion of the bile. All the functions of the liver are affected, and unless the liver is replaced by a transplant, cirrhosis is lethal (Fig. 11-2).

Although alcohol abuse causes 60% to 70% of cirrhosis in the United States, there are a number of other causes (Table 11-2). The cause of cirrhosis remains undetermined in approximately 10% to 20% of cases **(cryptogenic cirrhosis).**

Morphologically, cirrhosis can be classified as *micronodular,* if composed of small nodules measuring 5 to 10 mm in diameter, or *macronodular,* if the nodules are larger. The nodules may be uniform or vary in size. Alcoholic cirrhosis is usually micronodular and associated with fatty change of hepatocytes. If associated with broad areas of scarring, cirrhosis is called *postnecrotic,* under the assumption that it follows widespread liver necrosis caused by virus, drugs, or toxins.

Pathogenetically, cirrhosis is classified as portal or biliary. *Portal cirrhosis* results from liver cell injury by a virus, drugs, or toxins. *Biliary cirrhosis* presents in two forms: primary and secondary biliary cirrhosis. **Primary biliary cirrhosis** begins as a disease of the small bile ducts, which are destroyed by T-lymphocytes and macrophages.

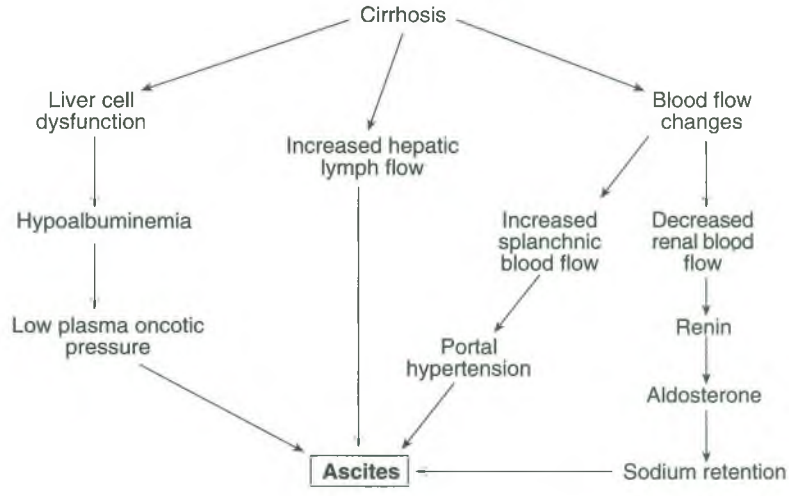


Figure 11-2.
Pathogenesis of ascites.

TABLE 11-2.
Causes of Cirrhosis

Cause	Percentage Occurrence
Alcohol abuse	60–70
Viral hepatitis (mostly HBV and HCV)	10
Genetic disorders	5
α_1-Antitrypsin deficiency	
Hereditary hemochromatosis	
Wilson disease	
Biliary disease	5
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Extrahepatic biliary obstruction	
Cryptogenic cirrhosis	10–20

Destruction of bile ducts is followed by fibrosis extending into the lobule and the development of cirrhosis. Primary biliary cirrhosis is an autoimmune disease that affects women. It is associated with antimitochondrial antibodies, which are useful for diagnosis. Clinically, it presents as insidious jaundice with itching and hypercholesterolemia, ultimately leading to end-stage liver failure. **Secondary biliary cirrhosis** is a consequence of chronic cholestasis due to the obstruction of extrahepatic bile ducts.

TABLE 11-3.

Special Histologic and Biochemical Features of Common Forms of Chronic Hepatitis and Cirrhosis

Diseases	Histologic Features	Diagnostic Tests
Viral infection		
Chronic HBV hepatitis	"Ground-glass" hepatocytes; "sandy nuclei" of hepatocytes	HBsAg, HBeAg
Chronic HCV hepatitis	Fatty change; bile ductular inflammation	Anti-HCV
Chronic alcohol abuse	Mallory (alcoholic) hyaline	No specific test
	Fatty change of hepatocytes	Elevated gamma glutamyltransferase, alanine aminotransferase
Immune disease		
Primary biliary cirrhosis	Bile ductule destruction; portal tract granulomas	Antimitochondrial antibodies
Autoimmune (lupoid) hepatitis	Plasma cell infiltrates	Antinuclear antibodies, anti–smooth muscle antibodies
Genetic metabolic diseases		
Hereditary hemochromatosis	Hemosiderin in liver, Kupffer and bile duct cells	High saturation of serum transferrin
Wilson disease	High copper content	Low ceruloplasmin in serum
α_1-Antitrypsin deficiency	Periodic acid–Schiff + cytoplasmic globules	Low α_1-antitrypsin in serum

Cirrhosis is a feature of several genetic diseases. **Hemochromatosis** causes cirrhosis, which is associated with iron storage in hepatocytes, hyperpigmentation (bronzing) of the skin, and diabetes mellitus. **Wilson disease** is an inherited disorder of copper metabolism. Serum levels of ceruloplasmin, the copper-binding protein, are low, and copper deposits are found in many tissues. The liver disease begins in childhood as chronic hepatitis and progresses to cirrhosis. **Kayser-Fleischer rings** of the cornea and degeneration of basal ganglia of the brain are other constant signs of copper toxicity. **α_1-Antitrypsin deficiency** is associated with chronic lung disease and cirrhosis. Round bodies containing stored enzyme that have positive results with the periodic acid–Schiff test are found in hepatocytes (Table 11-3).

Clinical manifestations of cirrhosis can be related to **loss of metabolic function** normally performed by the liver; **portal hypertension** resulting from impeded blood flow through the liver; and **faulty excretion of bile.** The most common clinical features of cirrhosis are presented in Figure 11-3.

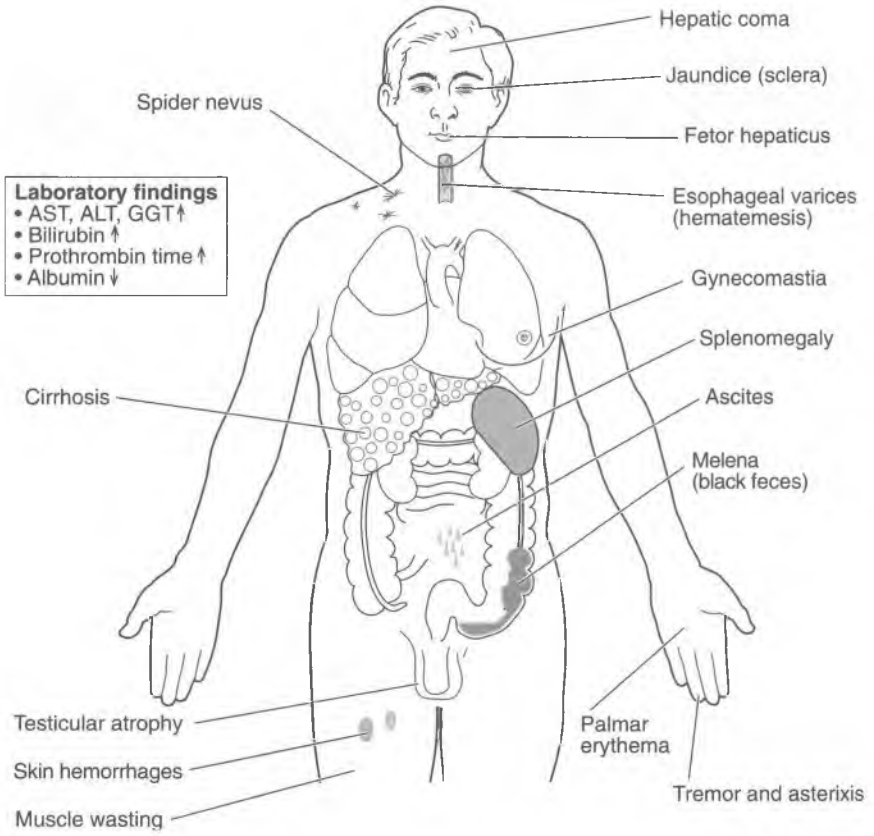


Figure 11-3.
Clinical manifestations of cirrhosis. (AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase.)

VASCULAR DISORDERS OF THE LIVER

Acute and chronic passive congestion are typical consequences of right-sided heart failure. In acute heart failure, the liver becomes congested, enlarged, and at times painful. Central vein and pericentral sinusoids dilate due to congestion with blood, and hepatocytes may undergo necrosis. If the central congestion develops slowly but persists, the hepatic parenchymal cells may undergo compression atrophy; over time, they are replaced by fibrous tissue. Cardiac cirrhosis develops in long-lasting disease, most often in conjunction with chronic constrictive pericarditis.

Obstruction of the hepatic vein by thrombi or tumors is called **Budd-Chiari syndrome.** It is a common complication of polycythemia.

HEPATIC NEOPLASMS

Benign Tumors of the Liver

The most common benign tumors of the liver are **hemangiomas.** These small blood-filled tumors composed of capillaries are of no clinical significance. **Hepatic adenoma** is a benign tumor composed of liver cells. It is seen primarily in young women, especially those taking oral contraceptives. **Nodular hyperplasia** is a hepatic tumor-like lesion, which is also more common in young women. Histologically, it is composed of liver cells arranged around a stellate fibrous scar. All of these benign lesions are usually asymptomatic and are accidentally discovered by surgeons during abdominal surgery or by radiologists during computed tomography. Subcapsular hepatic adenomas may rupture and cause massive bleeding.

Malignant Tumors of the Liver

Hepatocellular carcinoma of the liver is one of the most prevalent malignancies in humans. It is the most common tumor in sub-Saharan Africa and parts of Asia. Hepatocellular carcinomas almost always (90%) arise in cirrhotic livers and are often related to HBV and HCV infection.

On gross examination, hepatocellular carcinoma may present as a solitary mass, as multiple distinct nodules, or it may diffusely infiltrate the cirrhotic liver. To some extent, hepatocellular carcinoma cells resemble liver cells, but they are arranged in groups, acini, or solid sheets and never form sinusoids lined by Kupffer cells. Tumor cells invade hepatic veins and tend to metastasize hematogenously. Raised serum α-fetoprotein is a useful serum marker of hepatocellular carcinoma. Prognosis for these tumors is poor.

Cholangiocarcinoma is an adenocarcinoma of intrahepatic bile ducts. It is less common than hepatocellular carcinoma, but it also has a poor prognosis. Because the tumor has no distinctive features, it is difficult to distinguish from metastatic adenocarcinomas, especially in small liver biopsy samples.

Hepatoblastoma is a rare tumor of infants and young children. Histologically, it has a mixture of epithelial elements resembling fetal liver and primitive mesenchymal tissues. Serum α-fetoprotein is highly elevated in the blood. This tumor has a poor prognosis.

Sarcomas of the liver are very rare. Hemangiosarcomas of the liver have been causally linked to industrial exposure to vinyl chloride and medicinal exposure to thorium dioxide (Thorotrast),

a radioactive compound previously used as a radiographic contrast material.

Metastatic tumors in the liver are very common. Most often they are derived from primary carcinomas of the gastrointestinal tract, lung, or breast. Metastases present as multiple round tumor masses, which often have a necrotic center.

GALLBLADDER AND EXTRAHEPATIC BILIARY SYSTEM

The anatomy of the extrahepatic biliary system is quite variable, and minor abnormalities such as duplications or cysts are common. Agenesis of the gallbladder and atresia of extrahepatic biliary system are uncommon. **Extrahepatic biliary atresia** is nevertheless the most common cause of obstructive jaundice in infants. It requires surgical treatment, and in some cases the only solution is transplantation of the liver.

Cholelithiasis

Stones in the gallbladder and extrahepatic biliary system are extremely common in the United States and the Western world, affecting as many as 20% of adult men and 35% of women older than 75 years of age. In the United States, each year more than one million people undergo surgery for the removal of gallstones. The majority of gallstones (>75%) in the United States consist of cholesterol **(cholesterol stones)** and cholesterol mixed with calcium bilirubinate **(mixed stones).** In Asians, stones primarily consisting of calcium bilirubinate **(pigment stones)** are more common.

Gallstone formation is based on simple physical principles. The mixture of bile secreted by the liver contains bilirubin, bile salts (sodium and calcium salts of bile acids), cholesterol, and lecithin in a precarious equilibrium. Factors that favor precipitation of this metastable solution include increased cholesterol or decreased lecithin and some nidus of particulate material around which crystallization can occur. The human factors that seem to favor cholelithiasis include the five Fs: obesity (fat), female, fair complexion, middle age (40s), and multiple pregnancies (fertile). Most gallstones are clinically silent. Irritation of the gallbladder causes **cholecystitis**. Gallstones impacted in the neck of the gallbladder or in the cystic or common ducts may cause colic. Such attacks of pain are often produced by a fatty meal. Obstruction of the cystic duct may cause hydrops of the gallbladder. Obstruction of the common bile duct by a stone may cause jaundice (Fig. 11-4).

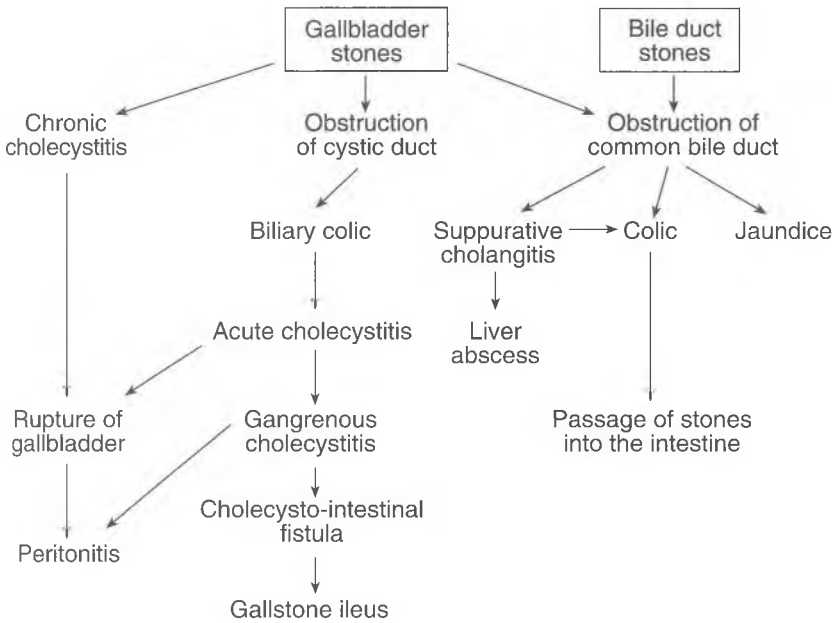


Figure 11-4.
Complications of cholelithiasis.

Acute Cholecystitis

Acute inflammation of the gallbladder occurs in two forms: the far more frequent *calculous* (stone-associated) and the less frequent *acalculous* form. In approximately 90% of cases, stones are present. The inflammation is caused by an ascending infection from the gastrointestinal tract along the peribiliary lymphatics or through the ducts. Obstruction of the biliary system is thought to play an important role. The gross findings include marked inflammation, edema, and hemorrhage of the gallbladder mucosa. The infection may extend to the peritoneal surface and cause localized peritonitis or necrosis of the entire wall **(gangrenous cholecystitis). Empyema** of the gallbladder is a term used to describe accumulation of pus inside the gallbladder. **Acalculous cholecystitis** may be a consequence of *Salmonella typhi* infection in asymptomatic carriers, shock, and autoimmune diseases such as polyarteritis nodosa.

Chronic Cholecystitis and Cholangitis

Chronic cholecystitis is a common disease. Essentially, all gallbladders reviewed for cholelithiasis show histologic signs of chronic inflammation. Bacteria, usually *Escherichia coli,* are only found in bile in approximately 30% of such cases. In the remaining 70% of cases, the bile is sterile, and it is assumed that the inflammation is caused chemically by bile or stones. Dystrophic calcification of the gallbladder wall in long-standing chronic cholecystitis is known as **porcelain gallbladder.**

Chronic cholangitis is, in most instances, a complication of gallstone disease and can be traced to an ascending bacterial infection.

Primary sclerosing cholangitis is a relatively rare fibrosis of the extrahepatic and intrahepatic bile ducts associated with inflammatory bowel disease, particularly ulcerative colitis. It most often occurs in male subjects and can lead to secondary biliary cirrhosis.

Tumors of the Biliary System

Benign tumors rarely occur in the extrahepatic biliary system and gallbladder. Most are epithelial tumors such as a **papilloma** or **mucous gland adenoma.**

Malignant neoplasms are most frequently found, in decreasing order, in the gallbladder, periampullary region of the common duct, common duct proper, and cystic and hepatic ducts as they approach the liver. All these tumors are adenocarcinomas.

Adenocarcinoma of the gallbladder represents approximately 5% of gastrointestinal malignancies. It is also more frequent in women and is strongly associated with gallstones. By the time it produces symptoms, it usually has spread to regional nodes or by direct extension to the liver. Prognosis is poor, with a 5-year survival rate of <5%.

Adenocarcinomas of the common bile duct are most often located in the periampullary region and usually present as jaundice. They have an approximately 35% overall 5-year survival rate, reflecting the fact that these tumors become symptomatic early when they can be treated by total resection.

Chapter 12

Pancreas

CONGENITAL AND HEREDITARY DISORDERS

Congenital anomalies such as **annular pancreas,** which surrounds the duodenum, are fairly common but most often are asymptomatic. If symptoms occur, usually later in life, surgery may be required. Ectopic acinar pancreas can be found in a variety of locations including Meckel diverticula, the wall of the duodenum, the stomach or jejunum, and even the liver. It usually does not produce any problems. **Congenital cysts** lined by cuboidal epithelium are fairly common in the pancreas, but are of no clinical significance.

Cystic fibrosis is the most important genetic disease of the pancreas. It affects mucus secretion, causing plugging of the ducts. Obstruction of the ducts by viscid mucus leads to gradual atrophy of the acinar tissue, which is ultimately replaced by fibrous tissue. Atrophy of the pancreas results in malabsorption and steatorrhea.

INFLAMMATION

Pancreatitis is the most common and potentially most serious nonneoplastic disease of the exocrine pancreas. It may occur as an *acute* fulminant disorder or a more indolent *chronic* disease.

Acute Pancreatitis

Acute pancreatitis represents, in most instances, a sterile inflammation of the pancreas associated with destruction of acini and autodigestion of tissues brought about by the enzymes released from the damaged pancreatic cells (Fig. 12-1). Approximately 80% of all cases of acute pancreatitis are related to either **alcoholism** or obstruction of the common bile duct by **gallstones.** Other causes are less common. It is thought that alcohol-induced spasm of the sphincter of Oddi or obstruction of the bile flow causes a reflux of bile into the

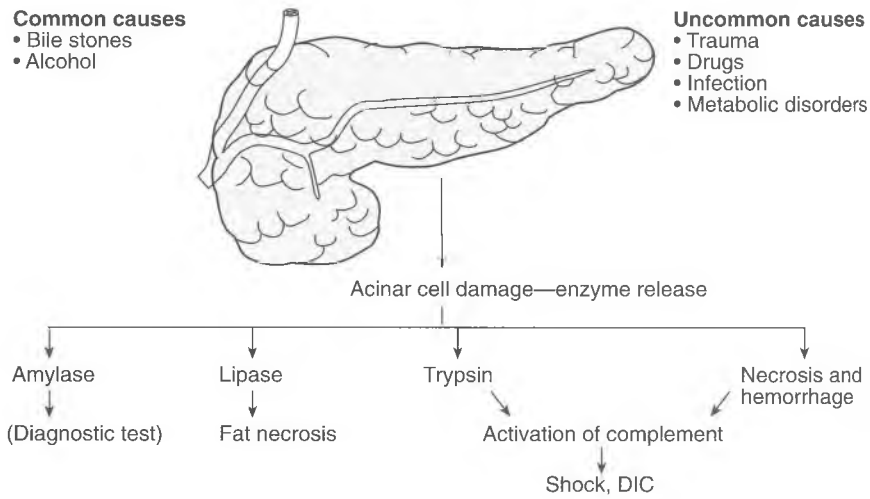


Figure 12-1.
Causes and pathogenesis of acute pancreatitis. (DIC, disseminated intravascular coagulation.)

main pancreatic duct, which leads to intrapancreatic activation of digestive enzymes. Proteases such as trypsin and lipases activated inside the pancreas get into the tissues, causing destruction of the pancreas and adjacent fat tissue (fat necrosis). Enzymes such as chymotrypsin may activate complement in serum and thus attract neutrophils to the pancreas. Necrosis of the tissues is accompanied by an acute inflammation response. Destruction of blood vessels provokes massive bleeding. Ascites rich in digestive enzymes is a common feature. Hemorrhage may convert the entire pancreas into a retroperitoneal hematoma. Autodigestion of tissue may lead to the formation of a pancreatic **pseudocyst** filled with tissue debris and enzymes. Vascular collapse and shock may occur in severe cases.

Pancreatic enzymes such as amylase and lipase are released into the serum. Lipase leaking out from the blood vessels may cause enzymatic fat necrosis in distant sites such as subcutaneous tissue or breasts. Measurement of serum amylase and lipase are important for the diagnosis of acute pancreatitis. Fat necrosis around the pancreas or other sites leads to the formation of calcium soaps and, accordingly, serum calcium concentrations decreases 2 to 3 days after an acute attack of pancreatitis.

Most patients recover after an episode of acute pancreatitis, but some have relapses that could ultimately destroy the pancreas entirely and cause pancreatic insufficiency. Acute pancreatitis has a mortality of 5% to 10%.

Chronic Pancreatitis

Chronic pancreatitis is also associated with alcohol abuse and with chronic **cholecystitis** and **cholelithiasis.** In **alcoholic pancreatitis,** the

ducts are often seen to be blocked by eosinophilic mucinous concretions. The acini are atrophic, and the interstitium is greatly expanded by fibrosis. Calcification is evident grossly and microscopically. Inflammation is present, consisting mostly of lymphocytes, but usually it is not severe. In addition to the plugging, the duct may show metaplasia to squamous epithelium and periductal fibrosis. Intraductal calculi may be present. Focal tissue calcification is also seen.

Clinically, the disease presents as a **malabsorption syndrome** due to lack of pancreatic enzymes. Dull abdominal pain is a common feature. Destruction of islet cells may cause diabetes mellitus, which is found in 30% of cases. Pseudocysts, that is, cystic spaces lined by fibrous tissue and lacking an epithelial lining, or true cysts representing dilated ducts are found in 20% of cases.

NEOPLASIA

Tumors of the pancreas can originate from the exocrine cells (ducts and acini) or the endocrine cells (islets of Langerhans). They can be benign or malignant or secretorily active or afunctional.

Tumors of the Exocrine Pancreas

Benign neoplasms of the exocrine pancreas are rare and most often found in women in their seventh and eighth decades. They are usually cystic and commonly multiloculated and are usually classified as **serous or mucinous cystadenomas.** Serous cystadenomas are lined by cuboidal cells and contain thin watery fluid. Mucinous cystadenomas have tall columnar cells with mucin secretion lining the cysts and are more difficult to distinguish from well-differentiated adenocarcinomas that have become cystic. Both are thought to arise from pancreatic ducts.

Malignant neoplasms are the fifth most common cause of cancer deaths in the United States. The incidence of pancreatic cancer has been increasing for no obvious reason. The causes of this cancer are unknown, and there are no means to prevent or treat it. Almost all malignant tumors of the pancreas are **adenocarcinomas** originating from ducts (99%), with only approximately 1% of acinar origin. **Ductal carcinoma** is a disease of later life, arising in the head (60%), body (15%), or tail of the pancreas (5%). All have a poor prognosis, with a 2% 5-year survival rate.

Clinical diagnosis of pancreatic cancer is delayed because in most cases the symptoms of disease are nonspecific, such as dull abdominal pain and weight loss. Tumors of the head of the pancreas often present with obstruction of the common duct and painless jaundice with an enlarged gallbladder (Courvoisier sign). Migratory

thrombophlebitis (**Trousseau syndrome**) is associated with a release of tissue thromboplastin or enzymes that promote coagulation.

Islet Cell Tumors

Pancreatic endocrine tumors are rare. Most tumors are hormonally active and produce well-defined hormonal syndromes. Accordingly, they are called *glucagonomas, insulinomas, somatostatinomas,* and so forth. **Insulinoma** is the most common endocrine tumor. Most insulinomas (90%) are benign, but 10% are malignant. In contrast, 60% to 80% of other islet cell tumors are malignant. Most islet cell tumors occur randomly unrelated to other diseases, but some are found in the context of familial **multiple endocrine neoplasia syndrome.**

Alpha cell tumors (glucagonomas) are associated with a syndrome consisting of anemia, mild diabetes, and a necrotizing rash, especially of the lower body.

Beta cell tumors (insulinomas) produce a syndrome of sweating, severe hypoglycemia, hunger, and nervousness. Mental confusion may be evident and may progress to coma.

Delta cell tumors (somatostatinomas) are exceedingly rare and are rarely diagnosed before they are discovered at laparotomy. The syndrome includes mild diabetes, cholelithiasis, malabsorption-like symptoms, and steatorrhea. Hypochlorhydria may be present.

Delta$_1$ cell tumors (VIPomas) produce a syndrome called the *Verner-Morrison* or *WDHA syndrome,* consisting of **w**atery **d**iarrhea, **h**ypokalemia, and **a**chlorhydria.

Pancreatic gastrinomas cause **Zollinger-Ellison syndrome.** Hypergastrinemia produces peptic ulcers, which are often multiple and resistant to the usual medical treatment and which may occur in unusual locations such as the jejunum or Meckel diverticulum. Approximately 50% of patients have diarrhea.

DIABETES MELLITUS

Diabetes mellitus is a disorder of intermediate metabolism of carbohydrates, lipids, and proteins related to insulin deficiency, insulin resistance, or both. Hyperglycemia accompanied by glucosuria is always present. It occurs in two forms: **insulin-dependent diabetes mellitus, or type I,** which is most frequent in juveniles, and **non–insulin-dependent diabetes mellitus, or type II,** which occurs in adults. Some ethnic groups (e.g., Pima Indians) show a higher incidence, whereas other groups (e.g., Eskimos) are rarely affected. Diabetes affects approximately 7% of the population of the United States (15,000,000), of whom approximately 15% have type I diabetes and the remaining 85% have type II diabetes.

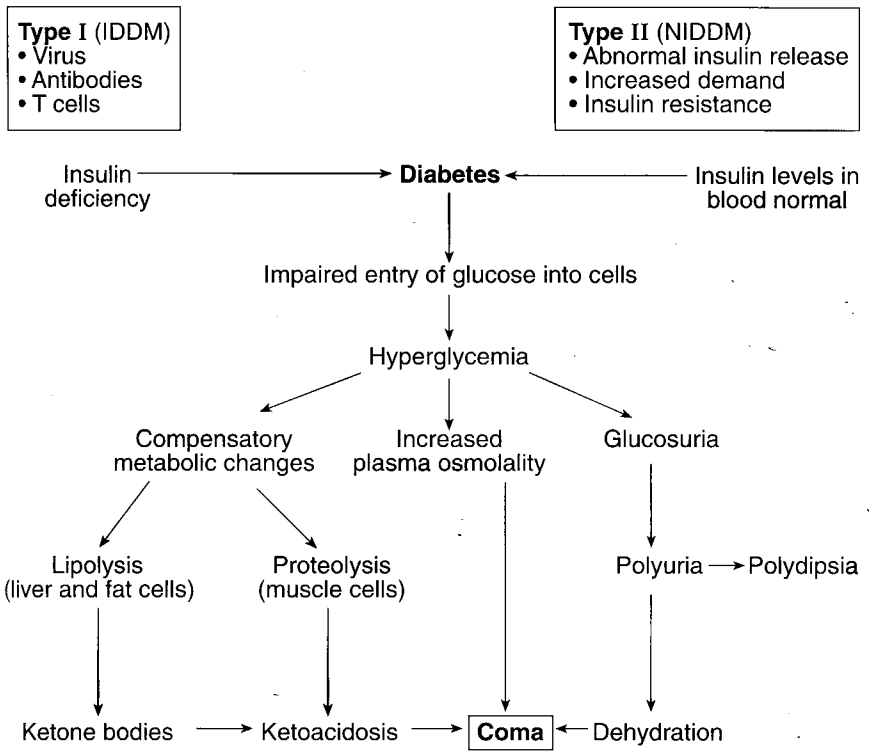


Figure 12-2.
Pathogenesis of diabetes mellitus. (IDDM, insulin-dependent diabetes mellitus; NIDDM, non–insulin-dependent diabetes mellitus.)

Type I diabetes usually has an abrupt onset, but there is a prodromal period that may last weeks to several years. Type I diabetes is an autoimmune disease that results from β-cell destruction, but the antigen triggering the response is uncertain. There is a substrate of genetic susceptibility, with many patients having the class II histocompatibility complex DR-3 or DR-4. A candidate protein of approximately 64 kD, which may be glutamic acid decarboxylase, has been identified, and antibodies to glutamic acid decarboxylase are typically found in type I diabetes.

Type II diabetes is more complex and probably multifactorial. There is a high concordance among twins, suggesting a hereditary component. Affected individuals are usually obese, and their blood sugar can be controlled by diet alone in ≤50% of cases. The pathogenesis of hyperglycemia is complex, but it can be explained in terms of **inappropriate secretion of insulin,** insulin resistance in fat and muscle (two tissues most dependent on insulin for glucose uptake), and decreased uptake and increased secretion of glucose by the liver. The pathogenesis of diabetes is shown in Figure 12-2. Table 12-1 compares type I and type II diabetes mellitus.

Complications of diabetes are the same for both groups, with the exception that type II diabetics are unlikely to develop ketoacidosis but

TABLE 12-1.
Comparison of Type I and Type II Diabetes Mellitus

Feature	Type I: Insulin-Dependent	Type II: Non–Insulin Dependent
Age at onset	Usually before 20 years	Usually after 30 years
Type of onset	Sudden	Gradual
Body weight	Normal	Increased
Monozygotic twins	50% concordant	90% concordant
HLA associations	Yes	No
Antibodies to beta cells	Yes	No
Islet lesions	Inflammation	None or minor and nonspecific changes
	Loss of β-cells and fibrosis	Amyloidosis (70%)
Blood insulin	Markedly reduced	Elevated or normal
Clinical management	Insulin and diet	Diet; if unresponsive, drugs or insulin

do develop hyperosmolar coma, which is unlikely in type I disease. Most complications develop over a 10-year period. The presence of **hypertension,** found more often in type II patients, may be an accelerating factor, particularly for the widespread vascular disease seen in long-standing diabetics. **Atherosclerosis** and its complications such as **stroke, myocardial infarction,** and **aneurysms** are common in diabetics, especially if hypertension is also present. Retinopathy with proliferation of retinal vessels increases the incidence of blindness. Peripheral neuropathy and peripheral vascular disease are prevalent, causing gangrene of the foot and often necessitating amputation of lower limbs. Renal failure is a major cause of death in diabetics. It includes **glomerular disease** (diffuse or nodular glomerulosclerosis [Kimmelstiel-Wilson syndrome]), renal vascular disease, predisposition to pyelonephritis, and papillary necrosis (Fig. 12-3).

Pathologic changes in the islets of Langerhans are disappointingly few. Very early in type I diabetes, an infiltration by lymphocytes is seen. Later, there is a loss of β-cells, which are replaced by fibrous tissue. Hyalinization with amyloid deposition is demonstrated in ≤70% of type II diabetics. The amyloid is derived from the islet-associated polypeptide, also known as **amylin,** a peptide related to the calcitonin gene-regulating peptide.

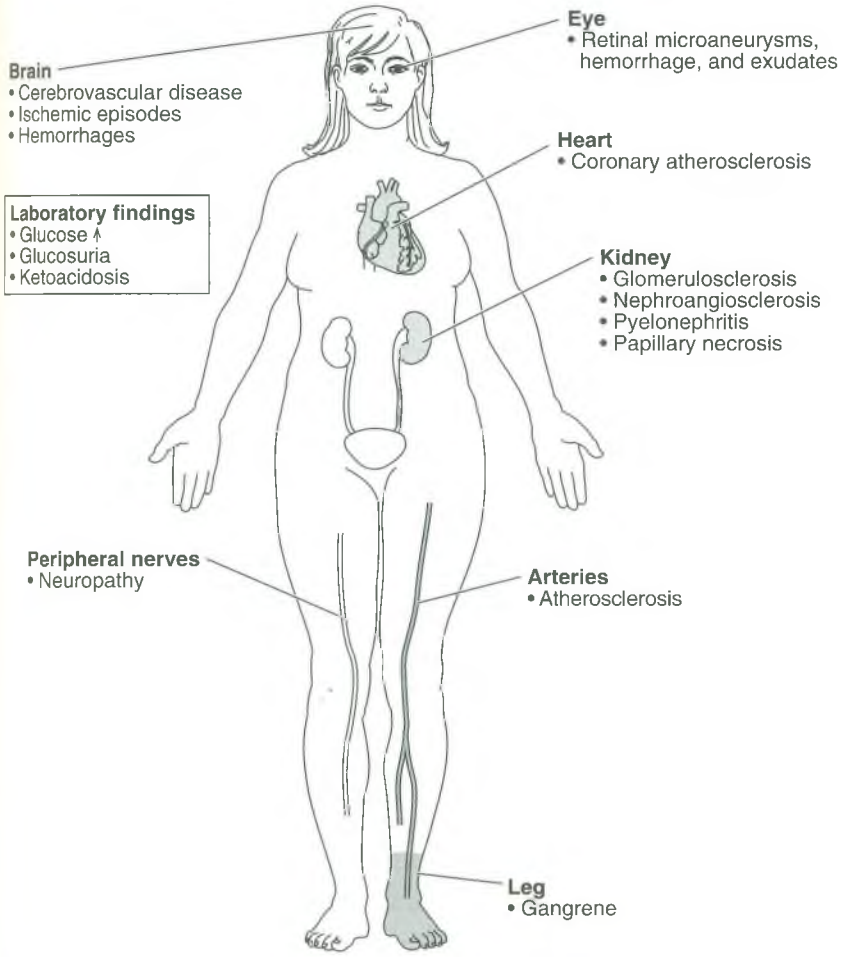


Figure 12-3.
Complications of diabetes mellitus.

Chapter 13

Kidneys and Urinary Tract

The principal diseases of the urinary tract are

- Developmental disorders
- Immune disorders involving the glomeruli or renal tubules
- Infectious diseases
- Metabolic diseases
- Neoplasms

Many symptoms and clinical findings are indicative of urinary tract disease, and several clinical syndromes are recognized. The most important clinicopathologic terms are presented.

Polyuria, oliguria, and anuria are terms pertaining to the amount of excreted urine, meaning, respectively, a lot, a little, or no urine. **Polyuria** is a symptom of overhydration, diabetes mellitus, or diabetes insipidus, but it may also occur in tubular necrosis and polycystic kidney disease such as acute glomerulonephritis. **Oliguria** is a feature of dehydration. It is found in many renal diseases and can also result from reduced glomerular filtration rate in prerenal failure (e.g., heart disease) or urinary tract obstruction. **Anuria** has similar causes to oliguria.

Proteinuria, hematuria, pyuria, and glucosuria are terms describing abnormal urine, as determined by biochemical analysis or microscopic examination of the urinary sediment. **Proteinuria** typically results from glomerular or tubular disease of the kidneys. **Hematuria** may be renal, but more often it is caused by inflammation of the lower urinary tract (e.g., cystitis), urinary stones, or tumors. **Pyuria** (i.e., pus in urine) is a sign of infection. **Glycosuria** is a feature of diabetes mellitus.

Nephrotic syndrome is defined by the presence of the triad of proteinuria, hypoproteinemia, and edema. Typically, it is of glomerular origin and is typical of diseases such as membranous nephropathy, lipoid nephrosis (nil disease), or systemic lupus erythematosus (SLE).

Nephritic syndrome is characterized by proteinuria, hypoalbuminemia, generalized edema, hypertension, oliguria, and hematuria. It is caused by inflammatory glomerular diseases such as acute poststreptococcal glomerulonephritis or SLE.

Acute renal failure is characterized by sudden cessation of renal functions and anuria. It may be caused by rapidly progressive

glomerulonephritis or renal tubular necrosis. It is most often a feature of shock, in which case it is of prerenal origin and related to circulatory failure.

Chronic renal failure is the clinical equivalent of end-stage renal disease. It is characterized by a number of metabolic disturbances **(uremia)** resulting from incomplete excretion of waste products and minerals in urine. These include elevated blood urea nitrogen, creatinine, potassium, and phosphate (Fig. 13-1).

DEVELOPMENTAL DISORDERS

Developmental disorders of the kidneys and ureters are common (2% to 3% of all people have them), but most often they are asymptomatic and of limited clinical significance. The best examples are **ectopic kidneys** (i.e., kidneys located outside of their normal location), double ureters, horseshoe kidney, and unilateral renal hypoplasia or renal agenesis, which are all usually discovered by chance. Bilateral renal agenesis (Potter syndrome) is a rare disease incompatible with life.

Cystic Diseases of the Kidney

Cystic diseases of the kidney are relatively common and account for a considerable number of renal disorders from childhood to adulthood. Several distinct entities are recognized, the most important of which are autosomal dominant adult polycystic kidney disease, autosomal recessive childhood polycystic kidney disease, and cystic renal dysplasia.

Autosomal dominant polycystic kidney disease occurs at a rate of 1:1,000 and accounts for approximately 10% of all patients on chronic renal dialysis or renal transplantation services. Approximately 90% of cases are caused by a mutation of the autosomal dominant polycystic kidney disease 1 gene on chromosome 16. The disease is always bilateral. Cystic dilatation of renal tubules leads to formation of **fluid-filled cysts,** which cause tremendous enlargement of the kidneys, which could weigh as much as 3,000 g (normal, 150 to 200 g). Symptoms of renal insufficiency begin appearing in the fourth decade of life, progressing steadily to uremia, which develops approximately 10 years later. Cystic dilatation of intrahepatic bile ducts **(polycystic liver disease),** which is usually asymptomatic, is found in approximately 50% of patients. **Berry aneurysms of the circle of Willis** are found in approximately 20% of patients, those at risk of intracranial hemorrhage, especially because many have hypertension.

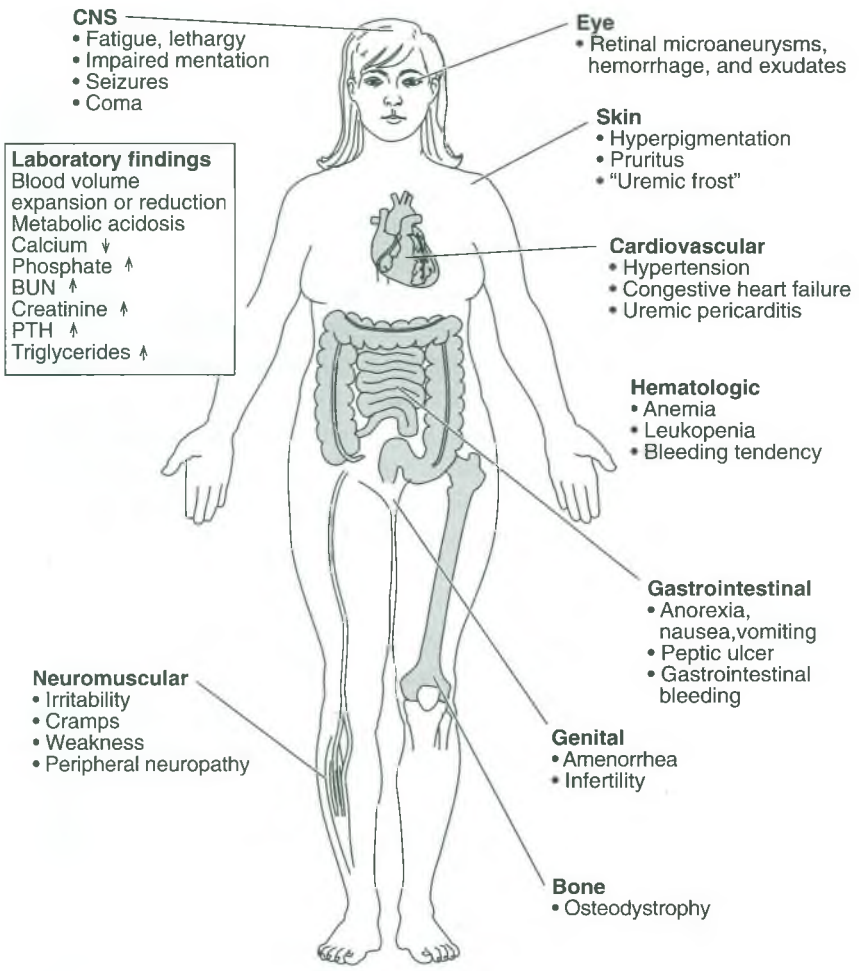


Figure 13-1.
Clinical and laboratory findings in chronic renal failure (uremia). (CNS, central nervous system; BUN, blood urea nitrogen; PTH, parathyroid hormone.)

Autosomal recessive kidney disease is a less common disease than autosomal dominant polycystic kidney disease. It occurs in several forms, defined by the time of its appearance as perinatal, infantile, or childhood. It is always bilateral, and renal failure develops early in all but the mildest cases. All patients have hepatic cysts, which may lead to formation of hepatic fibrosis in those who survive childhood.

Cystic renal dysplasia is a developmental disorder that may involve one or both kidneys due to the abnormal development of the kidney. The parenchyma is disorganized and composed of cysts and solid mesenchymal tissue, which differentiates into cartilage. Bilateral disease results in death shortly after birth. Unilateral cystic renal dysplasia presents as a mass that can be palpated through the thin abdominal wall of the baby.

GLOMERULAR DISEASES

Glomerular diseases may present as **isolated kidney diseases** such as acute glomerulonephritis, minimal charge disease, or IgA nephropathy, or **renal manifestations of systemic diseases** such as nephritis of SLE or **diabetic glomerulopathy.**

Pathogenically, glomerular diseases can be classified as *hereditary* (e.g., Alport syndrome), *immune-mediated* (e.g., membranous nephropathy), of *presumptive immune pathogenesis* (e.g., minimal change disease), or *metabolic* (e.g., diabetic nephropathy).

Clinically, glomerular diseases may present in six forms: nephrotic syndrome, nephritic syndrome, rapidly progressive glomerulonephritis, asymptomatic proteinuria, hematuria, or chronic renal failure (uremia).

Nephrotic Syndrome

Nephrotic syndrome is defined as proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia. It is typically a manifestation of glomerular disease, which may be immune mediated or metabolic.

Minimal change disease (also known as *nil disease* or *lipoid nephrosis*) is the most common cause of nephrotic syndrome in children, but it may also occur in adults. On histologic examination, the glomeruli appear normal and contain no immune deposits. By electron microscopy, the glomerular basement membrane (GBM) is normal, but the foot processes of the epithelial cells are fused. The disease responds well to corticosteroid treatment and has an excellent prognosis.

Focal and segmental glomerulosclerosis may be a variant of minimal change disease that does not respond adequately to corticosteroids and thus has a worse prognosis. The same morphologic changes (i.e., sclerotic obliteration of glomerular capillary loops in a focal and segmental pattern) can occur without an obvious cause (idiopathic focal and segmental glomerulosclerosis) or as a secondary reaction to a variety of insults such as heroin abuse or acquired immunodeficiency syndrome.

Membranous nephropathy is the most common form of nephrotic syndrome in adults. It occurs in an **idiopathic** form, the cause of which is unknown, and a **secondary** form, in which the glomerular injury is caused by immune complexes containing known antigens. Such secondary membranous nephropathy can occur in patients who have tumors, syphilis, hepatitis B virus infection, or SLE. In some cases of idiopathic membranous nephropathy, the antigen seems to be a component of cell membrane of the glomerular epithelial cells. On histologic examination, the glomeruli are normocellular but have markedly thickened basement membranes. Immunofluorescence microscopy shows that the

immune complexes are evenly spaced along the GBM in a granular manner. These deposits can also be seen by electron microscopy as dense aggregates on the subepithelial side of the GBM. As the disease progresses, which typically occurs over a period of 10 to 15 years, the deposits of immune complexes become incorporated into the GBM, contributing to its thickening and functional deterioration of glomerular function. Membranous nephropathy does not respond to corticosteroid therapy. End-stage kidney failure develops approximately 10 to 15 years after the onset of nephrotic syndrome.

Diabetes mellitus is the most common nonimmune cause of nephrotic syndrome. Only a minority of patients with diabetes develop nephrotic syndrome. Typically, it occurs in patients who do not control their hyperglycemia. Pathologically, the glomeruli may show diffuse thickening of the GBM **(diffuse sclerosis)** or thickening of the membrane with nodular widening of the mesangial areas (**nodular sclerosis** of Kimmelstiel-Wilson syndrome).

Amyloidosis affecting glomeruli may present as nephrotic syndrome. It may be classified as **primary,** which is caused by multiple myeloma in primary amyloidosis, or **secondary,** which develops in response to a chronic systemic infection, in which case the deposits are composed of the light chain or immunoglobulin (so-called amyloid of the AL type), whereas in secondary amyloidosis the deposits are composed of AA amyloid. Amyloid deposits are found in the GBM, small blood vessels, and in the tubular basement membranes in the advanced stages of the disease. Such extensive deposits usually cause kidney failure. Amyloidosis is an incurable disease.

Nephritic Syndrome

Nephritic syndrome is defined as proteinuria, glomerular hematuria, oliguria, hypoalbuminemia, generalized edema, and hypertension (Fig. 13-2). **Clinical features** reflect **glomerular inflammation** that obstructs the glomerular capillaries, reducing the renal blood flow and causing oliguria. **Renal hypoperfusion** also causes renin release and hypertension. The injury of the GBM, which becomes permeable to proteins and allows the passage of red blood cells (RBCs) and leukocytes into the urine, accounts for **proteinuria** and **hematuria**. These cells are trapped in protein-rich primary filtrate inside the proximal tubules, forming so-called RBC casts composed of fragmented RBCs or granular casts, which are composed of cell detritus and fragments of white blood cells, tubular cells, and RBCs. These casts are the foremost sign of glomerular hematuria and are important for distinguishing it from hematuria caused by lower urinary tract diseases, in which the urine contains dispersed RBCs and no casts or fragmented RBCs. Nephritic syndrome may occur as an acute or chronic *primary* kidney disease such as acute poststreptococcal glomerulonephritis or membranoproliferative glomerulonephritis, respectively, or as a manifestation of a systemic disease such as SLE.

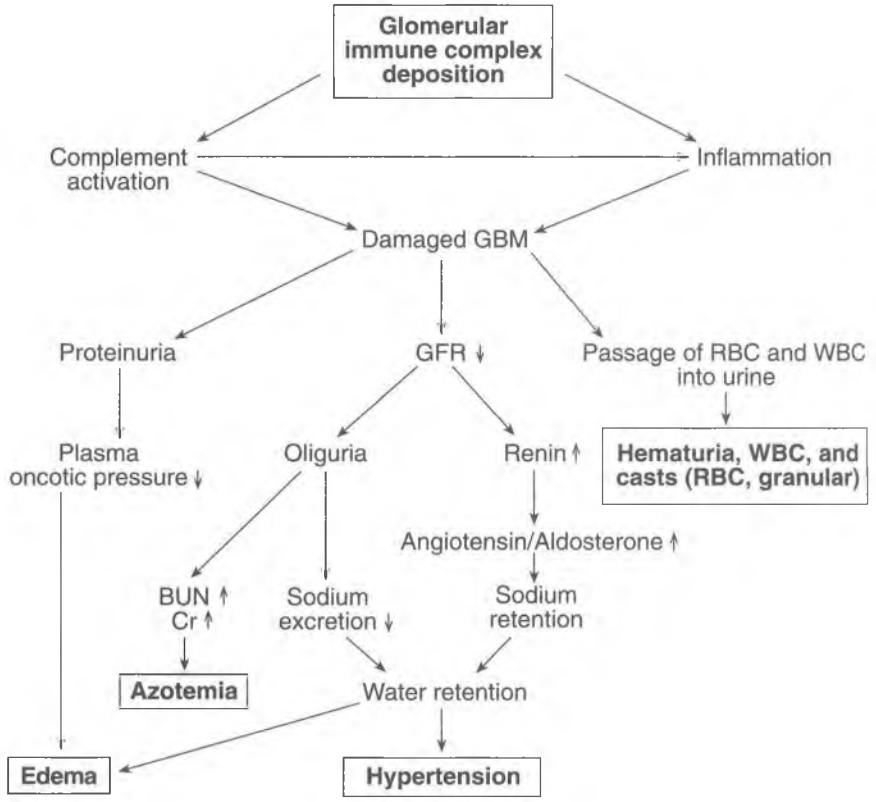


Figure 13-2.
Pathogenesis of nephritic syndrome. (GBM, glomerular basement membrane; GFR, glomerular filtration rate; RBC, red blood cells; WBC, white blood cells; BUN, blood urea nitrogen; Cr, creatinine.)

Acute poststreptococcal glomerulonephritis develops 2 to 3 weeks after a throat infection caused by **group A β-hemolytic *Streptococcus*.** Only certain "nephritogenic" types of *Streptococcus* known to have the capsular M protein cause renal problems. Typically, it is a disease of children, and in many underdeveloped countries it occurs in epidemic outbreaks, usually in late winter or spring. Less often, it is found in adults.

The disease has a sudden onset and usually heals spontaneously after 1 to 2 weeks. Microscopically, the glomeruli appear hypercellular due to the proliferation of mesangial and endothelial cells and infiltrates of inflammatory cells. Deposits of Ig and complement are found in all glomeruli and are usually irregularly distributed in the mesangium and along the GBM. These immune deposits may not be visible by electron microscopy, but the larger aggregates appear as dense subepithelial humps. These glomerular changes disappear spontaneously in most people, but in approximately 2% of cases the disease recurs, and in 2% it does not resolve and progresses to chronic glomerulonephritis. In approximately 1% of cases, the disease, which has a rapidly progressive course, presents as a crescentic glomerulonephritis. Epidemiologic data show that acute poststreptococcal

glomerulonephritis of adults has a less favorable prognosis than when the disease occurs in children, and the cases that occur at random have a worse prognosis than those that occur in a seasonal epidemic form.

Clinically, **postinfectious glomerulonephritis** resembles the disease that follows strep throat. It may be a complication of bacterial infections such as staphylococcal respiratory tract infection but also of malaria or toxoplasmosis. Bacterial endocarditis may be complicated by glomerulonephritis. These patients have circulating immune complexes that deposit in the glomeruli and produce glomerulonephritis.

Membranoproliferative glomerulonephritis is an uncommon disease, but still accounts for approximately 10% of all glomerular diseases. It may be *primary* (i.e., without an obvious cause) or *secondary* to a systemic disorder. It occurs in two forms, type I and type II, which can be distinguished from each other on the basis of immunofluorescence microscopy and electron microscopic findings. By light microscopy, both types show the same changes, which include mesangial widening and hypercellularity and reduplication of basement membranes due to new GBM formation ("tram track appearance" of GBM). This immune-mediated disease has a slowly progressive course and does not respond to corticosteroid treatment.

In 75% of cases, **SLE** is accompanied by renal disease. Clinically, these patients may have only mild proteinuria and hematuria or a full-blown nephrotic syndrome. Most have signs of glomerulonephritis, both clinically and on renal biopsy. Glomerular changes can be pathologically graded on a scale from I to V. Grade I implies no glomerular changes; II is associated with mesangial cell proliferation; III is focal proliferation and obliteration of capillaries; IV is diffuse proliferation; and V is equivalent to membranous nephropathy. All forms of glomerulonephritis of SLE respond well to treatment with corticosteroids or cyclophosphamide, except type V, in which the symptoms of nephrotic syndrome persist despite treatment.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis is a term used to describe a group of diseases that causes severe glomerular injury and presents as **crescentic glomerulonephritis.** In such cases, the GBM is usually disrupted, and the inflammatory cells enter through the hole in the GBM into the glomerular urinary space delimited by the Bowman capsule, surrounding and compressing the glomerular capillary tuft like a crescent. This type of glomerular injury typically results in oliguria and even anuria, which develops over several weeks, reflecting massive loss and destruction of glomeruli.

Rapidly progressive glomerulonephritis can be caused by a number of diseases (Table 13-1). In some, such as Goodpasture syndrome or Wegener granulomatosis, crescentic glomerulonephritis is the usual renal presentation of the disease. Crescentic glomerulonephritis may occur in the course of SLE or membranoproliferative glomerulonephritis, but this is rare. Similarly, it is only 1% of all

TABLE 13-1.
Diseases Presenting as Rapidly Progressive (Crescentic) Glomerulonephritis

Common
Goodpasture syndrome
Wegener granulomatosis
Polyarteritis nodosa
Idiopathic (50% of all cases)
Uncommon
Systemic lupus erythematosus
Poststreptococcal glomerulonephritis
Membranoproliferative glomerulonephritis

cases of poststreptococcal glomerulonephritis that occurs in the form of crescentic glomerulonephritis.

Other Forms of Glomerulonephritis

Berger disease (IgA nephropathy) is considered to be the most common glomerular disease diagnosed in clinical practice worldwide. It is a disease of unknown origin, characterized histologically by mesangial cell proliferation and mesangial widening. By immunofluorescence microscopy, mesangial areas contain deposits of IgA, which can also be seen by electron microscopy. The disease occurs most often in children and young adults and is typically preceded by a mild respiratory, urinary, or gastrointestinal infection. Most patients have only mild hematuria and proteinuria and no systemic symptoms. Despite this rather innocuous presentation, the disease tends to progress, and approximately 50% of patients develop end-stage kidney disease over a period of 20 years. The disease does not respond to any treatment.

IgA nephropathy has the same glomerular changes as another poorly understood disease, **Henoch-Schönlein purpura.** Henoch-Schönlein purpura is a systemic disease of unknown etiology, usually affecting children and young adults. It is characterized by episodes of bleeding into the skin (purpura), gastrointestinal bleeding (hematochezia), and hematuria. Glomeruli show mesangial proliferation and deposits of IgA, but on occasion the disease may have a more severe course and present as crescentic glomerulonephritis. The symptoms of the disease tend to recur. In children, it has a good prognosis, but in adults, it may progress over a long period of time to end-stage disease.

Chronic Glomerulonephritis

Chronic glomerulonephritis is not a single entity, but the end result of many glomerular diseases. In most cases, the kidneys are so altered

that no signs of the primary disease can be recognized. The kidneys are typically small and uniformly shrunken and have a finely granular external surface. Histologically, most glomeruli are hyalinized, and tubules have been replaced by fibrous tissue. It should be noted that similar changes can result from chronic ischemia **(nephroangiosclerosis or arteriolonephrosclerosis)** and even chronic pyelonephritis. Nevertheless, the **end-stage renal disease** caused by atherosclerosis tends to have (V-shaped) surface scars, corresponding to previous infarcts. Pyelonephritis tends to form irregular (U-shaped) scars corresponding to healed abscesses and defects of renal parenchyma caused by bacterial infection. Histologically, the glomeruli may be more preserved in such primarily tubulointerstitial diseases than in primary glomerulonephritis.

TUBULOINTERSTITIAL DISEASES

The diseases affecting the tubules and the renal interstitial tissue are grouped under one heading, because in most instances it is not possible to tell whether the disease began as a tubular injury with an interstitial reaction or an interstitial inflammation that ultimately destroyed the tubules. The causes of tubulointerstitial diseases are listed in Table 13-2.

Renal Infections

Acute pyelonephritis is a term used for all bacterial infections of the renal parenchyma, even those that do not involve the calices and pelves of the kidney. The infection can be ascending or descending. Ascending infections are typically caused by uropathogens (i.e., gram-negative bacteria such as *Escherichia coli, Klebsiella, Proteus,* and *Enterobacter*).

Acute pyelonephritis is characterized by infiltrates of polymorphonuclear leukocytes, which are found in the tubules or the interstitium where they can produce small abscesses. Larger abscesses that result from confluent smaller abscesses can be seen on gross examination at autopsy, and occasionally the entire kidney and pelves are transformed into a purulent mass **(pyonephros).** Clinically, the disease presents as acute febrile episode accompanied by flank pain. Dysuria and pus in urine **(pyuria)** may be found. Results of bacterial culture of urine are positive. The disease responds well to antibiotics, but if not treated, it may progress to chronic pyelonephritis.

Chronic pyelonephritis is a late complication of acute pyelonephritis. Like acute pyelonephritis, it may involve one or both kidneys. If both kidneys are involved, it presents as **end-stage kidney disease** and is indistinguishable clinically from chronic glomerulonephritis. On gross examination, the kidneys are small and irregu-

TABLE 13-2.
Tubulointerstitial Diseases

Infections
- Acute pyelonephritis
- Chronic pyelonephritis

Drug-induced
- Analgesic abuse nephropathy
- Acute tubulointerstitial nephritis due to hypersensitivity

Metabolic
- Urate nephropathy
- Diabetes mellitus
- Multiple myeloma nephropathy

Physical factors
- Obstructive nephropathy
- Radiation nephritis

Immunologic
- Transplant rejection
- Tubulointerstitial nephritis of autoimmune disease (e.g., systemic lupus erythematosus)

Ischemic
- Atherosclerosis
- Diabetes mellitus

larly scarred, and the pelves and calices are distorted. Histologically, the normal renal parenchyma is replaced by fibrous tissue that contains foci of chronic inflammation. The remaining tubules are atrophic and filled with proteinaceous material resembling thyroid follicles (thyroidization). In most cases of chronic pyelonephritis, the kidney parenchyma no longer contains bacteria, and the urine may be sterile. Chronic pyelonephritis does not respond to any medical treatment, and most patients with bilateral disease must have dialysis or require renal transplants.

Drug-Induced and Metabolic Diseases

Analgesic abuse nephropathy is a form of tubulointerstitial nephritis seen predominantly in women who ingest phenacetin on a daily basis for many years. Typically, it affects the medullary part of the kidney and presents often as papillary necrosis.

Acute tubulointerstitial nephritis is most often caused by an adverse reaction to drugs. Typically, it is a cell-mediated hypersensitivity reaction in which the interstitial spaces are infiltrated with lymphocytes and eosinophils. The disease may respond well to antiallergic drugs, but in some cases it may persist even after the causative drug has been withdrawn.

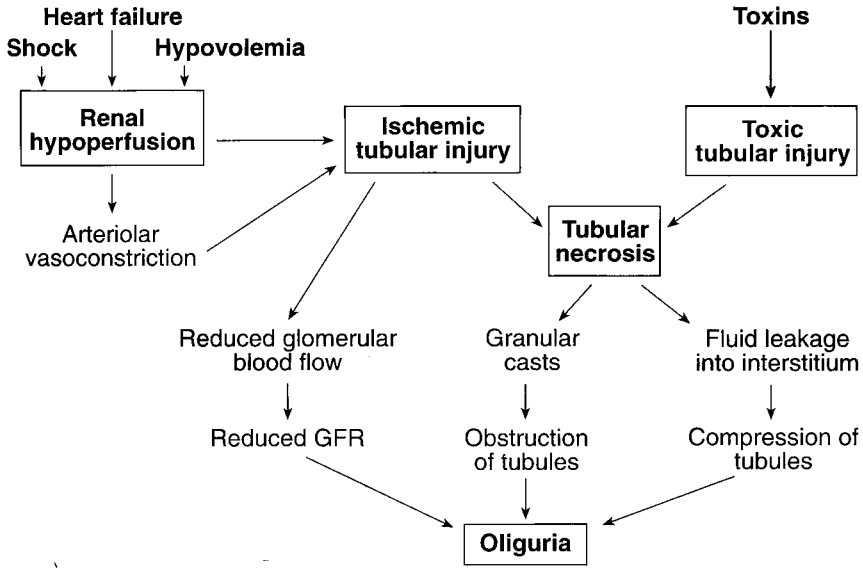


Figure 13-3.
Pathogenesis of oliguria in tubular necrosis. (GFR, glomerular filtration rate.)

Metabolic diseases that affect the kidney are legion, but the most important of these is diabetes mellitus. **Diabetes** may affect glomeruli, as mentioned previously, or blood vessels and tubules. It also predisposes to infections and is the most important cause of papillary necrosis. Deposits of uric acid in **gout** and deposits of Bence Jones protein or amyloid in **multiple myeloma** are important causes of tubular injury in these diseases. Metabolic diseases also lead to formation of renal stones, which may cause obstruction of the urine outflow tract **(hydronephrosis),** which predisposes to infections.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is a clinicopathologic syndrome characterized by widespread **necrosis** of renal tubules and a loss of renal function, which can be relatively mild and reversible or severe and potentially lethal (Fig. 13-3). ATN is the most common cause of renal failure of sudden onset. It can be caused by ischemia or toxins. **Ischemic ATN** is common and is found in almost all conditions that cause renal hypoperfusion, such as hypotension due to cardiac failure, hypovolemic shock due to massive blood loss, or peripheral blood pooling in endotoxic shock. **Toxic ATN** occurs after ingestion of toxins such as carbon tetrachloride, organophosphorous compounds, or heavy metals such as mercury. Renal failure that develops quickly is marked by low urinary output **(oliguria)** and **metabolic disturbances** (e.g., hyperkalemia), which may last several days and, if not treated, may be lethal. With proper treatment **(dialysis),** patients overcome the

initial crisis, and if the renal tubules are given sufficient time to regenerate, most fully recover. The regenerative phase is characterized by polyuria and hypokalemia, which must be treated appropriately.

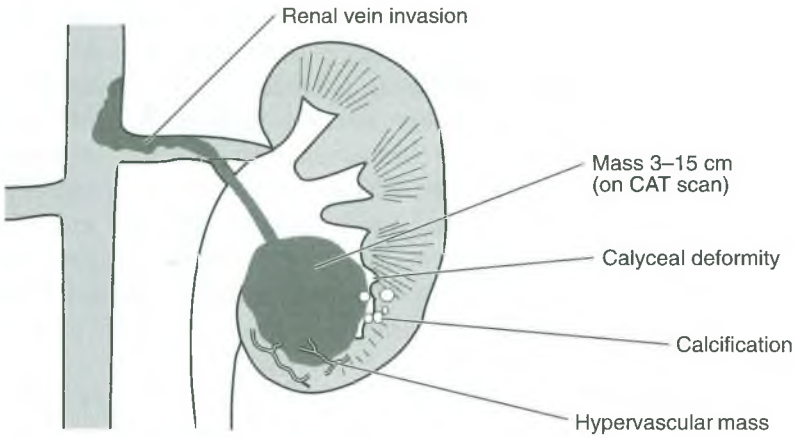
UROLITHIASIS

Stones may form under a variety of conditions in any part of the urinary system, but are found most often in the renal calices and pelves. It is estimated that 5% to 10% of all adults will have renal stones sometime during their life, but in some families and in certain conditions, such as gout or chronic intestinal diseases, the likelihood is much higher. Male subjects are affected more often than female subjects. Chemically, the urinary stones can be classified into four major groups: calcium, struvite, uric acid, and cystine. Approximately 75% of stones are composed of **calcium salts,** mostly oxalate, phosphate, or both. Such stones typically develop in patients who excrete calcium in high amounts without a well-understood reason. Only 5% of these hypercalciuric patients have hypercalcemia. Excess excretion of uric acid **(hyperuricosuria)** is found in approximately 20% of patients with calcium stones and is yet another risk factor. Urinary tract infection makes the urine alkaline, which predisposes to the formation of magnesium, ammonium, and phosphate calcium stones. These **struvite stones** may resemble antlers and are often called *staghorn calculi.* Pure **uric acid** stones are found in patients with hyperuricemia and gout. In approximately 50% of cases, there is no hyperuricemia; why uric acid stones are formed is not known. **Cystine stones** are found in cystinosis. Calcium stones are visible on radiography, whereas those composed of uric acid and cystine are not dense enough to be seen. Urinary stones may cause colic or hydronephrosis by obstructing the ureter. Like any other obstruction, stones predispose to infection.

TUMORS OF THE KIDNEYS

Renal tumors can originate from tubular cells, stromal cells, vascular cells, or the epithelium of the pelvis. The most important tumors are renal cell carcinoma, nephroblastoma, Wilms tumor, and transitional cell carcinoma of the renal pelvis.

Renal cell carcinoma is the most common malignant tumor of the adult kidneys. It accounts for approximately 2% of all human visceral tumors (Fig. 13-4). It is more common in men (3:1) and



- Most common renal tumor
- Age: 50–70; M:F = 3:1
- Yellow mass; clear cells arranged into tubules
- Metastasize early by venous blood
- Symptoms vary ("internist's tumor")
- Classic triad (hematuria, flank pain, mass) only in 10%
- No response to chemotherapy
- Prognosis: 40% 5-year survival

Figure 13-4.
Renal cell carcinoma. (CAT, computed axial tomography.)

has peak incidence at approximately 60 years of age. No definitive causative agents have been identified. The tumor appears more often than expected in families affected by the **von Hippel–Lindau syndrome,** a condition related to a defect in the vHL tumor-suppressor gene on chromosome 3. This tumor-suppressor gene most likely plays an important role in the pathogenesis of renal carcinomas. On gross examination, the tumor appears as a yellow, relatively circumscribed mass, which tends to extend into the hilus and invade the renal vein. Metastases occur hematogenously to the lungs and bones or through the perirenal lymphatics to abdominal sites. Histologically, the tumor is composed of clear cuboidal cells rich in lipid and glycogen. These cells are arranged into tubules or solid nests and to some degree resemble renal tubular cells.

Clinically, the tumor may present with a variety of symptoms, usually unpredictable. The typical triad comprising hematuria, flank pain, and a palpable mass is found in only 10% of patients. Erythrocytosis related to tumor-induced production of erythropoietin and hypertension related to renin, hypercalcemia, and amyloidosis are the most common paraneoplastic syndromes associated with renal cell carcinoma. Metastases are present at the time of diagnosis in 25% of patients. The tumors do not respond to chemotherapy, and surgery is the only treatment. The overall 5-year survival rate is 45%.

Wilms tumor is the most common renal tumor of infancy and childhood, diagnosed typically in the 2- to 4-year-old age group. In a familial form, it is associated with the deletion of the tumor suppressor gene WT-1 found on chromosome 11. The defects of this

gene may be associated with the so-called **WAGR syndrome** (**W**ilms tumor, **a**niridia, **g**enital anomalies, and mental **r**etardation) or **Denys-Drash syndrome,** comprising gonadal dysgenesis and childhood nephropathy. Tumors are usually unilateral, but can be bilateral in 10% of cases. The tumor mass may replace the entire kidney and metastasize widely. Histologically, it is composed of immature embryonic cells that form tubules. Spindle cells form solid nests that may show aberrant differentiation into striated muscle or cartilage. The tumor responds well to combined surgical-medicamentous treatment, and the 5-year survival rate is in the range of 90%.

Transitional cell carcinoma of the renal pelvis is biologically the same tumor as similar transitional cell carcinomas of the ureter and urinary bladder. It begins as a papillary neoplasm protruding into the lumen of the pelvis, ultimately growing into a mass that completely fills it. The tumor is composed of papillae lined by transitional epithelium, which can be graded as low-, medium-, and high-grade malignancy. The prognosis depends on the size of the tumor and its histologic grade and stage. Overall, the prognosis is good for small well-differentiated tumors (70% for 5-year survival), but is less favorable for larger, less-differentiated neoplasms. In approximately 50% of cases, the tumors are multiple, most of which are in the urinary bladder.

URINARY BLADDER PATHOLOGY

The most important diseases of the urinary bladder are cystitis and cancer. Congenital developmental anomalies such as exstrophy of the bladder and urachal cysts are rare. Vesicoureteral reflux due to congenital incompetence of the abnormal ureterovesical junction is found in 2% to 3% of young girls, but this functional abnormality is not linked to a specific pathologic alteration.

Cystitis

Cystitis, inflammation of the urinary bladder, is an extremely common disease, most often related to an ascending infection. The most common pathogens are *E. coli, Proteus, Klebsiella,* and *Enterobacter.* Because the female urethra is much shorter than the male urethra, cystitis is more common in **female children** and **women of reproductive age** than in males of the same age. In older men, urinary stagnation due to prostatic hyperplasia is the most common cause of cystitis. Many infections are related to sexual activity ("honeymoon cystitis"). Pregnancy, cystoscopy, urinary stones, and chemotherapy also predispose to urinary bladder infection. According to

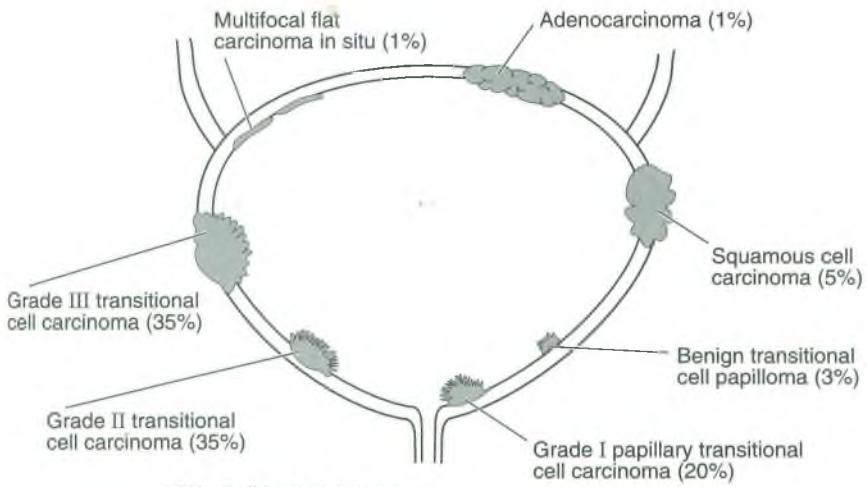


Figure 13-5.
Urinary bladder carcinoma.

its course, cystitis can be classified as acute, chronic, or recurrent. Pathologically, there are several variants such as hemorrhagic, ulcerative, suppurative, and pseudomembranous cystitis. **Chronic cystitis** is often associated with metaplastic changes (cystitis cystica, cystitis glandularis). A special form of chronic cystitis that occurs in women and is resistant to treatment is called **interstitial cystitis.** It is accompanied by fibrosis of the urinary bladder, inflammatory cell infiltrates rich in basophils, and ulceration (Hunner ulcer). Chronic cystitis in which the surface of the bladder is covered with soft yellowish plaques is called **malakoplakia.**

Tumors of the Urinary Bladder

Neoplasms of the urinary bladder account for 6% of all tumors and 3% of all tumor deaths (Fig. 13-5). Male subjects are more often affected (4:1). Most tumors arise from the transitional epithelium, and 95% are malignant. The most important risk factor is **cigarette smoking.** In some parts of the world, such as Africa and Asia where there is a high incidence of bladder cancer, *Schistosoma haematobium* infection plays an important pathogenetic role. **Chemical carcinogens** such as analines are prevalent in chemical industrial settings, and metabolites of certain drugs such as phenacetin and cyclophosphamide account for a minority of cases.

Pathologic features of urinary bladder cancer include typical gross and microscopic features. It presents as an exophytic mass or

polyp protruding into the lumen of the bladder. Often the tumors are multiple. Some tumors present as multifocal flat plaques of carcinoma in situ, which are prone to become invasive rather than to form exophytic masses. All malignant bladder tumors ultimately invade the bladder wall and infiltrate the adjacent organs. Distant metastases occur through the lymphatic and vascular channels. Histologically, most tumors (90%) are transitional cell carcinomas, but some are squamous cell carcinomas. At the bladder dome, the site of urachal insertion tumors may have the histologic features of adenocarcinoma. Treatment includes surgery and chemotherapy. The prognosis depends on the stage and grade of the tumor. Grade I tumors have excellent prognosis (>95% 10-year survival), whereas only 30% of patients with grade III tumors survive 10 years.

Chapter 14

Male Reproductive System

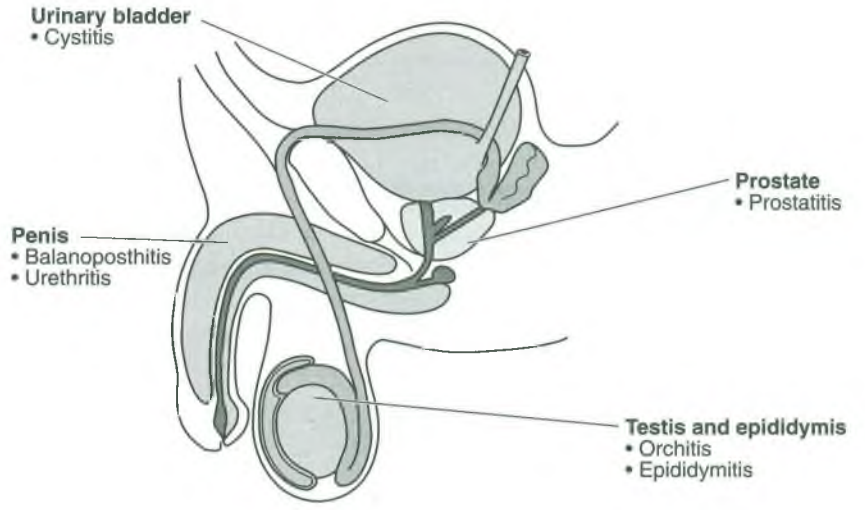
DEVELOPMENTAL DISORDERS

The most important developmental anomaly of the testis is **cryptorchidism,** or undescended testis, which is found in 0.5% of male subjects. Bilateral cryptorchidism is associated with infertility. The undescended testes are at a 10 to 20 times higher risk than normal testes for developing malignant germ cell tumors. Other developmental anomalies are rare and include **anorchia** (absence of one testis) or **polyorchidism** (three or more testes). Agenesis of the epididymis is rare except in men who have cystic fibrosis.

INFECTIONS

Infections of the male genital organs may involve the entire system or each organ separately (Fig. 14-1). **Orchitis,** inflammation of the testis, and **epididymitis,** inflammation of the epididymis, often occur simultaneously **(epididymo-orchitis).** In younger and middle-aged men, it is usually caused by an ascending spread of sexually acquired pathogens such as *Neisseria gonorrhoeae* or *Treponema pallidum.* In older men, epididymo-orchitis is secondary to urinary tract infections related to prostatic hyperplasia. These infections are caused by *Escherichia coli* and other gram-negative uropathogens such as *Klebsiella* or *Proteus.* Hematogenous epididymo-orchitis is rare, and it is usually a complication of bacteremia. Syphilitic gumma is also rare. Tuberculosis may spread to testes hematogenously from the kidney through the urine. It is rare in the United States. Mumps virus, which typically affects the salivary glands, may disseminate hematogenously and cause orchitis. **Clinical features** of epididymo-orchitis include scrotal swelling, pain, and tenderness on palpation. Bilateral epididymo-orchitis may cause infertility.

Infection of the prostate **(prostatitis)** is common in older men. **Urethritis** is a common disease in sexually active men. It may be caused by *N. gonorrhoeae, Chlamydia, Mycoplasma,* or uropathogens.



Sexually transmitted infection
- Herpes simplex virus
- *Chlamydia*
- *Mycoplasma*
- *Treponema pallidum*
- *Neisseria gonorrhoeae*
- HIV

Ascending urinary tract infection
- *Escherichia coli*
- *Klebsiella*
- *Proteus*

Blood-borne infections
- Mumps virus
- *Streptococcus*
- *Staphylococcus*

Figure 14-1.
Infections of the male reproductive system. (HIV, human immunodeficiency virus.)

TESTICULAR TUMORS

Testicular tumors account for 1% of all tumors in male subjects. The peak incidence of these tumors is in the 25- to 40-year-old age group. Germ cell tumors, most of which are malignant, account for 95% of all neoplasms, whereas the remaining 5% represent tumors of sex-cord cells (Sertoli cell tumors and Leydig cell tumors) or lymphomas and metastatic malignancies from abdominal organs (Table 14-1).

Germ cell tumors, as the name indicates, originate from germ cells. On malignant transformation, the carcinomatous germ cells remain inside the seminiferous tubules and are recognized as carcinoma in situ or **intratubular testicular neoplasia.** Invasive tumors form from the malignant cells. It is clinically convenient to subdivide these tumors into two major groups: **seminomas** and **nonseminomatous germ cell tumors** (NSGCTs) (Fig. 14-2). Seminomas and NSGCTs have a peak incidence in the 25- to 45-year-old age group and account for the vast majority of testicular tumors. Other germ cell tumors, such as yolk sac tumor of infancy, premature teratoma of childhood, and spermatocytic seminoma are rare.

TABLE 14-1.
Tumors of the Testis*

- **Germ cell tumors**
  - Seminoma
    - Nonseminomatous germ cell tumors
      - Embryonal carcinoma
      - Teratoma
      - Teratocarcinoma
      - Yolk sac carcinoma
      - Choriocarcinoma
    - Mixed germ cell tumor (seminoma + nonseminomatous germ cell tumors)
    - Teratoma of childhood
    - Yolk sac tumor of infancy (endodermal sinus tumor)
    - Spermatocytic seminoma
- **Sex cord cell tumors**
  - Leydig cell tumor
  - Sertoli cell tumor
- **Metastatic tumors**
  - Lymphoma
  - Carcinoma (prostate, colon)

The most important tumors can be remembered using the mnemonic TESTICLES, which stands for **teratoma, **e**mbryonal carcinoma, **s**eminomas, **t**eratocarcinoma, **i**nterstitial cell (Leydig cell) tumor, **c**horiocarcinoma, **l**ymphoma, **e**ndodermal sinus tumor (yolk sac tumor), and **s**ertoli tumor.*

Seminoma is the most common subtype of testicular germ cell tumor. It is composed of polygonal cells with clear glycogen-rich cytoplasm. Tumor cells are arranged in groups surrounded by fibrous septa, which contain numerous lymphocytes and macrophages. Seminoma cells resemble fetal germ cells and express, like the fetal germ cells, placental-like alkaline phosphatase, which can be demonstrated by immunohistochemistry in the plasma membrane of tumor cells. Seminomas do not secrete any tumor markers in the blood. Like all the testicular tumors, they metastasize first to abdominal pancreatic lymph nodes and then to the lungs and other internal organs. Seminomas are radiosensitive and can be cured by surgery and radiation in 90% of cases.

NSGCTs are a heterogenous group of tumors. These tumors are very malignant, and without modern chemotherapy have a high mortality. With chemotherapy, a cure rate of 90% can be achieved. NSGCTs may occur as pure tumors composed of a single cell type

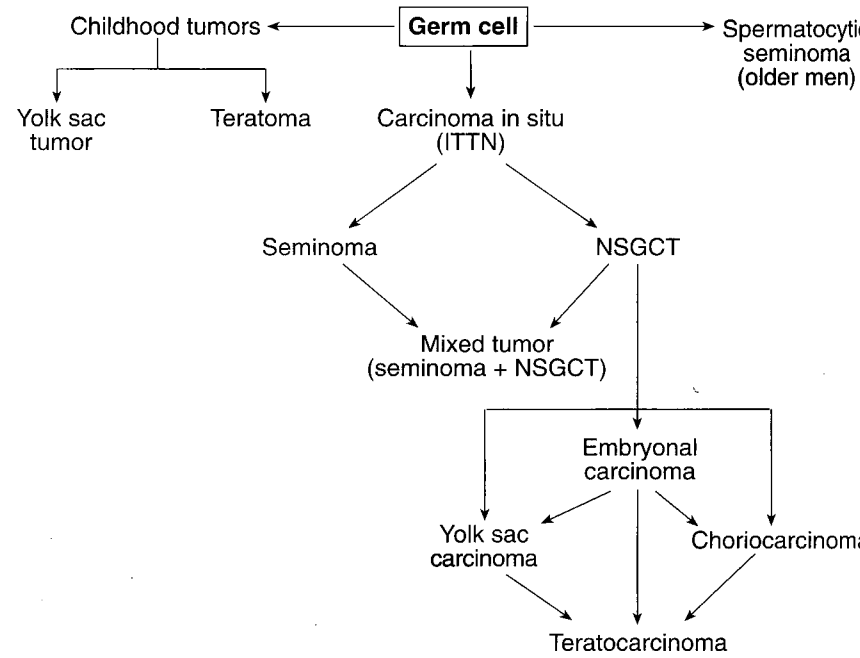


Figure 14-2.
Histogenesis of germ cell tumors. Intratubular testicular neoplasia (ITTN) is considered to be a precursor of seminomas and all nonseminomatous germ cell tumors (NSGCTs) of the adult testis. Yolk sac tumors of infancy, teratomas of childhood, and spermatocytic seminomas have a different histogenesis. These tumors do not originate from ITTN and are most likely derived from activated germ cells that have not undergone malignant transformation. This could account for the benign nature of these tumors.

(e.g., embryonal carcinoma, choriocarcinoma, or yolk sac carcinoma) or stem cells corresponding to embryonal carcinoma cells and various somatic tissues (e.g., skin, brain, bone) admixed with choriocarcinoma and yolk sac carcinoma cells. When all of these elements are combined and found in a single tumor, such as NSGCT, it is then called **teratocarcinoma.**

Embryonal carcinoma is composed of cells that resemble undifferentiated embryonic cells from early stages of development. In teratocarcinomas, they differentiate (like normal embryonic cells) into other tissues. **Yolk sac carcinoma** cells resemble those in the yolk sac, a temporary extraembryonic structure that is attached to the embryo until week 16 of pregnancy, involuting thereafter. Like the normal yolk sac, yolk sac carcinoma cells secrete into the blood α-fetoprotein (AFP), which can serve as a tumor marker. **Choriocarcinoma** is composed of cells resembling trophoblast of the placenta: mononuclear cytotrophoblastic and multinuclear syncytiotrophoblastic cells. Like the normal placenta, these cells secrete **human chorionic gonadotropin (hCG),** which is yet another tumor marker. Teratocarcinomas, the most common form of NSGCT, contain both yolk sac carcinoma and choriocarcinoma cells; thus patients with such tumors have elevated serum AFP and hCG.

Clinically, it is important to note that most malignant stem cells in most NSGCTs are embryonal carcinoma cells, and that these cells respond well to chemotherapy based on organic platinum compounds. It is also important to note that 80% of all NSGCTs secrete AFP, hCG, or both, which can be measured in the serum as tumor markers.

All other germ cell tumors besides seminomas and NSGCTs are rare. **Yolk sac tumor** of infancy (also known as *endodermal sinus tumor*) is a slow-growing tumor. In the newborn to 4-year-old age group, it is the most common testicular tumor. Surgery provides a 99% cure rate. **Teratoma** is a rare benign tumor of prepubertal boys. **Spermatocytic seminoma,** which despite its name has nothing in common with seminoma, is a benign tumor that occurs in older men (peak age, 55 years).

Other Tumors

Sex cord cell tumors are rare, accounting for approximately 3% of all testicular tumors. They are classified as Leydig cell tumors or Sertoli cell tumors.

Leydig cell tumors are composed of polygonal cells with well-developed eosinophilic cytoplasm and round nuclei. These cells resemble Leydig cells and may contain cytoplasmic crystals of Reinke and secrete androgens. Some tumors secrete estrogens, and some are afunctional. Leydig cell tumors occur in all age groups. In children, they may cause precocious puberty and penile enlargement. In adults, androgen-secreting tumors are recognized primarily because of the local mass effect. Estrogen-secreting tumors may cause gynecomastia and impotence.

Sertoli cell tumors are composed of cells resembling normal Sertoli cells, which are arranged into tubules. Most of the tumors are benign and hormonally inactive, but some may have estrogenic effects.

Metastatic tumors are rare in the testis. **Lymphomas** are the most common malignancy to spread to the testis. This usually occurs either in preschool children or the elderly. Other tumors that metastasize to the testes are carcinomas of the prostate and colon.

DISEASES OF THE PROSTATE

The most important diseases of the prostate are benign prostatic hyperplasia (BPH) and prostatic carcinoma, both of which typically occur in the elderly.

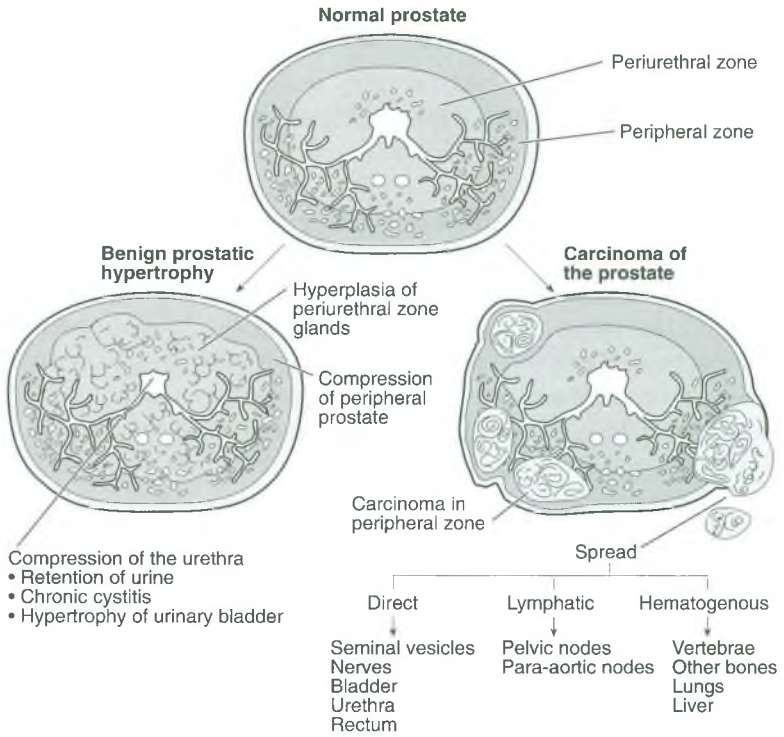


Figure 14-3.
Pathology of the prostate. The normal prostate has two major parts: a periurethral zone, which gives rise to benign prostatic hyperplasia; and the peripheral zone, which is the most common site of prostatic carcinoma.

Benign Prostatic Hyperplasia

BPH is a disease of unknown etiology. Some degree of prostatic hyperplasia is found in almost all men older than 60 years of age. BPH develops presumably under the influence of steroid sex hormones, which act on both the glands and the fibromuscular stroma of the prostate. The hyperplastic glands and stromal cells form nodules, which are most prominent in the central periurethral zone (Fig. 14-3). These nodules of the lateral lobes may compress the urethra, whereas the hyperplastic median lobe may protrude into the urinary bladder and obstruct the internal urethral orifice. Typical symptoms include urinary retention, **dysuria,** or frequent urgency to urinate. Retention of urine predisposes to infection of the bladder **(chronic cystitis)** and leads to hypertrophy and hyperplasia of the smooth muscle in the wall of the urinary bladder **(trabeculation)**. BPH is treated surgically by transurethral resection or suprapubic prostatectomy.

Carcinoma of the Prostate

Carcinoma of the prostate is the most common malignant tumor occurring in men. The prevalence of cancer increases with age,

similar to the prevalence of BPH, although the two conditions appear to be independent of each other. Carcinoma usually originates in the posterior lobe and is most often subcapsular in location. Many tumors are present for a long time without being suspected. Histologically, tumors are adenocarcinomas, usually of the desmoplastic type. When such carcinomas metastasize to bones, they form osteoblastic lesions, which appear dense on radiography. Metastases are most often found in the regional lymph nodes, pelvic bones, and the spine. *Prostate-specific antigen* and *prostatic acid phosphatase* levels in the serum are typically *elevated.* Serum alkaline phosphatase is elevated in patients with osteoblastic metastases to the bones. Tumors restricted to the prostate can be resected surgically, but those that have spread outside the prostate are incurable. The prognosis is determined taking into account the extent of tumor spread (staging), typically on a scale from A to D, and histologic grading, which is done according to the system developed by Glisson. Patients with stage B tumors have an 80% 5-year survival rate, but those with stage D tumors have a 5-year survival rate of only 20%. Chemotherapy is of no use for prostatic carcinoma.

PATHOLOGY OF THE PENIS

Developmental Disorders

Congenital anomalies of the penis are rare, except in hermaphrodites and pseudohermaphrodites. In genetic males, the anomalies usually involve the penile urethra. In **hypospadias,** the urethral opening of the urethra is on the lower surface of the penis, whereas in **epispadias,** which is very rare, the opening of the urethra is on the dorsal side. **Phimosis** is a narrowing of the prepuce so that it cannot be retracted over the glans.

Infections

Infections of the glans penis and the surrounding prepuce are called **balanoposthitis.** Nonspecific balanoposthitis owing to poor hygiene is more common in men who are not circumcised. Most other infections of the penis are acquired by sexual intercourse. **Gonorrhea** is characterized by a purulent urethral discharge, **syphilis** by ulcers on the glans penis, and **herpes** by vesicles on the glans or the skin of the shaft (see Fig. 14-1). **Condyloma acuminatum** is a genital wart caused by the human papillomavirus, typically found on the glans or terminal urethra.

Neoplasms

Carcinoma of the penis is uncommon in the United States, but is prevalent in many underdeveloped countries in South America and Africa. Histologically, these tumors are **squamous cell carcinomas.** Clinically, such tumors are recognized as persistent ulcerations, indurations, or exophytic verrucous lesions. Prognosis depends on the stage of the tumor at the time of diagnosis; overall, 60% of men survive 5 years after diagnosis.

Chapter 15

Female Reproductive System

The most important diseases of the female genital system are infections, hormonally induced lesions, and tumors, which may be interrelated. For example, infection of the cervix with human papillomavirus (HPV) may lead to carcinoma. Endometrial hyperplasia induced by estrogen may evolve into adenocarcinoma. Some ovarian tumors are hormonally active (e.g., theca cell tumors secrete estrogen, which may induce endometrial hyperplasia).

INFECTIONS

Infections may be acquired by sexual contact or nonsexually. **Sexually transmitted diseases** (STDs) predominate during reproductive life and include infections caused by **viruses** (herpesvirus, HPV), **bacteria** (*Neisseria gonorrhoeae, Treponema pallidum*), **protozoa** (*Trichomonas vaginalis*), and **chlamydia** (*Chlamydia trachomatis*).

Infections can be acute or chronic and localized to a portion of the female genital system or widespread (e.g., pelvic inflammatory disease [PID]).

Vulvovaginitis usually presents as a chronic disease. Vulvar infections are similar to those on the skin (e.g., vesicles caused by herpesvirus). The vagina is resistant to invasions, and the pathogens remain intraluminal. Symptoms are itching, irritation due to the discharge, pain (herpes), and dyspareunia (painful intercourse). The diagnosis is established by Papanicolaou (Pap) smear and other laboratory tests. Specific forms of vulvovaginitis are listed in Table 15-1.

Cervicitis is most often a chronic infection. It often remains unrecognized, but may be detected on vaginal examination and Pap smear results. Bacteria invade the endocervix and cause mucopurulent discharge. Viruses (herpesvirus and HPV) and chlamydia invade cervical squamous epithelium. Herpesvirus is recognized by intranuclear inclusions ("ground-glass" appearance) and by multinucleation.

TABLE 15-1.
Important Vulvar Infectious Lesions

Grouped vesicles: herpesvirus
Condyloma acuminatum (genital wart): human papillomavirus
Bartholin gland abscess: *Neisseria gonorrhoeae*, *Staphylococcus*, *Streptococcus*
Indurated "hard" chancre: *Treponema pallidum* (primary syphilis)
Condyloma latum (perineal skin): *T. pallidum* (secondary syphilis)
Chancroid "soft" chancre: *Haemophilus ducreyi*
Granuloma inguinale: *Calymmatobacterium donovani*

HPV causes koilocytic changes ("raisin-like nuclei" in the clear cytoplasm of cervical cells).

Endometritis is uncommon during reproductive life because of monthly endometrial shedding. If present, it causes infertility and is usually associated with PID.

Salpingitis is the most common infection of internal female genital organs and is the most typical presentation of PID. It is most often an STD, with mixed bacterial flora superimposed on it. The fallopian tubes are distended with pus and distorted ("retort-like"). The external surface is red and covered with fibrinopurulent exudate. Chronic adhesions are found between the fallopian tubes and adjacent pelvic organs. Infertility because of the obliteration of the tubal lumen is the most important consequence of PID.

HORMONALLY INDUCED LESIONS

Endometrial Hyperplasia

Endometrial hyperplasia is a consequence of **hyperestrinism.** This may be exogenous (e.g., hormonal treatment) or endogenous (e.g., ovarian hyperproduction in polycystic ovary syndrome or theca cell tumor). Lack of ovulation **(anovulatory cycle)** results in hyperestrinism unopposed by progesterone, which normally is secreted at the time of ovulation when the ovulated follicle transforms into the corpus luteum.

Histologically, three forms of hyperplasia are recognized:

- **Simple,** composed of cystic dilated glands resembling Swiss cheese
- **Complex,** composed of crowded glands that are hypercellular but show no nuclear atypia

- **Complex with atypia,** composed of irregularly shaped glands showing nuclear atypia

This histologic classification is of prognostic significance. Simple hyperplasia is a self-limited disease with no potential for malignancy. Complex hyperplasia can be successfully treated by curettage, and only 2% of cases evolve into adenocarcinoma. Complex hyperplasia with atypia should be treated as a premalignant lesion because it progresses to cancer in 25% of cases. Symptoms are nonspecific. Dysfunctional bleeding (i.e., spotting, bleeding in the middle of the cycle) is the most common finding. Massive bleeding (menorrhagia), however, is uncommon.

Endometriosis

Endometriosis is the appearance of foci of endometrial tissue outside the uterus. Pathogenesis is not known, but there are several hypotheses, two of which are most plausible:

- According to the **regurgitation theory,** the endometrial tissue shed during menstruation flows back into the fallopian tube and seeds on the serosa of the peritoneal cavity.
- The theory of **endometrial metaplasia** is based on the fact that endometrium is derived from fetal peritoneal epithelium (celomic epithelium) that invaginates and gives rise to the müllerian epithelium. It has been proposed that the peritoneal surfaces of the adult pelvis may also differentiate into endometrial tissue like the fetal peritoneum.

Pathologic changes are distinctive. The serosal surface of the pelvic organs is sprinkled with small punctate lesions that are red, bluish ("gunpowder mark" lesions), or yellow. Histologically, foci of endometriosis consist of hemorrhagic endometrial stroma and glands. **Large blood-filled cysts** ("chocolate cysts") measuring 3 to 5 cm or larger may be found on the ovaries. Endometriosis shows cyclic changes synchronous with endometrium. The most common sites of endometriosis are the ovary and pelvic peritoneum.

Symptoms are related to the cyclic enlargement and interstitial bleeding, which cause pelvic pain, most pronounced at the time of menstruation. Oral contraceptives suppress cyclic changes and provide relief. Infertility is the most common complication, although why it occurs is not known. Fibrosis and adhesions also occur.

Ovarian Cysts

Non-neoplastic ovarian cysts may be solitary or multiple. Solitary cysts are classified as follicular, theca-lutein, or luteal cysts. **Follicular** or **theca-lutein** cysts represent unruptured ovarian follicles lined by granulosa and theca cells. **Luteal** cysts represent persistent cystic corpora lutea.

Polycystic ovary syndrome is characterized by bilateral ovarian enlargement, cortical fibrosis, and multiple follicular cysts. Polycystic ovary syndrome is a complex disturbance of the hypothalamic-pituitary-ovarian-adrenal axis. Biochemically, it is characterized by an excess of androgens and luteinizing hormone and low levels of follicle-stimulating hormone. Some women have amenorrhea or do not ovulate regularly and show signs of virilization (e.g., facial hair) and are infertile.

NEOPLASMS AND RELATED DISORDERS

Tumors of the female reproductive system are an important cause of morbidity. They may be benign or malignant. Benign tumors are more common. Malignant tumors account for 15% of all malignancies in women. The uterus is the most common site of tumors in the female reproductive system. Risk factors have been identified for several tumors, the most important of which are HPV and STD for carcinoma of the cervix and hyperestrinism for endometrial adenocarcinoma.

Tumors of the Vulva and Vagina

Vulvar carcinoma in 95% of cases is a squamous cell carcinoma. Invasive cancer is preceded by vulvar intraepithelial neoplasia, which is graded I to III in a manner similar to preinvasive carcinoma of the cervix. Vulvar intraepithelial neoplasia III is also called *carcinoma in situ* or *Bowen disease.* On gross examination, carcinoma presents as leukoplakia (white plaques), ulceration, and exophytic verrucous lesion.

Extramammary Paget disease is a rare malignancy of vulvar glands that extends through the ducts into the mucosa, similar to Paget disease of the breast.

Vulvar cancer must be distinguished from non-neoplastic epithelial disorders of the vulva, also known as *vulvar dystrophies.* Clinically, the non-neoplastic epithelial disorders present as discoloration of vulvar mucosa. Most common are whitish plaques **(leukoplakia).** Histologically, non-neoplastic epithelial disorders are classified as atrophic **(lichen sclerosus),** hyperplastic **(squamous cell hyperplasia or hyperplastic dystrophy),** and mixed dystrophy. These benign lesions must be distinguished histologically from vulvar neoplasia and chronic skin diseases, which also may present as leukoplakia.

Vaginal carcinoma is a rare form of squamous cell carcinoma. It may coexist with vulvar and cervical cancer and contain HPV. **Clear cell carcinoma** is a rare form of adenocarcinoma of the vagina that develops in young women who were exposed transplacentally to diethylstilbestrol (DES). DES was used in the 1950s for threatening

abortions and is no longer used during pregnancy. The most common DES lesion is vaginal adenosis, which may persist as such or evolve into carcinoma.

Tumors of the Cervix

Cervical carcinoma accounts for 20% of gynecologic cancer. The incidence of invasive cancer has decreased because of early diagnosis by Pap smears at the preinvasive stage, **cervical intraepithelial neoplasia** (CIN), which is curable. Cervical carcinoma remains prevalent in underdeveloped countries.

Several risk factors have been identified. HPV plays an important pathogenetic role. High-risk HPV serotypes 16, 18, and 31 are found in a significant number of tumors. Other epidemiologic risk factors include STD, especially herpesvirus, multiple sexual partners, early age of first intercourse, and multiparity.

Most tumors originate from the transitional zone and are **squamous cell carcinomas.** Histologically, squamous cell carcinoma is indistinguishable from squamous cell carcinomas in other sites, such as skin. Invasive carcinoma is preceded by CIN. CIN I or mild dysplasia shows disorderly maturation limited to basal and parabasal layers, whereas CIN III shows atypical cells through the entire thickness of the epithelium **(carcinoma in situ).** CIN is labeled as stage 0, whereas the invasive cancer is staged I through IV, depending on the extent of tumor spread. Tumor stage is the primary determinant of prognosis.

Symptoms are nonspecific. Vaginal spotting, especially postcoital, may be present. The diagnosis is made by colposcopy and biopsy, but also may be made by Pap smear. Treatment includes surgical resection or radiation therapy.

Endocervical adenocarcinoma accounts for 10% of cervical cancer. It is composed of mucus-secreting glandular cells. Clinically, it is grouped with adenocarcinoma of the endometrium.

Tumors of the Endometrium

Tumors of the endometrium include adenocarcinoma, endometrial stromal sarcoma, and mixed müllerian tumors.

Adenocarcinoma of the endometrium is the most common gynecologic malignancy and accounts for 50% of all gynecologic cancers. Risk factors include several endogenous and exogenous influences, of which hyperestrinism is the most important. The causes of hyperestrinism are listed in Table 15-2. Other epidemiologic risk factors include nulliparity, obesity, diabetes mellitus, and hypertension.

Pathologically, more than 95% of endometrial cancers are adenocarcinomas. There are several histologic variants such as adenosquamous carcinoma, adeno-acanthomatous carcinoma, and papillary adenocarcinoma. However, histologic subtyping is of no

TABLE 15-2.
Causes of Hyperestrinism

- Exogenous estrogen
- Anovulatory cycle
- Polycystic ovary syndrome
- Tumors
  - Ovarian theca cell and granulosa cell tumors
  - Adrenal tumors

clinical significance. Other endometrial malignancies such as endometrial stromal sarcoma (composed of stromal cells) or mixed müllerian tumor (composed of glandular and stromal malignant cells) are rare. Invasive adenocarcinoma can be staged I through IV. The stage determines the prognosis.

Tumors of the Myometrium

Tumors originating from smooth muscle cells of the myometrium are classified as leiomyomas or leiomyosarcomas. Benign leiomyomas account for 98% of all myometrial tumors. **Leiomyoma** is the most common tumor of the female reproductive system. The tumor develops from estrogen-sensitive smooth muscle cells, but also contains estrogen-insensitive fibroblasts. Fibroblasts may predominate and render the tumor firm, which accounts for the frequently used synonym **fibroids.** Leiomyomas are tumors of reproductive age and do not occur before puberty. After menopause, the tumors shrink and become fibrotic because of a loss of estrogen-sensitive smooth muscle cells. During pregnancy, the tumors may increase in size in response to hormonal stimulation.

Tumors are classified as submucosal, intramural, or subserosal, depending on location. Leiomyomas are often multiple. Tumors are composed of benign smooth muscle cells and show almost no mitotic activity. Secondary changes are common and include ischemic necrosis leading to softening, cystic changes, hyalinization, and calcification.

Symptoms depend on the location of the tumor. Submucosal tumors may cause bleeding and dysmenorrhea. Infertility due to impeded implantation is another finding. Intramural tumors produce enlargement of the uterus, which may attain gigantic proportions and fill the entire pelvis. Such tumors compress the urinary bladder and rectum and may cause discomfort. The pedunculated subserosal tumors may twist around their stalk and undergo painful infarction.

Leiomyosarcomas of the uterus are rare malignant tumors. These tumors arise de novo and do not resemble leiomyomas. Leiomyosar-

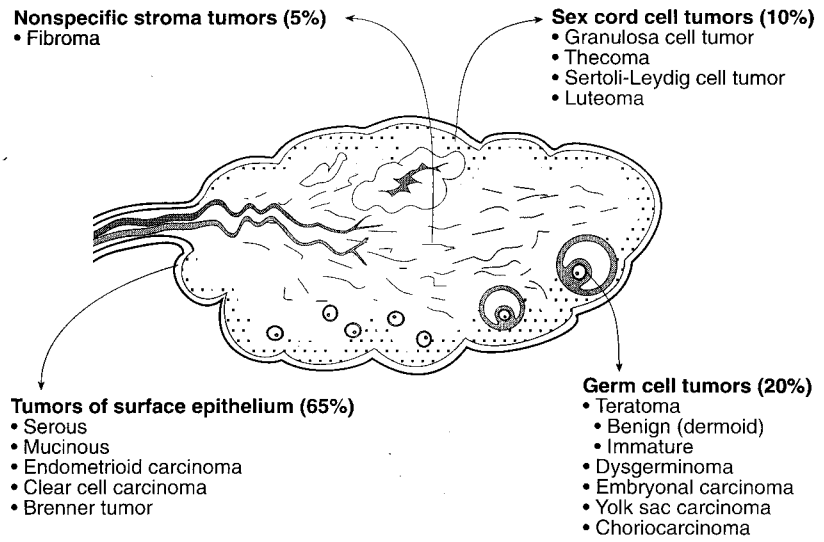


Figure 15-1.
Histogenesis of ovarian tumors. Tumors can originate from the surface epithelium, germ cells, sex cord cells, and nonspecific stroma.

comas occur in older women who have only a 40% 5-year survival rate. Histologically, they resemble leiomyomas, but generally the tumor cells show more pleomorphism and many more mitoses. Malignant transformation of leiomyomas is extremely rare.

Tumors of the Ovary

Clinicopathologically, it is important to note that ovarian tumors are a heterogeneous group, in contrast to tumors of other parts of the female reproductive system, which are histologically monomorphous. Histologic classification and grading of tumors has prognostic significance.

Malignant ovarian tumors account for 20% of gynecologic cancer and 50% of mortality from gynecologic cancer. This high mortality reflects the inability to diagnose ovarian cancer early and to treat the established cancer effectively.

Pathogenetically, the ovarian tumors can be classified according to their cell of origin into four groups: tumors of epithelial surface epithelium, germ cell tumors, sex cord cell tumors, and nonspecific stromal cell tumors (Fig. 15-1).

Surface epithelial cell tumors include serous and mucinous cystic tumors, endometrioid adenocarcinoma, clear cell carcinomas, and Brenner tumors. These tumors have been compared histologically with the epithelium derived from müllerian ducts: Serous tumors correspond to the epithelium of fallopian tubes, mucinous to endocervical epithelium, and endometrioid to endometrial epithelium.

Serous and mucinous tumors are cystic, and their cysts contain either serous clear fluid or mucus. Histologically, these tumors are

classified as benign cystadenoma or malignant cystadenocarcinomas, with the prefix serous or mucinous. The malignant cystadenocarcinomas contain highly malignant tumors and low-grade tumors (i.e., tumors of borderline malignancy). The benign tumors are lined by simple single-layered well-differentiated epithelium; the malignant tumors show marked epithelial irregularity, papillary structure formation, and invasion; the borderline tumors range in between.

Endometrioid carcinomas and clear cell carcinomas are solid malignant tumors and do not have benign equivalents. **Brenner tumor** is a benign tumor composed of islands of transitional epithelium included in nonspecific ovarian stroma.

Germ cell tumors include teratomas, dysgerminomas, embryonal carcinoma, yolk sac carcinoma, and choriocarcinoma. These tumors are equivalent to testicular germ cell tumors.

Teratomas occur in two forms: benign teratoma and immature teratoma. **Benign teratomas** are the most common ovarian tumor in women under the age of 25 years. These tumors contain tissues derived from all three embryonic germ layers (i.e., ectoderm, mesoderm, and endoderm). Tumors are typically cystic and lined from inside with skin, hence the synonym **dermoid.** The skin is covered with hair and sebum secreted by the skin glands. The cyst wall may contain other well-differentiated tissues such as teeth, brain, and bronchial glands. Teratomas are benign tumors, but if left untreated, the skin may undergo secondary malignant transformation, usually over a 20- to 30-year period.

All other germ cell tumors are rare. These tumors are solid masses, affect young women, and are clinically malignant. **Yolk sac carcinoma** secretes α-fetoprotein and choriocarcinoma secretes human chorionic gonadotropin (hCG), which serve as serologic markers for these tumors. **Sex cord cell tumors and stromal tumors** are rare tumors with a peak incidence between 25 and 45 years. This group includes granulosa and theca cell tumors, both of which secrete estrogens, and **Sertoli-Leydig cell tumors,** which secrete androgens. **Theca cell tumors** are benign, granulosa cell tumors are low-grade malignant, and the Sertoli-Leydig cell tumors may be benign or malignant.

Fibroma is the most common tumor of nonspecific ovarian stroma. This hormonally inactive tumor presents as a firm (fibrotic) mass expanding or completely replacing the ovary. It may be associated with pleural effusion **(Meigs syndrome). Metastases** to the ovaries are rare. Most arise from primary tumors in the contralateral ovary, uterus, and breast. Carcinoma of the gastrointestinal tract, especially carcinoma of the stomach, has a tendency to form bilateral ovarian metastases (so-called **Krukenberg tumor**).

Ovarian cancers tend to spread into the peritoneal cavity, but also involve the pelvic and abdominal lymph nodes. Peritoneal seeding leads to the formation of malignant ascites. Mucinous adenocarcinomas secrete mucus that fills the peritoneal cavity **(pseudomyxoma peritonei)**.

Symptoms of ovarian cancer are nonspecific and usually occur late in the course of the disease. Because most tumors are

TABLE 15-3.
Biochemical Markers of Ovarian Tumors

Tumor	Marker
Granulosa cell tumor	Estrogen
Theca cell tumor	Estrogen
Sertoli-Leydig cell tumor	Androgen
Yolk sac carcinoma	α-Fetoprotein
Choriocarcinoma	Human chorionic gonadotropin

Adenocarcinomas of ovarian surface epithelium may release glycolipid antigens CEA or CA-125, used for monitoring tumor treatment.

diagnosed in stage II or III and higher, the prognosis is poor, and the overall 5-year survival rate is only 30%. Diagnosis can be aided by using certain tumor markers listed in Table 15-3. Unfortunately, there are no dependable tumor markers for the most common ovarian malignant tumors (i.e., those originating from the surface epithelium).

PATHOLOGY OF PREGNANCY

Diseases of pregnancy can be classified as related to abnormal fertilization, abnormal implantation of the conceptus, pathology of the placenta, and maternal diseases of pregnancy.

Pathology of Fertilization and Implantation

Infertility can be caused by female and male factors, which could be further classified as infectious (e.g., PID), hormonal (e.g., polycystic ovary syndrome), immune, or idiopathic. Idiopathic infertility is the most common form of infertility.

Ectopic pregnancy results from the implantation of the conceptus outside the uterine cavity. Most often, ectopic pregnancy occurs in the fallopian tube, but it may also occur on the ovary, cervix, or peritoneal surfaces. Such pregnancy cannot be brought to term and usually results in **spontaneous abortion. Rupture of the fallopian tube** eroded by the ectopic placenta may result in rupture and massive hematoperitoneum and death due to exsanguination.

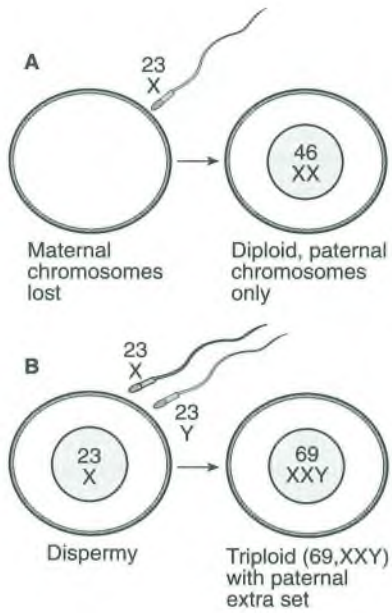


Figure 15-2.
Pathogenesis of hydatidiform mole. *A:* Complete. *B:* Partial.

Pathology of the Placenta

Gestational trophoblastic disease results from abnormal formation of the placenta. It includes four entities: hydatidiform mole, invasive mole, placental site trophoblastic tumor, and choriocarcinoma.

Hydatidiform mole represents marked swelling of chorionic villi associated with variable degrees of trophoblastic cell hyperplasia (Fig. 15-2). If all the villi are involved, the mole is *complete,* and if only part of the villi are involved, the mole is *partial.* Other differences between complete and partial mole are listed in Table 15-4.

Hydatidiform mole develops due to abnormal fertilization. The complete mole results from **androgenesis,** a process in which the fertilized ovum loses the maternal chromosomes but retains the paternal chromosomes. The male haploid chromosomal complement 23,X reduplicates, and thus in 90% of complete moles the karyotype is 46,XX and all the chromosomes are paternal. The incomplete moles have a triploid karyotype (69,XXY or 69,XYY) and contain one female haploid set and two male haploid sets of chromosomes. These are **diandric** (i.e., they are the result of double fertilization of the ovum). Hydatidiform mole occurs once in 2,000 pregnancies in the United States. However, in Southeast Asia, the incidence is 1 in 200. Most moles abort spontaneously; if they do not abort, curettage and evacuation are curative. However, 2% to 3% of complete moles tend to become invasive, recur after evacuation, and can give rise to choriocarcinoma.

Choriocarcinoma is a rare malignant tumor composed of trophoblastic cells, mononuclear cytotrophoblastic cells, and multinuclear syncytiotrophoblastic cells. It occurs in 1 in 30,000 pregnancies in the United States and 1 in 2,000 pregnancies in parts of Asia and Africa. In 50% of cases, it is a complication of hydatidiform mole; in 25%, it follows abortion; and in 25%, it occurs after a normal pregnancy. This is a

TABLE 15-4.
Hydatidiform Mole

Feature	Complete	Incomplete
Karyotype	46,XX (90%) 46,XY (10%)	69,XXY or 69,XYY
Villous edema	All villi	Partial
Trophoblastic proliferation	++	+/–
Fetal parts	–	+
Human chorionic gonadotropin very high	++	+
Choriocarcinoma	2–3%	Infrequent

highly invasive tumor with a tendency to hematogenous metastases. Despite widespread metastases, cure in excess of 75% has been achieved by chemotherapy regimens that contain methotrexate. Only tumors metastatic to the brain have poor prognosis. hCG typically produced in large amounts is a good tumor marker for choriocarcinomas.

Maternal Diseases of Pregnancy

The most important systemic disease of pregnancy is toxemia of pregnancy. It presents in two forms: preeclampsia and eclampsia. **Preeclampsia** is defined clinically as a syndrome that occurs in pregnancy and typically presents with proteinuria, edema, and hypertension. **Eclampsia** has these same symptoms, but is more severe and also causes convulsions. The pathogenesis of this systemic disease is not known, but it may be related to reduced uteroplacental blood flow. The resulting endothelial cell dysfunction leads to activation of intravascular coagulation and disseminated intravascular coagulation. Renal microvascular changes result in reduced glomerular filtration rate, proteinuria, and hypertension. Microvascular occlusion and ischemia of the brain may result in convulsions typical of eclampsia with life-threatening consequences.

BREAST DISEASES

Diseases of the breast can be classified as developmental, inflammatory, hormonal, and neoplastic. **Neoplasia** is the most important dis-

ease of the breast. The so-called fibrocystic change is actually more common, but should be considered an age-related phenomenon rather than a disease. Developmental and inflammatory breast lesions are rare. Agenesis of a breast or multiple breasts (polymastia) are rare developmental disorders.

Acute mastitis is a bacterial infection that typically affects the breast during lactation. Incomplete evacuation of the milk and minor skin trauma caused by the suckling (fissures of the nipple) predispose to bacterial invasion. The disease presents with reddening and swelling and pain, usually relieved by milking. **Breast abscess,** the most serious complication of acute mastitis, requires antibiotic therapy and occasionally even surgical incision.

Fibrocystic Change

The term *fibrocystic change* includes a series of gross microscopic changes related to the cumulative effects of aging and cyclic hormonal changes affecting the epithelium and stroma of the adult female breast. Typically, the changes are bilateral and produce irregular nodular (bead-like) lumps and fibrotic thickening of the breast parenchyma, which is more prominent and often painful prior to menstruation.

Fibrocystic change is found in approximately 50% of women over the age of 40. It is the most common histologic diagnosis on breast tissue biopsies. Histopathology of the fibrocystic change is characterized by a mixture of epithelial and stromal changes, mentioned previously. It is important to distinguish simple fibrocystic change (80%), which consists of fibrosis and cysts, from proliferative fibrocystic change (20%), which shows prominent intraductal proliferation. These epithelial cells may acquire atypical features and progress to cancer in 3% to 5% of cases.

Fibroadenoma

Fibroadenoma is a benign tumor composed of proliferated ducts and intralobular stroma. It is the most common tumor in young women, with a peak incidence in the 20- to 25-year-old age group. Giant fibroadenomas are called **phyllodes tumors.** Ordinary fibroadenomas are always benign. Phyllodes tumors are most often benign, but may also be low-grade malignant.

Carcinoma of the Breast

Breast carcinoma is the most common female malignancy. One of every 12 women can expect to develop breast cancer during her lifetime. Breast cancer accounts for 20% of cancer deaths in the United States. The prognosis depends on the stage of the tumor at diagnosis. Only the small tumors recognized by systemic screening

TABLE 15-5.
Risk Factors for Breast Cancer

Sex	Female > male = 100:1
Race	Caucasians > Asians = 5:1
Age	50 years > 30 years = 10:1
Family history	Positive:negative = 10:1
Pregnancy	Nulliparous > multiparous Late age at first pregnancy > early pregnancy No breast-feeding > breast-feeding
Other pathology	Proliferative fibrocystic disease Cancer of contralateral breast Ovarian cancer

TABLE 15-6.
Histologic Classification of Breast Carcinoma

Ductal carcinoma
Noninfiltrating
- Intraductal carcinoma
  - Comedo-type
  - Papillary carcinoma

Infiltrating
- Infiltrating ductal carcinoma NOS* (70%)
- Medullary carcinoma
- Mucinous (colloid carcinoma)
- Tubular carcinoma
- Paget disease

Lobular carcinoma
- Lobular carcinoma in situ
- Invasive lobular carcinoma

**Most common.*
NOS, not otherwise specified.

(self-palpation and mammography) are completely curable. The most important risk factors are listed in Table 15-5.

Most tumors originate in the outer upper quadrant. At the time of diagnosis, most tumors measure 2 to 4 cm in diameter and are firm. By mammography, most tumors appear dense and show focal calcification. Histologically, all breast tumors are adenocarcinomas, which can be subdivided into several types (Table 15-6).

Ductal carcinoma, not otherwise specified, is also referred to as the "garden variety breast cancer," which accounts for approximately

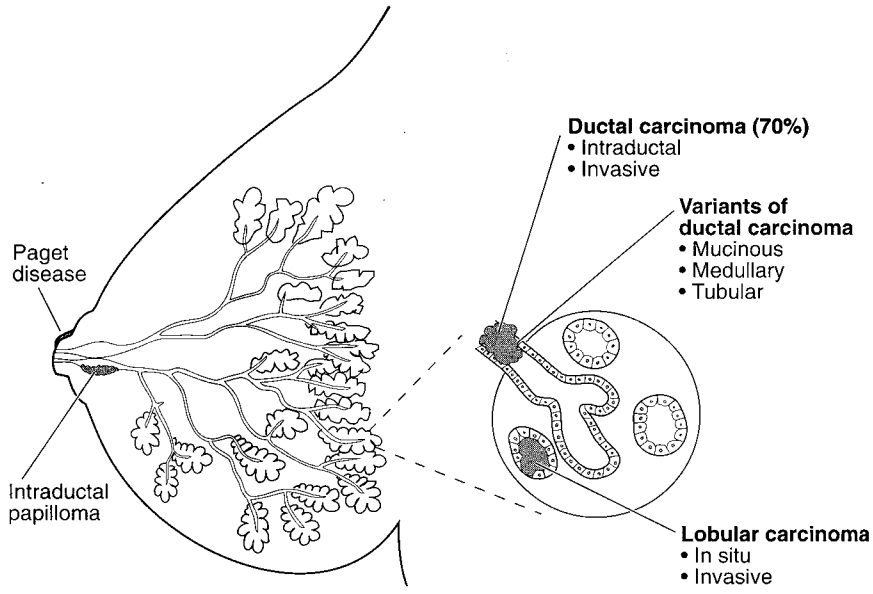


Figure 15-3.
Breast carcinoma. Tumors originate from ductal or lobular cells.

70% of all breast carcinomas. Such tumors are composed of atypical ducts and produce a strong desmoplastic reaction **(scirrhous carcinoma),** which accounts for their firm consistency (rock hard, gritty on sectioning) and puckering of the overlying skin (peau d'orange) or the inversion and retraction of the nipple. The invasive lobular carcinoma has the same gross features and prognosis (Fig. 15-3).

Intraductal carcinoma is not invasive and therefore has a better prognosis. It may be present as comedo or papillary type. In comedotype carcinoma, the ducts are filled with tumor cells that undergo necrosis centrally and can be expressed from the large ducts of the nipple as **comedo** (skin blackheads). **Papillary** carcinomas grow within the large duct and cause bleeding. The detached papillae can be recognized in cytologic smears of the material expressed from the nipple. Variants of ductal carcinoma are less common. **Medullary carcinoma** is composed of solid nests of tumor cells. **Mucinous carcinoma** is composed of mucus-secreting cells, which seem to be floating in the sea of extracellular mucus. Medullary and mucinous carcinomas contain scant connective tissue and are therefore soft. Both portend a better prognosis than the infiltrating duct carcinoma, not otherwise specified. **Tubular carcinoma** is composed of well-differentiated tubules infiltrating the breast parenchyma. Despite its invasiveness, this cancer has an excellent prognosis. **Paget disease** is a form of breast cancer that originates in the ducts and spreads intraductally to invade the skin of the nipple. It is an invasive cancer and thus has an unfavorable prognosis.

Lobular carcinoma differs from ductal carcinoma regarding only its primary site of origin. In the preinvasive form (lobular carcinoma in situ), which cannot be palpated and is discovered only by biopsy, the tumor cells fill the lobules but do not invade the surrounding tis-

TABLE 15-7.
Causes of Gynecomastia

- Physiologic: puberty
- Liver diseases: cirrhosis
- Tumors
  - Leydig cell tumor
  - Adrenal cortical carcinoma
- Exogenous hormones: estrogens
- Drugs
  - Psychotropic drugs
  - Cimetidine

sue. The tumor must be treated as a true malignancy because ultimately it becomes invasive. A contralateral breast biopsy is also indicated, because these patients have contralateral breast cancer in 30% of cases. **Invasive lobular carcinoma** resembles infiltrating duct carcinoma in that it is also a scirrhous carcinoma. Histologically, the lobular carcinoma cells are smaller and tend to infiltrate the connective tissue as single cell columns ("Indian file patterns").

Breast carcinoma has a tendency to metastasize to local lymph nodes, most often those located in the axilla or those along the internal mammary artery. Distant hematogenous metastases are found in the lungs, liver, brain, adrenals, and ovaries.

Symptoms of breast carcinoma are nonspecific. The majority of cases are detected by self-palpation as a small parenchymal nodule. Nipple retraction, nipple discharge, and breast inflammation are rare but important signs. Some tumors are recognized by lymph node involvement, mostly in the axilla or distant metastases. Paraneoplastic findings such as hypercalcemia are found in advanced disease.

The prognosis depends primarily on the stage of the tumor and to a lesser extent on the histologic type. Treatment is based on surgical resection of the breast and adjuvant chemotherapy.

Pathology of the Male Breast

Male breast pathology is of lesser clinical significance than female breast pathology. **Gynecomastia** is an enlargement of the male breast, usually in response to relative hyperestrinism. The causes of gynecomastia are listed in Table 15-7. High serum concentrations of estrogen may be related to estrogen-secreting tumors of the testis or the adrenal. Low or relatively mild elevations of serum may be related to drugs or cirrhosis of the liver. Carcinoma of the male breast is 100 times less common than carcinoma of the female breast. Histologically, it is most often of the infiltrating duct type.

Chapter 16

Endocrine System

PITUITARY GLAND

The pituitary gland, sometimes referred to as the *master gland*, exerts influence over several other endocrine glands including the thyroid, adrenal cortex, ovary, and testis. The most important diseases of the pituitary are hyperpituitarism, hypopituitarism, and posterior pituitary syndromes.

Hyperpituitarism

Hyperpituitarism is a disorder most commonly produced by **adenomas.** Pituitary carcinomas or idiopathic hyperfunction of the hypothalamus are rare causes of this disorder. Adenomas can be classified as microadenomas (<10 mm) or macroadenomas (>10 mm). These tumors may be confined to a portion of the anterior lobe or by expansile growth, replace the entire cloud, extend out of the sella turcica, or erode through the bone and impinge on adjacent structures. Microscopically, adenomas have a uniform appearance with polygonal cells arranged in sheets, cords, or nests. The stroma is delicate and vascularized. Ischemic necrosis or hemorrhages are secondary changes seen focally in larger tumors. The incidence of various pituitary adenomas is given in Table 16-1.

Somatotropic adenomas account for approximately 15% of pituitary tumors. Clinically, the tumors present with either acromegaly or gigantism. **Acromegaly** occurs in adults and presents with enlargement of the head, hands, feet, jutting jaw, large tongue, and soft tissue enlargement (Fig. 16-1). Generalized visceromegaly (e.g., cardiomegaly, hepatomegaly) and metabolic disorders (e.g., hyperglycemia) are also present. Childhood somatotrophic adenomas that occur before closure of the epiphysis of long bones cause **gigantism.** This is now a rare condition. Approximately one-third of somatotropic adenomas also secrete prolactin.

Prolactinomas are the most common functional pituitary adenomas, accounting for approximately 30% of all pituitary tumors. These neoplasms suppress normal gonadal functions in both men and women. In men, this may lead to impotence. In women, pro-

TABLE 16-1.
Pituitary Adenomas

Tumor	Incidence (%)
Somatotropic	15
Prolactinoma	30
Corticotropic	10
Gonadotropic	5
Thyrotropic	1
Nonfunctioning	20–30

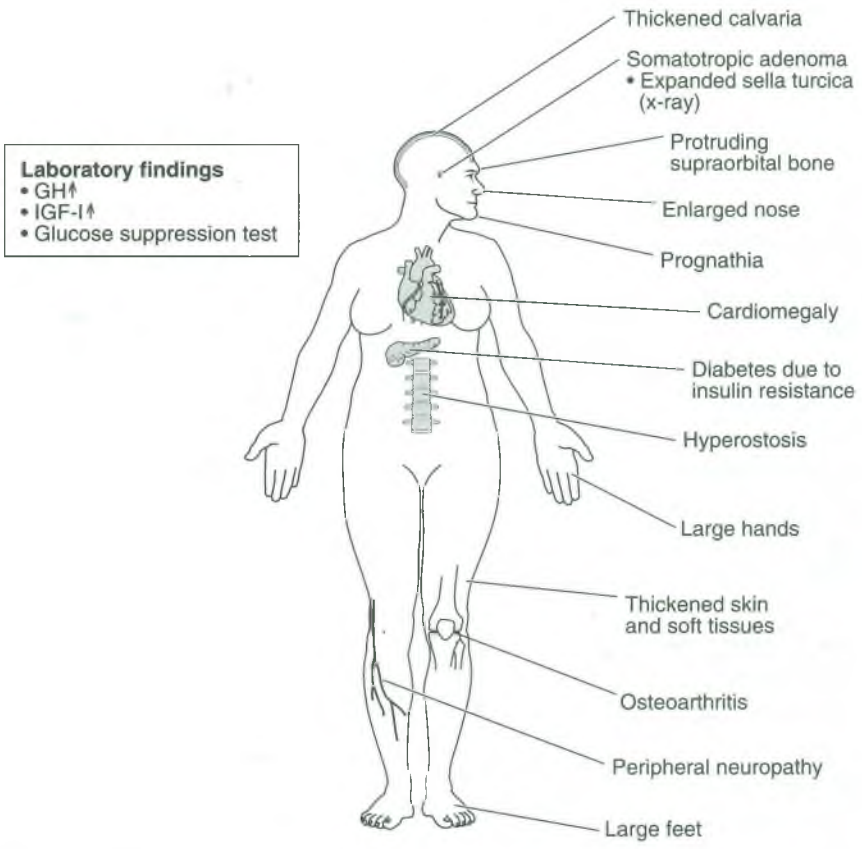


Figure 16-1.
Acromegaly. (GH, growth hormone; IGF, insulin-like growth factor.)

lactinomas cause galactorrhea and amenorrhea. Only one-third of these adenomas are macroadenomas, which may cause expansion of the sella turcica and local compression effects, whereas all others are microadenomas (i.e., <10 mm).

Corticotropic adenomas, most of which are microadenomas, secrete **adrenocorticotropic hormone** (ACTH). This stimulates the production of cortisol by the adrenal cortex, resulting in **Cushing disease.** In contrast, patients with primary adrenal hypercorticism have **Cushing syndrome** without ACTH-producing pituitary tumors.

Gonadotropic adenomas are usually macroadenomas, causing local compression symptoms such as headaches and visual disturbances. Gonadal functional disturbances are variable. Hypogonadism in men is associated with elevated serum levels of **follicle-stimulating hormone** (FSH), but **luteinizing hormone** (LH) levels are usually within normal limits. In women, there is often no detectable elevation of either FSH or LH.

Hypopituitarism

Hypopituitarism results from lesions in the anterior pituitary or hypothalamus. The vast majority of cases (90%) are associated with destructive lesions in the anterior pituitary. Clinically, hypopituitarism becomes manifest only if 75% or more of the anterior lobe is destroyed. Although hypopituitarism is uncommon, three clinical pathologic entities are discussed in this review: nonsecretory chromophobe pituitary adenomas, Sheehan syndrome, and craniopharyngiomas.

Nonsecretory pituitary adenomas account for 20% to 30% of pituitary tumors. There are no recognizable clinical effects of excess secretion of anterior lobe hormones. Rather, patients present with clinical signs referable to local compression effects such as visual field abnormalities; headaches; or hypofunction of target organs such as the thyroid, adrenals, or gonads. The tumors are generally large when discovered. Microscopically, these tumors are chromophobic null cells or oncocytomas composed of afunctional cells with abundant eosinophilic cytoplasm packed with mitochondria.

Sheehan syndrome (postpartum pituitary necrosis) is an acute anterior lobe infarction generally related to obstetric hemorrhage or shock. The pituitary enlarges considerably during pregnancy and compresses adjacent vessels. Bleeding or shock during delivery can cause acute hypotension, which in turn produces vasospasm and infarction of the anterior lobe of the pituitary while sparing the posterior lobe. Causes of pituitary infarction in nonpregnant women and men include disseminated intravascular coagulation, sickle cell anemia, thrombi in the cavernous sinus, temporal arteritis, and vascular trauma. Clinically, 90% to 95% of the gland is usually destroyed, resulting in panhypopituitarism evidenced by lactation failure in the puerperium, hypothyroidism, and adrenocortical insufficiency. With less extensive loss, patients may be asymptomatic or demonstrate loss of only a single trophic hormone. In the initial stages, the pituitary appears soft, pale, or hemorrhagic. Over time it becomes scarred.

Craniopharyngiomas are hypothalamic suprasellar tumors arising from remnants of the embryonic primordium of the pituitary, the Rathke pouch. These tumors are found in or above the sella tur-

cica. Because of their location, they often impinge on the optic nerve, other nerves, and the floor of the third ventricle. Histologically, they are composed of nests or cords of stratified squamous or columnar cells in a loose fibrous connective tissue stroma. These structures mimic the fetal primordia of the enamel organ of the tooth and are considered to be closely related to odontogenic tumors (adamantinomas). The majority contain foci of calcification or metaplastic bone that can be seen on radiography. These tumors are generally seen in children and young adults who generally complain of vision loss, headaches, or vomiting. Obesity, delayed pubescence, and diabetes insipidus are typically found, but the tumor may also cause panhypopituitarism.

Posterior Pituitary Syndromes

Disorders of the posterior pituitary gland are rare. Most are caused by suprasellar hypothalamic lesions and relate to deficiencies or inappropriate secretion of **antidiuretic hormone** (ADH), also known as **arginine vasopressin.**

Diabetes insipidus is caused by a deficiency of ADH. The disease is characterized by excessive thirst, polydipsia, and hypotonic polyuria. Hypotonic polyuria is defined as urine with osmolality <200 to 300 mosm/kg and output >2,000 ml/day. This syndrome results from an injury of the hypothalamohypophysial axis. The causes include inflammation at the base of the brain (e.g., abscesses, meningitis, tuberculosis, sarcoidosis), suprasellar hypothalamic neoplasms, or physical injury (e.g., surgery, irradiation, head trauma). In 30% of cases, no cause can be established, although some causes are inherited.

Syndrome of inappropriate ADH secretion can be caused by lesions of the central nervous system such as intracerebral hemorrhage, thrombosis, subarachnoid hemorrhage, or subdural hematomas. More often, it is related to paraneoplastic secretion of ADH by tumors, usually small cell bronchogenic carcinomas of the lung. Tumoral secretion of ADH is persistent and not influenced by plasma osmolality. Because of excess water reabsorption by the kidneys, the extracellular fluid volume is increased, resulting in hemodilution and hyponatremia.

THYROID GLAND

Developmental Disorders

Thyroglossal duct remnants and cysts are the most frequent congenital anomalies typically found in children. If the embryonic duct fails to completely involute, a cystic remnant can be found anywhere from the

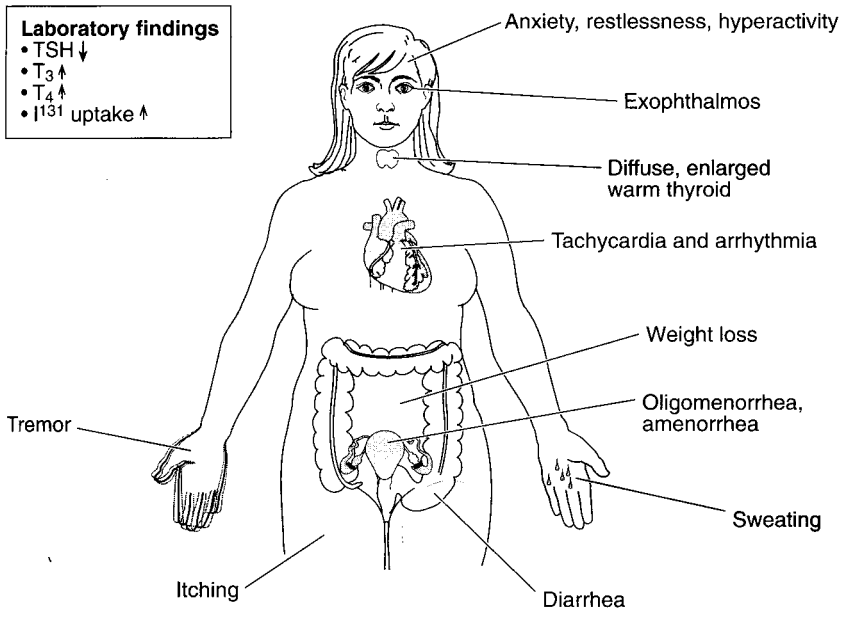


Figure 16-2.
Features of hyperthyroidism. (TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.)

tongue to the isthmus of the thyroid. The cysts are lined with squamous or respiratory-type epithelium attached to atrophic thyroid follicles.

Agenesis of the thyroid due to failure of embryonic induction occurs at a rate of 1 per 4,000. It results in congenital hypothyroidism.

Hyperthyroidism

Hyperthyroidism due to hyperfunction of the thyroid is most frequently observed in women. **Serum triiodothyronine (T_3)** and **thyroxine (T_4)** levels are elevated. Clinical features include nervousness, heart palpitations, rapid pulse, fatigability, weight loss in spite of good appetite, muscular weakness, and diarrhea. In addition, heat intolerance, excessive perspiration, warm skin due to peripheral vasodilation, and increased blood flow are observed. Finally, emotional lability, irregular menses, fine tremors of the hand, retraction of the upper eyelid yielding a stare, and proptosis due to inflammation of the retro-orbital tissues are prominent features, along with cardiomegaly due to increased workload (Fig. 16-2).

Graves disease is the most common cause of hyperthyroidism (85%), whereas toxic multinodular goiter and toxic adenoma account for the remaining 15%. In Graves disease, the entire thyroid is diffusely enlarged, hyperemic, and warm on palpation. In toxic multinodular goiter, the thyroid consists of numerous nodules that vary in size and shape. Toxic adenoma is usually a solitary nodule encased in the gland, which is of normal size.

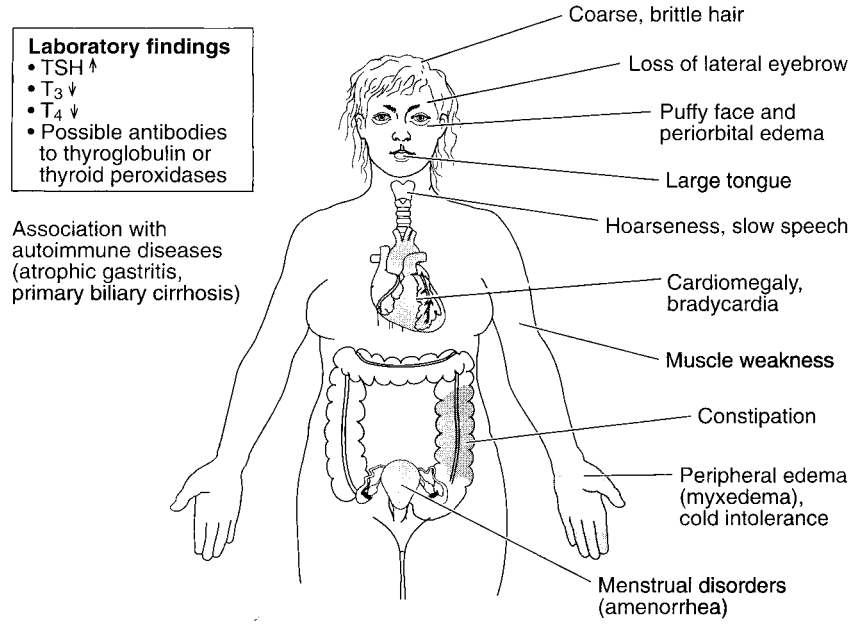


Figure 16-3.
Features of hypothyroidism. (TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.)

Hypothyroidism

Hypothyroidism manifests itself as a **hypometabolic** state caused by structural or functional changes that reduce or impair the normal output of thyroid hormone. Approximately 60% to 70% of all cases are assumed to be autoimmune. Perhaps, in these patients, the autoantibodies to thyroid-stimulating hormone (TSH) receptors inhibit proper stimulation of the thyroid. In some cases, the disease begins as **Hashimoto thyroiditis,** which destroys the thyroid parenchyma and then burns out. Other cases present as end-stage **atrophic thyroiditis**, the nature of which cannot be deciphered with certainty. Most other cases are iatrogenic and related to surgical resection or radiation of the thyroid. Hereditary defects of hormone biosynthesis, iodine deficiency, and certain drugs, such as lithium, may interfere with thyroid hormone synthesis. Finally, pituitary or hypothalamic lesions interfering with TSH secretions may cause the same clinical symptoms. All of these conditions are rare (Fig. 16-3).

Cretinism is a term used to denote mental retardation caused by hypothyroidism of infancy. This condition can be *endemic* in areas where there are dietary deficiencies of iodine, or it can be *sporadic* in the face of congenital developmental defects of the thyroid or biosynthetic defects affecting thyroxin. It is associated with physical and mental retardation. Individuals have dry, rough skin; widely set eyes with periorbital edema; a flattened, broad nose; and an excessively large tongue that protrudes from the mouth.

Myxedema is the name for the clinical syndrome caused by hypothyroidism in adults. Initially, the disease is characterized by

fatigue, lethargy, and cold intolerance, but as it progresses, it affects the speech and intellectual functions. Eventually, there is periorbital edema, the tongue is enlarged, the skin becomes thick and dry, and peripheral edema occurs, characterized by doughy thickening of the skin, which is resistant to pitting. The edema of the eyes and skin is due to accumulation of hydrophilic mucopolysaccharides in connective tissue. Similar changes occur in the heart, which becomes dilated and flabby (myxedema heart). Constipation, due to decreased peristalsis, is a common complaint. Reproductive function may be affected.

Thyroiditis

Thyroiditis can be divided into two major groups: infectious, which is rare, and immune mediated, which is common. **Infectious thyroiditis** may result from hematogenous or local spread of bacteria such as *Staphylococcus, Streptococcus,* and *Salmonella,* or fungi such as *Candida, Aspergillus,* and *Mucor.* Some forms of thyroiditis are presumably of viral origin. **Riedel fibrous thyroiditis (Riedel struma),** characterized by thyroid atrophy and fibrosis with adhesions to adjacent structures, is considered to be idiopathic. Immune-mediated thyroiditis accounts for most cases encountered in clinical practice. It occurs in several forms, the most important of which are Hashimoto thyroiditis, subacute granulomatous thyroiditis, and chronic lymphocytic thyroiditis.

Hashimoto thyroiditis is an autoimmune disease in which the immune system produces antibodies to thyroid antigens. It is the most common identifiable cause of hypothyroidism in the United States. It is characterized by either a goiterous enlargement or, less often, an atrophy of the thyroid. Patients' serum contains many autoantibodies such as those to thyroglobulin and TSH. Autoantibodies to thyroid peroxidases are considered most important because they seem to destroy thyroid follicles or inactivate thyroid cells, transforming them into eosinophilic Hürthle cells. Histologically, the thyroid gland in the **goiterous form** is characterized by marked infiltrates composed of lymphocytes, plasma cells, and macrophages, sometimes arranged into lymphoid follicles. Thyroid cells are lost, and many of the remaining follicles are small, contain intensely staining colloid, and are lined by Hürthle cells. In the **atrophic form,** the thyroid shows abundant fibrosis, replacing the follicles with a less dense cellular infiltrate.

The disease is found predominantly in women, its incidence increasing with age. Typically, the disease begins as a goiterous enlargement of the thyroid, with slowly evolving signs of hypothyroidism. Serum levels of TSH are high and T_3 and T_4 levels are low. Antibodies to thyroid peroxidase are present in high titer. In the atrophic form, functional signs predominate: There is no thyroid enlargement. On occasion, patients may present with hyperthyroidism, which subsides and then slowly progresses to hypothyroidism. Hypothyroidism can be treated effectively with thyroid hormone–replacement therapy.

Subacute (granulomatous, de Quervain, or giant cell) thyroiditis is a distinct form of thyroiditis characterized by a granulomatous inflammatory response. It is thought to be of viral etiology because it is often preceded by viral infections such as mumps or measles. Histologically, characteristic features include rupture of the follicles, which are surrounded by macrophages and giant cells. With time, chronic inflammatory cells and fibrosis supplant these granulomas. The condition is predominately observed in 20- to 50-year-old women. Clinically, it may present as an acute, febrile illness, a sudden painful enlargement of the thyroid gland, or transient hyperthyroidism with less painful enlargement. T_3 and T_4 levels are increased due to the release of hormones from damaged follicles. TSH levels are low and associated with low uptake of radioactive iodine into the thyroid. The disease is self-limiting, and recovery occurs 6 to 8 weeks after the initial attack.

Chronic lymphocytic thyroiditis is commonly diagnosed at autopsy. Clinically, it is usually silent, but occasionally it may be found associated with goiter or even hypothyroidism. In some cases, it represents remnants of a burned-out Hashimoto thyroiditis.

Graves Disease

Graves disease is an **autoimmune disease,** accounting for 85% of all cases of hyperthyroidism. It is found in approximately 2% of all women in the United States, but is rare in men. **Hyperthyroidism** is associated with thyroid enlargement, exophthalmus, and a diffuse infiltrative dermatopathy. The disease is characterized by the appearance of IgG antibodies to TSH receptor on the follicular cells of the thyroid. These antibodies stimulate follicular cells to become hyperactive and also to proliferate. Hypertrophy and hyperplasia of thyroid cells are evident histologically: The follicles are enlarged and lined by columnar epithelium, often forming papillae projecting into the lumen of the follicle. The amount of colloid is reduced and presents a scalloped appearance at its interface with the follicular cells. It stains pale pink and has a thin watery appearance. The interfollicular stroma is highly vascularized and infiltrated with lymphocytes.

Clinically, the disease is found predominantly in 20- to 40-year-old women and is associated with a triad of hyperthyroidism, exophthalmus, and dermatopathy. In addition, patients present with weight loss, sometimes nervousness, heat intolerance, and fatigue. Tachycardia and diarrhea may be present, reflecting the increased metabolic rate. The clinical diagnosis is supported by laboratory findings, which include decreased levels of TSH and increased levels of free T_3 and T_4 and increased radioactive iodine uptake.

Goiter

Goiter refers to **thyroid enlargement,** which may be diffuse or nodular. Goiter involves the entire gland and is generally associated with no

functional disturbance, although occasionally it may present with hyperfunction or hypofunction. In most cases in the United States, the cause is unknown. In certain parts of the world, it occurs in an endemic form, which is related to a decreased intake of iodine. **Iodine deficiency** leads to decreased synthesis of thyroid hormone, with increased production of TSH leading to focal compensatory follicular cell hypertrophy and hyperplasia. Goiters occasionally can be traced to the intake of goitrogens, such as calcium and fluorides in water supplies, or vegetables such as cabbage, cauliflower, and Brussels sprouts.

Histologically, goiter has a variegated appearance and consists of hyperplastic and atrophic nodules. Follicles are often arranged in nodules surrounded by fibrous tissue. Secondary degenerative changes include broad areas of fibrosis, foci of hemorrhage, or calcification.

Clinically, most patients with nontoxic goiter are euthyroid. The enlarged thyroid may cause local compression symptoms and even gross deformity of the neck. Occasionally, goiter may be associated with mild hyperthyroidism. Hypothyroidism is rarely a manifestation of goiter in the United States, but it may be prominent in endemic areas with inadequate iodine supply, as in the mountainous parts of South America or the Himalayas.

Tumors of the Thyroid Gland

Tumors of the thyroid are common. Fortunately, most tumors are benign. Thyroid cancer is rare, accounting for approximately 3% of malignant tumors and 1% of all cancer-related deaths in the United States.

Benign Tumors of the Thyroid

Adenomas present as discrete, solitary masses derived from follicular epithelium. Microscopically, they can be classified as fetal, embryonal, microfollicular, or macrofollicular, but this subtyping has no clinical significance. Clinically, most adenomas produce no symptoms. Occasionally, they present as a palpable mass. These tumors need to be differentiated from malignancies, especially if they do not take up radioactive iodine ("cold nodules"). In addition, as they increase they can compress other neck structures. Because of rapid enlargement due to hemorrhage, they may cause sudden pain. Rarely, adenomas may cause hyperthyroidism. Malignant transformation of adenomas is rare, but it should be considered in progressively enlarging nodules.

Malignant Tumors of the Thyroid

Malignant tumors of the thyroid gland are rare. They mainly affect women, and the majority are **carcinomas.** Lymphomas and sarcomas are rare. There is an increased risk of thyroid carcinoma in individuals with a history of irradiation to the head and neck in the first two

decades of life. In addition, nontoxic nodular goiter is also associated with a highly increased risk, especially in endemic areas. Finally, Hashimoto disease carries an increased risk of lymphoma and, to a lesser degree, carcinoma. Important features of thyroid carcinomas are summarized in Table 16-2.

Papillary carcinoma accounts for approximately 70% of thyroid carcinomas. It is found most often in 20- to 50-year-old women. It may be cystic or solid, encapsulated or invasive, and is often multifocal. Tumor cells tend to invade the thyroid parenchyma and lymphatics, leading to regional lymph node metastasis. Cervical lymph node metastasis is commonly present at the time of diagnosis, but spread beyond this point is unusual. Histologically, tumor cells form papillary structures, which may be intermixed with solid nests and follicles. Tumor cells have clear hypochromic nuclei ("Orphan Annie" or ground-glass nuclei), with nuclear grooves and invaginations of cytoplasm, which appear as eosinophilic intranuclear inclusions. Stromal calcifications *(psammoma bodies)* are common and often diagnostic. Despite lymph node metastasis, the prognosis is excellent for most papillary carcinomas. Some rarer variants of papillary carcinoma, such as the tall cell form, have a less favorable prognosis because these tumors invade blood vessels, resulting in local and distant metastases.

Follicular carcinoma accounts for 20% of thyroid malignancies. They are most often diagnosed in women in their fifth and sixth decades. These tumors are often encapsulated, but the tumor cells typically penetrate the capsule. Invasion of blood vessels is accompanied by distant metastases, most often to bone, lungs, and liver. Histologically, the tumor cells form follicles and solid nests. Clinically, follicular carcinomas present as slow-growing, painless thyroid nodules that do not take up radioactive iodine *(cold nodules)*.

Some tumors may take up radioactive iodine, which is often used in the treatment of distant metastases. Prognosis depends on the size of the primary tumor, the extent of capsular and vascular invasion, and the degree of cellular differentiation. The overall 10-year survival rate is 60%.

Anaplastic carcinomas account for 5% of thyroid malignancies. They occur most frequently in the elderly and are more common in areas of endemic goiter than in the United States. Histologically, these tumors are composed of undifferentiated spindle, giant, or small cells. Typically, tumors present as large lesions that grow rapidly, enlarging the neck over a period of months. They metastasize widely. Death occurs usually within the first year of diagnosis and is caused by invasion of trachea or distant metastases.

Medullary carcinomas of the thyroid are neuroendocrine neoplasms arising from C cells. Most secrete calcitonin, although they may secrete a variety of other biologically active substances. Many have an amyloid stroma, and approximately 20% to 25% are associated with multiple endocrine neoplasia (MEN) syndromes (types 2A and 2B). Sporadic tumors occur in the fifth and sixth decades of life, whereas those associated with MEN syndromes may be diagnosed

TABLE 16-2.

Thyroid Carcinomas

Type of Tumor	Incidence (% of All Thyroid Cancers)	Epidemiology	Pathology	Biological Features	10-Year Survival Rate
Papillary	70	F:M 3:1 20–50 yrs	Often cystic, with papillae, psammoma bodies	Early regional lymph node metastasis	90%
Follicular	20	F:M 3:1 40–60 yrs	Encapsulated, generally microfollicular; contains colloid and thyroglobulin	Invade capsule and blood vessels; distant metastases to lung and bone can be treated with ^{131}I	65%
Medullary	5	F = M 40–60 yrs, but in familial form (15–25 yrs)	Discrete tumors in one lobe or multiple nodules in both lobes; calcitonin-rich polygonal or spindle cells in amyloid stroma	Sporadic or familial (25%) multiple endocrine neoplasia 2A or 2B	Sporadic 30–50%; familial 90%
Anaplastic	5	F = M >50 yrs	Undifferentiated cells (spindle, giant cells)	Rapid invasive local growth and widespread metastases	Invariably fatal within 1 yr

even earlier. The sporadic tumors are usually confined to one lobe, whereas the familial tumors are multicentric.

Histologically, tumors are composed of cells that are usually arranged in solid nests separated by fibrovascular stroma, which contains amyloid in 50% of cases. Electron microscopy reveals intracytoplasmic membrane–bound neuroendocrine secretory granules containing calcitonin and other polypeptide hormones. The biological behavior of these tumors is highly variable. The familial medullary carcinoma syndrome has a good prognosis (90% 10-year survival rate); the sporadic tumors are more aggressive (30% to 50% 10-year survival).

PARATHYROID GLANDS

Parathyroid glands, which occur in two pairs, are yellow-brown nodules, each measuring 5 to 8 mm or more in diameter and weighing 35 to 40 mg combined. The two superior glands are generally located close to the upper posterior side of the thyroid. The inferior glands can be anywhere from the posteroinferior end of the thyroid to the mediastinum. Approximately 10% of individuals only have two or three glands.

The principal diseases of the parathyroid glands include hyperparathyroidism and hypoparathyroidism.

Hyperparathyroidism

Hyperparathyroidism is classified as primary or secondary, depending on its cause. **Primary hyperparathyroidism** is caused by parathyroid lesions (e.g., adenomas, primary hyperplasia, and carcinomas) that result in excess secretion of parathyroid hormone (PTH). Excess PTH results in increased bone resorption and calcium mobilization from bones, increased renal tubular resorption and retention of calcium, increased gastrointestinal resorption of calcium due to increased renal synthesis of $1,25\text{-}(OH)_2D$, and decreased renal resorption of phosphates.

Adenomas account for 75% to 80% of the cases of hyperparathyroidism. They are generally solitary, causing an expansile growth of one of the four glands, while the other three are of normal size. Histologically, they are composed of chief cells that, with some exception, appear normal. The enlarged gland contains no fat cells.

Primary hyperplasia accounts for 10% to 15% of cases of hyperparathyroidism. It may occur spontaneously or as part of the MEN syndromes 1 and 2A. Classically, all four glands are involved and show enlargement. Histologically, the hyperplasia may be diffuse or nodular, and most often chief cells predominate. The cells are arranged into solid nests or strands or gland-like structures. Stromal fat cells are inconspicuous or absent.

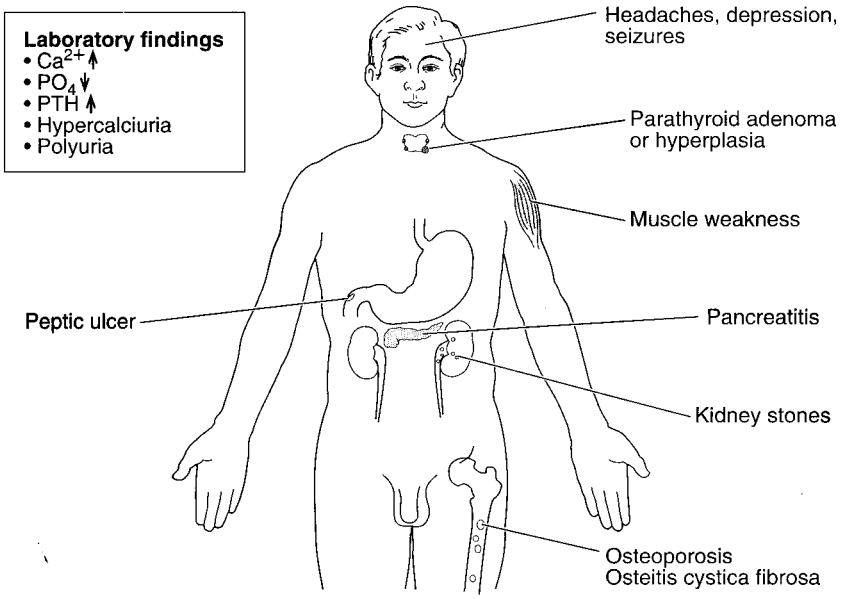


Figure 16-4.
Features of hyperparathyroidism. (PTH, parathyroid hormone.)

Carcinomas of the parathyroids are rare, accounting for <5% of cases of hyperparathyroidism. They usually involve one gland that is enlarged and often attached to adjacent structures. Histologically, the cells are most often well differentiated and arranged in nodular or trabecular patterns. Local invasion and metastasis are the only reliable diagnoses of malignancy. Local recurrence occurs in approximately one-third of patients and distant metastasis in another third. The prognosis for long-term survival is favorable.

Clinically, most cases of hyperparathyroidism occur in women in their sixth decade and older. The disease may present with nephrolithiasis, bone lesions (osteitis fibrosis cystica), pancreatitis, peptic ulceration, headaches, seizures, and depression. Symptoms are often nonspecific and include muscle weakness, fatigue, thirst or polyuria, constipation, and anorexia. As many as half the cases may be asymptomatic, and the diagnosis is based on the incidental finding of hypercalcemia and hypophosphatemia. Immunoassays for measuring serum PTH are essential for a definitive diagnosis. The clinical features of hyperparathyroidism are summarized in Figure 16-4.

Secondary hyperparathyroidism is most often seen in patients with chronic renal failure and, to a lesser degree, severe vitamin D deficiency or osteomalacia. Renal failure causes phosphate retention and hypocalcemia, which stimulates synthesis of PTH and hyperplasia of parathyroid glands. In addition, the renal disease may contribute to a reduction in the synthesis of 1,25-$(OH)_2D$, which leads to diminished calcium absorption by the small intestines. Histologically, parathyroid glands demonstrate stromal or nodular hyperplasia, primarily of chief cells, with concomitant reduction of stromal fat cells. Clinically, bone lesions are common, similar to

those in primary hyperparathyroidism, and include osteitis fibrosa cystica and osteomalacia.

Tertiary hyperparathyroidism is a term used to denote parathyroid adenomas that develop in patients with secondary hyperparathyroidism. These tumors show PTH secretion that does not respond to normal inhibitory feedback.

Hypoparathyroidism

Hypoparathyroidism is most often a *consequence of surgical removal of parathyroid glands.* Congenital absence or autoimmune disease are less common causes. It is characterized by **hypocalcemia,** which typically causes increased neuromuscular excitability and muscle spasm, causing irritability or depression. Despite hypocalcemia, calcifications can occur in basal ganglia causing parkinsonism, elevations in cerebrospinal fluid pressure, and papilledema. Calcification of the lens leads to cataracts. Cardiac conduction abnormalities are also common. Diagnosis is established by demonstrating hypocalcemia and low serum PTH.

Pseudohypoparathyroidism is due to abnormal PTH receptor complexes that fail to respond to PTH stimulation. Hypocalcemia is observed concomitant with elevated levels of PTH.

PATHOLOGY OF THE ADRENAL CORTEX

The adrenal glands are located immediately superior to each kidney. In the adult, each adrenal weighs approximately 4 g, although the glands may weigh less due to the lipid depletion caused by stress or chronic illness. The adrenal glands are divided into the cortex, the source of corticosteroids, and medulla, which produces catecholamines. The cortex is divided into three zones: zona glomerulosa, zona fasciculata, and zona reticularis.

Adrenal cortical diseases can present as hypofunction or hyperfunction. Three distinct forms of hyperadrenalism are recognized: **Cushing syndrome,** due to excess of cortisol; **hyperaldosteronism,** due to excess of aldosterone; and **adrenogenital syndrome,** due to excess of androgens.

Cushing Syndrome

Cushing syndrome may be caused by prolonged therapeutic use of corticosteroids, adrenal adenoma or carcinoma, or by ectopic ACTH secretion by nonpituitary tumors (Fig. 16-5).

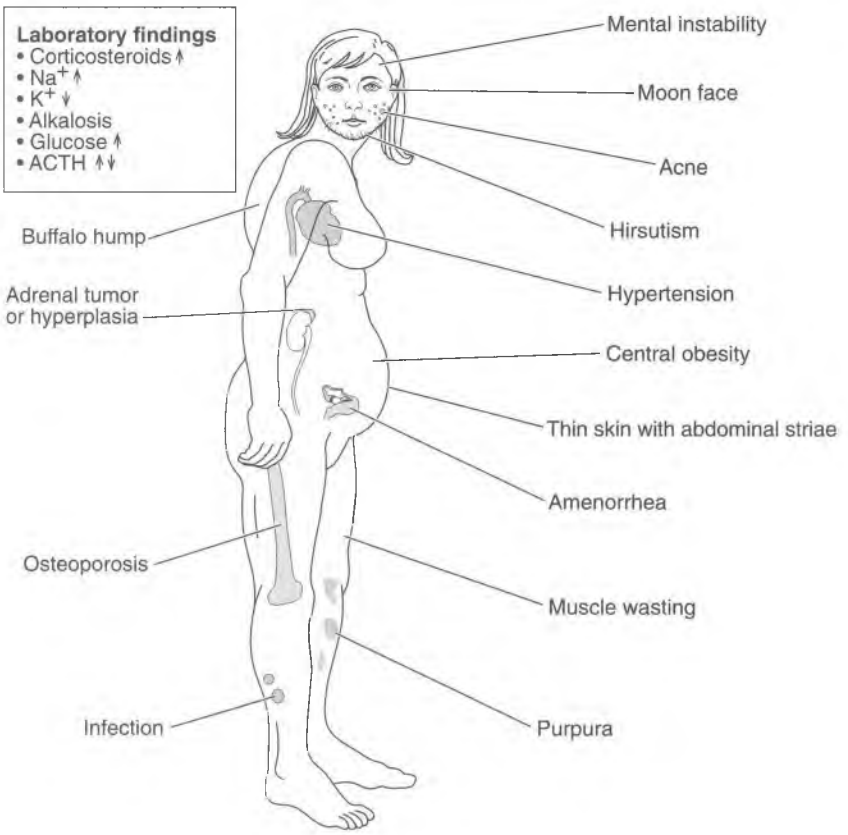


Figure 16-5.
Features of Cushing syndrome. (ACTH, adrenocorticotropic hormone.)

Exogenous corticosteroids are the most common cause of Cushing syndrome. Corticosteroids are widely used in the treatment of many diseases such as rheumatoid arthritis and autoimmune, kidney, and skin diseases.

Adrenal adenomas or **carcinomas** account for most endogenous cases of Cushing syndrome. In these cases, hypersecretion of cortisol is associated with suppression of ACTH secretion, which in turn leads to atrophy of nontumorous adrenal cortex. Hypercortisolism is most severe in patients with carcinomas, because these tumors are usually large. **Ectopic ACTH secretion** by nonpituitary tumors is responsible for approximately 10% to 15% of endogenous cases, most of whom are older men. The tumors most often associated with this condition include small cell carcinoma of the lung. Other tumors that secrete ACTH are carcinoids of the bronchus, pancreatic cell tumors, thymomas, pheochromocytomas, and thyroid medullary carcinomas.

The clinical features of Cushing syndrome are summarized in Figure 16-5. Diagnosis is based on laboratory data, which include elevated plasma levels of cortisol or its metabolites. If ACTH is ele-

vated, it is important to determine whether it is of pituitary origin or from a nonpituitary tumor. Radiography or computed tomography (CT) of the sella turcica may be useful. If ACTH is low and the patient is not being treated with corticosteroids, corticosteroids are most likely secreted by an adrenal tumor, which is best localized by CT or ultrasonography.

Primary Hyperaldosteronism

Primary hyperaldosteronism is caused by adrenal lesions that secrete aldosterone independently of the renin-angiotensin system. In this respect, it differs from *secondary hyperaldosteronism,* a form of hypertension caused by renal diseases in which the hypersecretion of aldosterone is related to high renin release. Approximately 65% of cases are caused by a solitary aldosterone-secreting adenoma **(Conn syndrome),** 30% of cases are caused by idiopathic bilateral hyperplasia of the adrenals, and the remaining 5% are related to rare diseases.

Aldosterone-secreting adenomas are generally solitary small encapsulated nodules that are bright yellow on the cut surface. Microscopically, they are composed of cells that are uniform in size and shape and well differentiated. Adenomas are more common in women than men. Bilateral hyperplasia is characterized by diffuse and focal hyperplasia of cortical cells.

Clinically, hyperaldosteronism is characterized by hypertension, which is accompanied by hypernatremia and hypokalemia resulting from renal potassium wasting. Hypertension results from sodium retention, which expands the extracellular fluid volume. Additional findings include muscle weakness, paresthesias, and visual disturbances. Diagnosis of primary hyperaldosteronism is confirmed by demonstrating elevated plasma levels of aldosterone concomitant with depressed levels of renin. Adenomas are treated surgically, and idiopathic bilateral hyperplasia is treated medically with aldosterone antagonists.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is a group of **inborn errors of metabolism** of corticosteroid hormones that presents in several forms depending on the specific enzyme deficiency. The most common is **21-hydroxylase deficiency**, in which the patient cannot form cortisol, aldosterone, or both. The intermediate corticosteroid metabolites are instead metabolized into androgens, which cause virilization of external female genitalia. Lack of aldosterone may result in excessive salt loss. The treatment includes cortisol, which corrects most of the metabolic disturbances and suppresses ACTH, thus reducing steroidogenesis and the production of androgens.

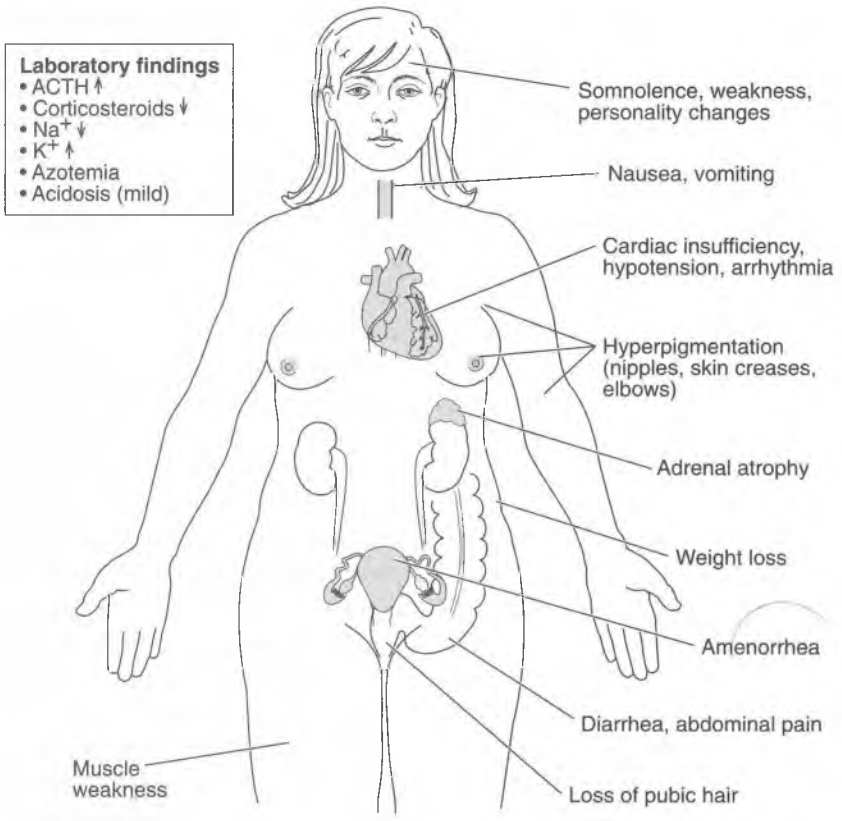


Figure 16-6.
Features of Addison disease. (ACTH, adrenocorticotropic hormone.)

Hypofunction of the Adrenal Cortex

Hypofunction of the adrenal cortex occurs as a result of ACTH deficiency or structural or functional conditions in the cortex that impair the production or synthesis of corticosteroids. Adrenocortical insufficiency may present clinically in several forms: primary acute adrenocortical insufficiency (adrenal crisis), primary chronic adrenocortical insufficiency **(Addison disease),** and secondary adrenocortical insufficiency (Fig. 16-6).

Primary acute adrenocortical insufficiency is uncommon but can result from any acute stress that requires more corticosteroids than the adrenals can provide. This is typically seen after a withdrawal of corticosteroids after long-term administration or in massive destruction of the adrenals such as that seen in neonates following prolonged or complicated delivery. Massive adrenal hemorrhage is a rare but well-known complication of bacteremia, especially those cases caused by *Neisseria meningitidis* **(Waterhouse-Friderichsen syndrome)** and conditions characterized by disseminated intravascular coagulation.

Primary chronic adrenocortical insufficiency or **Addison disease** is a rare and chronic debilitating disease caused by destruction of the adrenal cortex. It is caused most often by autoimmune adrena-

litis, which accounts for 70% of cases. Infections such as tuberculosis, amyloidosis, and metastatic cancer are less common causes of adrenal insufficiency, which develops only if more than 90% of the total adrenal cortex is destroyed. Certain drugs (e.g., ketoconazole) can also cause adrenal insufficiency.

Metastatic cancers to adrenals may cause Addison disease if bilateral. Destructive metastases, which must be bilateral to produce symptoms, are most often derived from carcinoma of the lungs, breast, and stomach.

Clinically, Addison disease has an insidious onset, presenting with a variety of nonspecific symptoms such as weakness, fatigue, weight loss, anorexia, and nausea and vomiting. Muscle wasting and hypotension are common, and the skin may show hyperpigmentation. Blood levels of cortisol and aldosterone and their metabolites are low, whereas ACTH levels are elevated. Blood levels of sodium, chloride, bicarbonate, and glucose are also low, whereas levels of potassium are generally elevated. Adrenal stimulation with synthetic ACTH, which typically causes an increase in the blood concentration of cortisol and aldosterone in normal people, does not produce positive results in Addison disease. Generally, the condition is easily treated with corticosteroids, which must be given for life.

Secondary adrenocortical insufficiency occurs because of reduced ACTH output caused by hypothalamic and pituitary lesions such as metastatic cancer, infection, infarction, and irradiation. Long-term use of corticosteroids can also reduce the levels of circulating ACTH by a negative feedback mechanism. In contrast to primary adrenocortical insufficiency, there is no hyperpigmentation, because ACTH, which acts as melanotrophic hormone, is not elevated. In secondary adrenocortical insufficiency, there is deficiency of cortisol and androgens, but the production of mineralocorticoids is not affected because the zona glomerulosa produces aldosterone, even without ACTH stimulation. Consequently, hyponatremia and hyperkalemia are not observed in secondary adrenocortical insufficiency.

TUMORS OF THE ADRENAL MEDULLA

Pheochromocytoma

Pheochromocytomas are tumors composed of well-differentiated cells resembling those of the normal medulla. Like normal medullary cells, tumor cells secrete **catecholamines** and can induce hypertension. Approximately 90% of pheochromocytomas occur sporadically, and the remaining 10% occur in familial syndromes. Approximately 90% of pheochromocytomas are benign, and 90% arise in the medulla of the adrenal (i.e., those arising in extra-

adrenal paraganglia). The extra-adrenal tumors are more often malignant than those found in the adrenals.

The tumors vary in size and shape, but most often they are encapsulated. They have vascularized fibrous septa dividing them into lobules. On the cut surface, they are pale gray to brown but turn brown-black when fixed in dichromate-containing fixatives due to oxidation of stored catecholamines (chromaffin reaction). Microscopically, several patterns are observed, but most often the cells are arranged into groups surrounded by vascular stroma. Benign tumors cannot be distinguished from the less common malignant tumors on the basis of histology. Metastases from malignant tumors occur most commonly in related lymph nodes, liver, lungs, and bones. Metastases are the only proof that a pheochromocytoma is malignant.

Clinically, the **sporadic neoplasms** occur in adults and at the same rate in men and women. However, the tumors of familial syndromes arise in childhood and are found predominantly in male children. Typical symptoms include headache, tachycardia, and sweating. Hypertension is invariably present. It can be sustained with paroxysmal attacks (33%), intermittent (33%), or sustained without the paroxysmal attacks (33%). When present, the paroxysms of hypertension can be induced by emotional stress, exercise, change in posture, or palpation of the tumor. The sudden release of catecholamines elevates blood pressure and may acutely cause congestive heart failure, pulmonary edema, myocardial infarction, and even cerebral hemorrhage.

Diagnosis is established by measuring urinary catecholamines and their metabolites, especially metanephrine and vanillylmandelic acid. The localization of the tumor can usually be defined by CT, magnetic resonance imaging, or ultrasonography.

Neuroblastoma and Ganglioneuroma

Neuroblastoma is a malignant tumor composed of undifferentiated cells resembling the neuroblastic precursors in the fetal neural tube. It accounts for approximately 15% of childhood cancer deaths and is one of the most common solid neoplasms in children. Approximately 25% to 35% arise in the adrenal medulla. The remainder occur anywhere in the sympathetic chain, but particularly in the paravertebral region of the posterior mediastinum. Histologically, the neoplasms are composed of small undifferentiated cells with dark nuclei and little cytoplasm. Occasionally neuroblastoma cells differentiate into ganglion cells, which may be found scattered among the undifferentiated neuroblastic cells. Such tumors are called **ganglioneuroblastomas.** Tumors composed of nondividing sympathetic ganglion cells are called **ganglioneuromas.**

Clinically, most neuroblastomas are found **primarily in young children** younger than 2 years of age. They present as large abdominal masses, causing fever and possible weight loss. In older children, they may not be diagnosed early because the tumors remain asymptomatic until metastases have occurred. Symptoms include

bone pain, respiratory symptoms, or gastrointestinal complaints, reflecting the widespread dissemination of the tumor.

MULTIPLE ENDOCRINE NEOPLASIA

MEN comprises three autosomal dominant syndromes, characterized by either hyperplasia or tumors of several endocrine glands occurring concomitantly.

Multiple Endocrine Neoplasia Type 1 (Wermer Syndrome)

MEN 1 is characterized by **tumors of the pituitary, parathyroid, and pancreatic islets.** In addition, there may be hyperplasia in the parathyroids. Kidney stones resulting from the hypercalcemia are among the most common presenting findings. Most of the fatalities result from the pancreatic islet cell lesions, which are usually malignant gastrinomas or insulinomas. Gastrin secreted by pancreatic tumor causes the **Zollinger-Ellison syndrome,** whereas insulin may cause severe hypoglycemia. Hyperplasia or adenomas of the adrenal cortex lead to adrenocortical hyperfunction, and C-cell hyperplasia of the thyroid occurs in rare instances. A mutation in chromosome 11q11–q13 has been identified in the majority of cases.

Multiple Endocrine Neoplasia Type 2A (Sipple Syndrome)

MEN 2A syndrome includes **medullary carcinomas** of the thyroid, pheochromocytomas, and, to a lesser degree, adenomas or hyperplasia of the parathyroid. The medullary thyroid carcinomas are frequently multifocal and invariably associated with elevated serum levels of calcitonin. The pheochromocytomas are often bilateral and often extra-adrenal. MEN 2A is linked to a germ line mutation on chromosome 10q11.2. Although medullary carcinoma is a malignant tumor capable of metastasis, treated patients have a good prognosis.

Multiple Endocrine Neoplasia Type 2B

Patients with MEN 2B have medullary thyroid carcinoma, pheochromocytomas, but also neuromas or ganglioneuromas of the lips, oral cavity, eyes, respiratory tract, and gastrointestinal tract, which distinguish them from patients with MEN 2A.

Chapter 17

Skin

Skin diseases can be classified as those infections environmentally caused, immune disorders, metabolic disturbances, and diseases of unknown etiology. Morphologically, skin diseases present in several forms and can be classified as follows:

- **Macule,** a flat lesion presenting as a localized discoloration of the skin
- **Papule,** a slightly elevated lesion, called a *plaque* if >5 mm
- **Nodule or tumor,** which may appear as an epidermal or dermal often protruding mass
- **Vesicle and bulla,** which are filled with fluid
- **Pustule,** which contains pus
- **Ulcer,** which presents as an epidermal defect
- **Crust (scab),** formed of coagulated plasma or blood
- **Scale and squame,** composed of layers of keratin that can be removed by scratching

Histologic terms used to describe these lesions include the terms of general pathology, such as necrosis, abscess, and ulcers, but also by the following specific dermatopathologic terms:

- **Acanthosis,** thickening of the epidermis
- **Hyperkeratosis,** thickening of superficial keratin layer composed of squames devoid of nuclei
- **Parakeratosis,** thickening of stratum corneum with retention of nuclei
- **Acantholysis,** loss of contact between keratinocytes that leads to formation of intradermal vesicles
- **Spongiosis,** separation of cells by intercellular edema, but the cells remain attached to one another by desmosomes

CHRONIC DERMATITIS

Chronic dermatitis, also known as *eczema,* may develop due to obvious exogenous causes, but often it may be an expression of internal

diseases, hypersensitivity reactions, or it may evolve for unknown reasons. **Exogenous eczema** is classified as irritant contact dermatitis, usually caused by exposure to soil, dust, or chemicals in the workplace, or **allergic contact dermatitis**, which develops after sensitization by specific allergens, such as gold rings or rubber gloves. Examples of endogenous chronic dermatitis include

- **Atopic dermatitis,** a common skin disease of infants and children, thought to be of allergic origin and related to adverse IgE-mediated reactions to food and environmental allergens
- **Seborrheic dermatitis,** a disease of unknown origin presenting with excessive dandruff, redness, scaling, and itching of the hairy skin of the chest and intertriginous areas of adults
- **Asteatotic chronic dermatitis** (dry skin) that develops during the winter, especially in the elderly

Chronic dermatitis can be treated successfully if the cause is known. If the cause cannot be identified, the treatment is symptomatic and includes emollient creams and mild topical corticosteroid ointments.

Erythematous Scaly Eruptions

Eczema can be distinguished from several defined clinicopathologic entities, which can be identified on the basis of typical clinical and histologic features evident in skin biopsies. These diseases do not have a known cause and are classified as idiopathic. The most common among them are **psoriasis** and **lichen planus.**

Psoriasis is a chronic disease of unknown etiology that presents with recurrent eruptions of erythematous or silvery plaques and scales. It affects approximately 2% of the total population. The lesions, which are thought to originate because of the abnormally rapid proliferation of basal epidermal cells, appear as pearly papules most often on elbows, knees, the lower back, and scalp. Nails may be involved, and some patients suffer from psoriatic arthritis. Eruptions, which are typically nonpruritic, appear without any obvious reason, but occasionally they may be related to trauma, emotional crisis, infections, and certain drugs such as lithium and β-blockers. Histologically, the papules consist of thickened epidermis **(acanthosis)** showing extended projections into the dermis **(papillomatosis)** and surface parakeratosis. In the parakeratotic surface layer, there are microscopic abscesses **(Munro abscess).** The rete ridges contain elongated thin-walled blood vessels, which can bleed if the surface layer of the papule is scratched off.

Lichen planus presents with highly pruritic red papules on the flexor sides of the extremities, genital organs, and mucous membranes, especially in the mouth. Histologically, the lesions consist of infiltrates of T-lymphocytes in the upper dermis invading the epidermis and causing destruction of the basal layer. These histologic findings suggest a possible immune mechanism. Occasionally, the

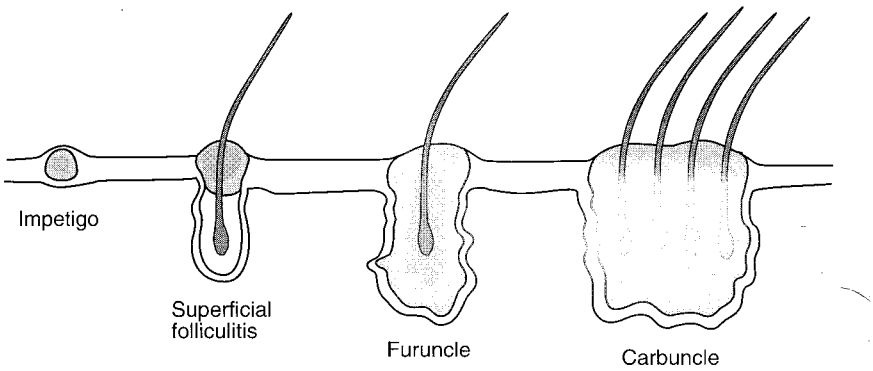


Figure 17-1.
Bacterial infections of the skin.

eruptions are linked to an intake of certain drugs or exposure to chemicals such as film developers. The lesions of lichen planus last for a short period and then heal spontaneously.

INFECTIOUS SKIN DISEASES

Bacterial Infections

Suppurative bacterial infections of the skin are extremely common (Fig. 17-1). Such infections occur in all age groups and are caused by a wide variety of pathogens. Bacteria usually enter skin through small skin defects, cuts, or scratches. **Impetigo** is a superficial skin infection typically caused by streptococci or staphylococci, presenting as superficial pustules and yellow crusts. It is most common on the face and arms of children who tend to transmit the disease to other children by close contact or hands. **Furuncles** are abscesses within the confines of hair follicles, usually caused by the bacteria *Staphylococcus aureus.* Confluent furuncles are called **carbuncles (boils).** Suppurative infection of apocrine glands, most common in the axilla and groin, is called **hidradenitis suppurativa.**

Erysipelas presents as redness of the skin overlying an infection of the upper subcutis, usually caused by streptococci that spread through the lymphatics. **Cellulitis** is an infection of the deep subcutis extending into the adjacent soft tissues.

Chronic granulomatous dermatitis may be caused by *Mycobacterium leprae* or *Mycobacterium tuberculosis,* but such infections are rare in the United States. Leprosy or tuberculosis present as induration of the skin, often with destruction of underlying tissue and disfigurement. **Gumma** of the skin and **condyloma latum** are features of secondary syphilis.

Acne vulgaris is an inflammatory disease related to the obstruction of the pilosebaceous units. Acne predominantly affects teenagers; however, in approximately 5% of women and men, the disease may persist into adulthood. Most often the lesions appear on the face, upper chest, and back. Pathogenetically, it is related to an infection with anaerobic bacterium, *Propionibacterium acnes,* which thrives in stagnant sebum. Hormonal influences, genetic predisposition, and all drugs that stimulate the production of sebum promote the development of lesions. Clinically, acne presents as **seborrhea** (greasy skin), reflecting hypersecretion of sebum and comedos, which are stagnant sebum in hair follicles. Comedos are classified as open (blackheads) or closed (whiteheads). Infection superimposed on seborrhea and comedos leads to formation of pustules, which may become confluent **(acne conglobata).** Deep infection may result in scarring. Treatment with systemic or local antibiotics usually controls the eruptions. In severe cases, retinoic acid creams and hormonal treatment may be indicated.

Viral Infections

Viral infections of the skin may cause acute or chronic lesions. Many common childhood viral diseases present with skin eruptions.

Measles cause a maculopapular rash. It appears 2 to 4 days after the onset of fever, first on the face or behind the ears. The rash spreads to the trunk and finally reaches the extremities, but then it disappears without any consequences.

Varicella or chicken pox presents with vesicles, which appear first on the face, scalp, or body. Later, the eruption extends to the arms and legs. Unless the vesicles are scratched or infected, they heal without residues.

Herpes simplex virus (HSV) infection causes vesicles in defined anatomic sites. HSV-1 causes vesicles on the lips; HSV-2 causes genital vesicles; and herpes zoster causes eruptions of vesicles along specific somatic nerves (shingles). HSV-8 causes hemorrhagic lesions of Kaposi sarcoma in homosexual male AIDS patients.

Human papillomaviruses cause warts, which occur in several variants: common wart or **verruca vulgaris,** which occurs most often on arms and legs; flat **plantar warts;** and large genital warts **(condyloma acuminatum).**

Fungal Infections

Fungal infections of the skin are classified as superficial or deep. **Superficial fungal infections** are most often caused by **dermatophytes** (such as *Trichophyton, Epidermophyton,* or *Microsporum* spp.), which live in the scales of the superficial epidermis. Typical infections are presented here:

- **Tinea capitis,** found on the head and presenting as patches of hair loss and scarring
- **Tinea cruris** (jock itch), found in the groin and presenting as itchy scaly patches
- **Tinea corporis** (also known as *ringworm*), which appears as pale patches with raised margins
- **Tinea pedis** (also known as *athlete's foot*), which occurs between the toes

Deep fungal infections caused by *Blastomyces, Madurella,* and similar pathogens typically occur in the tropics and are rare in the United States. Such lesions present as induration of the dermis and may cause disfigurement or tissue destruction. Histologically, these fungi cause a granulomatous reaction accompanied by suppuration.

Skin Diseases Caused by Insects

Insect-related skin diseases are most often caused by insect stings or bites. Mosquitoes, ticks, chiggers, fleas, and lice all cause papillomacular, often indurated skin lesions, which are transient and rarely have any consequences unless infected during scratching. Many insects, however, transmit systemic diseases, which may appear weeks or even months after their bites.

Scabies, a chronic skin infection caused by *Sarcoptes scabiei* and capable of invading the deep epidermis, is characterized by migratory maculopapular rashes. It is transmitted by close body contact.

IMMUNE DISEASES OF THE SKIN

Skin is often exposed to foreign substances that may immunize the body and cause a hypersensitivity reaction. Skin can be affected by all four types of hypersensitivity reactions (Fig. 17-2).

Atopic dermatitis is an example of a type I hypersensitivity reaction, mediated by IgE attached to mast cells. Binding of antigen to IgE on the surface of mast cells triggers a release of histamine from these cells, causing local increased permeability of the blood vessels, edema, and itching. **Pemphigus vulgaris** is the best example of type II or cytotoxic hypersensitivity reaction. It is a blistering disease caused by cytotoxic antibodies that bind to the surface of keratinocytes in the epidermis. Antibodies disrupt the cell-to-cell contact junction, which leads to formation of intraepidermal vesicles and bullae. **Bullous pemphigoid** is caused by a deposition of cytotoxic antibodies along the basement membrane of the epidermis.

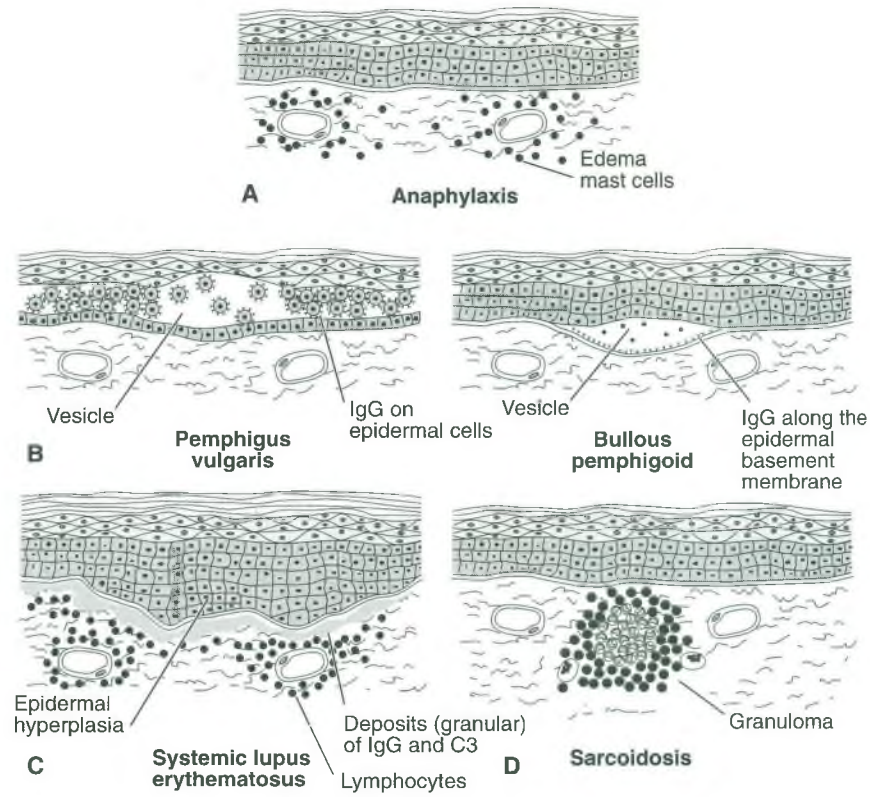


Figure 17-2.
Immunologic skin diseases. *A:* Type I hypersensitivity reaction is mediated by histamine released from mast cells in the dermis. There is edema of dermis and epidermis. *B:* Type II hypersensitivity reaction can be mediated by IgG to epidermal cells, as in pemphigoid vulgaris, or IgG against the basement membrane, as in bullous pemphigoid. *C:* Type III hypersensitivity reaction is mediated by granular deposits of immune complexes along the epidermal basement membrane. *D:* Type IV hypersensitivity reaction is marked by granulomas in the skin.

These antibodies disrupt the contact between the basal layer of the epidermis and the basement membrane, causing formation of subepidermal bullae.

Discoid lupus erythematosus and **systemic lupus erythematosus** are examples of the type III hypersensitivity reaction. In these diseases, the circulating immune complexes are deposited along the basement membrane at the epidermal-dermal junction. Deposition of immune complexes activates the complement cascade, which incites a dermal and epidermal inflammation. Skin lesions are most prominent on the face and other areas exposed to sunlight.

Type IV or **cell-mediated hypersensitivity** reaction is mediated by T-lymphocytes and is typically the underlying cause of skin lesions in **sarcoidosis,** a systematic disease that often presents with subcutaneous nodules. Histologically, these lesions are noncaseating granulomas. Most forms of **contact dermatitis,** such as allergy to gold rings

or **poison ivy reactions,** represent a cell-mediated type IV hypersensitivity reaction.

Graft-versus-host reaction in patients who have received bone marrow transplants is also mediated by T-lymphocytes derived from the donor. The disease presents as extensive desquamation and peeling of epidermis.

SKIN MANIFESTATIONS OF SYSTEMIC DISEASES

Many internal diseases present with skin lesions. Liver disease presents with spider nevi and palmar erythema. **Porphyria cutanea tarda** may present with skin blisters. **Rheumatoid arthritis** may present with subcutaneous rheumatoid nodules. Skin hyperpigmentation is a feature of Addison disease. **Hyperthyroidism** presents with sweating, warm moist skin (hyperhidrosis), whereas in **hypothyroidism,** the skin is dough-like, soft and pliable **(myxedema). Xanthomas** are yellow papules or nodules composed of lipid-laden macrophages in the dermis of persons who have hyperlipidemia.

Acanthosis nigricans is a pigmentation of the skin on the neck and intertriginous areas, found as a paraneoplastic syndrome in patients who have carcinoma of the gastrointestinal tract.

Dermatitis herpetiforms is a chronic skin disease found in 20- to 30-year-old patients with sprue and hypersensitivity to gluten. It is characterized by vesicular eruptions. Histologically, the vesicles are related to deposits of IgA along the epidermal-dermal junctions associated with microabscesses in the dermal papillae.

TUMORS AND RELATED LESIONS

Skin tumors can originate from epithelial cells of the epidermis, pigmented cells (melanocytes), neuroendocrine cells (Merkel cells), dermal connective tissue cells, and migratory cells, such as blood-derived white blood cell precursors (Table 17-1).

Epithelial tumors and **melanomas** in many cases may be induced by ultraviolet light and occur with greater frequency among people exposed to sunshine (e.g., farmers, sailors) and those of light complexion. Some dermal tumors are genetically determined, such as multiple dermatofibromas (neurofibromatosis type I). The etiology of most skin tumors, however, is not known.

TABLE 17-1.
Neoplasms of the Skin

Cell of Origin	Benign	Malignant
Keratinocyte	Seborrheic keratosis	Actinic keratosis Bowen disease (carcinoma in situ) Basal cell carcinoma Squamous cell carcinoma
Melanocyte	Nevocellular nevus	Malignant melanoma
Merkel cell	—	Merkel cell carcinoma
Dermal mesenchymal cells	Hemangioma	Angiosarcoma Kaposi sarcoma
	Dermatofibroma	Dermatofibrosarcoma
	Neurofibroma	Neurofibrosarcoma
Lymphocyte	—	Mycosis fungoides (T cell) Lymphoma (B cell)
Mast cell	Urticaria pigmentosa	Systemic mastocytosis
Dermal adnexal cells	Adenoma	Carcinoma

Epithelial Tumors

Epithelial tumors may be benign or malignant (Fig. 17-3). The most common benign epithelial tumor is **seborrheic keratosis,** also known as *basal cell epithelioma*, which presents as wart-like, mildly pigmented brown lesions on the skin of older people. The most common malignant tumor of the skin is **basal cell carcinoma,** a locally invasive neoplasm of low malignant potential. Most basal cell carcinomas are located on the face and other sun-exposed areas. Histologically, these tumors are composed of cells resembling those of the basal layer of the epidermis. The cells are arranged into nests and strands, and although the tumor is usually locally invasive, distant metastases almost never occur. Excellent results are obtained by surgical resection, which must ensure that the entire tumor is removed to prevent local recurrence.

Squamous cell carcinoma differs from basal cell carcinoma in that it is both locally invasive and prone to metastasis. Squamous cell carcinoma also occurs on sun-exposed skin. It is often preceded by preinvasive, intraepithelial neoplastic changes known as **senile or actinic keratosis.** Actinic keratosis may present as an atrophy of the skin or as locally hyperkeratotic lesions. Transition to squamous cell carcinoma is characterized by induration of the skin, due to tumor invasion, accompanied by a desmoplastic dermal reaction or an exophytic outgrowth leading to formation of nodules and surface ulceration.

Pigmented Lesions

Pigmented skin lesions are classified as benign or malignant. Most benign pigmented lesions are not true tumors, but rather hamartomas composed of normal pigmented cells showing abnormal distributions (Fig. 17-4). **Freckles** (ephelis) are pigmented macules composed of melanocytes that become more pigmented when exposed to sunlight. **Lentigo** is also composed of melanocytes, but such lesions do not become darker under the influence of ultraviolet light.

Nevus is a hamartoma composed of melanocytic cells. Nevi are classified as *congenital,* if present from birth, or *acquired,* if first noticed in adult life. Histologically, nevi are classified according to location of the pigmented cells as dermal, if the cells are in the dermis; junctional, if located at the dermal-epidermal junction; or compound, if the lesions show both junctional activity and dermal location. Most nevi are benign, but in some cases they show histologic atypia and are classified as dysplastic. **Dysplastic nevi,** which may occur at an increased rate in some families, must be watched carefully because they tend to progress to invasive malignant melanomas.

Malignant melanomas are invasive malignant neoplasms arising from melanocytes residing in a previously melanocytic normal skin or nevi. Histologically, malignant melanomas are classified as *superficial spreading, nodular, or acrolentiginous.* All melanomas are most often located on **sun-exposed skin,** except the acrolentiginous melanomas, which typically occur on distal parts or extremities and are often subungual. Melanomas are more common in people who live in the southern United States, but rarely occur among blacks and dark-skinned people. The prognosis of malignant melanoma depends on the extent of spread of tumor at the time of diagnosis. Level I tumors restricted to the epidermis have the best prognosis; level II tumors invading the papillary dermis have a 90% survival rate; level III tumors filling the papillary dermis have a 70% survival rate; and level IV tumors invading the reticular dermis have only a 40% 5-year survival rate.

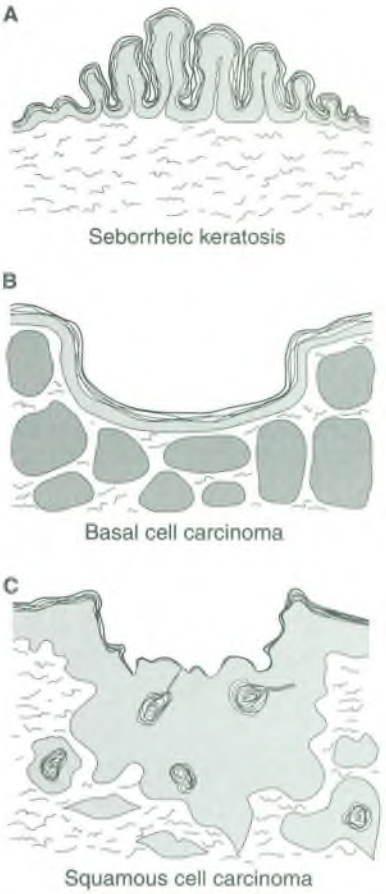


Figure 17-3.
Epithelial skin tumors.

Other Tumors

The most common mesenchymal tumor of the dermis is **hemangioma.** Other connective tissue tumors are most often benign and usually histologically classified as dermatofibroma, neurofibroma, lipoma, or leiomyoma. Malignant dermal tumors (sarcomas) are less common. **Kaposi sarcoma** is a malignant tumor of small blood vessels, which occurs most often in people affected with AIDS. Infiltrates of myelogenous leukemia cells in the dermis may present as yellow-green nodules known as **chloroma.** Both B- and T-cell lymphoma cells may infiltrate the skin. Low-grade malignant lymphoma, composed of mature T cells that show remarkable dermatotropism, is called **mycosis fungoides. Urticaria pigmentosa** is a disease of children and young adults in which the skin is infiltrated with mast cells.

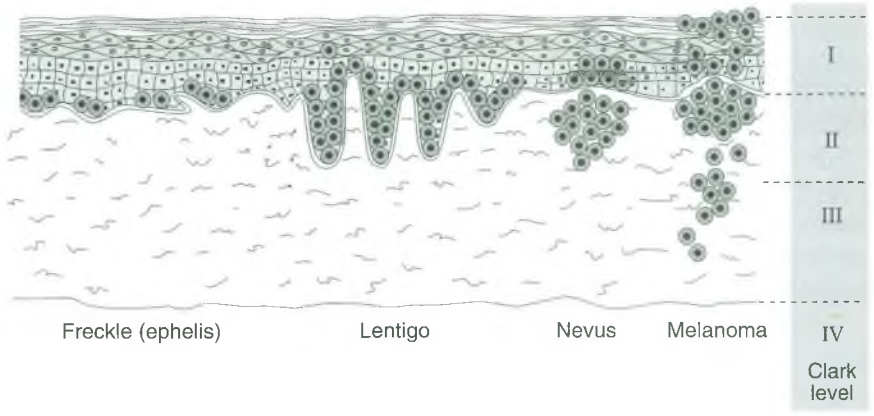


Figure 17-4.
Pigmented skin lesions.

Urticaria pigmentosa usually heals spontaneously by the time of puberty, and it is debatable whether it represents a neoplasm at all.

Neuroendocrine tumors of the skin are rare but unfortunately very malignant. They originate from Merkel cells and, therefore, are called **Merkel cell carcinomas.** Tumors originating from **skin appendages** are usually benign and are classified as apocrine or eccrine or sweat gland adenomas. Carcinomas of these glands are less common.

Chapter 18

Bones and Joints

DEVELOPMENTAL BONE DISORDERS

Developmental bone disorders can be classified as **genetic,** if related to mutations of specific genes encoding structurally important proteins of the bone (e.g., osteogenesis imperfecta), or **metabolic** (e.g., congenital hypothyroidism or vitamin C deficiency).

Achondroplasia

Achondroplasia is the most common genetic form of **dwarfism,** inherited as an autosomal dominant trait. The defect lies in the gene encoding the fibroblast growth factor receptor. The lack of fibroblast growth factor receptor affects bone growth and results in thin epiphyseal plates and abnormal endochondral ossification. The secondary ossification centers, the articular cartilage and intramembranous bone formation, are normal. Hence, bones of the limbs are short, but thick. The bones of the head are large compared with the bones of the face. The spine is of normal length.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a group of diseases characterized by abnormal type I collagen synthesis. There are at least four types of osteogenesis imperfecta (types I–IV), which are distinguished from each other by their mode of inheritance and clinical signs.

Osteogenesis imperfecta type I is characterized by multiple fractures after birth, blue sclerae, deafness, misshapen bluish teeth, kyphoscoliosis, and flat feet. The bones are extremely thin on radiography and abnormally curved and prone to fracture. The number of fractures and their severity diminish with age. Progressive hearing loss and deafness result from the fusion of the auditory ossicles.

Osteogenesis imperfecta **type II** presents with multiple intrauterine or perinatal fractures. The disease is invariably lethal. Most infants are either stillborn or die within a few days of delivery.

Osteogenesis imperfecta **type III** is characterized by multiple fractures, some present at birth, retarded growth, and blue sclerae that turn white shortly after birth. Kyphoscoliosis and tooth abnormalities are seen in older children. Short stature results from repetitive fractures and kyphoscoliosis.

Osteogenesis imperfecta **type IV** is similar to type I except that these patients have normal sclerae and show no dental disease. Cortical bone appears immature for prolonged periods of time. The frequency of fractures diminishes as the cortex matures over a period of years.

METABOLIC BONE DISEASES

Osteoporosis

Osteoporosis is characterized by a reduction of the bone mass. Radiologically, it is recognized as osteopenia (i.e., bone loss). It can be *localized* (e.g., disuse atrophy) or *generalized* (e.g., metabolic diseases). The *primary form* is associated with advanced age, most often affecting postmenopausal women. The *secondary form* can result from a variety of conditions:

- **Endocrine disturbances** (e.g., hyperparathyroidism, hyperthyroidism, Cushing disease, hypogonadism)
- **Neoplasms** (e.g., multiple myeloma)
- **Gastrointestinal disorders** (e.g., malabsorption, rheumatoid disorders)
- **Drugs** (e.g., corticosteroids, chemotherapy)
- **Miscellaneous conditions** (e.g., immobilization and pulmonary disease)

The osteoporosis of older age is a multifactorial disease that has genetic, nutritional, and metabolic components. Reduced physical activity and low serum estrogen also play an important role. Morphologically, the entire skeleton is involved, but the vertebral bodies are most severely affected. Spontaneous fractures are common. Histologically, bone trabeculae are thin and prone to fractures.

Clinically, fractures of thoracic and lumbar vertebrae lead to reduction in height, kyphoscoliosis, and lordosis ("dowager hump"). Hip fracture is the most serious complication, which accounts for many deaths in elderly patients with osteoporosis. Serum calcium and phosphate levels are within normal limits.

Rickets and Osteomalacia

Rickets, a disease of children, and osteomalacia, a disease of adults, result from dietary vitamin D deficiency, inadequate vitamin D

absorption, or metabolism. The resulting defects in bone metabolism cause delayed or inadequate mineralization, leading to excess unmineralized osteoid. In **rickets,** there is the addition of deranged endochondral bone growth resulting from inadequate mineralization of the epiphyseal cartilage. Histologically, there is overgrowth of inadequately mineralized epiphyseal cartilage and osteoid, which project into the marrow cavity. The overgrowth of capillaries and connective tissue contributes to the fibrosis of the marrow. Because the bones are soft, they can be easily bent and deformed, giving rise in children to bowlegs, lumbar lordosis, frontal bossing, "rachitic rosary" of the costochondral junction, and anterior protrusion of the sternum (pigeon-breast deformity). **Osteomalacia** in the adult is not as dramatic, and skeletal deformities are rarely seen. Radiographic evidence of cortical thinning and loss of bone density correlates with histologic changes, such as a reduction of ossified bone and increased osteoid and increased osteoclastic activity.

Osteitis Fibrosa Cystica (von Recklinghausen Disease of Bone)

Osteitis fibrosa cystica is a manifestation of severe **primary hyperparathyroidism.** It is characterized by widespread osteoclastic resorption of cortical bone. Subperiosteal resorption produces thin cortices and loss of the lamina dura around teeth. Histologically, osteoclasts move along the bone spicules and enlarge haversian and Volkmann canals in a characteristic pattern. In cancellous bone, osteoclasts dissect along the length of the trabeculae, producing "dissecting osteitis." Concomitant repair causes filling of marrow spaces with fibrovascular tissue. Microfractures produce cystic hemorrhagic foci, which become infiltrated by macrophages and osteoclastic giant cells (brown tumors). Clinically, the disease presents with bone pain, expansile bone lesions, and fractures. Control of hyperparathyroidism leads to regression or resolution of the bony lesions.

Renal Osteodystrophy

Renal osteodystrophy describes the skeletal changes induced by chronic renal disease. These changes include increased osteoclastic activity resembling osteitis fibrosa cystica, osteomalacia, osteosclerosis, and osteoporosis.

Renal failure causes increased retention of phosphate, leading to hyperphosphatemia and hypocalcemia, which is magnified by the kidney's inability to convert vitamin D metabolite 25-(OH)-D to the more active metabolite 1,25-$(OH)_2$-D. Plasma phosphate interferes with the renal hydroxylase involved in the conversion of the 25-(OH)-D to the more active derivative. The low levels of 1,25-$(OH)_2$-D also reduce the intestinal absorption of calcium. The hypocalcemia stimu-

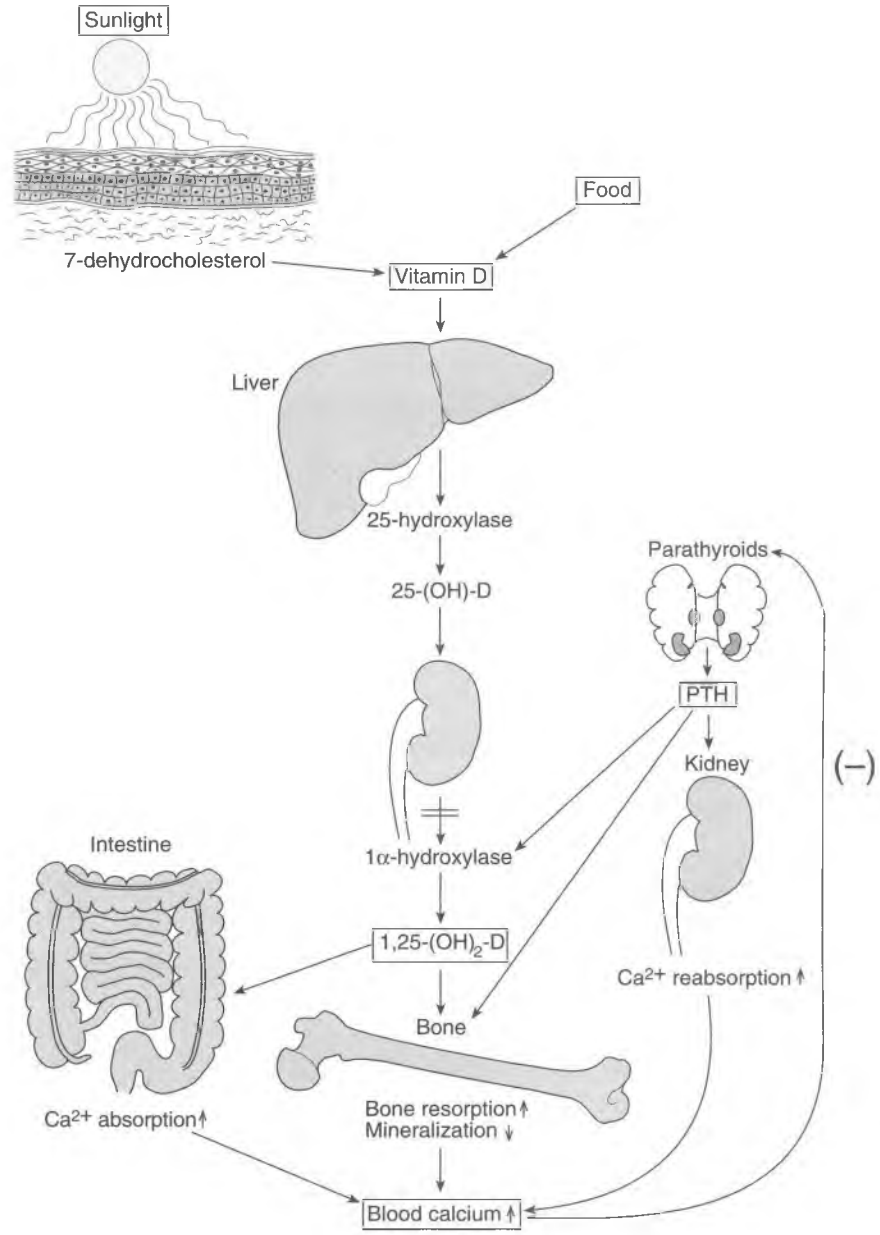


Figure 18-1.
Pathogenesis of renal osteodystrophy.

lates the production of parathormone by the parathyroid glands. This secondary hyperparathyroidism stimulates osteoclastic activity and further contributes to bone loss (Fig. 18-1).

Osteopetrosis

Osteopetrosis is a group of inherited diseases characterized by abnormally dense bone. It occurs in an autosomal recessive (malig-

nant) form and an autosomal dominant (benign) form. The *malignant* form affects infants and children and can sometimes be fatal as a result of anemia, cranial nerve entrapment, hydrocephalus, and infections. The *benign* form occurs in adolescents and adults. It is associated with mild anemia or can be asymptomatic.

The cause of osteopetrosis is unknown; however, there is faulty bone remodeling, which appears to be related to osteoclast function. The bones are short, heavy, and radiodense. Because their structure is disorganized, however, the bones are weak and easily fractured. Histologically, the bone is disorganized, the cortex is thick, and the marrow cavity is reduced.

Clinically, **severe anemia** results from the replacement of hematopoietic cells by bone trabeculae. The liver, spleen, and lymph nodes enlarge as a result of extramedullary hematopoiesis. Cranial nerve compression may cause blindness and deafness.

Paget Disease (Osteitis Deformans)

Paget disease is characterized by **osteoclastic bone resorption** followed by reactive osteoblastic activity, which outpaces resorption, leading to a net gain in bone mass and osteosclerosis. Histologically, the lamellar bone has a mosaic pattern, giving it the appearance of a jigsaw puzzle. The new bone may be initially woven or lamellar, but all of it is eventually remodeled into dense lamellar bone, arranged into coarsely thickened trabeculae. Clinically, it is seen slightly more frequently in men than women in the fifth decade. It may be *monostotic,* involving tibia, ileum, femur, skull, vertebra, and humerus (in approximately 15% of cases) or, in the majority of cases, *polyostotic,* which affects the pelvis, spine, and skull. The axial skeleton or proximal femur are involved most frequently.

Clinically, the disease is often asymptomatic. However, pain due to microfractures and bone overgrowth compressing spinal and cranial nerve roots is the most common presentation. In addition, there may be a variety of postural deformities, including inability to hold the head erect and anterior bowing of the long leg bones. Paget disease can be complicated by high output heart failure due to high blood flow through the bones. **Osteosarcomas** occur at an increased rate, especially in patients with severe polyostotic Paget disease.

INFECTIONS OF BONE

Osteomyelitis

Suppurative osteomyelitis is inflammation of the bone and bone marrow. It is generally caused by pyogenic bacteria, such as *Staphylococcus aureus,* which is responsible for 80% to 90% of cases. The organisms

reach the bone via the hematogenous route, by extension from an adjacent site such as skin ulcers or direct implantation of bacteria in gunshot wounds. The **hematogenous infections** typically involve the metaphysis of **long bones** and are most often seen in children and teenagers. Histologically, acute inflammation, ischemic necrotic bone fragments, and granulation tissue are found. Subperiosteal abscesses may lead to the formation of draining sinuses. In chronic inflammation, bone resorption, fibrosis, and deposition of reactive bone on the periphery occur with time.

Clinically, hematogenous osteomyelitis presents as an acute systemic illness with marked pain over the involved area. Local spread may cause suppurative arthritis, usually in infants. Complications of chronic osteomyelitis include pathologic fractures, secondary amyloidosis, endocarditis, or sepsis. Squamous cell carcinomas may arise on the skin above the sinus tracts and rarely, sarcomas form in the infected bone. Treatment requires surgical drainage and antibiotics.

Tuberculous osteomyelitis is rare today. It results from blood-borne infection in which the mycobacteria are carried to the bones from an active lesion in the lungs or some other organs. The lesions are usually solitary, but may be multiple in AIDS patients. Spinal disease (Pott disease), previously the most common form of skeletal tuberculosis, may involve multiple vertebrae and adjacent soft tissue. Clinically, patients present with pain on motion; fever, chills, and weight loss; and localized tenderness. Complications include abscesses of the psoas muscles and sinus tracts. Vertebral compression fractures lead to scoliosis or kyphosis.

BONE TUMORS

Tumors of bone are rare. They can be benign or malignant. Histogenetically, they can be classified as follows:

- **Bone-forming tumors** (e.g., osteoma or osteosarcoma)
- **Cartilagenous tumors** (e.g., chondroma or chondrosarcoma)
- **Fibroblastic tumors** (e.g., fibrosarcoma)
- **Tumors of undifferentiated cells** (e.g., Ewing sarcoma)
- **Hematopoietic tumors** (e.g., leukemia and multiple myeloma)

Approximately one-half of all malignant bone neoplasms are hematopoietic (see Chapter 9). The most common sites of bone tumors are shown in Figure 18-2.

Benign Tumors

Osteoid osteoma and **osteoblastoma** are benign tumors that have identical histologic features. By definition, osteoid osteomas are <2 cm in greatest dimension, and osteoblastomas are larger. Grossly, they are

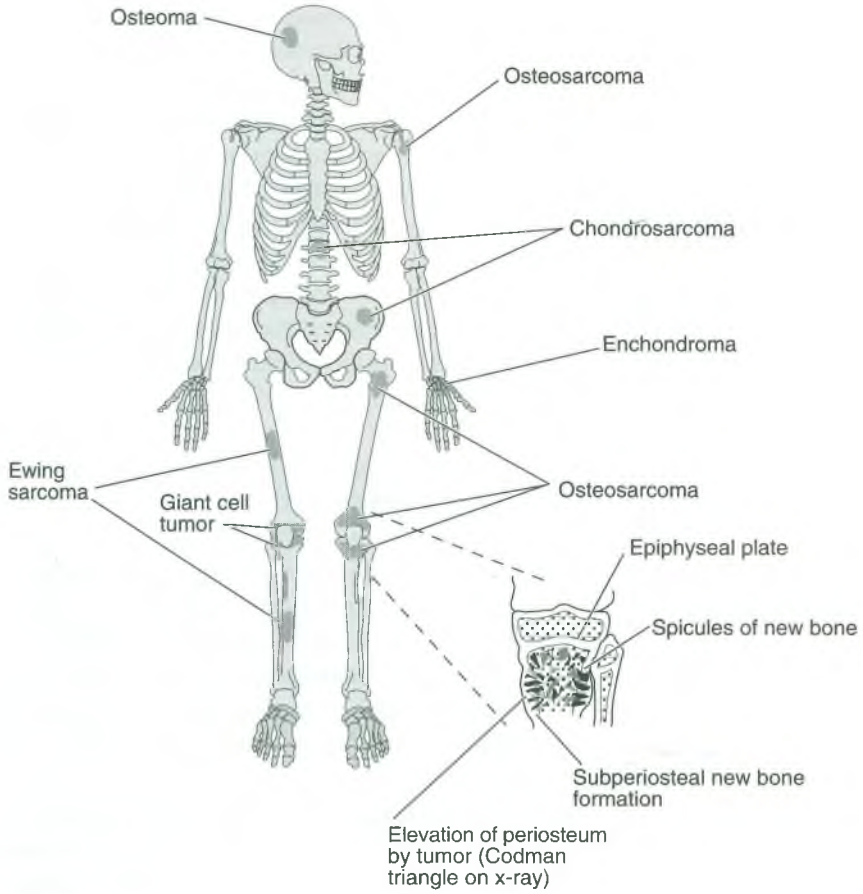


Figure 18-2.
The most common sites of bone tumors.

round to oval, tan, gritty, and hemorrhagic. Histologically, the lesions are well circumscribed and composed of trabeculae of bone, which are connected randomly and lined by osteoblasts living in a fibrovascular stroma. **Osteoid osteomas** are often surrounded by reactive bone, particularly when they arise in the subperiosteum. Clinically, both are found in the second and third decades of life, with men outnumbering women 2 to 1. Osteoid osteomas are most often found in the femur and tibia and are quite painful due to excessive prostaglandin 17β-estradiol production. The pain is relieved by aspirin. **Osteoblastomas** occur in the same age group and are also more common in men. They are much less painful and most often involve the vertebrae and, to a lesser degree, the long bones. Both osteoid osteomas and osteoblastomas are readily treated surgically; malignant transformation is exceptionally rare.

Giant cell tumors are usually benign, but 10% are malignant. They generally arise in the epiphysis and metaphysis of distal femur and proximal tibia but can be found elsewhere; in adolescents, they are confined to the metaphysis. Most are large, solitary, red-brown, and often cystic. Histologically, they are composed of uniform mono-

nuclear cells with indistinct cytoplasm, and frequent mitoses are admixed with osteoclast-type giant cells. Necrosis, hemorrhage, hemosiderin deposition, and reactive bone formation may be observed. These tumors arise in the third to fifth decades of life and are found in women slightly more often than men. Patients present with complaints of bone or joint pain because the tumor may compress the joints or cause pathologic fractures. Radiographically, the tumors are large lytic lesions that are eccentric and erode into subchondral bone. If the cortex is destroyed, they present as a bulging soft tissue mass. Giant cell tumors are histologically benign, but may frequently recur if treated by curettage. Approximately 10% are malignant and metastasize, usually to the lung.

Malignant Tumors

Osteosarcomas are malignant neoplasms that produce bone matrix. They account for approximately 20% of primary bone malignancies. The vast majority arise in the metaphysis of long bones. The favored sites in descending order include distal femur, proximal tibia, proximal humerus, and proximal tibia. Mutations of RB-1 (retinoblastoma) and *p53* suppressor genes have been associated with both inherited and noninherited forms.

Grossly, these tumors are tan-white and gritty and may have cysts and areas of hemorrhage. They often destroy the cortex and extend into adjacent soft tissue. Histologically, the cells are spindle shaped like osteoblasts, but may vary in size and shape. Tumor cells produce osteoid and bone, which is coarse and formed in sheets or trabeculae. The tumors spread in the medullary cavity, and less often they penetrate the epiphysis and enter the joint space or grow along the tendons and ligaments entering the joint.

Clinically, osteosarcomas occur at any age, but the majority occur in patients younger than 20 years. In the elderly, osteosarcomas are often a complication of Paget disease. Male subjects are at higher risk than female subjects. Osteosarcomas present as painful, enlarging masses or, to a lesser degree, sudden fractures. Approximately 20% of patients may have pulmonary metastases at the time of diagnosis. Radiographically, they present as destructive lytic masses, which also show bone formation. They commonly break through the cortex lifting the periosteum **(Codman triangle).** Metastasis to lungs, bones, brain, and elsewhere is via the hematogenous route. With modern chemotherapy, the long-term survival rate is approximately 60%.

Chondrosarcomas are malignant neoplasms of cartilage-forming cells. They are most commonly found in the pelvis, shoulder, and ribs. Grossly, they are nodular, gray-white, translucent, and glistening. Histologically, they are composed of malignant cartilage infiltrating marrow spaces and surrounding bone trabeculae. The adjacent cortex may be thickened or eroded. Cellularity varies depending on the grade of the tumor. The grading of tumors (I–III) has clinical significance.

Clinically, chondrosarcomas are found twice as often in men as in women. Most patients are in their fourth decade or older. Symptoms usually stem from the local effects of the progressively enlarging tumor mass. Tumors >10 cm are more aggressive and tend to metastasize to the lungs more often than smaller tumors.

Ewing sarcoma is a primary malignant tumor of bone composed of undifferentiated small round cells. The nature of these cells remains undetermined, and it is customary to include them in the group of "small blue cell tumors," such as retinoblastoma, medulloblastoma, rhabdomyosarcoma, and neuroblastoma, all of which correspond to embryonic blastema-like cells. Although Ewing sarcomas account for <10% of primary malignant bone tumors, they are second to osteosarcoma as the most frequent sarcoma of bone in children. The peak incidence is in the 10- to 15-year-old age group, and most patients are younger than 20 years of age. They occur more often in men, and whites are afflicted more often than blacks.

Ewing sarcomas arise in the **medullary cavity.** Histologically, the cells are round and arranged in nests and sheets with areas of necrosis and hemorrhages. Tumor cells have little cytoplasm, which is often clear and contains glycogen. **Homer-Wright pseudorosettes** may be present, suggesting neural differentiation. The stroma is scanty.

Clinically, Ewing sarcoma is a tumor of the diaphysis of long tubular bones, such as the femur, and flat bones of the pelvis. It presents as a painful enlarging mass that is tender and warm. There may also be systemic signs such as fever, leukocytosis, increased sedimentation rate, and anemia. Radiographic findings include bone lysis, with a characteristic "onion skin" periosteal reaction due to the formation of concentric layers of reactive bone. A 50% long-term cure rate can be achieved with surgery, chemotherapy, and radiation.

Fibrosarcoma and malignant fibrous histiocytoma are neoplasms composed of fibroblasts. They have similar clinical, radiographic, and pathologic features, although they differ histologically. They occur at any age, but have a predilection for the middle-aged and elderly. Malignant fibrous histiocytoma affects men more than women, but fibrosarcoma affects both genders equally. A small number of both tumors arise secondary to conditions such as Paget disease, benign tumors, and irradiated areas. The vast majority, however, arise spontaneously. Grossly, these tumors are large, tan-white, and often hemorrhagic. They destroy bone and invade into soft tissue. **Fibrosarcomas** consist of spindle-shaped malignant fibroblasts arranged in interlacing bundles that produce a herringbone pattern. Histologically, they can be classified as low- or intermediate-grade tumors. **Malignant fibrous histiocytomas** are composed of spindle-shaped fibroblasts in a storiform pattern admixed with large, multinucleated giant cells and are considered to be high-grade tumors. Both neoplasms present as painful masses on the metaphysis of long bones and flat bones of the pelvis. On radiography, they appear as lytic lesions and frequently invade adjacent soft tissue; pathologic fractures are common. The prognosis is poor for high-grade lesions, which have a 20% 5-year survival rate.

The salient features of primary malignant bone tumors are summarized in Table 18-1.

Metastatic tumors of bone represent the most common form of malignancy in the skeleton. Neoplasms reach bones hematogenously or by local spread, as in prostate carcinoma invading the pelvis and lumbar vertebra. The most common primary sites are carcinomas of the breast, prostate, lung, kidney, and thyroid. The common sites of metastases in descending order include axial skeleton, proximal femur, and humerus. On radiography, the lesions may be **lytic** (lucent) or **osteoblastic** (dense). Lytic lesions are associated with hypercalcemia. Osteoblastic lesions are associated with elevated serum alkaline phosphatase levels, a marker of osteoblastic proliferation. In children, bone metastases are a common feature of neuroblastoma. Multiple bone lesions of Ewing sarcoma represent either metastases or multifocal primary tumors, originating simultaneously.

JOINTS

Joints are divided into two groups: **synovial** (diarthrodial) joints, which are movable (e.g., elbow and knee) and lined by a synovial membrane; and **synarthroses** joints, which show little movement and are classified according to the type of connective tissue that bridges the bones (e.g., **fibrous synarthroses,** as cranial sutures, and **cartilaginous synarthroses,** as pubic symphyses).

The inner surface of synovial joints, with the exception of the articular cartilage, is lined by synovium. The synovium is composed of two types of cells. One population is phagocytic and secretes hyaluronic acid. The other population is fibroblast-like and produces matrix proteins, such as collagen type I. Synovial cells are not surrounded by a basement membrane, but merge with the underlying stromal cells.

DEGENERATIVE JOINT DISEASE

Osteoarthritis

Osteoarthritis is a **degenerative joint disease** characterized by erosion of articular cartilage and reactive changes in the adjacent bone. It can be *primary, idiopathic,* or *secondary* to some underlying cause such as traumatic injury, congenital joint and bone malformations, or diabetes. The primary form appears to result from intrinsic alterations in the cartilage favoring its breakdown. Morphologically,

TABLE 18-1.

Comparison of Malignant Bone Neoplasms

Neoplasms	Frequency	Age and Gender Ratio (M:F)	Sites Most Often Affected	Behavior	Prognosis
Osteosarcoma	Overall, most common primary malignant tumor of bone	Peak incidence <20 yrs, second minor peak in elderly, Paget disease–related (2:1)	Distal femur, proximal tibia, jaw, metaphysis of long bones	Painful, progressively enlarging masses; lung metastasis	Long-term survival approximately 60% with chemotherapy
Chondrosarcoma	Most common malignant bone tumor in 40- to 60-yr age group	Fourth decade or older (2:1)	Pelvis, shoulder, ribs, long bones, axial skeleton	Painful, progressively enlarging masses; slow growing; metastasizes to lungs	Depends on size and grade; 5-yr survival 45–90%; resistant to chemotherapy
Ewing sarcoma	6–10% of primary malignant bone tumors; second most common bone sarcoma in children	Children and teenagers; blacks rarely affected	Diaphysis of long bones (femur), pelvic flat bones	Painful, progressively enlarging masses; may be multifocal	Long-term survival approximately 50% with chemotherapy
Fibrosarcoma/ malignant fibrous histiocytoma	—	Middle age and elderly (1:1)	Metaphysis of long bones and flat bones of the pelvis	Painful, progressively enlarging masses; pathologic fracture	High grades, 5-yr survival 20%; resistant to chemotherapy
Giant cell tumor	—	Third to fifth decade (1:1)	Epiphysis and metaphysis around knee most frequent	Painful; pathologic fractures; metastasis infrequent (10%)	Recurs frequently after surgery in 30%; 10% are malignant; does not require chemotherapy

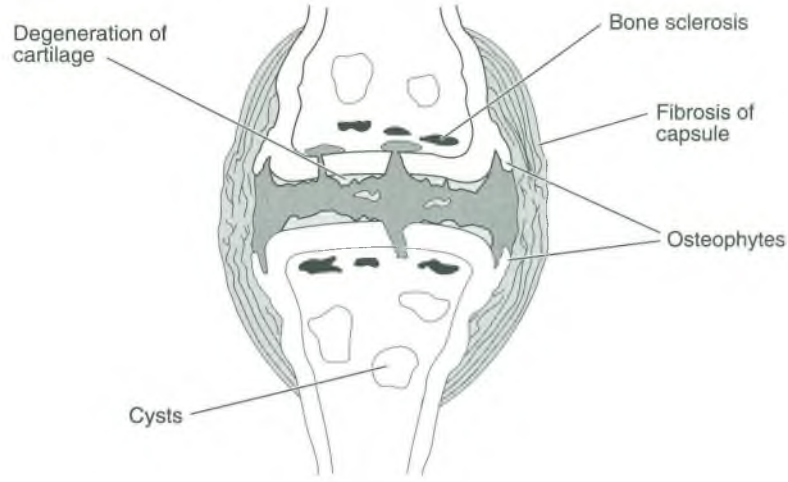


Figure 18-3.
Osteoarthritis.

there is fraying and erosion of articular cartilage, which may be completely lost, exposing the bone to undue pressure. Dislodged cartilage and bone detach and float in the joint space as free bodies ("joint mice"). The reactive changes in the underlying bone include osteosclerosis, fibrosis, and cyst formation. **Osteophytes (bone spurs)** develop at the margins of the articular surface (Fig. 18-3).

Clinically, primary osteoarthritis is a disease of the elderly. Symptoms include deep aching pain, stiffness, crepitus, and limitation of movement. The weight-bearing joints such as hips, knees, and those between the lower lumbar and cervical vertebrae are commonly affected. Distal interphalangeal joints of the fingers show osteophytes (Heberden nodes), but first carpometacarpal joints and first tarsometatarsal joints of the feet also may be deformed. There is no medical treatment for osteoarthritis. Severe incapacitating joint lesions must be replaced by artificial joints made of metal.

Infections of Joints

Infections reach the joints most often by a hematogenous route. **Suppurative arthritis** is most commonly caused by *S. aureus; Neisseria gonorrhoeae* infection is a complication of gonorrhea. The large joints are most frequently involved. Clinically, the joints are hot and swollen, and there is fever and leukocytosis. Antibiotics are the treatment of choice. Destruction of articular cartilage and spread to the bones may occur in inadequately treated cases.

Arthritis is a common feature of **Lyme disease.** It occurs from weeks to years after the infection with the spirochete *Borrelia burgdorferi.* Knees, shoulders, elbows, and ankles are most often involved in

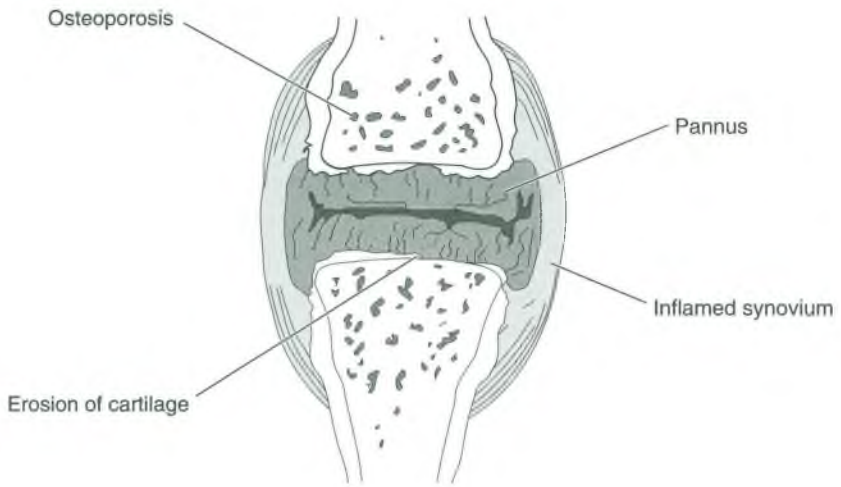


Figure 18-4.
Rheumatoid arthritis.

a fleeting (migratory) manner. Attacks can last for weeks to months. Histologically, there is chronic papillary synovitis marked by hyperplasia of synovial cells and fibrin deposition. The inflammatory infiltrate consists mostly of **$CD4^+$ helper/inducer T cells.** Concentric onion-skin thickening of arterioles may be a prominent feature. Spirochetes are rarely detected in the joint fluid, but serologic tests for Lyme disease are diagnostic.

Autoimmune Disease of Joints

Rheumatoid arthritis (RA) is a chronic autoimmune multisystemic inflammatory disorder of unknown etiology that affects joints and many other tissues and organs such as skin, blood vessels, heart, lungs, and muscle. The exact pathogenesis of RA is not known. Most patients (90%) have IgM autoantibodies reacting with their own IgG (rheumatoid factor), which points to the immune nature of the disease. Although the joints may contain deposits of rheumatoid factor, it is not known whether rheumatoid factor has a pathogenetic role in inflammation. Genetic susceptibility (the majority of patients are HLA-DR4 or -DR1) may be important. The role of infectious agents (e.g., Epstein-Barr virus) has been explored but not proven.

Morphologically, the synovium is edematous and infiltrated by lymphoid follicles (primarily $CD4^+$ helper T cells), plasma cells, and macrophages. The hyperplastic inflamed, hyperemic synovium **(pannus)** forms a cover extending over the articular cartilage and causing its erosion. Mediators released during this process activate osteoclasts, leading to osteoporosis of underlying bone. Fibrous and then bony ankylosis with obliteration of the articular space is a late feature of RA (Fig. 18-4).

Extra-articular manifestations of RA are found at a variable rate. Rheumatoid nodules (fibrinoid necrosis surrounded by epithelioid cells) are noted in the skin in regions subjected to pressure, such as the ulnar aspect of the forearm, elbow, and occiput. Rheumatoid lung disease may present with lung destruction and formation of cavities surrounded by fibrosis. In severe cases, rheumatoid vasculitis is observed, which may be accompanied by skin ulcers, gangrene, and even neuropathy.

Clinically, the onset of the disease has a peak between the third and fifth decades, and women are three to five times more often affected than men. Involved joints are hot, swollen, and stiff. Initially, small joints such as metacarpophalangeal and proximal interphalangeal joints are involved. Later in the course, larger joints become affected. Because of the destructive nature of the disease, various deformities are observed. These include radial deviation of the wrist, ulnar deviation of the fingers, and flexion-hyperextension abnormalities of the fingers, which are referred to as *swan-neck* or *boutonnière* deformities. *Diagnosis is based on any four of the following observations:* (1) morning stiffness, (2) arthritis in three or more joints, (3) arthritis of hand joints, (4) symmetric arthritis, (5) rheumatoid nodules, (6) serum rheumatoid factor, and (7) typical radiographic findings. In approximately 20% of cases, the disease has a limited course, but in most patients it has a chronic course. In approximately 10% of cases, the disease is associated with incapacitating deformities. Treatment is mostly symptomatic. Gastrointestinal bleeding resulting from chronic aspirin or nonsteroidal anti-inflammatory drug use and infections resulting from corticosteroid use are important complications.

Gout

Gout is a multisystemic disease that results from **hyperuricemia** and deposition of **uric acid crystals** in tissues. It is characterized by transient acute arthritis that eventually leads to chronic arthritis and the deposition of urate masses (tophi) in the joints and other sites, most often including the kidney. *Primary gout,* not fully understood, accounts for approximately 90% of cases. *Secondary gout* includes metabolic disorders such as Lesch-Nyhan syndrome, chronic renal disease, and other conditions marked by hyperuricemia for gout.

Morphologically, four distinct lesions are typical of gout. These include acute arthritis, chronic tophaceous arthritis, tophi in a variety of locations, and gouty nephropathy. **Acute arthritis,** most often involving the first tarsometatarsal joint, is marked by infiltration of the joint by neutrophils, which respond to deposits of monosodium urate crystals in the synovium. **Chronic tophaceous arthritis** results from repetitive urate crystal deposition during acute attacks. The synovium becomes hyperplastic, fibrotic, and thickened, forming a pannus that, together with the tophaceous nodules, destroys the

underlying cartilage and erodes the bone. In severe cases, the joints show deformities and ankylosis.

Tophi are nodules composed of sodium urate crystals surrounded by mononuclear inflammatory cells, and foreign body giant cells. Tophi are found in the joints, ligaments, tendons, and subcutaneous soft tissues such as the earlobes.

Gouty nephropathy results from the deposition of monosodium urate crystals, and sometimes tophi, in the medullary interstitium of the kidneys. Precipitates of crystals or free uric acid crystals are also seen in the tubules. Urate stones formed in the renal pelvis may cause obstruction and predispose to pyelonephritis.

Clinically, gout has four stages: (1) asymptomatic uricemia, (2) acute gouty arthritis, (3) intercritical gout, and (4) chronic tophaceous gout. The first attack usually occurs 20 to 30 years after the onset of hyperuricemia. The metatarsophalangeal joints are most often affected. Attacks present as excruciating pain with sudden onset, hyperemia, warmth, and severe tenderness. Drugs such as colchicine are available for treatment of acute attacks. Long-term treatment is directed at the reduction of uric acid deposits.

Tumors and Tumor-Like Conditions of the Joints

Tumors of the joints are rare. The most common benign neoplastic proliferation of synovial cells is called **pigmented villonodular synovitis.** Despite its name, this is a tumor and not an inflammatory lesion. It is characterized by reddish brown finger-like protrusions of synovium that fill the articular cavity. The color of the lesion stems from extravasated blood that is taken up and stored as hemosiderin in phagocytic cells.

Chapter 19

Skeletal Muscles

The response of skeletal muscles to injury includes the following reactions:

- **Atrophy** is caused by inactivity (e.g., immobilization of a leg in a cast after bone fractures), malnutrition, aging, chronic disease, or denervation (e.g., spinal cord trauma).
- **Hypertrophy** can be induced by prolonged strain or exercise (e.g., weightlifting). This enlargement of muscles is due mostly to an increased size of type II muscle fibers.
- **Necrosis** or cell death can be a consequence of external injury (e.g., toxic myopathy) or internal structural disturbances as in genetic disorders (e.g., Duchenne muscular dystrophy). Necrosis may be accompanied by abortive regeneration of reserve cells, which appear as small cells with basophilic (RNA-rich) cytoplasm.
- **Rhabdomyolysis** (lysis of muscle cells) is a form of focal necrosis of muscle fibers due to hyperexertion, toxins, or viruses. Like any other form of necrosis, it is accompanied by a release of creatine kinase (CK) into the circulation.
- **Inflammation (myositis)** is characterized by infiltration of muscles with inflammatory cells. Inflammation may be a response to muscle cell necrosis, as in viral infections, or it may be a hypersensitivity reaction in which the T-lymphocytes or B cells infiltrate the muscle and damage it. Often it is not possible to state which came first, the muscle cell injury or inflammation.
- **Fibrosis** is the common response to muscle cell loss. Because muscles have a limited capacity for regeneration, repair by fibrosis is the only way to preserve the structural integrity of the muscles. Fibrotic muscles lack strength and cannot either stretch or contract as normal muscles can.

Overall, the non-neoplastic muscle diseases are classified into three categories (Fig. 19-1 and Table 19-1):

- **Neurogenic muscle atrophy** is secondary to denervation.
- **Myopathy** or primary muscle disease, characterized by destruction and loss of muscle cells. Myopathies include **muscular dystrophies,** a heterogeneous group of genetic disorders involving structural proteins of muscle fibers; **congenital myopathies,** genetic disorders of intermediate metabolism of glycogen, lipids, or pro-

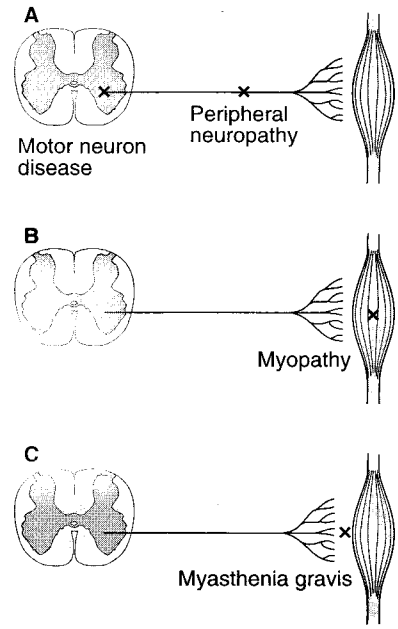


Figure 19-1.
Three forms of muscle diseases. *A:* Denervation atrophy. *B:* Myopathy. *C:* Neuromuscular junction disorder.

teins; **inflammatory myopathies,** which are caused by infections or autoimmune disorders; and **toxic and metabolic myopathies** caused by toxins (e.g., botulism), drugs (e.g., corticosteroids), or systemic metabolic diseases such as diabetes.

- **Diseases of the neuromuscular junction,** such as myasthenia gravis and Lambert-Eaton myasthenic syndrome, represent disturbances of nerve impulse transmission at the neuromuscular junction. Despite considerable muscle weakness, the muscle shows no pathologic changes.

NEUROGENIC ATROPHY

Denervation atrophy of skeletal muscles may involve the entire muscle or large muscle fascicles **(fascicular atrophy),** as in spinal cord injury; or individual muscle fibers, as in ischemic neuropathies characterized by a loss of small branches of motor neuron axons. Single cell atrophy is common in diabetic neuropathy, which is probably the most common cause of neurogenic atrophy seen clinically. In fascicular atrophy, atrophic fibers are grouped, whereas in single fiber atrophy, triangulated atrophic fibers are scattered randomly among normal fibers (Fig. 19-2).

Atrophy represents a reversible change: On reinnervation, muscle fibers regain their normal size. Reinnervated muscles can be best recognized by enzyme histochemistry. Instead of the typical haphazard arrangement of type I and type II muscle fibers, in a checker-

TABLE 19-1.
Classification of Muscle Diseases

- Neurogenic muscle disease
- Myopathy
  - Muscular dystrophies
  - Congenital myopathies
  - Toxic or metabolic myopathy
    - Toxins
    - Drugs
    - Metabolic diseases
  - Inflammatory myopathy
    - Infectious
    - Autoimmune
- Diseases of the neuromuscular junction
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome
- Neoplasms

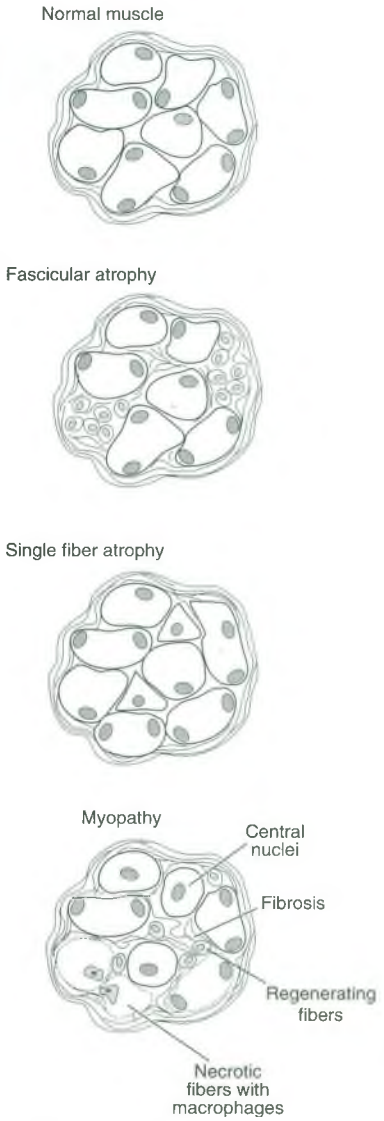


Figure 19-2.
Histopathologic changes typical of neurogenic atrophy and myopathy.

board pattern, the reinnervated muscles show grouping of type I and type II fibers.

Clinically, atrophy of the muscle is most often related to the following conditions:

- **Spinal cord injury,** most often caused by trauma
- **Anterior horn diseases,** reflecting destruction of motor neurons of spinal cord. Typical diseases in this group are amyotrophic lateral sclerosis (ALS) and poliomyelitis.
- **Peripheral neuropathies** such as diabetic, carcinomatous, or alcoholic neuropathy
- **Congenital spinal muscular atrophy,** which includes rare genetic disorders presenting as "floppy baby syndrome" (e.g., Werdnig-Hoffmann disease) or progressive childhood muscle weakness (e.g., Kugelberg-Welander syndrome)

MUSCULAR DYSTROPHY

The term *muscular dystrophy* includes several hereditary diseases, all of which are characterized by progressive destruction and loss of muscle fibers due to a genetically determined abnormality of integral components of muscle fibers. Necrosis of muscle fibers is accompanied by an elevation of CK in blood and muscle wasting

TABLE 19-2.
Muscular Dystrophies

Type of Dystrophy	Inheritance	Incidence	Age at Onset (yrs)	Features
Duchenne	XR	1:3,500	2–6	Most common and most severe dystrophy; progressive wasting of pelvic and leg muscles, becomes generalized
Becker	XR	1:35,000	10–30	Milder, adult form of Duchenne dystrophy, 10× less common
Limb-girdle	AR	1:40,000	Variable	Wasting of muscles of pelvic girdle, then shoulders and limbs; variable course, usually mild to moderate
Facioscapulohumeral	AD	1:20,000	10–20	Wasting of facial and shoulder muscles; slow clinical progression
Myotonic	AD	1:8,000	20–30	Most common adult-onset dystrophy; wasting of facial and limb muscles with myotonia Typical electromyographic findings Extramuscular findings: baldness, gonadal atrophy, diabetes, cataract, low IQ, cardiomyopathy

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

and weakness. The most important muscular dystrophies are listed in Table 19-2.

Duchenne Dystrophy

Duchenne dystrophy represents a defect of the gene for **dystrophin,** a structural protein of the muscle that links the cytoskeleton to the plasma membrane. The dystrophin gene is on the X chromosome, and its mutations are transmitted in an X-linked recessive manner according to which only the male offspring of female carriers are affected. Only exceptionally, the disease may appear in women. Approximately 30% of cases represent new mutations, in which case there is no previous family history of the disease.

In the absence of dystrophin, muscle cells cannot regulate the influx of calcium and tend to disintegrate, causing muscle wasting and weakness.

The symptoms of **muscle weakness** may appear when the infant begins to walk or later in preschool years. The disease progresses relentlessly. By school age, most children are confined to a wheelchair, and by the age of 20 years, they usually die. There is

marked muscle wasting, although some muscles replaced by fat cells may be thicker than normal (pseudohypertrophy). Affected children have a tendency to develop contractures, which cause deformities of the body and limit the patient's mobility even more. Death is usually caused by respiratory failure or cardiomyopathy because the respiratory muscles and heart muscle are also affected in a manner similar to the skeletal muscles of the extremities. The clinical diagnosis can be confirmed by laboratory studies. CK is elevated in serum, reflecting the extent of muscle cell necrosis, and also may be elevated in amniotic fluid, which is important for the prenatal diagnosis. Muscle biopsy is useful because it shows typical features of dystrophy such as muscle fiber necrosis, myophagocytosis, endomysial fibrosis, and fat replacing the lost fibers. Molecular biological data on dystrophin gene provide the definitive diagnosis and are useful for characterizing the gene defect.

Becker Dystrophy

Becker dystrophy is a milder form of Duchenne dystrophy of late onset. It is 10 times less common than Duchenne dystrophy. It is also related to dystrophin gene, but apparently the defect involves a smaller gene segment than in the Duchenne dystrophy. Histologically, the muscle shows the same features. although the changes are less pronounced than in Duchenne dystrophy. Symptoms of Becker dystrophy appear in the second or even third decade. **Muscle wasting** is less incapacitating but still progressive, and most patients die in their 40s or 50s.

Myotonic Dystrophy

Myotonic dystrophy, the second most common dystrophy, is inherited as an **autosomal dominant trait** causally linked to a gene that shows triple nucleotide CGG repeats on chromosome 19. The symptoms of the disease begin appearing between 20 and 30 years of age. **Progressive muscle wasting** is especially prominent on the face, giving the person a somber appearance ("hatchet-man face"). **Muscle weakness** is accompanied by myotonia (i.e., prolonged spasm of muscles that cannot relax after contraction, such as persistent clasp after handshake). The pathologic changes in the muscle biopsy are highly variable and include atrophy of type I fibers, internally placed nuclei, and structural changes seen by electron microscopy. Necrosis of muscle fibers is not prominent. Affected persons also show signs of mild mental retardation, frontal baldness, and endocrine disorders such as diabetes and gonadal atrophy. Respiratory muscle weakness and cardiomyopathy are the most common causes of death.

TOXIC AND METABOLIC MYOPATHIES

Toxic and metabolic myopathies are closely interrelated. Muscles may be injured by many toxins, drugs, or metabolites. **Alcohol** is probably the most common cause of toxic myopathy because it acts directly on muscle cells. Chronic alcoholics have also a metabolic myopathy because alcohol damages the liver and causes changes in the metabolism of lipids and carbohydrates. Examples of toxins that affect the muscle are bacterial toxins (e.g., tetanus, gas gangrene), organophosphorous toxins, and metals.

Congenital metabolic myopathies are rare and occur as part of a generalized metabolic disturbance. The best examples are various glycogenoses, most of which are characterized by muscle symptoms. In **Pompe disease** (glycogenosis II, caused by acid maltase deficiency), muscle weakness is associated with cardiomyopathy. In **McArdle disease** (glycogenosis type IV, muscle phosphorylase deficiency), muscle weakness is the predominant symptom.

Acquired metabolic myopathies are typical of several endocrine disorders such as diabetes mellitus, Cushing syndrome, Addison disease, hypothyroidism, and hyperthyroidism. Hormones are essential for muscle metabolism, and a hormonal imbalance usually adversely affects the muscles, causing weakness, easy fatigability, and other functional disturbances. In diabetes, which causes peripheral neuropathy, muscle may also show signs of neurogenic atrophy. In other diseases, the muscle biopsy may show no changes or only type II muscle fiber atrophy, which is a nonspecific reaction and is found in many conditions such as prolonged immobilization, hypothyroidism, and cortisone therapy.

MYOSITIS

Inflammation of the muscles is found in the course of many infectious or autoimmune diseases. Infectious diseases are most often systemic, and the symptoms of muscle diseases are typically overshadowed by other more serious ailments. **Infectious myositis** may be caused by **viruses** (e.g., coxsackievirus B) or **bacteria** (e.g., streptococci). Myositis is a common feature of **trichinosis,** a disease caused by *Trichinella spiralis,* a parasite that has a tendency to encyst in the striated muscle (Table 19-3).

Polymyositis is an autoimmune disease affecting the muscles. Histologically, it is characterized by foci of inflammation in which macrophages and T-lymphocytes predominate. Clinically, it is characterized by muscle pain and weakness, which tends to be more prominent in proximal muscles, in contrast to neurogenic muscular atrophy,

TABLE 19-3.
Causes of Myositis

Cause	Pathogens or Disease
Bacterial infection	Various bacteria
Wound infection	Tetanus and gas gangrene
Trauma	
Spread from adjacent structures	
Sepsis	
Viral infection	Coxsackievirus, influenza virus
Parasitic infection	*Trichinella spiralis*
	Taenia solium (cysticercosis)
Protozoal infection	*Toxoplasma gondii*
Autoimmune	Polymyositis
	Dermatomyositis
	Systemic lupus erythematosus
	Sarcoidosis

which involves more distal limb muscles. Elevated CK level in blood is indicative of muscle cell necrosis, but does not provide information on whether a muscle disease is infectious or immune mediated. Positive serologic tests such as antinuclear antibodies (ANAs) or anti–Jo-1 antibodies are positive in autoimmune disorders. Electromyographic changes and muscle biopsy are also important for diagnosis. Polymyositis may be associated with skin disease (dermatomyositis) or other autoimmune disorders (e.g., systemic lupus erythematosus).

Dermatomyositis typically affects 10- to 20-year-old girls who present with signs of muscle weakness and skin rash. Typically, they show lilac discoloration around the eyes (heliotrope rash) and rash of the upper chest and extensor surface of the arms. Serologic test results indicate that the disease is immune mediated. In older patients, dermatomyositis may be a paraneoplastic syndrome. In such cases, ANA and other serologic test results are negative.

Sarcoidosis may involve muscles. As in other organs, this T-cell–mediated disease presents with noncaseating granulomas.

MYASTHENIC SYNDROMES

Myasthenia gravis is an autoimmune disease characterized by the presence of **autoantibodies to acetylcholine (ACh) receptors** at the neuromuscular junction (Fig. 19-3). The binding of antibodies to

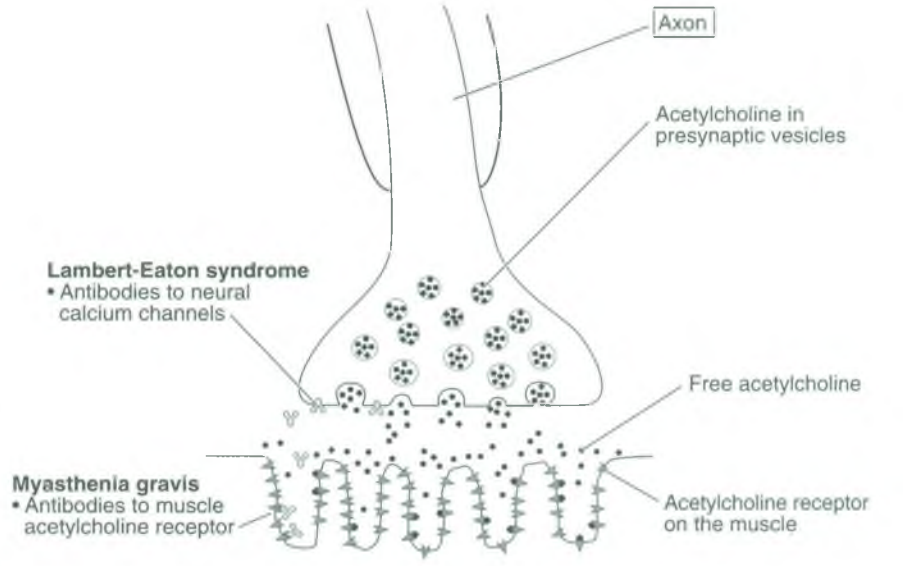


Figure 19-3.
Myasthenic syndromes. At the normal neuromuscular junction, acetylcholine is released from the nerve endings. It binds to specific acetylcholine receptors on the muscle end plate, thus stimulating the muscle contraction. In myasthenia gravis, antibodies to acetylcholine-receptor inhibit the binding of acetylcholine to the muscle end plate. In Lambert-Eaton myasthenic syndrome, antibodies to calcium channel protein inhibit the release of acetylcholine from the nerve terminal.

the receptor prevents the transmission of neural impulses, which impairs the contraction of skeletal muscles. Anti–ACh receptor antibodies are found in the serum of 85% of patients. Histologically, the muscle shows no pathologic changes.

The disease presents with fatigue and muscle weakness. Typically, it involves eye muscles, causing double vision or drooping of eyelids. Weakness of the laryngeal muscle causes dysphonia. Other muscles become affected as the disease progresses. Death may result from respiratory muscle failure. A diagnosis that is suspected clinically can be confirmed by the injection of edrophonium (cholinesterase inhibitor), which restores muscle strength. Electromyographic changes are typical. Many patients, especially those who are young and female, have thymic lesions, such as thymic hyperplasia or thymoma. Muscle symptoms of these patients improve after thymectomy. In older patients, medical treatment with inhibitors of cholinesterase or plasmapheresis to remove the harmful antibodies from circulation may give temporary relief, but in most cases, the disease is incurable.

Lambert-Eaton myasthenic syndrome is any autoimmune paraneoplastic disease resembling myasthenia gravis. In contrast to progressive weakness of muscles in myasthenia gravis, in this syndrome the muscle weakness improves with movement. It is caused by **antibodies to calcium channel proteins** at the nerve terminal, which impede the release of ACh. Most cases have oat cell lung carcinoma, which presumably leads to autoimmunization of the patient's body

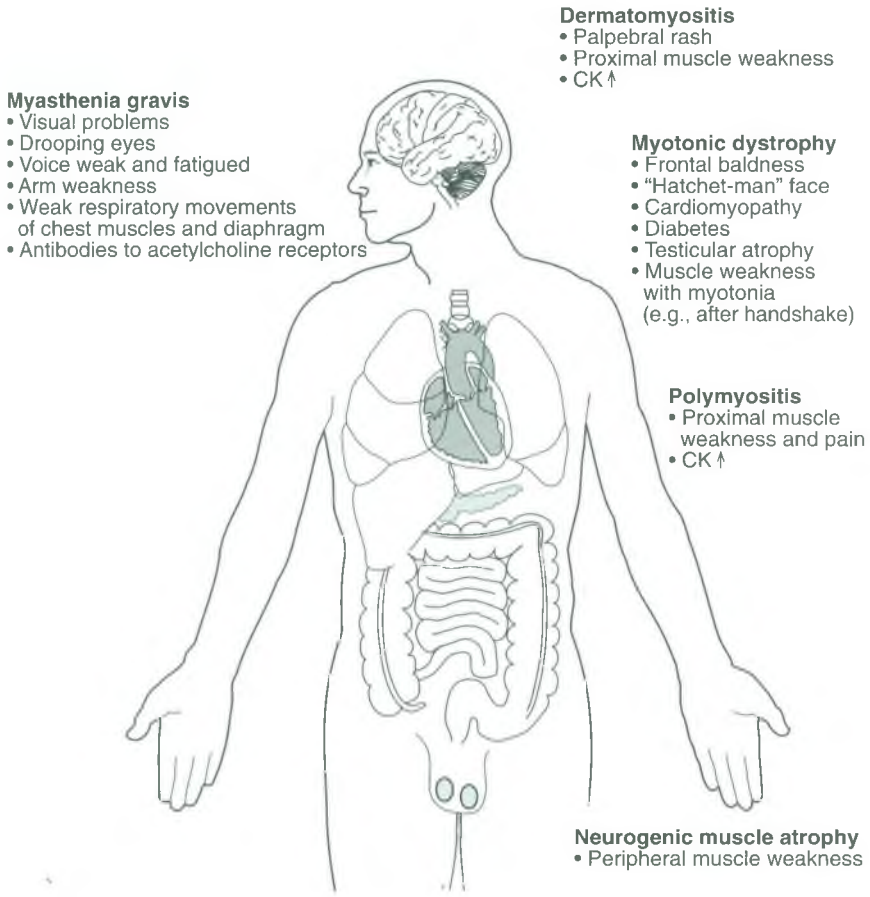


Figure 19-4.
Clinical features of important muscle diseases. Electromyography may show changes typical of each of these diseases. Creatine kinase (CK) is elevated in the serum of patients who have dermatomyositis and polymyositis, but it is normal in other diseases that do show muscle cell necrosis. Muscle biopsy changes are seen in all of these diseases, except myasthenia gravis, which causes no visible histologic changes in the muscle.

to calcium channel proteins. Treatment is symptomatic, because most patients have incurable cancer.

Clinical features of myasthenia gravis are presented in Figure 19-4 and compared with those of dermatomyositis/polymyositis, myotonic dystrophy, and neurogenic atrophy.

NEOPLASMS

Tumors of skeletal muscle are rare. These tumors are clinically grouped with other **soft tissue tumors** and may be benign or malignant. Most tumors are of **connective tissue** origin and are classified as

TABLE 19-4.
Soft Tissue Sarcomas

Tumor Type	Cell of Origin	Most Common Sites	Peak Incidence (yrs)
Rhabdomyosarcoma	Striated muscle	Various sites	Children (5–10)
Malignant fibrous histiocytoma	Mesenchymal stem cell	Leg, arm, retroperitoneum	Adults (40–60)
Synovial sarcoma	Mesenchymal stem cell	Leg	Young adults (10–40)
Liposarcoma	Fat cell	Leg, retroperitoneum	Adults (40–60)
Leiomyosarcoma	Smooth muscle	Retroperitoneum	Adults (40–60)
Angiosarcoma	Blood vessel cells	Head and neck	Adults (30–50)

fibroma, myxoma, and lipoma if benign; or fibrosarcoma, malignant fibrous histiocytoma, and liposarcoma if malignant (Table 19-4).

Rhabdomyosarcoma is a tumor originating from the striated muscle reserve cells. It most often occurs on the arms and legs of children. Rhabdomyosarcomas in adults are less common. Typically, they originate from smaller muscles, such as the retro-orbital muscles of the external eye. Surgical resection with chemotherapy is the treatment of choice. The prognosis of malignant tumors of soft tissues depends on their size and location, but overall the treatment results are not favorable.

Chapter 20

Nervous System

The central nervous system (CNS) is composed of neurons and glia cells. **Neurons** vary in size and shape, but have a body (called *perikaryon* because it surrounds the nucleus) and cytoplasmic projections that receive or transmit signals to or from other cells; dendrites carry incoming impulses, and axons carry the outward signals. Neurons are very sensitive to injury such as anoxia or toxins. In response to injury, the neurons may swell (ballooning or hydropic degeneration) or show a loss of cytoplasmic basophilia of the Nissl substance (chromatolysis). Ischemic neurons have shrunken eosinophilic cytoplasm ("pink neurons"). Neurons atrophy in a variety of neurodegenerative diseases. They also may contain cytoplasmic inclusions (e.g., neurofibrillary tangles in Alzheimer disease or Lewy bodies in Parkinson disease) or nuclear inclusions (e.g., viral inclusion in herpes simplex viral infection).

Astrocytes are star-shaped large glia cells forming close contacts with neurons and blood vessels. In response to injury, astrocytes may enlarge (become gemistocytic) or proliferate, contributing to gliosis of the brain, an equivalent of scarring in other organs.

Oligodendroglia cells are myelin-producing cells of the CNS, equivalent to Schwann cells of peripheral nerves. Injury to these cells results in **demyelination,** as typically seen in multiple sclerosis.

Ependymal cells line the four brain ventricles, the aqueduct, and the central canal of the spinal cord. These cells contribute nonspecifically to various forms of injury. During the repair of virus-induced lesions of the pons and medulla oblongata, in children ependymal cells proliferate, which may result in obstruction of CSF flow. In adults, their response to injury has little if any significance.

Microglia cells are phagocytic cells equivalent to tissue macrophages. In response to injury, they proliferate and may form microglial nodules. Around the infected brain tissue, these cells become lipid laden and have foamy cytoplasm (gitter cells).

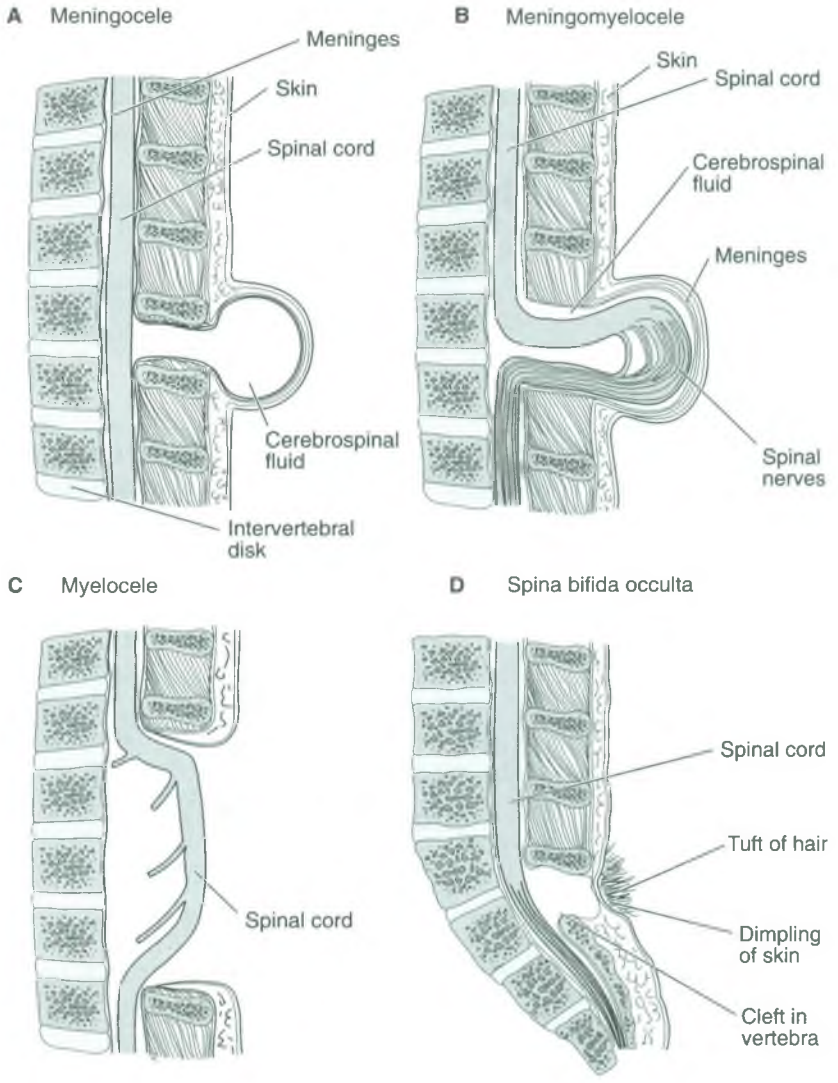


Figure 20-1.
Dysraphic malformations. *A:* Meningocele. *B:* Meningomyelocele. *C:* Myelocele. *D:* Spina bifida occulta.

CONGENITAL AND DEVELOPMENTAL DISORDERS

The most important diseases in this group of congenital and developmental disorders are **dysraphic disorders,** which result from incomplete closure of the fetal neural tube. These include anencephaly and a variety of defects caused by incomplete closure of the spinal cord and vertebrae such as meningocele, myelomeningocele, and spina bifida. **Anencephaly** is incompatible with life. **Spina bifida aperta,** in which the spinal cord is exposed, is a severe disease, whereas **spina bifida occulta** may have only minor neurologic symptoms (Fig. 20-1).

Arnold Chiari malformation involves downward displacement of the cerebellum and elongation of medulla oblongata and the fourth

ventricle, resulting in hydrocephalus due to obstruction of normal CSF circulation. **Dandy-Walker malformation** is a hydrocephalus caused by occlusion of the foramina of Luschka and Magendie, related to abnormal development of the vermis of the cerebellum.

Phakomatoses

Phakomatoses is a group of heterogenous, developmental disorders unrelated to each other and characterized by distinct pathologic changes in the brain. Some of these disorders have been traced to abnormal genes, but the others remain poorly understood. The most important phacomatoses are tuberous sclerosis, von Hippel–Lindau disease, and neurofibromatosis.

Tuberous sclerosis presents with aggregates of glial cells and neurons and large cells intermediate between glia and neurons, forming grossly visible nodules (tubers) and subependymal hamartomas that may give rise to true neoplasms (astrocytomas). These brain lesions are associated with mental retardation and epileptic seizures. In addition, the patients have facial nodules (nevus sebaceus), skin patches ("shagreen patches"), areas of hypopigmentation, subungual fibromas, and hamartomatous nodules and cysts in internal organs.

von Hippel–Lindau disease presents with hemangioblastoma of the cerebellum, hemangioma of the retina, and cysts in the liver, kidney, and pancreas. Patients have a tendency to develop renal cell carcinoma and pheochromocytoma. A mutation in the von Hippel–Lindau tumor-suppressor gene on chromosome 3 accounts for the various neoplasms associated with this syndrome.

Neurofibromatosis occurs in two forms. Type I (von Recklinghausen disease) is an autosomal dominant disease characterized by multiple cutaneous neurofibromas, pigmented lesions of skin (café au lait lesions), pigmented foci of the iris (Lisch nodules), and less often meningiomas, optic gliomas, and acoustic schwannomas. It is associated with a mutation or deletion of the NF-1 tumor suppressor gene on chromosome 17q. Neurofibromatosis type II is also an autosomal dominant disorder, characterized by bilateral acoustic schwannomas and less commonly meningiomas and is associated with mutations of a gene on chromosome 22.

ACQUIRED DEVELOPMENTAL ABNORMALITIES

Congenital Hydrocephalus

Congenital hydrocephalus is usually caused by an **obstruction in the flow of cerebrospinal fluid** (CSF) due to an obstruction at the level of the fourth ventricle or the aqueduct of Sylvius. Aqueductal stenosis or atresia may result from intrauterine infections caused by viruses (e.g., rubella, cytomegalovirus, herpesvirus) and toxoplasma and is often

associated with calcification that can be recognized radiographically. The obstruction of flow of the CSF leads to the dilatation of the lateral ventricles and atrophy of the brain. Because the cranial sutures are not fused during the first few months postnatally, the head expands, resulting in macrocephaly with bulging fontanelles.

Cerebral Palsy

Cerebral palsy is a clinical term applied to a heterogeneous group of congenital CNS disorders presumably related to intrauterine brain injury. It affects 2 per 1,000 newborns. The etiology of the disease remains unknown, but it most likely represents a multifactorial prenatal brain injury. Intrauterine anoxia, toxicity, nutritional deficiencies, and to a lesser extent, mechanical brain trauma have been implicated, albeit without any final conclusive evidence. The symptoms, usually a combination of movement abnormalities, spastic paralysis, speech impairment, and intellectual deficits may be apparent at birth, but more often the first symptoms appear later during infancy and early childhood. Clinical symptoms do not correlate well with pathologic changes in the brain, and the severity of brain lesions does not reflect the extent of functional impairment.

TRAUMA OF THE CENTRAL NERVOUS SYSTEM

Trauma of the CNS can occur in several forms and is often associated with fractures of the skull or vertebra and various forms of bleeding (Fig. 20-2).

Concussion is a traumatic lesion of the brain that presents with temporary loss of consciousness and reflexes and depression of vital functions (e.g., apnea), but it is not associated with anatomic changes in the brain. The functional changes are reversible even though most patients develop amnesia about the events that preceded or followed trauma.

Contusion or bruise is a more severe form of brain injury, typically associated with foci of brain necrosis and hemorrhage. Contusion is typically bipolar and includes the so-called coup lesion at the site of impact and the contrecoup lesion at the opposite site of skull. It may result in permanent neurologic impairment, depending on the site of injury.

Epidural hematoma results from skull fracture lacerating the middle meningeal artery and causing a relentlessly progressive accumulation of blood between the dura and the skull bone. Typically, it is located over the lateral convexity of the cerebral hemispheres. Unless the bleeding is stopped and the clotted blood evacuated, epidural hematoma is lethal.

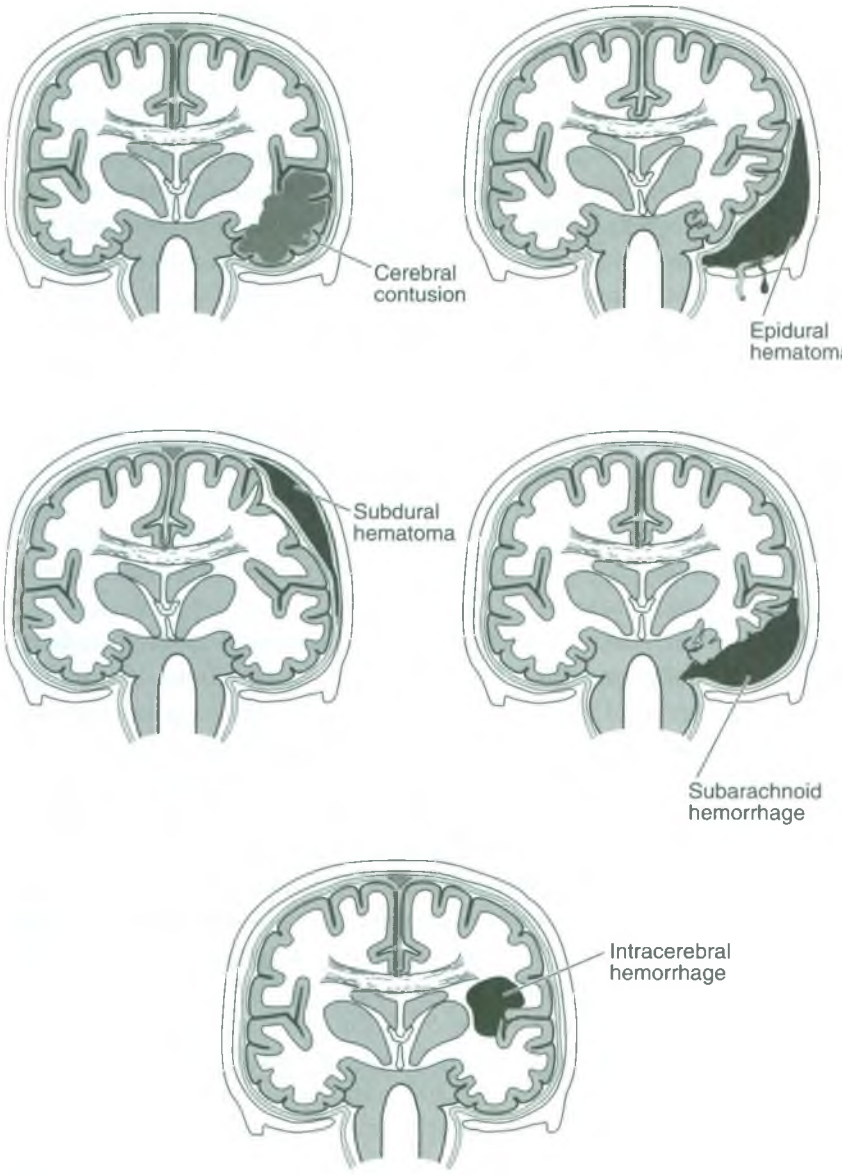


Figure 20-2.
Intracranial hemorrhages.

Subdural hematoma results from repeated bleedings from ruptured bridging veins crossing the subdural space between the cerebral hemispheres and the dural venous sinuses. Because the blood accumulates over time, which allows it to clot and become partially organized by the blood vessels growing into it from the arachnoid, it usually appears as a brown-red firm layer between the dura and the arachnoid. Subdural hematomas are typically found in boxers, alcoholics, and elderly persons prone to repeated falls or head injuries.

Intracerebral hematoma is typically found after bullet wounds or severe head trauma and is typically associated with marked brain destruction or laceration.

Spinal cord injury is typically caused by anterior or posterior displacement of the vertebral bodies, resulting in compression or transection of the spinal cord. If the impact hits the chin from below, an **overextension** injury of the anterior part of the spinal cord and **compression** of the posterior part result. Trauma to the occiput flexing the face downward causes the reverse (i.e., compression of the anterior part of cervical spine and overextension of the posterior part). These forms of trauma are often lethal, but if the patient survives, complete quadriplegia is the norm. Transection of the spinal cord in the thoracic or lumbar part results in paralysis of lower extremities and a loss of autonomic functions such as urination, defecation, and erection.

CIRCULATORY DISORDERS

Cerebrovascular diseases are caused by ischemia or hemorrhage, which are often combined. Pathogenetically, these events are related to congenital malformations of cerebral vasculature, atherosclerosis of cerebral vessels, and arterial hypertension.

Congenital malformations of cerebral vasculature may be asymptomatic, but often they can cause hemorrhages. The most common intraparenchymal lesion is the **arteriovenous malformation** composed of convoluted abnormal, usually dilated, and interconnected veins and arteries. Small saccular aneurysms, called **berry aneurysms,** are typically found along the arteries at the base of the brain. Most often they are located at the site of bifurcation or junction of the major arteries forming the circle of Willis. In approximately 20% of cases, these aneurysms are multiple. The rupture of a berry aneurysm results in subarachnoid hemorrhage, which is often lethal.

Cerebral Infarcts

Cerebral infarcts result from the occlusion of major cerebral arteries. The occlusion is most often caused by a **thrombus,** originating over a ruptured atheroma. The most common locations of thrombi are the carotid artery and its major branches and the basilar artery. Infarcts can also be caused by thromboemboli originating in the left side of the heart or major arteries of the aortic arch. Cerebral emboli arise as complications of myocardial infarcts, atrial fibrillation, and valvular heart disease, all of which are accompanied by thrombus formation in the left side of the heart. Thromboemboli carried by arterial circulation tend to lodge preferentially in the middle cerebral artery, but may also occlude any other cerebral vessel. Infarcts caused by either thrombi or emboli are initially pale and characterized by liquefactive necrosis of the affected brain region. Because of the dual blood supply of most regions of the brain, the embolic infarcts are

usually reperfused from collateral circulation and therefore tend to become hemorrhagic within the first 48 hours after infarct. Necrotic brain tissue elicits a glial reaction and an influx of macrophages, but no repair occurs. Ultimately the necrotic tissue is resorbed, and the infarct transforms into a cyst filled with fluid, which is clear or yellow (xanthochromic) if the infarct was hemorrhagic.

Hypotensive cerebral infarcts typical of hypotensive vascular episodes (e.g., myocardial infarct or shock) occur without complete occlusion of a major cerebral artery. Vascular collapse results in hypoperfusion of the brain, which affects mostly the border zone between the vascular supply regions of major arteries. This results in multiple watershed zone infarcts and laminar necrosis of deeper layers of the cerebral cortex. The most vulnerable area is the marginal zone between the supply region of the anterior and middle cerebral artery, Sommer sector of the hippocampus, and Purkinje cells of the cerebellum.

Acute cerebral ischemia results in a clinical picture known as stroke. **Stroke** is characterized by a complete or partial loss of consciousness and abnormal sensory and motor functions. Despite high mortality, most patients recover to some extent; many remain dysfunctional or bedridden for many years. Motor deficits are typical of the anatomic location of the infarct.

Ischemic encephalopathy results from widespread global ischemia of the brain due to atherosclerosis of the branches of the cerebral arteries. Atherosclerotic narrowing and occlusion of small blood vessels cause ischemic necrosis of neurons or multiple microinfarcts. These result in **transient ischemic attacks** and ultimately may severely impair the mental functions of the affected person **(microinfarct dementia).**

Hypertensive Cerebrovascular Disease

Hypertensive cerebrovascular disease may occur in an acute form, as cerebral hemorrhage, or in a chronic form. **Acute massive cerebral hemorrhage** is usually associated with high mortality. Most often these hypertensive hematomas are located in the basal ganglia–hypothalamic region (65%), pons (15%), or cerebellum (10%); they may occur in other parts of the brain or be multiple. Some patients die of **acute hypertensive encephalopathy,** characterized by a sudden onset of headache, vomiting, blurry vision, or convulsions and coma, and may not have any major hemorrhage. Instead, in such patients, the brain shows marked edema and minor hemorrhages from necrotic arterioles. Arterioles often show **lipohyalinosis** (i.e., accumulation of lipid in hyalinized vessel wall) and formation of **Charcot-Bouchard aneurysms,** which are prone to rupture and intraparenchymal hemorrhage.

Chronic hypertensive encephalopathy is characterized by multiple small cystic infarcts known as *lacunae.* A lacunar state is most prominent in the basal ganglia thalamus and internal capsule and pons. Clinically, it may be characterized by nonspecific neurologic symptoms.

Brain Edema

Brain edema is characterized by an accumulation of fluid in the brain parenchyma. Edema may result from circulatory disturbances, but also it may be provoked by trauma, inflammation, tumors, and metabolic and toxic injuries of the brain. Pathogenetically, there are two types of edema: (1) **vasogenic edema,** caused by increased vascular permeability and characterized by an increased amount of fluid in interstitial spaces of the white matter; and (2) **cytotoxic edema,** characterized by intracellular accumulation of fluid, predominantly affecting the gray matter. Vasogenic edema is more common and clinically more important because it can be treated more efficiently. Typically, it leads to widening of the white matter, narrowing of the sulci, widening of the gyri, and compression of ventricles, which appear narrow. The expanded brain causes herniations, which are typically found in three places: (1) subfalcine translocation of the gyrus cinguli of the cerebral hemisphere; (2) uncal herniation beneath the tentorium cerebelli; and (3) herniation of the cerebellar tonsils into the foramen magnum with compression of the medulla oblongata. Herniation of the cerebellar tonsils is the most common cause of death in patients suffering from brain edema, because it results in compression of the vital centers in the medulla oblongata.

INFECTIOUS DISEASES

Infections of the CNS may present in several forms, which include meningitis, encephalitis, brain abscess, or myelitis, all of which may occur in an isolated form or more often combined (e.g., meningoencephalomyelitis). The most important pathogens include **viruses** (e.g., HIV, herpesvirus, rabies virus, and various neurotropic arboviruses such as St. Louis encephalitis virus); **bacteria** (e.g., *Neisseria meningitidis, Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae*); **fungi** (e.g., *Cryptococcus, Aspergillus*); and **protozoa** (e.g., *Toxoplasma*).

The main routes of infection of the CNS are hematogenous from a distant site of infection in the body; local extension from infections of the ear, nose, and nasal sinuses; neurogenic along the axons, as commonly seen in herpesvirus infection and rabies; and by direct inoculation, as in trauma (Fig. 20-3).

Meningitis

Meningitis typically involves the arachnoid and is therefore also called *leptomeningitis*, in contrast to the less common pachymeningitis, which involves the dura. Most often, it is caused by viruses. **Viral**

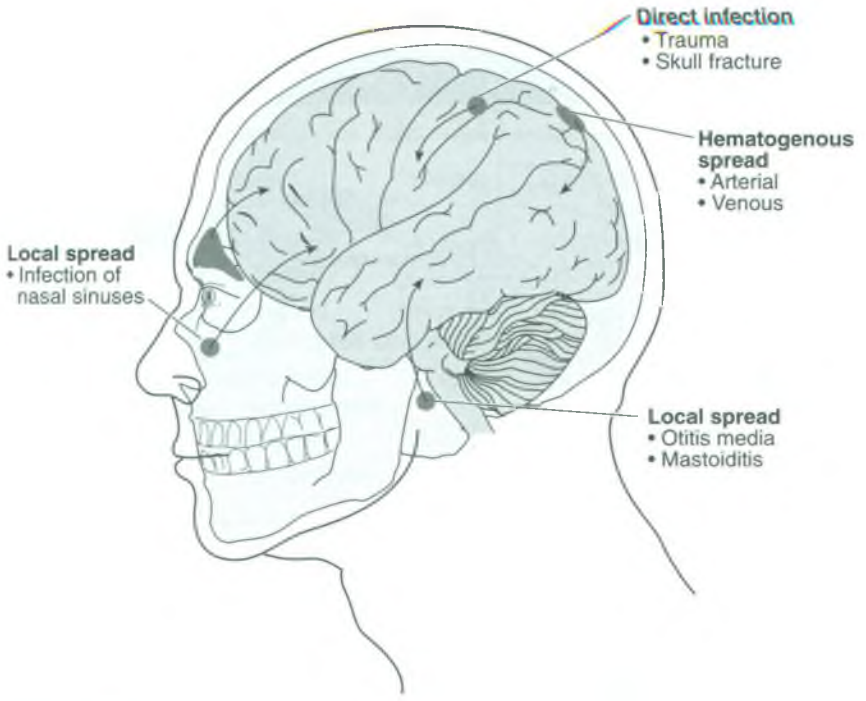


Figure 20-3.
Routes of infection of the brain.

meningitis that occurs typically during systemic viremia is usually mild and clinically suspected but rarely fully documented. Clinically, it is evidenced by somnolence or mild mental obtundation, rigidity of the neck, a positive Kernig sign (pain in the knee on flexing of the hip), and various nonspecific neurologic symptoms. Most patients recover spontaneously. **Bacterial meningitis** is a more serious disease. In newborns, it is most often caused by *E. coli*. In infants, *H. influenzae* predominates, whereas in adults, the disease is most often caused by *S. pneumoniae* and *N. meningitidis*. Bacterial infection leads to an exudation of neutrophils into the CSF. Signs of infection include fever, leukocytosis, and general malaise. There is severe headache, stiffness of the neck, and the Kernig and Brudzinski signs can be readily elicited. CSF is under increased pressure, and lumbar puncture typically yields purulent fluid, rich in protein and depleted of glucose. The causative bacteria can be seen in smears stained with Gram stain or cultured bacteriologically. Antibiotic treatment gives good results, but if the disease is not recognized or if it is associated with Waterhouse-Friderichsen syndrome (as occasionally seen in *N. meningitidis* infection), it may have high mortality.

Chronic meningitis was common at one time, but it is now rarely seen except in patients with AIDS. Previously, chronic meningitis was most often caused by *Mycobacterium tuberculosis*, which is still an important pathogen in underdeveloped countries. Tuberculous meningitis preferentially affects the meninges on the basal side of

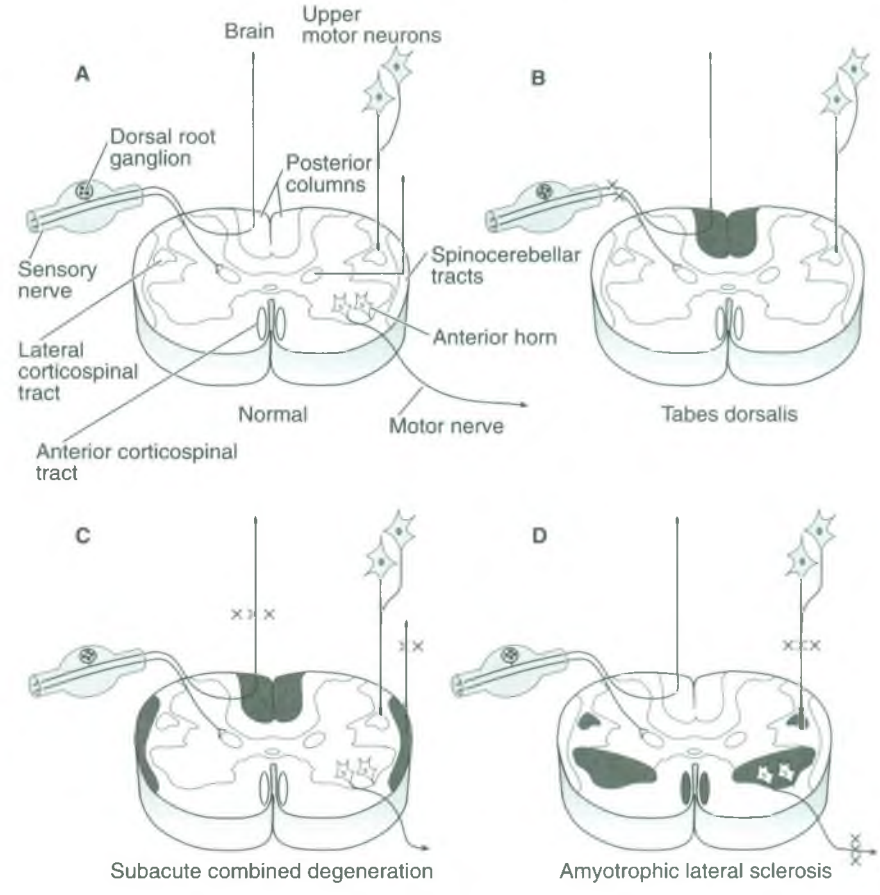


Figure 20-4.
Spinal cord injuries in various diseases. *A:* Normal spinal cord. *B:* Tabes dorsalis. *C:* Subacute combined degeneration (vitamin B_{12} deficiency). *D:* Amyotrophic lateral sclerosis.

the brain. On gross examination, meninges are cloudy, overlying the cisterns filled with gelatinous material. Histologically, the meninges contain an exudate composed of incompletely formed granulomas with giant cells and numerous lymphocytes extending into the sulci and encasing the cranial nerves. CSF shows lymphocytosis, increased concentration of protein, and low glucose.

Neurosyphilis

Neurosyphilis presents most often as **chronic meningitis** with prominent plasma cellular infiltrates around the meningeal blood vessels and obliterative endovasculitis **(meningovascular syphilis).** Construction of the posterior nerve roots of the spinal cord by the fibrotic granulation tissue and scars results in compression atrophy of the posterior columns of the spinal cord and a loss of sensory proprioceptive and pain-conducting tracts **(tabes dorsalis)** (Fig. 20-4). A

TABLE 20-1.
Cerebrospinal Fluid Changes in Various Forms of Meningitis

	Cells	Protein	Glucose	Appearance
Normal	0–4 lymphocytes/ml	40 mg/dl	50–70 mg/dl	Clear, colorless
Bacterial meningitis	Increased neutrophils	Increased	Decreased	Turbid yellow
Tuberculous meningitis	Increased lymphocytes	Increased	Decreased	Clear
Viral meningitis	Increased lymphocytes	Increased	Normal	Clear

loss of cortical neurons, partially due to meningeal vascular changes and in part due to spread of syphilis into the brain parenchyma, leads to **general paresis of the insane,** a form of syphilitic dementia accompanied by a variety of motor and sensory deficits.

The diagnosis of meningitis is best established by examining the CSF obtained by lumbar puncture. Typical findings in various forms of meningitis are given in Table 20-1.

Brain Abscess

Bacterial infection of the brain parenchyma **(cerebritis)** typically leads to localized suppuration and abscess formation. Such abscess presents as an expansile space-occupying lesion, showing central liquefactive necrosis and formation of a cavity that is enclosed by a glial capsule. The infection may spread into the surrounding brain tissue, resulting in satellite abscesses. The extension into the meningeal spaces may cause suppurative meningitis. Rupture of the abscess into the ventricles leads to the formation of **pyocephalus.**

Encephalitis

Encephalitis is a term reserved for nonbacterial infections of the brain, most of which are caused by **viruses** (Table 20-2). **HIV** is the most common pathogen today. Epidemics of viral encephalitis are caused by arthropod-borne neurotropic viruses such as Eastern or Western equine encephalitis or St. Louis encephalitis. These viruses show no predilection for specific anatomic parts of the brain and therefore produce a diffuse encephalitis. All of these viral infections cause lymphocytic exudates around the cerebral blood vessels (Virchow-Robin spaces).

TABLE 20-2.
Important Forms of Viral Encephalitis

Virus	Pathology	Features
Human immunodeficiency virus	Microglial nodules in white matter by other infections	Acquired immunodeficiency syndrome dementia complex; complicated
Herpesviruses		
Herpes simplex virus 1	Latent trigeminal ganglion infection leads to necrotizing encephalitis of temporal lobes	Intranuclear inclusions
Herpes zoster virus	Latent infection from dorsal root ganglia affects peripheral nerve	Skin eruption of vesicles in dermatomes
Cytomegalovirus	Focal encephalitis in immunosuppressed persons or intrauterine/neonatal infection	Intranuclear and cytoplasmic inclusions with cell enlargement
Rabies virus	CNS infection through peripheral nerves	Negri bodies diagnostic; lethal
Measles virus	Subacute sclerosing panencephalitis	Childhood disease
JC virus (papovavirus)	Progressive multifocal encephalitis	Immunosuppressed persons
Arbor virus	Diffuse encephalitis	Epidemic, arthropod-borne
Poliovirus	Spinal cord inflammation	Destruction of anterior horn neurons (paralysis)

CNS, central nervous system.

In contrast to the diffuse encephalitis caused by arthropod-borne virus, the infections caused by other viruses show predilection for certain parts of the brain. **Herpes simplex virus,** the most common pathogen in the United States, has a tendency to infect the temporal lobes. **Rabies virus** localizes preferentially in the brain stem, hippocampus, and cerebellum. **Poliomyelitis virus** affects preferentially the motor neuron cells of the anterior horn of the spinal cord and the bulbar motor nuclei. **Cytomegalovirus** (CMV) affects the periventricular white matter of fetuses and infants, but in adults it shows no predilection for any specific site. **Progressive multifocal leukoencephalopathy,** a disease caused by a papovavirus (JC) in immunocompromised hosts, affects the corticomedullary junction of the cerebral hemispheres.

Many of these viruses can be recognized on histologic examination of brain biopsies or autopsy material. Rabies produces typical cytoplasmic inclusions called **Negri bodies.** Herpesvirus infection and subacute sclerosing panencephalitis caused by measles virus are characterized by intranuclear inclusions, which may be surrounded by a halo. In progressive multifocal leukoencephalopathy, the intranuclear inclusions impart a ground-glass appearance to the

nuclei. CMV infection causes enlargement of the nuclei, which contain large basophilic inclusions surrounded by a halo. The CMV virus may be present in the cytoplasm as well. The important features of viral encephalitides are listed in Table 20-2. Protozoal encephalitis can be a feature of malaria or toxoplasmosis.

Acquired Immunodeficiency Syndrome–Related Encephalopathy

HIV may cross the blood-brain barrier and cause a variety of CNS disorders. HIV causes an **aseptic meningitis,** typically early in the course of the disease, which is followed by an **HIV encephalopathy** characterized by progressive loss of mental capacity. A deterioration of motor and autonomic functions is found in later stages of AIDS. **Vacuolar myelopathy** involving the posterior columns of the spinal cord, **peripheral neuropathy,** and **myopathy** are also features of AIDS. Immunosuppression caused by HIV infection predisposes the patients to various infections that are normally not seen in immunocompetent hosts. The most important are infections caused by **viruses** (herpes simplex virus, CMV, varicella zoster virus), **fungi** such as *Cryptococcus,* and **protozoa** such as *Toxoplasma.*

Spongiform Encephalopathies

Spongiform encephalopathies include several infectious diseases such as **Creutzfeldt-Jakob disease, kuru,** and **chronic spongiform encephalopathies** encountered in sheep, goats, and cows. All of these diseases are caused by minute infectious particles called **prions** (previously known as *slow viruses*) composed of protein and encoded by a host's gene. The pathologic hallmark of these diseases is formation of small vacuoles in the gray matter and the basal ganglia, imparting a sponge-like appearance **(spongiform degeneration)** to the brain. Clinically, spongiform encephalopathies present with progressive dementia, cerebellar symptoms such as ataxia, and corticospinal tract motor symptoms. These diseases are not curable.

DEMYELINATING DISEASES

Diseases characterized by a loss of myelin sheaths of cerebral axons belong to three pathogenetic groups: **inborn errors of metabolism** affecting myelin sheaths, demyelinating disorders such as **adrenoleukodystrophy,** and **Krabbe disease.** These genetic

diseases are characterized by defective synthesis of myelin, which tends to decompose spontaneously. In Krabbe disease, myelin degradation products accumulate in macrophages, which assume the appearance of so-called globoid cells.

In **inflammatory diseases** such as progressive multifocal leukoencephalopathy, the entry of papovavirus JC into oligodendroglia cells (i.e., glial cells that produce the myelin sheaths) impairs the metabolism of myelin; thus causing demyelination.

Autoimmune diseases are caused by presumably immunologic demyelination, as in multiple sclerosis (MS), acute disseminated encephalomyelitis, or acute hemorrhagic leukoencephalitis. MS is the most important of these diseases, with an incidence of 1 per 1,000 people. Acute disseminated encephalomyelitis is a rare complication of acute viral infections or antiviral immunization, characterized by multifocal perivenous demyelination and an acute onset of neurologic deficits or coma. Acute hemorrhagic leukoencephalitis has a more fulminant course and is characterized by widespread hemorrhagic necrosis of the white and gray matter. Both of these conditions are thought to represent a hypersensitivity reaction or an autoimmune response against myelin.

Multiple Sclerosis

MS is a chronic recurrent **progressive demyelinating disease** of unknown etiology. It affects the white matter of the brain, causing multifocal demyelination of cerebral axons. The demyelinated foci, most prominent around the ventricles in the optic nerve and the spinal cord, are called plaques. They can be seen by computed tomography and have been found to enlarge as the disease progresses. Histologically, the plaques consist initially of lymphocytes and macrophages, which destroy the myelin leaving denuded axons. The CSF contains increased amounts of immunoglobulin, which appear as oligoclonal bands. Demyelination is accompanied by a loss of motor function, vision problems, and, ultimately, sensory symptoms and a loss of coordinated neuromuscular action. The disease has an inexorable progressive course leading to complete incapacitation, usually over a period of 15 to 30 years. There is **no effective treatment.**

Subacute Combined Degeneration

Subacute combined degeneration represents a demyelination of the ascending posterior columns and descending lateral columns due to a lack of vitamin B_{12} (see Fig. 20-4). Like pernicious anemia, the main manifestation of vitamin B_{12} deficiency, it is usually associated with atrophic gastritis, which causes a deficiency of the intrinsic factor required for vitamin B_{12} absorption.

NEURODEGENERATIVE DISEASES

The term *neurodegenerative diseases* is used to denote a group of unrelated disorders of unknown etiology, which are characterized by degeneration of parts of the CNS, causing defined clinical symptoms. The most important among these diseases are Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and Huntington disease.

Alzheimer disease is a dementia (loss of mental function) that typically occurs in the elderly. The etiology of this disease is not known, albeit there are some familial cases, suggesting a genetic predisposition. Pathologically, it is characterized by atrophy of the brain evidenced as narrowing of the gyri and widening of the sulci and a hydrocephalus ex vacuo. Histologic hallmarks of Alzheimer disease include **neuritic (senile) plaques** composed of amyloid and filaments that can be impregnated with silver, neurofibrillary tangles in the cytoplasm of neurons, granulovacuolar degeneration of neurons, and deposition of amyloid in the small cerebral arteries. The first evidence of the disease is a loss of recent memory, but as the dementia evolves, all mental functions deteriorate and the patients become completely mentally incapacitated. Alzheimer disease is the leading cause of dementia among the elderly.

Parkinson disease is characterized by a **loss of pigmented neurons** in the substantia nigra and locus ceruleus. The remaining neurons often contain cytoplasmic Lewy bodies. Clinically, extrapyramidal symptoms dominate. Typically, the muscle movements are slow and lack fine coordination. There is rigidity, tremor at rest, and the face is expressionless (mask-like face). The patient is stooped and has a shuffling gait. Loss of mental functions and depression occur in advanced cases.

Amyotrophic lateral sclerosis, also known as *Lou Gehrig disease* after the baseball player who suffered from it, is characterized by a progressive **loss of motor neurons** from the anterior horn of the spinal cord, brain stem, and ultimately cerebral cortex. Loss of motor neurons is accompanied by demyelination of the lateral corticospinal tracts in the spinal cord and progressive atrophy of skeletal muscles (see Fig. 20-4). Loss of muscle fibers presents clinically with fasciculation, progressive weakness leading ultimately to immobility, slurred speech, and loss of coordination. Eye muscles are often affected. The mental capacity is preserved, however.

Huntington disease is an autosomal dominant hereditary disorder that presents in midlife with progressive dementia, movement disorders **(chorea and athetosis),** and emotional imbalance. The genetic defect is related to an expansion of CAG trinucleotide repeats on chromosome 4. Persons whose fathers were affected tend to develop symptoms earlier than those whose mothers were the carriers of the abnormal gene. Pathologically, the brain shows cortical atrophy and dilatation of the lateral ventricles, which appear as squares on cross sectioning (box-like) due to the loss of the lateral indentation of the caudate nuclei.

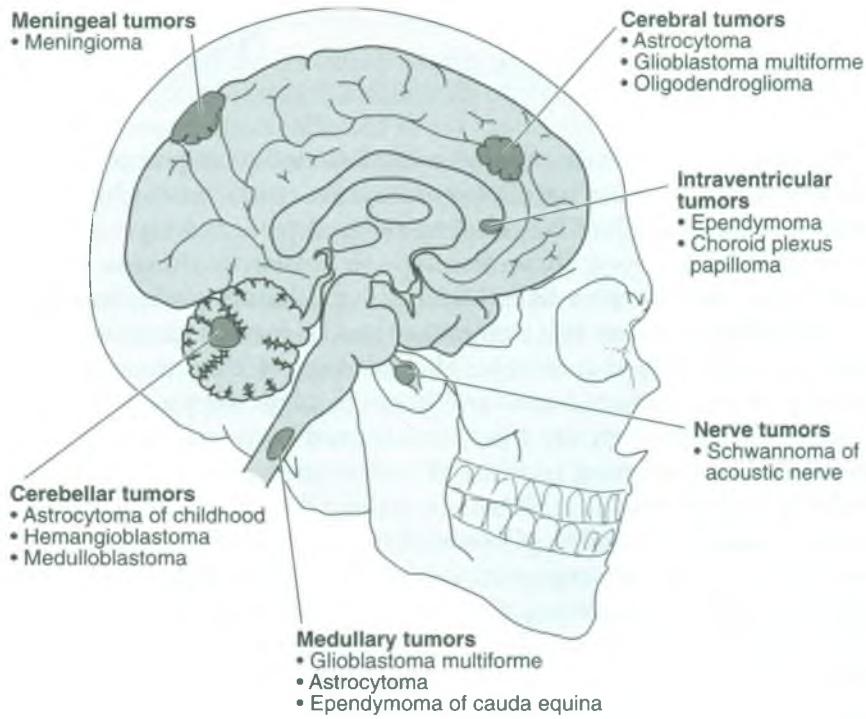


Figure 20-5.
Primary brain tumors.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

Tumors of the CNS are rare, representing only 2% of all human neoplasms. These tumors occur in all age groups. In children and young adults (i.e., age groups in which neoplasms are not common), CNS tumors account for 10% of cancer-related deaths, which is second only to leukemia. Most primary tumors of adults are supratentorial (i.e., in the cerebrum), whereas in children subtentorial tumors of the cerebellum predominate (Fig. 20-5). In older adults and the elderly, the primary tumors account for approximately one-third of all intracranial neoplasms, whereas all others are metastases. The most common primary malignancies metastasizing to the brain are carcinomas of the lungs, breast, gastrointestinal tract, and kidneys and melanomas.

The *primary tumors* of the CNS originate from glial cells, neuronal cell precursors, cranial nerves, and meninges. **Glial cell tumors** are the most common, accounting for approximately one-half of all primary tumors. The most important glial tumors are astrocytoma, glioblastoma multiforme, oligodendroglioma, and ependymoma. All glial tumors are malignant, albeit some, such as glioblastoma multiforme, are more malignant than others. **Neuronal tumors** develop mostly from neuronal precursor cells (neuroblasts) and typically are found in children. The most important tumors in this group are medulloblastoma and neuroblastoma. **Cranial nerve tumors,** schwan-

nomas, originate most often from the acoustic nerve in patients with neurofibromatosis. **Meningeal tumors** are called meningiomas.

Astrocytomas are low-grade malignant tumors. In children, they are most often cystic and located in the cerebellum, whereas in adults, they are usually in the cerebrum. **Glioblastoma multiforme,** the most common primary malignant CNS tumor, occurs most often in the cerebral hemispheres of adults, but may also involve other parts of the brain and spinal cord. It is a rapidly growing, highly malignant tumor named *multiforme,* because on gross examination, it has a variegated appearance imparted by broad areas of necrosis and hemorrhage. Histologically, it is also pleomorphic and composed of small, large, and even giant cells. **Oligodendrogliomas** are slow growing malignant tumors of the cerebral hemispheres of adults, composed of oligodendroglia cells, commonly speckled with foci of calcification. **Ependymomas** originate from the ependymal lining of the cerebral ventricles, central canal of the spinal cord, or the cauda equina. These rare tumors occur mostly in children and young adults and are characterized by slow but relentless growth. Choroid plexus adenomas or carcinomas are rare intraventricular tumors of children. **Medulloblastoma** are tumors of the cerebellum of children. These tumors are composed of primitive undifferentiated cells resembling primitive fetal cells in the neural tube. Despite responding well to radiation and chemotherapy, these tumors have a poor prognosis, mostly because of their close proximity to the vital centers. **Schwannomas** of cranial nerve VIII are slow-growing benign tumors, often bilateral, and usually associated with other stigmata of neurofibromatosis. These tumors are located in the cerebellopontine angle, compressing the cerebellum and the vital centers of the pons. They also cause deafness and vertigo due to the destruction of cranial nerve VIII.

Meningiomas are well-circumscribed benign tumors derived from the meninges. They are typically attached to the dura, compressing the brain from the outside. Histologically, meningiomas are composed of elongated meningothelial cells, usually forming interlacing whorls, with occasional calcifications **(psammoma bodies).** Most meningiomas are benign. These tumors can be surgically removed without any residual consequences. The medulla and spinal cord are less common important sites of origin of various gliomas and ependymomas, but still have a predilection for the cauda equina. Salient feature of the most important tumors of the CNS are listed in Table 20-3.

DISEASES OF PERIPHERAL NERVES

Trauma

Peripheral nerves are prone to traumatic injury, such as avulsion, transection, or compression. After transection of the nerve, the distal part of the axon undergoes **wallerian degeneration** and disinte-

TABLE 20-3.
Tumors of the Central Nervous System

Tumor	Cell of Origin/Histology	Incidence (%)	Most Common Location	Notes
Astrocytoma	Astrocyte well differentiated	20	Cerebrum (adults)	Good chance for 5-yr survival but always fatal; childhood tumors are cystic
Glioblastoma multiforme	Astrocyte multiple patterns	40	Cerebrum, but also other parts of the CNS	Most common primary tumor in adults; truly multiform (macro and micro)
Oligodendroglioma	Oligodendrocyte	3	Cerebrum	Slow growth, 10-yr survival; calcified, focally; best prognosis of all gliomas
Ependymoma	Ependymal cell; several patterns	3	Fourth ventricle; spinal canal; caudae quina	Poor prognosis because of inaccessibility
Medulloblastoma	Primitive neural cell precursors; masses of small blue cells	8	Cerebellum	Childhood tumor; accounts for 60% of childhood tumors of the CNS; poor prognosis (1–2 yrs), even though it responds to radiation and chemotherapy
Meningioma	Meningeal cell; whorls in several patterns	20	Meninges on the convexity of the brain	Benign, good prognosis, operable; malignant transformation rare; calcifications (psammoma bodies); may invade or erode bone of the skull
Schwannoma	Schwann cell; palisaded bundles	5	Acoustic nerve	Good prognosis; may be bilateral as part of neurofibromatosis type II; causes vertigo and loss of hearing

CNS, central nervous system.

grates. If the perikaryon of the nerve cell is intact, however, new axons sprout, extend to the periphery, and reinnervate the muscle.

Neuropathy

Injury of peripheral nerves may be caused by a variety of exogenous and endogenous insults (Table 20-4). **Toxic nerve injury** may be caused by industrial toxins, heavy metals (lead), or drugs. **Nutritional neuropathies** are often caused by a deficiency of vitamins such as thiamine **(beriberi neuropathy),** vitamin B_{12}, pyridoxine, or niacin. **Metabolic injury** is found in systemic diseases such as uremia, porphyria, or diabetes. **Diabetic neuropathy,** one of the most common forms of peripheral nerve injury, is only partially induced by metabolic disturbances of diabetes and to a large extent is secondary to diabetic

TABLE 20-4.
Common Causes of Peripheral Neuropathies

- Toxic
  - Alcohol
  - Cytotoxic drugs
  - Lead and heavy metals
- Nutritional: vitamin deficiencies (vitamins B_1, B_{12}, E)
- Metabolic
  - Diabetes
  - Uremia
  - Porphyria
- Infections
  - Herpes
  - Leprosy
  - Lyme disease
- Autoimmune: Guillain-Barré syndrome, polyarteritis, sarcoidosis
- Paraneoplastic

microangiopathy, which impedes the blood supply to nerves, thus causing axonal atrophy and degeneration. **Viral infections,** such as herpes zoster (**shingles**) and **AIDS,** and **bacterial infections,** such as leprosy, also affect peripheral nerves. The peripheral nerves can also be affected by demyelinating diseases, the most important of which is the **Guillain-Barré syndrome.** In this syndrome, which develops usually after a viral disease or following immunization, the nerves are infiltrated with lymphocytes, causing focal demyelination. Although the disease may present with extensive motor defects and even extensive paralysis, most patients recover completely within a few weeks. Peripheral sensorimotor neuropathy characterized by axonal degeneration and occasional focal demyelination is found in some patients with cancer as a form of **paraneoplastic neuropathy.**

Several **hereditary diseases** that cause peripheral neuropathies have been identified. The most important among these is the **hereditary motor and sensory neuropathy,** which occurs in several forms. Hereditary motor and sensory neuropathy type I, also known as **Charcot-Marie-Tooth disease,** is inherited as an autosomal dominant trait, causing extensive demyelination of nerves with subsequent concentric Schwann cell proliferation ("onion bulb formation").

Tumors of the Peripheral Nerves

Tumors of the peripheral nerves are usually benign and are histologically classified as neurofibromas or schwannomas. Malignant peripheral nerve tumors, **neurofibrosarcomas,** are rare and are most often encountered in patients with pre-existing neurofibromatosis type I.

Chapter 21

Sensory Organs

EYE

Developmental Disorders

The disorders of organogenesis of the eye are rare. These include **cyclopia** (one eye), **anophthalmia** (no eyes), **microphthalmia** (small eye), **cataracts,** and **coloboma** (persistence of the choroid fissure). **Congenital glaucoma** occurs due to dysgenesis of the venous system around the iris, incomplete regression of the hyaloid artery, and persistence of the pupillary membrane.

Much more common are developmental and genetic disorders that affect vision but show no obvious organic defects. Nearsightedness **(myopia)** and farsightedness **(hypermetropia)** result from structural and functional changes in the development of the eye, many of which are hereditary. Red-green color blindness is inherited as an X-linked trait, and thus affects only males.

Traumatic Lesions

Eyes can be injured by physical objects, heat, irradiation, and exposure to chemicals. Penetrating or perforating injuries, particularly those complicated by infection, may result in loss of the eye and, if bilateral, may cause blindness.

Vascular Disorders

Vascular diseases are major causes of vision impairment in middle-aged and elderly individuals. **Retinal ischemia** is caused by vascular stenosis or occlusion associated with atherosclerosis, vasculitis, thrombosis, or emboli. The inner two-thirds of the retina becomes ischemic when the central retinal artery is involved and the outer retinal layers when there is involvement of the posterior ciliary artery. Occlusion of retinal vessels causes extravasation of plasma from capillaries (exudation). These exudates appear as yellow streaks when viewed with the ophthalmoscope. Lesions due to

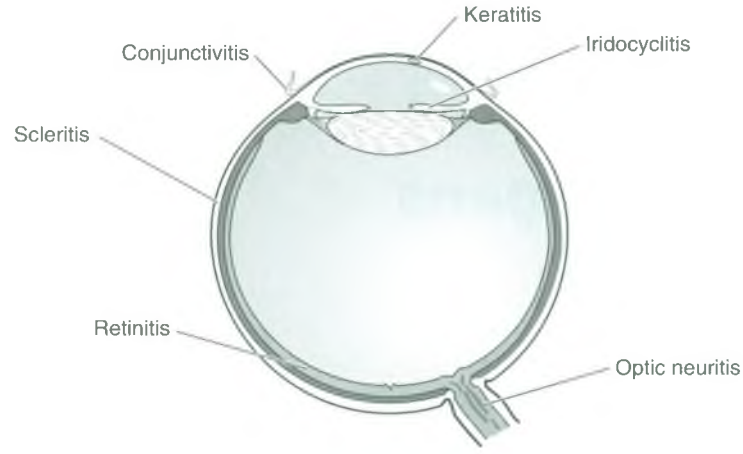


Figure 21-1.
Infections of the eye and its adnexa.

microinfarcts of the retinal ganglia and nerve fibers are known as **cotton-wool spots.**

Diabetic retinopathy includes a spectrum of changes such as dilatation and increased tortuousity of veins, microaneurysms and dilatation of capillaries, exudates, neovascularization, hemorrhages, and cotton-wool spots.

Hypertension produces cotton-wool spots, flame-shaped hemorrhages, variations in the caliber of arterioles due to thick walls, and decreased arteriolar tortuousity.

Neovascularization is a response to retinal ischemia, hemorrhage, or macular degeneration. It is characterized by the proliferation of small vessels around the edge of the lesions or in the vitreous. Newly found vessels in the vitreous often rupture, causing hemorrhage. Macular lesions often cause a loss of central vision.

Inflammatory Diseases

Inflammatory diseases of the eye can be infectious or noninfectious. Any part of the eye can be affected, but the external layers of the eye are the most susceptible. Hence, **conjunctivitis** is the most common inflammatory eye disease (pink eye). Choroiditis, iridocyclitis, or generalized eye infection known as **uveitis** are less common, but pose a greater danger and may result in loss of vision (Fig. 21-1).

Infectious diseases can be bacterial, viral, chlamydial, protozoal, or parasitic. They stem from hematogenous spread, from adjacent tissues, or from the eye surface.

Bacterial infections usually present as conjunctivitis, but they may spread internally to the lens and vitreous. *Staphylococcus aureus* is a common cause of purulent infection. Acute purulent conjunctivitis in children is often caused by *Haemophilus influenzae.*

Viral infections generally cause conjunctival or corneal lesions. Viral **conjunctivitis** is most often caused by adenoviruses. **Herpes simplex virus 1** may cause epithelial keratitis or stromal keratitis and is the major infectious cause of corneal blindness in the United States. **Stromal keratitis** is immune mediated and responds to corticosteroid therapy. Conjunctivitis and keratitis can also be caused by varicella zoster virus.

Chlamydia trachomatis can produce two types of lesions. **Trachoma,** a form of chronic keratoconjunctivitis, is common in Asia and Africa and is a leading cause of blindness worldwide. **Inclusion conjunctivitis,** a disease of infants born to infected mothers, is characterized by edema, hyperemia, and a mononuclear cell infiltrate.

Toxoplasma gondii is the most important protozoal pathogen affecting the eyes. The infection may occur during intrauterine life and present as chorioretinitis, microphthalmos, and blindness.

Parasitic diseases of the eye are rare except in the tropics. *Toxocara canis* infection is acquired in childhood from ova-containing dog feces. Ingestion of the ova results in a systemic disease **(visceral larvae migrans)** that may also affect the eyes. Granulomas that result in response to dead larvae cause blindness. *Onchocerca volvulus* infection, the cause of river blindness in Africa, presents with sclerosing keratitis, iridocyclitis, and retinitis.

Noninfectious Inflammatory Diseases

Noninfectious inflammatory diseases include sarcoidosis and a variety of autoimmune diseases. **Sarcoidosis** affects the eye in approximately 20% of cases. Most often it presents as an inflammation of the lacrimal gland. Iritis or iridocyclitis is less common, but may be unilateral or bilateral and may lead to glaucoma, corneal opacities, or both. The disease is characterized by the formation of **noncaseating granulomas.**

Among the autoimmune diseases, **Graves disease** most often affects the eyes. It causes **exophthalmus** characterized by lymphocytic infiltrates in the extraocular eye muscles and retro-orbital fat. Inflammation is accompanied by edema, deposition of mucopolysaccharides, and fibrosis, which may impair eye movement and cause diplopia and ophthalmoplegia.

Degenerative Lesions

Cataracts are opacifications of the lens due to changes in the lens proteins. Normally, these proteins are transparent; however, under certain conditions, opacities form. Due to structural changes in its components, the lens loses elasticity and can become more compact, resulting in severe vision loss. Lens dislocation and glaucoma secondary to mechanical obstruction of the anterior chamber are less common. Cataracts are commonly seen in the elderly. In the young, they result from congenitally acquired rubella infection. In

addition to rubella, cataracts are also associated with Down syndrome, senile degeneration, tears in lens capsule, irradiation, uveitis, diabetes mellitus, and corticosteroid therapy.

Glaucoma is a condition in which the pressure of intraocular fluid is elevated above normal (15 to 20 mm Hg). Intraocular hypertension may reduce the blood supply to the retina and cause blindness. The intraocular pressure depends on the rate of fluid production and the resistance to its outflow. Consequently, anything causing obstruction anywhere in the outflow track can lead to glaucoma. Clinically, glaucoma is manifested by central visual defects due to retinal ischemia, bullous keratopathy due to corneal edema, scleral bulges **(staphylomas)** due to scleral stretching, and in infants, enlargement and distention of the fibrous coats of the eye **(buphthalmos).** There are two major types of glaucoma, both of which can occur in a primary and a secondary form.

Closed-angle glaucoma is caused by an obstruction of the iridocorneal angle, impeding the flow of aqueous humor from the anterior chamber. In the primary form, it occurs in middle-aged or elderly patients who have a shallow anterior chamber and narrow anterior chamber angle. In the secondary form, it occurs after inflammation or hemorrhage around the iridocorneal angle. Acute attacks are characterized by pain precipitated by dilatation of the pupil, as is usually done for an eye examination. Blindness may develop unless emergency treatment is given.

Open-angle glaucoma occurs in the elderly when there is progressive fibrosis within the trabeculae and extracellular space of the outflow system. There is a slow increase in intraocular pressure, which manifests itself as a central visual field defect due to pressure-induced ischemia. Optic disk degeneration seen as optic disk cupping on eye examination leads to the widening of the blind spot (scotoma). Blindness develops slowly, but can be prevented by pilocarpine or laser surgery (trabeculoplasty). Primary open-angle glaucoma accounts for 90% of all cases of glaucoma. In the secondary form, which is less common, it may be caused by inflammation, hemorrhage, or neoplasms.

Neoplasms

Melanoma is the most common primary malignant tumor of the eye in adults. Melanomas of the eye arise from melanocytes of the uvea. There are two histologic types. In the **spindle cell** type, the cells have elongated nuclei and variable amounts of cytoplasmic melanin. In the **epithelioid cell** type, the noncohesive cells have abundant, sometimes pigmented cytoplasm. Tumors of the spindle cell are slow growing and less prone to metastasize than those of the epithelioid cells. Melanomas metastasize through blood vessels. Removal of the tumor-bearing eye **(enucleation)** is the treatment of choice. Long-term survival (≥15 years) can be expected in 50% of treated patients, although some develop late metastases.

Retinoblastoma is the most common malignant eye tumor of children and adolescents up to the age of 15 years. Most tumors are diagnosed in the first years of life. They can be sporadic or familial. Histologically, they are composed of small cells with round hyperchromatic nuclei and little cytoplasm. In more differentiated tumors, the cells are arranged in rosettes (Flexner-Wintersteiner rosettes). Clinically, tumors impair vision and cause strabismus, pain, and tenderness. They are fatal without treatment, but with treatment, most tumors can be cured. Patients with the familial form of this tumor are at risk of developing other tumors in later life, most often osteogenic sarcomas.

Metastatic carcinomas are most often derived from breast carcinomas in women and bronchial carcinomas in men.

EAR

Traumatic Lesions and Foreign Bodies

Trauma of the external ear results typically from fights, bites, or cuts. In boxers who suffer repeated injuries, the external ear may be lacerated and scarred (cauliflower ear). Mechanical or barotrauma may lacerate the eardrum **(rupture of tympanic membrane)** and cause deafness. Trauma of the vestibular organ may result in vertigo and loss of balance.

Impacted cerumen, the wax-like secretion that is normally found in the external auditory canal, may cause temporary hearing loss, a feeling of fullness of the ear canal, and even tinnitus. It results from desiccation of the normal secretions or excessive desquamation of scaly epidermis, which becomes admixed with the normal secretions, making them firmer and stickier. Impacted cerumen must be softened with ear drops so that it can be easily removed by rinsing the ear. Occasionally, it needs to be removed instrumentally under otoscopic guidance.

Infections

Infections of the ear are common. **Otitis externa,** infection of the external ear canal, is commonly known as *swimmer's ear* and is the most common type of infection in adults. It is usually caused by bacteria invading the skin of the ear, moist from humid air or by prolonged swimming.

Otitis media is the most common type of infection in children. It occurs in two forms, classified as either serous or suppurative. **Serous otitis media** is characterized by an accumulation of clear fluid in the middle ear, causing the bulging of the tympanic membrane ("glue

ear"). In **suppurative otitis media,** the middle ear is filled with pus. In both instances, the disease is a consequence of the spread of an upper respiratory infection to the middle ear and engorgement of the eustachian tubes that fail to drain the exudate. The most common causes of suppurative otitis media are the bacteria *Streptococcus pneumoniae* and *H. influenzae.* Serous otitis media is caused by viruses, but also it may be a sign of residual fluid that has not cleared after a suppurative otitis media has been cured by antibiotics. Otitis media may cause rupture of the tympanic membrane, which results in deafness.

Repeated bacterial infections may cause extensive damage to the ear. **Chronic otitis media** typically presents with defects in the eardrum and often with a purulent discharge from the ear. The infection may spread to the mastoid bone **(mastoiditis)** and even into the cranium, causing cerebral abscesses or meningitis. Some chronically inflamed ears contain copious granulation tissue that forms inflammatory polyps. Some of the granulation tissue contains large amounts of cholesterol crystals (cholesterol granulomas). These should be distinguished from **cholesteatoma** cyst–like structures filled with keratin. The cause of cholesteatoma is not known, but most often it is associated with defects in the tympanic membrane. Cholesteatomas are located in the middle ear or the mastoid and act as benign tumors, compressing the adjacent normal structures.

Labyrinthitis is an infection of the semicircular canals of the inner ear. It may be caused by viral infection, but in many cases the cause remains unknown. It presents with vertigo and loss of balance, often accompanied by nausea and vomiting.

Degenerative Diseases and Diseases of Unknown Origin

Otosclerosis is an autosomal dominant disease characterized by formation of new bone between the stapes and the oval window. It is the most common cause of conductive deafness in young adults, but its incidence increases with age. It is an important cause of hearing loss because it affects, to some minor degree, 10% of all white and 1% of all black Americans. The disease is twice as common in women than in men.

Ménière disease is a labyrinthine disease characterized by an accumulation of fluid in the endolymphatic cochlea of the inner ear. The cause of the accumulation of fluid is not known. Typically, it presents with a triad that includes vertigo, tinnitus (ringing in the ears), and deafness. In approximately 50% of patients, the disease is bilateral. The symptoms seem to improve on administration of diuretics and a low-salt diet.

PATHOLOGY QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A patient with sepsis of 3 days' duration dies in respiratory failure. At autopsy, the lungs are wet, heavy, and congested. Histologically, there is pulmonary edema, and hyaline membranes line the alveoli. The most likely diagnosis of this patient is

   (A) acute fulminant lobar pneumonia
   (B) acute fulminant viral pneumonia
   (C) adult respiratory distress syndrome
   (D) desquamative interstitial pneumonia
   (E) Hamman-Rich syndrome

2. Exophthalmus is often associated with

   (A) diabetes mellitus
   (B) Down syndrome
   (C) hyperthyroidism
   (D) irradiation
   (E) seborrheic keratosis

3. Which is the correct sequence of vascular events accounting for the triple response that occurs in acute injury?

   (A) Arteriolar vasodilatation followed by slowing of the circulation, stasis of blood flow, and vasoconstriction
   (B) Arteriolar vasodilatation followed by slowing of the circulation, vasoconstriction, and stasis of blood flow
   (C) Arteriolar vasodilatation followed by vasoconstriction, slowing of the circulation, and stasis of blood flow
   (D) Arteriolar vasoconstriction followed by vasodilatation, slowing of the circulation, and stasis of blood flow and edema

4. Which of the following statements about labyrinthitis is true?

   (A) In children, it is most often caused by *Haemophilus influenzae*
   (B) In adults, it is most often caused by *Staphylococcus aureus*
   (C) It is more common in men than in women
   (D) It is the most common type of ear lesion in children
   (E) It presents with vertigo and a loss of balance

5. Intestinal carcinoma originates most often in the

   (A) ascending colon
   (B) cecum
   (C) ileum
   (D) jejunum
   (E) rectosigmoid

6. In most cases of childhood osteomyelitis, the infection results from

   (A) direct extension of a joint infection
   (B) direct implantation of microbes
   (C) hematogenous spread of bacteria from a distant site
   (D) lymphatic spread of infection
   (E) spread from muscle

7. The clinical triad of vertigo, tinnitus, and deafness is typical of

   (A) cholesteatoma
   (B) impacted cerumen
   (C) Ménière disease
   (D) otitis externa
   (E) otitis media

8. Hypercalcemia found in association with lung cancer is induced by

   (A) adrenocorticotropin hormone
   (B) osteocalcin
   (C) osteopontin
   (D) parathormone-like peptide
   (E) vitamin D

9. A 45-year-old man presents with chest pains of 6 hours' duration. Elevations of which of the following enzymes would be the most specific evidence that this patient had experienced a myocardial infarction?

(A) Acid phosphatase
(B) Alkaline phosphatase
(C) Aspartate aminotransferase
(D) Creatine kinase
(E) Lactic dehydrogenase

10. In men, the most common cause of cancer of the internal organs is carcinoma of the

(A) colon
(B) lung
(C) pancreas
(D) prostate
(E) stomach

11. Which of the following is the most common primary intraocular tumor of adults?

(A) Basal cell carcinoma
(B) Leiomyoma
(C) Melanoma
(D) Retinoblastoma
(E) Squamous cell carcinoma

12. Human chorionic gonadotropin is a good tumor marker for

(A) lung cancer
(B) nonseminomatous germ cell tumors
(C) ovarian cystadenocarcinoma
(D) pancreatic islet cell carcinoma
(E) prostatic adenocarcinoma

13. Pelvic inflammatory disease is most often caused by

(A) *Gardnerella vaginalis*
(B) herpes simplex virus type 2
(C) mixed bacterial flora
(D) *Neisseria gonorrhoeae*
(E) *Treponema pallidum*

14. Cotton-wool spots identified on ophthalmoscopic examinations are a complication of

(A) herpes simplex virus infection
(B) hypertension
(C) sarcoidosis
(D) *Staphylococcus aureus* infection
(E) trachoma

15. Estrogen has an important pathogenetic role in the development of carcinoma of the

(A) cervix
(B) endometrium
(C) ovary
(D) vagina
(E) vulva

16. A 60-year-old man has a history of mild, slowly progressive dyspnea. He is thin, barrel-chested, and has experienced marked weight loss over the past year. There are no abnormal sounds on auscultation. The most likely diagnosis of this patient is

(A) asthma
(B) bronchiectasis
(C) chronic bronchitis
(D) emphysema
(E) pneumothorax

17. Which of the following ovarian tumors is most often accompanied by ascites?

(A) Brenner tumor
(B) Granulosa cell tumor
(C) Mucinous cystadenoma
(D) Serous cystadenocarcinoma
(E) Sertoli-Leydig cell tumor

18. At the autopsy of a 30-year-old man who died of intracerebral hemorrhage, the heart valves are covered with fibrinous vegetations. The myocardium contain foci of fibrinoid necrosis surrounded by macrophages. These histologic lesions in the myocardium of this patient represent

(A) Aschoff bodies
(B) caseating granulomas
(C) emboli from endocardial lesions
(D) sarcoidosis
(E) Wegener granulomatosis

19. What is the most common site of ectopic pregnancy?

(A) Cervix
(B) Fallopian tubes
(C) Ovary
(D) Peritoneum of the pelvis
(E) Vagina

20. Which of the following infectious agents is the most important cause of corneal blindness in the United States?

(A) *Chlamydia trachomatis*
(B) Herpes simplex virus type 1
(C) *Onchocerca volvulus*
(D) *Staphylococcus aureus*
(E) *Toxoplasma gondii*

21. On gross examination, breast carcinomas are most often

(A) firm and gritty on sectioning
(B) hemorrhagic
(C) necrotic
(D) soft and bulky
(E) yellow and greasy

22. Obstructive atelectasis is usually seen in association with

(A) ascites
(B) asthma
(C) neonatal respiratory distress syndrome
(D) pleuritis
(E) pneumothorax

23. Which of the following is the simplest technique for a definitive diagnosis of pulmonary embolism?

(A) Chest radiography
(B) Measurement of lactic dehydrogenase in blood
(C) Measurement of respiratory capacity
(D) Pulmonary angiography
(E) Ventilation-perfusion scans

24. A lung biopsy from an elderly patient with dyspnea reveals diffuse interstitial fibrosis involving respiratory bronchioles, alveolar ducts, and alveolar sacs. Golden brown fusiform, beaded rods are seen within the fibrotic lung parenchyma. Some of the rods stain positively for iron. The most likely diagnosis of this patient is

(A) anthracosis
(B) asbestosis
(C) hypersensitivity pneumonitis
(D) sarcoidosis
(E) silicosis

25. A lung biopsy specimen discloses proteinaceous fluid in the alveoli. Round and oval pathogens are seen in silver-impregnated slides. There are no hyphae. What is the most likely cause of this patient's lung disease?

(A) *Aspergillus fumigatus*
(B) *Mycoplasma pneumoniae*
(C) *Mycobacterium tuberculosis*
(D) *Pneumocystis carinii*
(E) *Streptococcus pneumoniae*

26. Which of the following pathologic changes is typical of glaucoma?

(A) Blepharitis
(B) Flame hemorrhages
(C) Increased intraocular pressure
(D) Intraocular exudation
(E) Microaneurysms

27. The most common lung cancer in nonsmokers is

(A) adenocarcinoma
(B) bronchoalveolar carcinoma
(C) large cell carcinoma
(D) small cell carcinoma
(E) squamous cell carcinoma

28. Which of the following characterizes all forms of osteogenesis imperfecta?

(A) Failure of mineralization
(B) Hemarthrosis
(C) Malignant transformation
(D) Mutation of gene encoding collagen type I
(E) Osteomyelitis

29. The most common inherited form of dwarfism is

(A) achondroplasia
(B) cretinism
(C) osteogenesis imperfecta
(D) rickets
(E) scurvy

30. Which of the following is a histologic feature of osteoporosis?

(A) Disorganized trabeculae with cartilage cores
(B) Excessive unmineralized osteoid
(C) Marrow spaces filled with fibrovascular tissue
(D) Necrosis of osteocytes
(E) Thin trabeculae and widened haversian canals

31. The best example of healing by first intention is

(A) infected wound
(B) proud flesh
(C) ruptured abscess
(D) surgical excision
(E) uncomplicated surgical incision

32. Which of the following causes rickets?

(A) Epstein-Barr virus
(B) Hypocalcemia
(C) Myxovirus
(D) Vitamin C deficiency
(E) Vitamin D deficiency

33. An 18-year-old man complains of a painful enlarging mass in the metaphysis of the distal femur. Radiographically, the lesion is lytic and destructive and appears to lift the periosteum away from the bone. Chest radiography reveals multiple well-circumscribed densities in the lung parenchyma. This lesion is most likely a

(A) chondroblastoma
(B) chondrosarcoma
(C) Ewing sarcoma
(D) osteoblastoma
(E) osteosarcoma

34. An 18-year-old man complains of dyspnea and states that for the past 24 hours he has had a productive cough, rust-colored sputum, and a temperature of 38.3°C (101°F). At this stage of the disease, lung alveoli most likely contain

(A) fibrous scar tissue
(B) granulation tissue
(C) macrophages
(D) neutrophils
(E) plasma cells

35. Complement and IgG facilitate the phagocytosis of bacteria by acting as

(A) anaphylatoxins
(B) chemotactic factors
(C) mediators of vascular permeability
(D) opsonins
(E) oxygen-derived free radicals

36. Joint tissue biopsy is taken from a 50-year-old woman with a lengthy history of arthritis. The tissue consists of hyperplastic synovium covering the articular cartilage. The synovium is highly vascularized, edematous, and studded with lymphoid follicles and plasma cells. The most likely diagnosis of this patient is

(A) gouty arthritis
(B) Lyme disease
(C) osteoarthritis
(D) rheumatoid arthritis
(E) tuberculous arthritis

37. A biopsy of an infected wound reveals fibrosis, macrophages, lymphocytes, and granulation tissue. This type of inflammation is classified as

(A) acute
(B) allergic
(C) chronic
(D) granulomatous
(E) gummatous

38. Which of the following exudates results from an infection caused by pyogenic bacteria?

(A) Catarrhal
(B) Fibrinous
(C) Hemorrhagic
(D) Purulent
(E) Serous

39. The most common cause of delayed wound healing is

(A) administration of glucocorticoids
(B) inadequate angiogenesis
(C) infection
(D) ischemia
(E) vitamin C deficiency

40. A 9-month-old infant presents with recurrent bacterial conjunctivitis, pharyngitis, and bronchitis. There are no detectable immunoglobulins in the serum and virtually no B-lymphocytes in the blood. Lymph nodes contain no germinal centers. The thymus is normal. In this patient, these features are diagnostic of

(A) common variable immunodeficiency
(B) DiGeorge syndrome
(C) isolated IgA deficiency
(D) severe combined immunodeficiency diseases
(E) X-linked agammaglobulinemia of Bruton

41. Which of the following opportunistic infectious agents is the most common cause of lethal pneumonia in patients with AIDS?

(A) *Klebsiella pneumoniae*
(B) *Pneumocystis carinii*
(C) *Pseudomonas aeruginosa*
(D) *Staphylococcus aureus*
(E) *Streptococcus pyogenes*

42. Localized amyloidosis beta (Aβ) protein deposits are typically found in

(A) Alzheimer disease
(B) atherosclerosis of the aorta
(C) medullary carcinoma of the thyroid
(D) multiple myeloma
(E) small cell carcinomas of the lung

43. Barrett esophagus is characterized by foci lined by

(A) ciliated epithelium
(B) columnar epithelium
(C) small neuroendocrine cells
(D) squamous epithelium
(E) transitional epithelium

44. Jaundice characterized by elevation of serum levels of unconjugated bilirubin in blood is most likely caused by

(A) gallstones
(B) hemolysis
(C) pancreatic carcinoma
(D) toxic liver cell injury
(E) viral hepatitis

45. The uterus of a woman who is 20 weeks pregnant is enlarged to the size of a pregnancy in the twenty-eighth week. The human chorionic gonadotropin is elevated above the normal limits for this stage of pregnancy. No fetal sounds are heard. The ultrasound discloses an abnormal placenta. What is the most likely diagnosis of this patient?

(A) Abruptio placentae
(B) Choriocarcinoma
(C) Eclampsia
(D) Hydatidiform mole
(E) Placenta accreta

46. Acromegaly is most commonly produced by

(A) an adenoma
(B) a carcinoma
(C) hyperfunction of the hypothalamus
(D) hyperplasia of the anterior pituitary
(E) hyperplasia of the posterior pituitary

47. A 15-year-old girl presents with excessive thirst, polydipsia, polyuria (3 liters/day), and hypotonic urine. There is no evidence of glycosuria or proteinuria. The most likely cause of these findings is

(A) adenoma in the anterior pituitary
(B) craniopharyngioma
(C) diabetes mellitus
(D) glomerulonephritis
(E) postpartum pituitary necrosis

48. A 35-year-old white woman presents with nervousness, heat intolerance, and weight loss despite having a good appetite. Physical examination reveals diffuse enlargement of the thyroid, exophthalmus, and swelling of skin over the proximal tibia. A previous chest radiograph revealed cardiomegaly. Which of the following disorders is the most likely cause of these symptoms and findings?

(A) Graves disease
(B) Hashimoto disease
(C) Medullary carcinoma of the thyroid
(D) Myxedema
(E) Toxic thyroid adenoma

49. A 30-year-old woman presents with multiple nodules on the left side of the neck. Biopsy reveals that a thyroid neoplasm has metastasized to the lymph nodes. This tumor is most likely

(A) anaplastic carcinoma
(B) follicular carcinoma
(C) medullary carcinoma
(D) papillary carcinoma

50. Primary hyperparathyroidism is characterized by

(A) hypercalcemia
(B) hyperphosphatemia
(C) hypocalcemia
(D) hypocalciuria
(E) hypophosphaturia

51. Cushing syndrome is most commonly caused by

(A) an adrenal cortical carcinoma
(B) an adrenal gland adenoma
(C) an ectopic adrenocorticotropin hormone secretion
(D) exogenous corticosteroids
(E) a pituitary gland adenoma

52. A 50-year-old man presents with depression, a moon face, central obesity, and a history of hypertension and osteoporosis. Based on this history and physical findings, which of the following laboratory findings would you expect?

(A) Decreased plasma aldosterone
(B) Decreased plasma testosterone
(C) Elevated plasma cortisol
(D) Elevated plasma estrogen
(E) Elevated urine vanillylmandelic acid

53. In the United States, the most common cause of Addison disease is

(A) autoimmune adrenalitis
(B) disseminated intravascular coagulation
(C) histoplasmosis
(D) tuberculosis
(E) Waterhouse-Friderichsen syndrome

54. Which of the following mediators of inflammation is derived from mast cell granules?

(A) Bradykinin
(B) Complement
(C) Endotoxin
(D) Histamine
(E) Interleukin-1

55. Which of the following is found in or around the gumma of syphilis but not in granulomas of tuberculosis?

(A) Eosinophils
(B) Lymphocytes
(C) Mast cells
(D) Myofibroblasts
(E) Plasma cells

56. Clear yellow fluid is found in the left pleural cavity of a 20-year-old woman with viral pneumonia. This exudate is best labeled as

(A) fibrinopurulent
(B) fibrinous
(C) hemorrhagic
(D) purulent
(E) serous

57. Which of the following is an example of atrophy caused by a deficiency of a trophic hormone?

(A) Brain in Alzheimer disease
(B) Skeletal muscles of the limbs in traumatic paraplegia
(C) Skeletal muscle in poliomyelitis
(D) Thymus after puberty
(E) Uterus in postmenopausal women

58. A solitary nodule of the lung composed of cartilage, smooth muscle cells, and cuboidal epithelium represents a form of

(A) choristoma
(B) dysplasia
(C) hamartoma
(D) metaplasia
(E) teratoma

59. Hay fever is mediated by which immunoglobulin?

(A) IgA
(B) IgD
(C) IgE
(D) IgG
(E) IgM

60. Cushing syndrome is most often found in patients who have carcinoma of the

(A) brain
(B) esophagus
(C) lung
(D) stomach
(E) thyroid

61. An adenomatous polyp and an adenocarcinoma of the colon are morphologically similar because both

(A) are composed of columnar cells forming gland-like structures
(B) are encapsulated
(C) are pedunculated
(D) invade the bowel wall
(E) show metaplastic changes

62. Which of the following lesions is caused by human papillomavirus?

(A) Barrett esophagus
(B) Lichen sclerosus
(C) Oral leukoplakia
(D) Psoriasis
(E) Verruca vulgaris

63. Epstein-Barr virus is pathogenetically associated with

(A) Burkitt lymphoma
(B) Ewing sarcoma
(C) Hodgkin disease
(D) nasal papilloma
(E) Paget disease

64. Rhabdomyosarcomas are tumors of

(A) adipose tissue
(B) glial cells
(C) nerve sheath cells
(D) smooth muscle cells
(E) striated muscle cells

65. In children born to mothers who are older than 35 years of age, there is an increased incidence of

(A) Down syndrome
(B) Huntington disease
(C) Klinefelter syndrome
(D) Marfan syndrome
(E) Turner syndrome

66. Which of the following internal organs is often affected in progressive systemic sclerosis (scleroderma)?

(A) Brain
(B) Esophagus
(C) Ovary
(D) Thyroid
(E) Uterus

67. Which of the following diseases is often complicated by an extranodal lymphoma?

(A) Goodpasture syndrome
(B) Myasthenia gravis
(C) Polyarteritis nodosa
(D) Sjögren syndrome
(E) Wegener granulomatosis

68. Which of the following inflammatory diseases occurs most often in systemic lupus erythematosus?

(A) Encephalitis
(B) Glomerulonephritis
(C) Hepatitis
(D) Myocarditis
(E) Pneumonitis

69. Electron microscopy of the liver cells of a patient taking large doses of antiepileptic drugs will show changes of

(A) cytoskeleton
(B) mitochondria
(C) plasma membrane
(D) rough endoplasmic reticulum
(E) smooth endoplasmic reticulum

70. Which of the following organs is most radiosensitive?

(A) Adrenals
(B) Kidney
(C) Liver
(D) Testes
(E) Thyroid

71. At autopsy, a 60-year-old man is found to have brown induration of the lungs with hemosiderin-laden alveolar macrophages, nutmeg liver, and pleural effusion. These changes were caused by

(A) Goodpasture syndrome
(B) heart failure
(C) hemochromatosis
(D) primary biliary cirrhosis
(E) Wilson disease

72. A myocardial infarct is a good example of which type of necrosis?

(A) Caseous necrosis
(B) Coagulation necrosis
(C) Enzymatic fat necrosis
(D) Fibrinoid necrosis
(E) Liquefactive necrosis

73. Deep flask-shaped ulcers of the cecum are characteristic of

(A) amebiasis
(B) cholera
(C) *Escherichia coli* infection
(D) rotavirus infection
(E) shigellosis

74. Whitish plaque on the oral mucosa of a debilitated child is caused by

(A) *Actinomyces israelii*
(B) *Candida albicans*
(C) *Escherichia coli*
(D) *Histoplasma capsulatum*
(E) *Trichinella spiralis*

75. Which of the following opportunistic infectious organisms is the most common cause of malabsorption in patients with AIDS?

(A) *Cryptosporidium*
(B) *Mycobacterium avium intracellulare*
(C) *Mycobacterium bovis*
(D) *Mycobacterium tuberculosis*
(E) *Pneumocystis carinii*

76. Furuncles and carbuncles represent infections caused by

(A) fungi
(B) gram-positive bacteria
(C) protozoa
(D) spirochetes
(E) viruses

77. Which of the following conditions is characterized by thrombocytopenia?

(A) Asthma
(B) Chronic liver disease
(C) Disseminated intravascular coagulation
(D) Nephrotic syndrome
(E) Vitamin K deficiency

78. Within the past 50 years in the United States, tumors of which organ have shown a decreased incidence?

(A) Brain
(B) Large intestine
(C) Lungs
(D) Pancreas
(E) Stomach

79. Which of the following inflammatory disorders is a typical feature of rabies infection?

(A) Arthritis
(B) Encephalitis
(C) Hepatitis
(D) Myocarditis
(E) Thyroiditis

80. Which of the following diseases is mediated by IgE and leukotrienes?

(A) Asthma
(B) Polyarteritis nodosa
(C) Sarcoidosis
(D) Scleroderma
(E) Systemic lupus erythematosus

81. Which immunoglobulins cross the placenta to cause erythroblastosis fetalis and hemolysis of fetal red blood cells?

(A) IgA
(B) IgD
(C) IgE
(D) IgG
(E) IgM

82. Noncaseating epithelioid granulomas are typical of which condition?

(A) Polyarteritis nodosa
(B) Sarcoidosis
(C) Scarlet fever
(D) Scleroderma
(E) Ulcerative colitis

83. Chronic pancreatitis typically presents with

(A) achalasia
(B) ascites
(C) hematemesis
(D) hematochezia
(E) malabsorption

84. Gangrene of the intestine is typically a complication of

(A) adynamic ileus
(B) carcinoid syndrome
(C) diverticulosis
(D) embolization of the superior mesenteric artery
(E) infection with *Giardia lamblia*

85. Krukenberg tumors of the ovary are typically associated with

(A) carcinoma of the pancreas
(B) carcinoma of the stomach
(C) Crohn disease
(D) gastric sarcoma
(E) ulcerative colitis

86. Bacterial infection caused by *Helicobacter pylori* is associated with an increased incidence of

(A) intestinal villous atrophy
(B) peptic ulcer disease
(C) sprue
(D) ulcerative colitis
(E) Zollinger-Ellison syndrome

87. Increased levels of serum ceruloplasmin are typical of which disease?

(A) Budd-Chiari syndrome
(B) Gilbert disease
(C) Hereditary hemochromatosis
(D) Secondary hemochromatosis
(E) Wilson disease

88. Which of the following processes is the most common cause of transmural myocardial infarction?

(A) Embolus
(B) Hypotension
(C) Stenosis
(D) Thrombosis
(E) Vasospasm

89. A reportedly healthy 56-year-old man complains of a crushing chest pain, and a few minutes later he collapses and dies. The coroner suspects heart disease but cannot find any conclusive findings at autopsy. Which of the following mechanisms would most likely account for this man's sudden death?

(A) Arrhythmia
(B) Dressler syndrome
(C) Rupture of the chordae tendineae
(D) Rupture of the interventricular septum
(E) Ventricular rupture

90. Which of the following findings is typical of pernicious anemia?

(A) Fibroblastic hyperplasia of bone marrow
(B) High mean corpuscular volume of red blood cells
(C) Hyperacidity of gastric contents
(D) Macroglobulinemia
(E) Macroglossia

91. The most common congenital heart malformation that is diagnosed clinically is

(A) aortic stenosis
(B) atrial septal defect
(C) tetralogy of Fallot
(D) transposition of great vessels
(E) ventricular septal defect

92. Which of the following complications of leukemia accounts for most deaths in these patients?

(A) Anemia
(B) Bleeding tendency
(C) Hepatomegaly
(D) Hyperuricemia
(E) Reduced resistance to infections

93. A 22-year-old man with a 3-year history of congestive heart failure dies. His brother died at the age of 25 years, and his sudden death also was attributed to heart failure. An autopsy reveals an asymmetric hypertrophy of the left ventricle. Microscopically, there are large haphazardly arranged muscle fibers. No other pathologic findings are found. The most likely diagnosis of this patient is

(A) constrictive cardiomyopathy
(B) cor pulmonale
(C) dilated cardiomyopathy
(D) hypertensive heart disease
(E) hypertrophic cardiomyopathy

94. Which of the following pathologic findings is part of the tetralogy of Fallot?

(A) Atrial septal defect
(B) Coarctation of the aorta
(C) Mitral stenosis
(D) Tricuspid valvular defect
(E) Ventricular septal defect

95. Temporal arteritis is characterized by

(A) calcification of media
(B) deposition of IgA
(C) fibrinoid necrosis
(D) granulomatous inflammation
(E) pyogenic inflammation

96. The most appropriate test used to diagnose sickle cell anemia is

(A) Coombs test
(B) hemoglobin electrophoresis
(C) red cell fragility test
(D) reticulocyte count
(E) serum total iron-binding capacity

97. Burkitt lymphoma cells are

(A) B-lymphocytes
(B) monocytes
(C) natural killer cells
(D) plasmacytoid lymphocytes
(E) T-lymphocytes

98. Dissecting aneurysms of the aorta are most often pathogenetically associated with

(A) Ehlers-Danlos syndrome
(B) hypertension
(C) Marfan syndrome
(D) osteogenesis imperfecta
(E) syphilis

99. Which of the following is a T-cell neoplasm?

(A) Burkitt lymphoma
(B) Multiple myeloma
(C) Mycosis fungoides
(D) Polycythemia rubra vera
(E) Well-differentiated small cell lymphoma

100. Microscopic arterial aneurysms or aneurysms of small arteries detectable by contrast angiography are typical of

(A) Buerger disease
(B) hypertension
(C) Marfan syndrome
(D) polyarteritis nodosa
(E) Raynaud disease

101. Seminomas arise from the

(A) epididymis
(B) penile urethra
(C) prostate
(D) seminal vesicles
(E) testes

102. The most common cause of abdominal aortic aneurysm in a 70-year-old man is

(A) atherosclerosis
(B) cystic medial necrosis
(C) hypertension
(D) syphilis
(E) trauma

103. Bence Jones protein in urine is diagnostic of

(A) Burkitt lymphoma
(B) chronic lymphocytic leukemia
(C) Hodgkin disease
(D) multiple myeloma
(E) Sézary syndrome

104. In children younger than the age of 5 years, the most common form of leukemia is

(A) acute lymphoblastic
(B) acute myeloblastic
(C) chronic lymphocytic
(D) chronic myeloblastic
(E) erythroblastic

105. A patient being treated with chloramphenicol for a bacterial infection develops anemia, leukopenia, and thrombocytopenia. In addition to the low red blood cell count, the reticulocyte count is low, and the bone marrow appears hypocellular. This form of anemia is best classified as

(A) aplastic
(B) hemolytic
(C) hypochromic
(D) megaloblastic
(E) sideropenic

106. A 60-year-old coal miner presents with shortness of breath and diffuse nodular densities of the lungs. Most nodules are small (1 to 2 cm), but some appear larger. The lesions are more prominent in the upper zone of the lung. Open lung biopsy reveals nodules composed of concentrically layered dense collagenous connective tissue. The most likely diagnosis of this patient is

(A) anthracosilicosis
(B) asbestosis
(C) bagassosis
(D) Caplan syndrome
(E) siderosis

107. Interstitial infiltrates of lymphocytes and granulomas found in the lung biopsy of a mushroom farmer are evidence of

(A) aspergillosis
(B) asthma
(C) Goodpasture syndrome
(D) hay fever
(E) hypersensitivity pneumonitis

108. Cigarette smoking is a consistent risk factor for which of the following diseases?

(A) Buerger disease
(B) Henoch-Schönlein purpura
(C) Raynaud disease
(D) Takayasu arteritis
(E) Wegener granulomatosis

109. A 46-year-old previously healthy woman began bleeding from her nose. The bleeding could not be stopped, and she underwent a nasal biopsy. Radiography disclosed bilateral densities in her lungs. Vasculitis, granulomas, and areas of necrosis are found in both lungs and the nasal mucosa. These findings are most consistent with the diagnosis of

(A) bronchial asthma
(B) desquamative interstitial pneumonia
(C) sarcoidosis
(D) tuberculosis
(E) Wegener granuloma

110. Congenital α_1-antitrypsin deficiency is associated with

(A) bronchiectasis
(B) centriacinar emphysema
(C) hyaline membrane disease of the newborn
(D) interstitial fibrosis
(E) patchy atelectasis

111. A previously healthy 4-year-old child dies after a week-long febrile illness. Pulmonary hyaline membranes and intra-alveolar hemorrhages associated with focal alveolar cell necrosis and interstitial infiltrates of lymphocytes are found in both lungs. This is most consistent with the diagnosis of

(A) bronchiolitis obliterans
(B) bronchiectasis
(C) lipid pneumonia
(D) lobar bacterial pneumonia
(E) viral pneumonia

112. Which of the following diseases is caused by deposition of antigen-antibody complexes in tissues?

(A) Asthma
(B) Contact dermatitis
(C) Myasthenia gravis
(D) Sarcoidosis
(E) Systemic lupus erythematosus

113. Which of the following signs or conditions is typical of DiGeorge syndrome?

(A) Hypercalcemia
(B) Hyperplasia of the thymus
(C) Hypogammaglobulinemia
(D) Impaired delayed hypersensitivity reaction
(E) Interventricular septal defect

114. Kartagener syndrome is characterized by a ciliary defect. Therefore, it presents with

(A) asthma
(B) bullous emphysema
(C) chronic and recurrent bronchitis
(D) glossitis
(E) pneumothorax

115. A 45-year-old woman has routine mammography, which shows a small nodule in her breast. The physician recommends an additional mammographic x-ray examination. Densities visible by x-ray in the breast tissue of this woman represent foci of

(A) dystrophic calcification
(B) fat necrosis
(C) intratubular carcinoma
(D) medullary carcinoma
(E) metastatic calcification

116. Fat is transported from the intestines to the liver in the form of

(A) chylomicrons
(B) free fatty acids
(C) high-density lipoproteins
(D) low-density lipoproteins
(E) very low–density lipoproteins

117. Hyperplasia of the prostate is

(A) common in older men
(B) more common after castration than in normal men
(C) premalignant
(D) spontaneously reversible
(E) typically calcified

118. A 12-year-old girl is diagnosed with a cerebellar tumor, which is composed of small cells with hyperchromatic nuclei and scant cytoplasm. This tumor most likely represents

(A) an ependymoma
(B) a glioblastoma multiforme
(C) a medulloblastoma
(D) a meningioma
(E) an oligodendroglioma

119. Fungal meningitis in a patient with AIDS is most often caused by

(A) *Aspergillus fumigatus*
(B) *Candida albicans*
(C) *Cryptococcus neoformans*
(D) *Histoplasma capsulatum*
(E) *Mucor*

120. Periventricular demyelination seen on a CT scan of a 37-year-old woman suggests the diagnosis of

(A) Huntington disease
(B) Krabbe disease
(C) multiple sclerosis
(D) Parkinson disease
(E) Wilson disease

121. A 4-year-old child is diagnosed with anemia and deafness caused by nerve compression. The child has radiologically dense but brittle bones. These findings suggest the diagnosis of

(A) enchondromatosis
(B) osteogenesis imperfecta
(C) osteopetrosis
(D) osteoporosis
(E) rickets

122. Hypertensive intracerebral hemorrhages are most often found in the

(A) basal ganglia
(B) cerebellum
(C) frontal cortex
(D) medulla
(E) pons

123. A 25-year-old woman is bitten on her arm by a rabid dog. Rabies virus will reach the CNS via the

(A) arteries
(B) lymphatics
(C) peripheral nerves
(D) plasma
(E) veins

124. In chronic atrophic gastritis characterized by a deficiency of vitamin B_{12}, the CNS most often shows

(A) atrophy of the frontal cortex
(B) demyelination of the posterior columns of the spinal cord
(C) depigmentation of the substantia nigra
(D) loss of neurons from the anterior horn cells in the spinal cord
(E) widening of the lateral ventricles

125. Which of the following diseases is a spongiform encephalopathy caused by prions?

(A) Creutzfeldt-Jakob disease
(B) Huntington disease
(C) Metachromatic leukodystrophy
(D) Multiple sclerosis
(E) Parkinson disease

126. A cystic subtentorial tumor is diagnosed in a 12-year-old boy who has incurable headaches. The tumor is most likely

(A) an astrocytoma
(B) a craniopharyngioma
(C) a glioblastoma multiforme
(D) a neuroblastoma
(E) an oligodendroglioma

127. Multiple cerebral metastases are found in a 62-year-old woman with a 20-year history of cigarette smoking. The primary tumor is most likely

(A) an adenocarcinoma of the colon
(B) a chondrosarcoma
(C) a cystadenocarcinoma of the ovary
(D) a hepatocellular carcinoma
(E) a small cell carcinoma of the lung

128. A 10-year-old boy is hospitalized because of febrile illness for the past 3 days. He has experienced vomiting, blurred vision, and headaches that do not respond to pain medication. High protein, low glucose, and numerous neutrophils are found in the CSF of this child. These findings suggest the diagnosis of

(A) bacterial meningitis
(B) encephalitis
(C) multiple sclerosis
(D) tuberculosis of the brain
(E) viral meningitis

129. An epidural hematoma is caused by a hemorrhage from the

(A) middle cerebellar artery
(B) middle cerebral artery
(C) middle cerebral vein
(D) middle meningeal artery
(E) middle meningeal vein

130. Lymphomas of the CNS are a complication of infection with

(A) cytomegalovirus
(B) herpes simplex virus type 1
(C) herpes zoster virus
(D) human immunodeficiency virus
(E) rubella virus

131. Watershed infarcts are typically found as a complication of

(A) encephalitis
(B) hypertension
(C) hypotension
(D) syphilis
(E) vitamin B_{12} deficiency

132. Which of the following intracranial tumors has the best prognosis?

(A) Astrocytoma of the cerebrum
(B) Ependymoma of the lateral ventricle
(C) Glioblastoma multiforme
(D) Meningioma
(E) Oligodendroglioma

Questions 133–135

A 45-year-old woman complains of persistent itching. On physical examination, the physician notices that the patient is jaundiced. Blood test results show only slightly increased aspartate aminotransferase, significant elevation of alkaline phosphatase, and mild hyperbilirubinuria. She tests negatively for hepatitis A and hepatitis C antibodies and HBsAg. She denies any use of drugs. A liver biopsy discloses portal inflammation and destruction of small bile ducts.

133. A blood test of this patient will most likely show antibodies to

(A) cilia
(B) histones
(C) keratin filaments
(D) lysosomes
(E) mitochondria

134. Liver biopsy shows nonsuppurative cholangitis with destruction of small bile ducts. The most likely diagnosis of this patient is

(A) chronic active hepatitis
(B) Gilbert syndrome
(C) lupoid hepatitis
(D) primary biliary cirrhosis
(E) primary sclerosing cholangitis

135. Patients with these findings tend to develop

(A) acanthosis nigricans
(B) hyperkeratosis
(C) melanomas
(D) neurofibromas
(E) xanthomas

136. Zollinger-Ellison syndrome is usually caused by an islet cell tumor that produces

(A) gastrin
(B) glucagon
(C) insulin
(D) serotonin
(E) vasoactive inhibitory polypeptide

137. Which of the following intestinal polyps will most likely give rise to carcinoma?

(A) Adenomatous polyp
(B) Juvenile polyp
(C) Peutz-Jeghers polyp
(D) Tubular adenoma
(E) Villous adenoma

138. Which of the following pathologic processes is caused by *Clostridium difficile*?

(A) Crohn disease
(B) Hirschsprung disease
(C) Malabsorption syndrome
(D) Peptic ulcer disease
(E) Pseudomembranous colitis

139. Which of the following conditions is characterized by steatorrhea?

(A) Celiac disease
(B) Hemorrhoids
(C) Hirschsprung disease
(D) Peptic ulcer disease
(E) Ulcerative colitis

140. Multiple small, dark, red-to-brownish colored nodules on the ovary of an infertile 25-year-old woman are most likely evidence of

(A) adenomyosis
(B) choriocarcinoma
(C) endometrioid carcinoma
(D) endometriosis
(E) polycystic ovaries

141. Which of the following gynecologic tumors has the worst overall prognosis?

(A) Adenocarcinoma of the endometrium
(B) Dysgerminoma
(C) Mucinous cystadenocarcinoma of the ovary
(D) Serous cystadenoma of the ovary
(E) Teratoma of the ovary

Questions 142–145

A 4-year-old girl develops edema and is found to have proteinuria and hypoalbuminemia in her urine. The urinary sediment contains no inflammatory or red blood cells.

142. In the urine sediment of this patient, you will expect to find

(A) Bence Jones protein
(B) ketone bodies
(C) lipid casts
(D) pus
(E) white blood cell casts

143. The child is treated with corticosteroids with excellent results, and all of her symptoms disappear. The most likely diagnosis of this patient is

(A) acute glomerulonephritis
(B) IgA nephropathy
(C) amyloidosis
(D) membranous nephropathy
(E) minimal change disease

144. Using immunofluorescent microscopy, renal biopsy will show

(A) IgA deposits
(B) granular deposits of Ig and complement in the basement membrane of glomeruli
(C) intracapillary deposits of fibrin
(D) linear deposits of immunoglobulin
(E) no deposits of immunoglobulin

145. Using electron microscopy, you will see

(A) deposits of immunoglobulin on the subepithelial side of the basement membrane
(B) epithelial crescents
(C) fusion of the epithelial cell foot processes
(D) mesangial deposits
(E) rupture of the basement membrane

146. Mumps infection of salivary glands is most often complicated by

(A) epididymitis
(B) orchitis
(C) prostatitis
(D) urethritis
(E) vaginosis

147. Yellow radiolucent urinary stones composed exclusively of uric acid are

(A) associated with urinary infection
(B) found in patients with gout
(C) found only in women
(D) the most common type of urinary stones
(E) visible by radiography

148. In females younger than the age of 25 years, the most common ovarian tumors are derived from

(A) germ cells
(B) granulosa cells
(C) hilar cells
(D) surface epithelium
(E) theca cells

149. Bacteriuria is a typical finding in which disease?

(A) Acute poststreptococcal glomerulonephritis
(B) Acute pyelonephritis
(C) Acute tubular necrosis
(D) Glomerulonephritis of systemic lupus erythematosus
(E) Myeloma of the kidney

150. Gynecomastia is typically found in patients who have

(A) chronic pancreatitis
(B) cirrhosis
(C) end-stage kidney disease
(D) Graves disease
(E) Wegener granulomatosis

151. In the United States, which of the following bladder tumors occurs most commonly in men aged 60 to 80 years?

(A) Adenocarcinoma
(B) Rhabdomyosarcoma
(C) Squamous cell carcinoma
(D) Transitional cell carcinoma
(E) Wilms tumor

152. The most common cause of death in patients with bladder carcinoma is

(A) massive hemorrhage
(B) metastasis to the brain
(C) pulmonary embolus
(D) pulmonary insufficiency secondary to metastases
(E) renal failure

153. In degenerative joint disease (osteoarthritis), the subchondral periarticular bone shows

(A) amyloid deposition
(B) extramedullary hematopoiesis
(C) inflammation
(D) osteoporosis
(E) osteosclerosis

154. Hyperphosphatemia, hypocalcemia, and elevated serum parathyroid hormone levels suggest the diagnosis of

(A) hypervitaminosis D
(B) osteoporosis
(C) osteosclerosis
(D) parathyroid adenoma
(E) renal osteodystrophy

155. In most instances, which of the following diseases is inherited as an autosomal dominant trait?

(A) Alzheimer disease
(B) Amyotrophic lateral sclerosis
(C) Huntington disease
(D) Parkinson disease
(E) Tay-Sachs disease

156. In a 60-year-old man, which of the following diseases will most likely appear as a paraneoplastic process?

(A) Dermatomyositis
(B) Lupus erythematosus
(C) Rhabdomyolysis
(D) Sjögren syndrome
(E) Systemic sclerosis

157. Which of the following muscle changes results from lifting weights?

(A) Hyperplasia of myoblasts
(B) Hyperplasia of type I fibers
(C) Hyperplasia of type II fibers
(D) Hypertrophy of type I fibers
(E) Hypertrophy of type II fibers

158. Which of the following types of lymphoma has the best prognosis?

(A) Burkitt lymphoma
(B) Diffuse large cell type lymphoma
(C) Follicular small cell lymphocytic lymphoma
(D) Large cell immunoblastic lymphoma
(E) Lymphoblastic lymphoma

159. Which of the following is the most common benign endocrine tumor of the pancreas?

(A) Alpha cell tumor (glucagonoma)
(B) Beta cell tumor (insulinoma)
(C) Delta cell tumor (somatostatinoma)
(D) Delta-1 cell tumor (VIPoma)
(E) Gastrinoma

160. Philadelphia chromosome is typical of which form of leukemia?

(A) Acute lymphoblastic
(B) Acute myelogenous
(C) Chronic lymphoblastic
(D) Chronic myelogenous
(E) Hairy cell

161. Hepatomegaly and splenomegaly are typical of

(A) Budd-Chiari syndrome
(B) Hirschsprung disease
(C) Meigs syndrome
(D) Ménétrier disease
(E) Zollinger-Ellison syndrome

162. A bleeding tendency associated with low levels of fibrinogen and coagulation factors VII, IX, and X in plasma is typical of

(A) carcinoma of the esophagus
(B) chronic pancreatitis
(C) cirrhosis
(D) Crohn disease
(E) peptic ulcer disease

163. Hepatic cirrhosis associated with lesions involving the eye and the basal ganglia is a feature of an inborn error of metabolism of which trace element?

(A) Calcium
(B) Copper
(C) Iron
(D) Potassium
(E) Zinc

164. Patients with carcinoid heart disease invariably have tumor nodules in the

(A) appendix
(B) ileum
(C) jejunum
(D) liver
(E) stomach

165. A 38-year-old woman complains of fatigue and weakness and pain of the calf muscles. The only abnormality found biochemically is elevation of creatine kinase. The suspected diagnosis of this patient is confirmed by muscle biopsy, which shows signs of

(A) glycogenosis
(B) myasthenia
(C) myositis
(D) type I muscle cell atrophy
(E) type II muscle cell atrophy

166. Calcitonin is secreted by which of the following tumors?

(A) Follicular carcinoma of the thyroid
(B) Medullary carcinoma of the thyroid
(C) Papillary carcinoma of the thyroid
(D) Parathyroid adenoma
(E) Thymoma

167. Catecholamines are found in large quantities in the blood and urine of patients with a

(A) granulosa cell tumor
(B) hepatocellular carcinoma
(C) pheochromocytoma
(D) retinoblastoma
(E) seminoma

168. Papillary necrosis of the kidney is a complication of

(A) diabetes mellitus
(B) glomerulonephritis
(C) lipoid nephrosis
(D) nephrotic syndrome
(E) prerenal kidney failure

169. Nonbacterial thrombotic endocarditis typically is found in

(A) children
(B) adolescents
(C) young adults
(D) premenopausal women
(E) elderly people

170. Which of the following diseases most often presents with crescentic glomerulonephritis?

(A) Amyloidosis
(B) Goodpasture syndrome
(C) IgA nephropathy
(D) Lipoid nephrosis
(E) Pyelonephritis

171. Breast carcinoma is most often classified histologically as

(A) infiltrating duct carcinoma
(B) intraductal carcinoma
(C) medullary carcinoma
(D) mucinous carcinoma
(E) tubular carcinoma

172. Xerostomia is a feature of which disorder?

(A) Achalasia
(B) Esophageal varices
(C) Peptic ulcer disease
(D) Sjögren syndrome
(E) Vitamin D deficiency

173. Which of the following tumors is the most likely cause of intra-abdominal hemorrhage in young women taking oral contraceptives?

(A) Gallbladder carcinoma
(B) Leiomyoma of the uterus
(C) Liver cell adenoma
(D) Ovarian theca cell tumor
(E) Pancreatic carcinoma

174. Retinal microaneurysms are a complication of

(A) Addison syndrome
(B) diabetes mellitus
(C) gout
(D) hyperlipidemia
(E) nephrotic syndrome

175. Erysipelas is caused by

(A) fungi
(B) mycobacteria
(C) protozoa
(D) pyogenic cocci
(E) viruses

DIRECTIONS: Each of the numbered items or incomplete statements in this section is negatively phrased as indicated by a capitalized word such as EXCEPT, LEAST, or NOT. Select the ONE lettered answer or completion that is best in each case.

176. Each of the following is a complication of Paget disease EXCEPT

(A) compression of spinal nerve roots
(B) high output heart failure
(C) multiple microfractures
(D) osteosarcoma
(E) severe anemia

177. Each of the following is a complication of infectious endocarditis of the mitral valve EXCEPT

(A) immune complex glomerulonephritis
(B) mitral valve insufficiency
(C) pulmonary infarcts
(D) renal infarcts
(E) sepsis

178. Each of the following is a common feature or complication of primary pulmonary hypertension EXCEPT

(A) cor pulmonale
(B) hepatic congestion
(C) pneumonia
(D) pulmonary abscess
(E) pulmonary thrombi

179. Each of the following is associated with osteitis fibrosa cystica EXCEPT

(A) "brown tumors" composed of osteoclasts
(B) coarsely thickened trabeculae of bone
(C) fibrovascular tissue in marrow spaces of bone
(D) loss of lamina dura around teeth
(E) thin cortices

180. Each of the following proteins becomes elevated in the serum as a result of acute inflammation EXCEPT

(A) α_1-antitrypsin
(B) α_2-macroglobulin
(C) albumin
(D) ceruloplasmin
(E) fibrinogen

181. The human immunodeficiency virus invades all of the following cells EXCEPT

(A) $CD4^+$ T-lymphocytes
(B) follicular dendritic cells
(C) macrophages
(D) microglia cells
(E) neutrophils

182. Each of the following conditions predisposes a person to venous thrombosis EXCEPT

(A) cancer of the pancreas
(B) myocardial infarct
(C) pregnancy
(D) varicose veins of the lower extremities
(E) von Willebrand disease

183. Each of the following is a feature of hereditary hemochromatosis EXCEPT

(A) cirrhosis
(B) congestive heart failure
(C) dark skin
(D) diabetes mellitus
(E) volvulus

184. Each of the following is a documented complication of gallstones EXCEPT

(A) ascending cholangitis
(B) hepatocellular carcinoma
(C) hydrops of the gallbladder
(D) intestinal obstruction
(E) pancreatitis

185. Cirrhosis is a complication of each of the following diseases EXCEPT

(A) α_1-antitrypsin deficiency
(B) hereditary hemochromatosis
(C) viral hepatitis A
(D) viral hepatitis B
(E) viral hepatitis C

186. Each of the following diseases may have a leukemic phase or an equivalent leukemia EXCEPT

(A) chloroma
(B) Hodgkin disease
(C) lymphoblastic lymphoma
(D) mycosis fungoides
(E) well-differentiated lymphocytic B-cell lymphoma

187. Each of the following conditions is associated with splenomegaly EXCEPT

(A) cirrhosis
(B) Gaucher disease
(C) hereditary spherocytosis
(D) myelofibrosis
(E) sickle cell anemia

188. Adult respiratory distress syndrome may be caused by each of the following conditions EXCEPT

(A) disseminated intravascular coagulation
(B) drug overdose
(C) oxygen toxicity
(D) shock
(E) smoking

189. Complications of duodenal ulcers include each of the following EXCEPT

(A) carcinoma
(B) hemorrhage
(C) obstruction
(D) pneumoperitoneum
(E) shock

190. A 60-year-old chronic alcoholic who has smoked two packs of cigarettes a day for the past 40 years presents with progressive shortness of breath and relentless coughing. Radiographic examination shows a cavitary lesion of the right lower lobe of the lung. The LEAST likely diagnosis of this patient is

(A) abscess
(B) cancer
(C) fungal disease
(D) tuberculosis
(E) viral pneumonia

191. Depletion of adenosine triphosphate causes each of the following conditions EXCEPT

(A) degranulation of rough endoplasmic reticulum
(B) hyperplasia of smooth endoplasmic reticulum
(C) influx of sodium into the cell
(D) invagination of plasma membranes and formation of hypoxic vacuoles
(E) mitochondrial swellings

192. In acute pancreatitis, the histologic sections of the pancreas show each of the following findings EXCEPT

(A) edema
(B) fat necrosis
(C) hemorrhage
(D) infiltrates of neutrophils
(E) plasma cells

193. Each of the following tumors secretes hormones EXCEPT

(A) choriocarcinoma
(B) dysgerminoma
(C) granulosa cell tumor
(D) Sertoli-Leydig cell tumor
(E) theca cell tumor

194. Multiple myeloma is commonly associated with each of the following findings EXCEPT

(A) hypercalcemia
(B) hypergammaglobulinemia
(C) osteoblastic bone lesions
(D) plasma cell infiltrates in bone marrow
(E) radiolucent bone defects on radiography

195. Arterial hypertension occurs with each of the following diseases EXCEPT

(A) acute glomerulonephritis
(B) Addison disease
(C) adrenal cortical tumors
(D) adrenal medullary tumors
(E) chronic renal failure

196. Risk factors for adenocarcinoma of the uterus include each of the following EXCEPT

(A) hyperestrinism
(B) infertility
(C) multiple sex partners
(D) obesity
(E) theca cell tumor of the ovary

197. Each of the following is a typical feature, complication, or consequence of ulcerative colitis EXCEPT

(A) carcinoma of the colon
(B) granulomas
(C) hemorrhage
(D) megacolon
(E) pseudopolyps

198. Each of the following is a characteristic of scurvy EXCEPT

(A) defective collagen synthesis
(B) fragility of blood vessels
(C) impaired wound healing
(D) inadequate mineralization of cartilage
(E) subperiosteal hemorrhage

199. Which of the following inherited disorders is NOT associated with cirrhosis?

(A) α_1-Antitrypsin deficiency
(B) Cystic fibrosis
(C) Gilbert disease
(D) Hemochromatosis
(E) Wilson disease

200. Which of the following cells CANNOT regenerate?

(A) Enterocytes
(B) Hematopoietic stem cells
(C) Hepatocytes
(D) Neurons
(E) Osteoblasts

DIRECTIONS: Each set of matching questions in this section consists of a list of 3 to 26 options followed by several numbered items. For each numbered item, select the ONE lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

Questions 201–205

(A) Vitamin A
(B) Vitamin B_{12}
(C) Vitamin C
(D) Vitamin D
(E) Vitamin E

Match each of the following descriptions with the vitamin associated with it.

201. Converted to its active form in the kidney

202. Deficiency is found in atrophic gastritis

203. Essential for the synthesis of collagen

204. Deficiency results in vascular purpura

205. Deficiency results in abnormal gait

Questions 206–210

(A) *Candida albicans*
(B) *Chlamydia trachomatis*
(C) *Mycoplasma hominis*
(D) *Neisseria gonorrhoeae*
(E) *Treponema pallidum*

Match each of the following conditions or complications with the organism that is most likely to cause it.

206. Condyloma latum

207. Dementia is a major complication in untreated cases

208. Vaginal inflammation occurs with abundant discharge

209. Infectious arthritis is an extragenital complication

210. Ulceration occurs on the glans penis

Questions 211 and 212

(A) Air embolism
(B) Amniotic fluid embolism
(C) Bone marrow embolism
(D) Fat embolism
(E) Thromboembolism

For each description, match the embolism that is associated with it.

211. Emboli originating from the veins of lower extremities

212. Cause of postpartum disseminated intravascular coagulation

Questions 213–217

(A) Acute poststreptococcal glomerulonephritis
(B) Chronic glomerulonephritis
(C) Goodpasture syndrome
(D) IgA nephropathy
(E) Minimal change nephropathy

For each description, match the renal disorder that is most closely associated with it.

213. In a person with uremia, causes uniformly shrunken small kidneys

214. Has renal changes resembling those of Henoch-Schönlein purpura

215. Causes isolated proteinuria, hypoalbuminemia, and edema in a preschool-aged child

216. In most cases, heals spontaneously without treatment

217. Crescentic glomerulonephritis mediated by antibodies to collagen type IV

Questions 218–220

(A) Clear cell adenocarcinoma
(B) Endometrial adenocarcinoma
(C) Leiomyoma
(D) Squamous cell carcinoma
(E) Theca cell tumor

For each description below, match the tumor associated with the female reproductive system.

218. Malignant tumor of the vulva

219. Malignant tumor of the vagina caused by prenatal diethylstilbestrol treatment

220. Most common tumor of the uterus

PATHOLOGY ANSWERS AND DISCUSSION

1—C (Chapter 8) Patients dying in septic shock have adult respiratory distress syndrome. Neutrophils play a key role in the pathogenesis of this disease. They release mediators that injure endothelial cells, giving rise to edema, a fibrinous exudate, and hyaline membrane formation. At autopsy, the lungs of this patient are wet, heavy, and congested.

2—C (Chapter 21) Exophthalmus is typically associated with hyperthyroidism in Graves disease. Histologically, there are lymphocytic infiltrates in the extraocular eye muscles and retro-orbital fat, combined with a deposition of mucopolysaccharides and fibrosis. These changes can cause pain on eye movement, diplopia, and ophthalmoplegia.

3—D (Chapter 2) The initial condition is a transient vasoconstriction of arterioles. This is followed by arteriolar vasodilation, which increases blood flow to the region and opens new capillary beds. The circulation then slows down, and edema occurs.

4—E (Chapter 21) Vertigo and loss of balance are signs of labyrinthitis. It is usually idiopathic, although in some cases, viral infection is suspected.

5—E (Chapter 10) Intestinal carcinomas occur most often in the rectosigmoid part of the large intestine.

6—C (Chapter 18) Most cases of osteomyelitis result from hematogenous spread of pyogenic bacteria (e.g., *Staphylococcus aureus*).

7—C (Chapter 21) Ménière disease is an idiopathic condition characterized by the accumulation of fluid in the endolymphatic system of the cochlea in the inner ear. These changes cause vertigo, ringing in the ears (tinnitus), and ultimately deafness. It is bilateral in approximately 50% of cases.

8—D (Chapter 8) Squamous cell carcinomas of the lung, like the normal squamous epithelium of the skin, produce parathyroid hormone–like peptide. Like parathormone, this polypeptide can cause hypercalcemia.

9—D (Chapter 7) Creatine kinase is the first enzyme to increase in blood after a myocardial infarction. Typically, it becomes elevated 6 to 12 hours after coronary occlusion.

10—D (Chapters 4 and 14) The most common cancer of the internal organs in men is carcinoma of the prostate. Because this cancer affects mostly older men and because the number of aging men is increasing, the incidence of prostatic carcinoma is rising.

11—C (Chapter 21) Melanoma is the most common primary tumor of the eye in adults; in children, retinoblastoma is the most common primary malignant tumor of the eye. There are two histologic types of melanomas: spindle cell and epithelioid cell. Both types metastasize via blood vessels, but the spindle cell type is slow growing and metastasizes later than the epithelioid cell type.

12—B (Chapters 4 and 14) Human chorionic gonadotropin (hCG) is a good marker for testicular teratocarcinomas and related nonseminomatous germ cell tumors. Approximately 80% of these tumors contain trophoblastic cells that secrete hCG. hCG is present in the blood of pregnant women, but under physiologic conditions, it is not found in the blood of men.

13—C (Chapter 15) Pelvic inflammatory disease (PID) is a purulent infection of the upper part of the internal female genital organs. In most instances, the pus in the infected fallopian tubes or paraovarian abscesses contains a mixed bacterial flora. PID caused by *Neisseria gonorrhoeae* is much less common than PID caused by mixed bacterial infection. Other pathogens listed here predispose to an ascending infection of female genital organs, but they do not cause PID directly.

14—B (Chapter 21) *Cotton-wool spots* is the term used to describe the ophthalmoscopic appearance of microinfarcts of the retina, which are usually related to hypertension or diabetes mellitus.

15—B (Chapter 15) Hyperestrinism is associated with an increased risk of carcinoma of the endometrium. Estrogen stimulates the proliferation of endometrial glands and, if unopposed by progesterone, it may cause endometrial hyperplasia. Complex endometrial hyperplasia with atypia is considered to be a premalignant condition and, if untreated, it may progress to adenocarcinoma.

16—D (Chapter 8) Patients with emphysema appear dyspneic but well oxygenated ("pink puffers"). The dyspnea is characterized by forced expiration. The patient coughs but has no bronchitis and thus expectorates only a small amount of mucoid sputum, which grows no bacteria.

17—D (Chapter 15) Serous cystadenocarcinoma is a malignant ovarian tumor that tends to spread inside the peritoneal cavity. Peritoneal seeding of tumor cells is typically accompanied by accumulation of abdominal fluid (ascites). Other tumors listed in the question (i.e., Brenner tumor, granulosa cell tumor, mucinous cystadenoma, and Sertoli-Leydig cell tumor) are usually benign and do not metastasize over the peritoneal surfaces.

18—A (Chapter 7) Aschoff bodies pathognomonic of rheumatic carditis are characterized by central fibrinoid necrosis surrounded by histiocytes and multinucleated cells. They are found in connective tissue septa within the myocardium and ultimately undergo fibrosis. Other lesions of rheumatic arthritis include verrucous endocarditis and fibrinous pericarditis, and in the chronic form, valvular stenosis.

19—B (Chapter 15) Fallopian tubes are the most common site of ectopic pregnancy. Fallopian tubes are narrow, and any obstruction or narrowing of their lumen can interfere with the normal passage of the fertilized ovum into the uterus.

20—B (Chapter 21) In the United States, herpes simplex virus type 1 (HSV-1) is the leading cause of blindness caused by infections. HSV-1 can cause epithelial keratitis or stromal keratitis. Stromal keratitis is an immune disease and responds to corticosteroid therapy.

21—A (Chapter 15) More than two-thirds of breast carcinomas are infiltrating duct carcinomas that evoke a prominent desmoplastic reaction (i.e., formation of collagenous stroma). Because of abundance of stromal connective tissue, these tumors appear firm on palpation and gritty on sectioning.

22—B (Chapter 8) Mucus plugs in the bronchi of asthmatics can completely obstruct the airway, with subsequent resorption of air from that segment. Pleuritis with effusion or ascites and pneumothorax lead to compressive atelectasis. Atelectasis in neonatal respiratory distress syndrome is patchy and results from inadequate pulmonary surfactant.

23—D (Chapter 8) Pulmonary angiography is the definitive procedure for establishing the diagnosis of pulmonary embolism. Ventilation-perfusion scans are also useful but more complicated to perform.

24—B (Chapter 8) Asbestosis is characterized by diffuse interstitial fibrosis and the presence of beaded asbestos bodies coated with protein and iron. Lung biopsy of the patient with dyspnea reveals diffuse interstitial fibrosis involving respiratory bronchioles, alveolar ducts, and sacs.

25—D (Chapter 8) *Pneumocystis carinii* is a fungus that causes an alveolar exudate of proteinaceous fluid containing encysted pathogens. These can be impregnated with silver.

26—C (Chapter 21) The increased intraocular pressure typical of glaucoma results from impeded flow of aqueous humor. If the condition is not treated, it may cause retinal ischemia and blindness.

27—A (Chapter 8) Adenocarcinoma is the most common lung cancer in nonsmokers. It accounts for 25% to 40% of all lung cancers. Adenocarcinoma is mostly found in peripheral parts of the lung, and it grows more slowly than squamous cell carcinomas.

28—D (Chapter 18) All forms of osteogenesis imperfecta are characterized by an inability to form type I collagen. Multiple fractures, thin sclerae that take on the blue color of the underlying choroid, kyphoscoliosis, and misshapen teeth are found at variable rates in affected patients.

29—A (Chapter 18) Achondroplasia is the most common form of inherited dwarfism. It is transmitted as an autosomal dominant trait.

30—E (Chapter 18) Osteoporosis is characterized by increased porosity of the bone, leading to a reduction in skeletal mass. The bone trabeculae appear thin, and the haversian canals are widened.

31—E (Chapter 2) In an uncomplicated surgical incision, the incision margins are sutured with ideal approximation of the edges. This reduces the amount of hemorrhage and inflammation and allows healing by first intention.

32—E (Chapter 18) Rickets is caused by dietary deficiency of vitamin D or disturbances of its metabolism. This results in either delayed or inadequate or both delayed and inadequate mineralization, leading to excess unmineralized matrix (osteoid).

33—E (Chapter 18) Osteosarcomas are most often found in patients younger than 20 years of age. These tumors are destructive, lytic lesions that often lift the periosteum away from the bone, forming a triangular region seen on radiography (Codman triangle). Metastases to the lungs are common.

34—D (Chapters 2 and 8) Neutrophils predominate in the first 24 to 48 hours of an acute inflammatory response. Macrophages and granulation tissues appear later in the first week, and fibrosis (scarring) occurs only weeks to months later.

35—D (Chapter 2) Complement and IgG act as opsonins and cover bacteria to be phagocytized.

36—D (Chapter 18) Rheumatoid arthritis is more common in women than in men, usually beginning in the third to fifth decades. It is characterized by a nonsuppurative, proliferative synovitis. The hyperemic synovium (pannus) covers the articular cartilage. Aggregates of lymphocytes and plasma cells and the positive rheumatoid factor suggest that the disease is of an immune nature.

37—C (Chapter 2) Chronic inflammation is characterized by the presence of mononuclear inflammatory cells, granulation tissue, and fibrosis. Acute inflammation is characterized by neutrophils and edema. Granulomatous inflammation is a form of chronic inflammation characterized by nodules composed of epithelioid cells and giant cells. Gummas are associated with syphilis and are characterized by necrosis surrounded by macrophages and fibroblasts and plasma cells.

38—D (Chapter 2) Pyogenic bacteria cause a massive influx of neutrophils. The neutrophils and some parenchymal cells liquefy, causing a purulent (suppurative) exudate.

39—C (Chapter 2) Infections are the most common cause of delayed wound healing.

40—E (Chapter 3) X-linked agammaglobulinemia is observed in the latter half of the first year, after maternal immunoglobulins decline. It is characterized clinically by a lack of immunoglobulins and virtually no B-lymphocytes in the blood. Histologically, there are no germinal centers and no plasma cells in the lymph nodes and spleen.

41—B (Chapter 3) *Pneumocystis carinii* causes pneumonia in patients with AIDS and is the leading cause of death in these patients. This

encysted fungus measures 4 to 6 μm in diameter and can be diagnosed in bronchoalveolar fluid or transtracheal biopsy preparations stained with silver, Giemsa, or toluidine blue stains.

42—A (Chapter 20) Amyloid beta (Aβ) protein is the core protein found in cerebral plaques and the walls of cerebral blood vessels in Alzheimer disease.

43—B (Chapter 10) Barrett esophagus is lined by columnar epithelium resembling gastric or intestinal mucosa.

44—B (Chapter 11) Unconjugated hyperbilirubinemia is a feature of hemolytic jaundice.

45—D (Chapter 15) Enlargement of the uterus, lack of fetal sounds, high hCG levels, and abnormal placenta discovered by ultrasound suggest the diagnosis of hydatidiform mole.

46—A (Chapter 16) Acromegaly is most often caused by pituitary adenomas secreting growth hormone.

47—B (Chapter 16) Craniopharyngiomas are suprasellar neoplasms that occur in young persons and arise from remnants of Rathke pouch. These neoplasms may impinge on the optic nerve, other nerves, or the floor of the third ventricle, and destroy the hypothalamus. They can cause diabetes insipidus, as in the case presented in the question. Clinical presentations include vision loss, headaches, vomiting, obesity, and delayed puberty.

48—A (Chapter 16) Graves disease is an autoimmune disease responsible for approximately 85% of the cases of hyperthyroidism in patients younger than 40 years of age. The thyroid enlargement, exophthalmus, and pretibial swelling caused by the accumulation of fluid and glycosaminoglycans (infiltrative dermatopathy) are typical clinical findings.

49—D (Chapter 16) Papillary carcinomas account for approximately 70% of thyroid carcinomas. They occur in young women and often metastasize to local lymph nodes.

50—A (Chapter 16) Primary hyperparathyroidism most often is caused by parathyroid adenomas, which secrete parathyroid hormone. Parathyroid hormone causes hypercalcemia by mobilizing calcium from bones. It also stimulates renal tubular resorption and retention of calcium and inhibits renal resorption of phosphates, leading to hypophosphatemia and hyperphosphaturia.

51—D (Chapter 16) Exogenous corticosteroids, particularly those used in the treatment of autoimmune and other inflammatory conditions, are the most common cause of Cushing syndrome.

52—C (Chapter 16) A 50-year-old man presents with depression, a moon face, central obesity, and a history of hypertension and osteoporosis. The history and physical signs are compatible with a diagnosis of Cushing syndrome. Elevated plasma cortisol and, depending

on the cause, elevated adrenocorticotropic hormone levels would be expected in this man's condition.

53—A (Chapter 16) Autoimmune adrenalitis is the most common cause of adrenal insufficiency (Addison disease) in the United States. Worldwide, tuberculosis is still the most common cause of Addison disease.

54—D (Chapter 2) Histamine is released from granules of mast cells and basophils. This typically occurs in type I hypersensitivity reactions mediated by IgE.

55—E (Chapter 2) Plasma cells are found in or around the granulomas of syphilis (gumma), but they are not found in granulomas of tuberculosis.

56—E (Chapter 2) Clear yellow protein fluid is typically found in serous inflammation.

57—E (Chapter 1) The uterus undergoes atrophy after menopause due to a lack of estrogen, which acts as a trophic hormone for both the endometrial and myometrial cells.

58—C (Chapter 4) A pulmonary nodule composed of cartilage, smooth muscle cells, and bronchial epithelium (i.e., tissue components normally found in the lungs but arranged in an abnormal manner) represents a hamartoma.

59—C (Chapter 3) Hay fever is a type I hypersensitivity reaction mediated by IgE. IgE bound to mast cells reacts with the antigen, whereupon the signal is transmitted to the inside of mast cells, resulting in the release of mast cell granules rich in histamine.

60—C (Chapters 5, 8, and 16) Paraneoplastic Cushing syndrome is most often caused by adrenocorticotropic hormone secreted by oat (small) cell carcinoma of the lung.

61—A (Chapters 4 and 10) Both adenomatous polyps (tubular adenoma) and adenocarcinoma of the colon are composed of columnar cells forming gland-like structures. In the adenomatous polyp, these neoplastic glands are lined by uniform (benign) cells, whereas in carcinoma, the cells show marked pleomorphism and atypia and are considered malignant.

62—E (Chapter 7) Verruca vulgaris (wart) is caused by the human papillomavirus.

63—A (Chapters 4 and 9) Burkitt lymphoma cells contain Epstein-Barr virus, which is thought to play an important, yet undefined, role in the pathogenesis of this neoplasm.

64—E (Chapter 4) Rhabdomyosarcoma is a tumor of striated muscle cells.

65—A (Chapter 5) Children of mothers older than 35 years of age are at a greater risk to be born with Down syndrome than those whose mothers are younger at the time of conception.

66—B (Chapters 3 and 10) The esophagus is often affected by systemic sclerosis.

67—D (Chapter 3) Lymphoma of the salivary glands is an important complication of Sjögren syndrome, an autoimmune disease that typically affects the salivary glands.

68—B (Chapters 3 and 13) Glomerulonephritis is the most common inflammation of parenchymal organs in systemic lupus erythematosus. It is somewhat less common than dermatitis and arthritis, the two most constant features of systemic lupus erythematosus.

69—E (Chapter 1) Chronic ingestion of antiepileptic drugs increases the amount of smooth endoplasmic reticulum in liver cells. Smooth endoplasmic reticulum participates in the catabolism of drugs in the liver.

70—D (Chapter 2) The stem cells of the testes, like other mitotic stem cells such as those in the intestine or bone marrow, are very sensitive to x-radiation.

71—B (Chapter 6) Brown induration of the lungs, congestion of the liver, and pleural effusion are signs of heart failure.

72—B (Chapter 1) Myocardial infarct is a good example of coagulation necrosis.

73—A (Chapter 10) Deep flesh-shaped ulcers of the cecum are characteristic of amebiasis.

74—B (Chapter 10) Whitish plaques on the oral mucosa of a debilitated child (thrush) are caused by fungus *Candida albicans.*

75—B (Chapter 10) Infection of the small intestines with *Mycobacterium avium-intracellulare* is the most common cause of malabsorption in patients with AIDS.

76—B (Chapter 17) Furuncles and carbuncles are confluent follicular abscesses caused by gram-positive pyogenic bacteria.

77—C (Chapters 6 and 9) Disseminated intravascular coagulation is a consumptive coagulopathy in which both platelets and coagulation factors are consumed during the formation of intravascular microthrombi.

78—E (Chapter 4) Within the past 50 years in the United States, the incidence of stomach cancer has decreased.

79—B (Chapter 20) Rabies causes encephalitis.

80—A (Chapter 8) Asthma is a type I hypersensitivity reaction mediated by IgE, histamine, and leukotrienes (also known as *slow-reacting substances of anaphylaxis*, or SRS-A).

81—D (Chapter 5) IgG is the only immunoglobulin that can cross the placenta. In Rh^- mothers sensitized to Rh^+ blood, anti-Rh^+ IgG can cross the placenta, and if the fetus is Rh^+, it can cause erythroblastosis fetalis and hemolysis of fetal red blood cells.

82—B (Chapters 3 and 8) Noncaseating granulomas composed predominantly of epithelioid macrophages and a thin rim of lymphocytes are typical of sarcoidosis. These granulomas are not diagnostic of sarcoidosis and can be found in other type IV hypersensitivity reactions.

83—E (Chapter 12) Chronic pancreatitis presents with malabsorption caused by an inadequate supply of digestive pancreatic enzymes (e.g., trypsin, lipase, and amylase).

84—D (Chapter 10) Gangrene or infarction of the intestine is a typical outcome of embolism or thrombosis of one of the major mesenteric arteries. Thrombosis of mesenteric veins could have a similar outcome.

85—B (Chapters 10 and 15) Krukenberg tumors of the ovary represent metastases of gastrointestinal carcinoma, most often located in the stomach.

86—B (Chapter 10) Infection caused by *Helicobacter pylori* plays a role in the pathogenesis of peptic ulcer disease and chronic gastritis.

87—E (Chapter 11) Increased serum ceruloplasmin is typical of Wilson disease. Ceruloplasmin is the carrier protein for copper, which accumulates in large amounts in the liver in patients with Wilson disease.

88—D (Chapter 7) Transmural myocardial infarctions are precipitated by rupture of atherosclerotic plaques with superimposed thrombi that fully occlude the involved coronary vessel.

89—A (Chapter 7) Sudden cardiac death is usually attributed to arrhythmias or conduction system disorders caused by marked ischemia. The cause of death is ascribed to pump failure, but autopsy often does not provide a full explanation because myocardial cell death is not visible for the first 24 hours.

90—B (Chapter 9) Pernicious anemia is caused by vitamin B_{12} deficiency. Without adequate supply of vitamin B_{12}, which is essential for DNA synthesis, the precursors of red blood cells in the bone marrow do not mature appropriately and transform into megaloblasts. Red blood cells formed from megaloblasts are larger than normal (macrocytic) and have a high mean corpuscular volume.

91—E (Chapter 7) Ventricular septal defect is the most common congenital cardiac anomaly diagnosed clinically. This defect creates a left-to-right shunt that, over time, can present as late cyanosis. Ventricular defects occur in an isolated form, but are often associated with other defects such as in tetralogy of Fallot.

92—E (Chapter 9) Reduced resistance to infections is the most common cause of death in all patients with leukemias. Bleeding and metabolic changes are common complications, but they are less often lethal.

93—E (Chapter 7) A history of familial congestive heart failure with asymmetric left ventricular hypertrophy and haphazardly arranged

muscle fibers in the interventricular septum is highly suggestive of hereditary hypertrophic cardiomyopathy.

94—E (Chapter 7) Tetralogy of Fallot comprises ventricular septal defect, dextroposition of the aorta, pulmonary stenosis, and right-sided ventricular hypertrophy.

95—D (Chapter 7) Temporal arteritis is a granulomatous inflammation that may narrow the lumen of the vessel and cause ischemia.

96—B (Chapter 9) The abnormal hemoglobin S typical of sickle cell anemia is easily detected by electrophoresis, which is the most widely used test to diagnose this disease.

97—A (Chapter 9) Burkitt lymphoma is a B-cell tumor related pathogenetically to Epstein-Barr virus, which has a predilection to infect B-lymphocytes.

98—B (Chapter 7) Most adults who die of dissecting aneurysm of the aorta have hypertension.

99—C (Chapter 9) Mycosis fungoides is a T-cell lymphoma. Malignant T-lymphocytes are dermatotropic and tend to invade the skin.

100—D (Chapter 7) The fibrinoid necrosis weakens the wall of small arteries that are affected in polyarteritis nodosa. The blood pressure produces microaneurysms, which can be seen by angiography.

101—E (Chapter 14) Seminoma is a malignant germ cell tumor arising from spermatogonia in the seminiferous tubules of the testes.

102—A (Chapter 7) The most common cause of aneurysms of the aorta in the elderly is atherosclerosis.

103—D (Chapter 9) Bence Jones protein is typically found in the urine of patients with multiple myeloma. Bence Jones protein represents the light chain of the immunoglobulin secreted by neoplastic plasma cells.

104—A (Chapter 9) Acute lymphoblastic leukemia is the most common form of leukemia in children younger than the age of 5 years.

105—A (Chapter 9) Anemia, leukopenia, and thrombocytopenia are signs of *aplastic anemia*, a term used to denote bone marrow failure. Aplastic anemia can be idiopathic or due to an identifiable cause, such as, in this case, the drug chloramphenicol.

106—A (Chapter 8) Coal miners' lungs are black (anthracosis) from inhaled dust particles, which usually contain coal. Anthracosilicosis develops if the dust also contains quartz crystals (silica). In this disease, the lung parenchyma contains numerous fibrotic nodules composed of collagen fibers arranged concentrically around an imaginary central point. Coal particles impart a black color to these nodules. Silica crystals can be seen within the nodules by polarized light microscopy.

107—E (Chapter 8) Mushroom growers may develop hypersensitivity pneumonitis, a type IV hypersensitivity reaction characterized by

infiltrates of T-lymphocytes and granulomas in the alveolar septa and peribronchial stroma.

108—A (Chapter 7) Buerger disease, or thromboangiitis obliterans, is a form of vasculitis of unknown etiology that occurs almost exclusively in cigarette smokers.

109—E (Chapter 8) Wegener granulomatosis typically presents with a triad comprising upper respiratory tract inflammation, pneumonitis, and nephritis. In all three locations (i.e., upper respiratory tract, lungs, and kidneys), there are histologic signs of vasculitis, granuloma, and widespread necrosis.

110—B (Chapter 8) Congenital α_1-antitrypsin deficiency is a major risk factor for the development of centrilobular emphysema.

111—E (Chapter 8) The patient is diagnosed with viral pneumonia. Viruses invade and destroy alveolar lining cells and endothelial cells and elicit a lymphocytic inflammation, which is limited to alveolar septa. The alveolar cell defects are covered with hyaline membranes derived from fibrin that has seeped into the alveoli from damaged pulmonary capillaries. Vessel wall damage accounts also for the intra-alveolar hemorrhage.

112—E (Chapter 3) Systemic lupus erythematosus is an immune complex–mediated or type III hypersensitivity disorder. Immune complexes circulating in blood are deposited in the glomeruli, along the dermal-epidermal junction, in the choroid plexus, and on serosal surfaces (i.e., anatomic sites in which plasma is filtered to produce urine or another kind of bloody fluid such as CSF).

113—D (Chapter 3) DiGeorge syndrome is characterized by a congenital aplasia of parathyroid glands, resulting in hypercalcemia shortly after birth. Aplasia of the thymus adversely affects the development of T-lymphocytes. Because the T-cell system cannot develop without the thymus, children born with DiGeorge syndrome cannot mount cell-mediated immune reactions.

114—C (Chapter 8) Kartagener syndrome is a structural inborn defect of cilia. Because the cilia cannot move efficiently to and from the bronchi, and therefore cannot clear the mucus from the bronchi, affected persons are susceptible to infections and experience chronic bronchitis.

115—A (Chapter 1) Calcifications in the breast tissue seen by mammography represent foci of dystrophic calcification. Calcium salts are deposited into breast tissue destroyed by the cancer or dead tumor cells. Calcifications unrelated to breast carcinoma most likely represent calcified foci of traumatic fat necrosis or small fibrotic scars.

116—A (Chapter 1) Fat is transported from the intestines to the liver in the form of chylomicrons.

117—A (Chapter 14) Prostatic hyperplasia is extremely common in older men. It is not premalignant—it actually occurs in the peri-

urethral zone of the prostate, whereas cancers arise from the peripheral part of the prostate. Prostatic hyperplasia does not heal spontaneously. Calcifications are not a typical feature of this disease. Prostatic hyperplasia does not develop in castrated men.

118—C (Chapter 20) Medulloblastoma is the most common subtentorial brain tumor in children. It is typically composed of undifferentiated cells ("small blue cells") that have oval-to-round hyperchromatic nuclei and little cytoplasm.

119—C (Chapter 20) Fungal meningitis in AIDS patients is most often caused by the fungus *Cryptococcus neoformans*. This fungus has a proteoglycan-rich capsule that can be best demonstrated in the CSF by using India ink preparations.

120—C (Chapter 20) Plaques of periventricular demyelination seen by computed tomography in women aged 20 to 50 years are highly indicative of multiple sclerosis. Krabbe disease is yet another demyelinating disease, but it is rare and usually diagnosed in childhood.

121—C (Chapter 18) Anemia due to the replacement of the bone marrow by bone trabeculae is a feature of osteopetrosis. Abnormal bone can also compress cranial nerves and typically cause deafness.

122—A (Chapter 20) Approximately 70% of all hypertensive hemorrhages are found in the basal ganglia, 15% are found in the cerebellum, and 10% in the pons and medulla oblongata.

123—C (Chapter 20) Rabies virus travels along the peripheral nerves to the spinal cord and from there to the cerebrum.

124—B (Chapter 20) Vitamin B_{12} deficiency results in pernicious anemia and a loss of myelinated nerves of the posterior columns of the spinal cord. These spinal cord lesions affect the transmission of sensory impulses and proprioception, resulting in abnormal gait.

125—A (Chapter 20) Creutzfeldt-Jakob disease is the most common spongiform encephalopathy caused by prions. Other diseases in this category, such as kuru, are less common.

126—A (Chapter 20) Most cystic subtentorial intracranial tumors of children are classified as astrocytomas.

127—E (Chapters 8 and 20) Small cell carcinoma of the lung has a predilection to metastasize to the brain. All tumors could theoretically metastasize to the brain, but those listed here (i.e., adenocarcinoma of the colon, chondrosarcoma, cystadenocarcinoma of the ovary, and hepatocellular carcinoma) are much less common than lung cancer to be the source of brain metastases.

128—A (Chapter 20) High protein, low glucose, and numerous neutrophils in the CSF are typical of bacterial meningitis.

129—D (Chapter 20) Epidural hematoma is typically caused by a traumatic rupture of middle meningeal artery.

130—D (Chapter 20) Lymphomas of the central nervous system are an important complication of AIDS.

131—C (Chapter 20) Watershed infarcts are a typical cerebral hypoperfusion lesion caused by hypotension, as in heart failure or hypotensive shock following a massive hemorrhage.

132—D (Chapter 20) Meningioma has the best prognosis of all tumors of the brain and its coverings.

133—E (Chapter 11) The clinical and pathologic findings indicate that this 45-year-old woman has primary biliary cirrhosis, an autoimmune disease characterized by the presence of antimitochondrial antibodies.

134—D (Chapter 11) Laboratory findings typical of jaundice resulting from cholestasis and positive serologic data in a middle-aged woman are most suggestive of primary biliary cirrhosis. The liver biopsy showed destruction of bile ducts, which confirms the diagnosis.

135—E (Chapter 11) Patients who have primary biliary cirrhosis have hyperlipidemia and develop xanthomas. Xanthomas are skin nodules composed of lipid-laden macrophages in the dermis.

136—A (Chapter 12) Zollinger-Ellison syndrome is caused by gastrin-secreting islet cell tumors. Gastrin stimulates hypersecretion of hydrochloric acid in the stomach, which leads to formation of peptic ulcers. These ulcers may be multiple and are typically resistant to treatment.

137—E (Chapter 10) Of all colonic polyps, villous adenomas have the highest tendency for malignant transformation, which occurs in approximately 50% of cases. Tubular adenomas can also give rise to cancer, but do so at a much lower rate (1% to 2%).

138—E (Chapter 10) Intestinal overgrowth of *Clostridium difficile* will typically cause pseudomembranous colitis.

139—A (Chapter 10) Malabsorption of fat in the small intestine, which is characterized by bulky fatty stools (steatorrhea), is a feature of celiac disease.

140—D (Chapter 15) Small hemorrhagic nodules on the peritoneal surfaces of the fallopian tubes, ovary, or pelvis represent endometriosis.

141—C (Chapter 15) Of all the tumors listed (i.e., adenocarcinoma of the endometrium, dysgerminoma, serous cystadenoma of the ovary, and teratoma of the ovary) mucinous cystadenocarcinomas of the ovary have the worst prognosis.

142—C (Chapter 13) The 4-year-old girl has a nephrotic syndrome; hyperlipidemia found in this disease may produce lipid casts in the urine. Ketone bodies and Bence Jones protein are not visible by microscopy.

143—E (Chapter 13) Minimal change disease typically responds well to corticosteroids.

144—E (Chapter 13) Minimal change disease shows no changes in glomeruli by either light or immunofluorescence microscopy.

145—C (Chapter 13) Fusion of the foot processes of glomerular epithelial cells (podocytes) can be seen by electron microscopy.

146—B (Chapter 14) In approximately 30% of cases, mumps virus infection of the salivary glands is complicated by orchitis (i.e., inflammation of one or both testes).

147—B (Chapter 13) Uric acid stones are found in hyperuricemia and form in acidic urine. In contrast, struvite stones form during urinary infections, which makes the urine alkaline. Uric acid stones account for a small fraction of all urinary stones. They do not contain calcium and are not visible by radiography.

148—A (Chapter 15) Teratoma, a germ cell tumor, is the most common ovarian tumor in females younger than the age of 25 years.

149—B (Chapter 13) Bacteriuria is typical of acute pyelonephritis, a term used for all renal bacterial infections.

150—B (Chapters 11 and 15) Gynecomastia, enlargement of the male breast, is a feature of cirrhosis.

151—D (Chapter 13) Transitional cell carcinoma is the most common bladder tumor and is found not only in the elderly but in all age groups except children. Its incidence increases with age.

152—E (Chapter 13) Bladder carcinoma has a tendency to invade adjacent pelvic organs. Obstruction of ureters leads to postrenal renal failure.

153—E (Chapter 18) Osteoarthritis is characterized by degeneration and fraying of articular cartilage and mechanical stress-induced condensation of the underlying bone (osteosclerosis).

154—E (Chapter 18) End-stage kidney disease is characterized by hyperphosphatemia and hypocalcemia and by secondary hyperparathyroidism, which causes typical bone changes known as renal osteodystrophy.

155—C (Chapter 20) Huntington disease is inherited in an autosomal dominant manner. Tay-Sachs disease is inherited as an autosomal recessive trait. Although there are hereditary forms of amyotrophic lateral sclerosis and Alzheimer and Parkinson diseases, most cases are not inherited as mendelian traits.

156—A (Chapters 3 and 19) Dermatomyositis of adults is a relatively common paraneoplastic syndrome in patients with cancer. Dermatomyositis of young women is usually an autoimmune disorder unrelated to cancer.

157—E (Chapter 19) Weight lifting leads to hypertrophy of type II (slow) muscle fibers. On the other hand, inactivity leads to atrophy of type II fibers. Striated muscle cells cannot undergo hyperplasia.

158—C (Chapter 9) Follicular small cell (well-differentiated) lymphocytic lymphoma that is positive for the *bcl*-2 oncogene has the best overall prognosis. Most patients who have the disease survive 7 to 8 years, even without any medical treatment. Because the well-differentiated tumor cells do not react to cytotoxic drugs, it is customary not to give any chemotherapy.

159—B (Chapter 12) In general, β-cell tumor or insulinoma is the most common endocrine tumor of the pancreas. Most insulinomas (90%) are benign, in contrast to other pancreatic endocrine tumors, which more often are malignant.

160—D (Chapter 9) Philadelphia chromosome (i.e., the shortened chromosome 22 due to a 22 to 9 translocation) is typical of chronic myelogenous leukemia.

161—A (Chapter 11) Hepatomegaly, splenomegaly, and portal hypertension are features of Budd-Chiari syndrome (obstruction of hepatic vein). This syndrome typically is caused by thrombi or tumors.

162—C (Chapters 9 and 11) Bleeding tendency caused by low plasma levels of fibrinogen and coagulation factors VII, IX, and X is typical of end-stage liver disease (cirrhosis). All these plasma proteins are synthesized in the liver and are found in low concentrations in plasma when the synthetic function of the liver is compromised.

163—B (Chapter 11) Wilson disease, an inborn error of copper metabolism, presents with cirrhosis, Kayser-Fleischer ring of the cornea, and degeneration of basal ganglia of the brain.

164—D (Chapter 10) Carcinoid heart disease is caused by serotonin and polypeptide hormones secreted by carcinoid tumors into the systemic venous circulation. Gastrointestinal carcinoids secrete these bioactive substances into the portal circulation, which carries them to the liver, where they are inactivated. Only carcinoids that have metastasized to the liver can secrete these substances into the systemic venous circulation and bypass the inactivating effects of the liver.

165—C (Chapter 19) Limited proximal muscle weakness and pain associated with elevated levels of creatine kinase in the blood in an adult suggests the diagnosis of myositis (polymyositis). Muscle cell atrophy and myasthenia cause muscle weakness in patients of the same age, but they are not associated with pain and elevated creatine kinase levels. Glycogenosis is a generalized myopathy of infants and children, who usually experience widespread muscle weakness rather than localized muscle disease, as did the patient described in the question.

166—B (Chapter 16) Calcitonin is secreted by normal C cells of the thyroid as well as by medullary carcinomas of the thyroid that originate from these cells.

167—C (Chapter 16) Hypertension is a typical manifestation of pheochromocytoma. Like the adrenal medullary cells, from which these tumors most often arise, pheochromocytomas secrete adrenergic amines (epinephrine or norepinephrine) that stimulate the

contraction of the heart and arteriolar smooth muscle cells, thus increasing the blood pressure. The degradation products of these catecholamines are found in urine.

168—A (Chapter 13) Papillary necrosis is an important renal complication of diabetes mellitus. Other causes of papillary necrosis are pyelonephritis, hydronephrosis, and chronic abuse of analgesics such as phenacetin.

169—E (Chapter 7) Nonbacterial thrombotic endocarditis typically is found in elderly patients emaciated by chronic disease. It is also known as marantic endocarditis.

170—B (Chapter 13) Goodpasture syndrome, an autoimmune renal and pulmonary disease, usually presents as a crescentic, rapidly progressive glomerulonephritis.

171—A (Chapter 15) Infiltrating duct carcinoma, which accounts for approximately 70% of all breast cancers, represents the most common histologic type of this disease.

172—D (Chapters 3 and 10) Xerostomia (dryness of the mouth) is a manifestation of autoimmune salivary gland disease typically found in Sjögren syndrome.

173—C (Chapter 11) Liver cell adenoma is a benign tumor pathogenetically linked to oral contraceptives and estrogens. The tumor is highly vascular and prone to rupture and bleeding.

174—B (Chapters 12 and 21) Retinal microaneurysms are a complication of diabetes mellitus and arterial hypertension.

175—D (Chapter 17) Erysipelas is a skin disease caused by the bacteria *Streptococcus pyogenes* and other pyogenic cocci.

176—E (Chapter 18) Paget disease is characterized by osteoclastic bone resorption, followed by osteoclastic and osteoblastic activity and leading to a net gain in bone mass. This thickened bone can compress nerve roots. It requires more blood, and it could cause heart failure. It is more prone to fractures than normal bone. Severe anemia, a feature of the autosomal recessive form of osteopetrosis, is not observed in Paget disease.

177—C (Chapter 7) Pulmonary infarcts are a complication of tricuspid valvulitis, but they do not occur with mitral valve endocarditis. Vegetations detached from the mitral valve can cause arterial emboli, sepsis, or glomerulonephritis.

178—D (Chapter 8) Pulmonary abscesses are not a common complication of pulmonary hypertension.

179—B (Chapter 18) Osteitis fibrosa cystica is caused by enhanced osteoclastic activity due to severe primary hyperparathyroidism. Subperiosteal resorption of bone produces thin cortices that give a characteristic radiographic pattern. In addition, the lamina dura of the teeth is lost. Brown tumors result from hemorrhages caused by

microfractures, which also evoke a response of macrophages and reactive proliferation of osteoblasts. The marrow spaces are filled with fibrovascular tissue and osteoclastic multinucleated cells.

180—C (Chapter 2) α_1-Antitrypsin, α_2-macroglobulin, ceruloplasmin, and fibrinogen are acute phase reactants (i.e., serum proteins that become elevated in acute inflammation). Albumin concentration decreases in acute inflammation.

181—E (Chapter 3) The human immunodeficiency virus targets $CD4^+$ lymphocytes and destroys them over time, which leads to immunosuppression. It appears that macrophages, microglia cells, and follicular dendritic cells are targeted, but are resistant to lysis. The virus appears to replicate in these cells and is transported by them.

182—E (Chapter 9) von Willebrand disease is a bleeding disorder. The other conditions listed (i.e., cancer of the pancreas, myocardial infarct, pregnancy, and varicose veins of the lower extremities) are associated with a predisposition to venous thrombosis.

183—E (Chapter 1) Hemochromatosis may present with dark skin, cirrhosis, congestive heart failure, or diabetes mellitus. Volvulus is not a condition associated with hemochromatosis.

184—B (Chapter 11) Gallstones may cause ascending cholangitis, pancreatitis, intestinal obstruction (gallstone ileus), and hydrops of the gallbladder, but they bear no pathogenetic relationship to hepatocellular carcinoma.

185—C (Chapter 11) Hepatitis A virus infection does not progress to cirrhosis, in contrast to hepatitis B virus and hepatitis C infections, which may progress to cirrhosis. Cirrhosis is a well-known complication of hereditary hemochromatosis and α_1-antitrypsin deficiency.

186—B (Chapter 9) Hodgkin disease, a disease of lymph nodes, may involve the spleen, bone marrow, or liver, but it does not have a leukemic form. All the other entities listed have a leukemic equivalent: Well-differentiated lymphocytic B-cell lymphoma is related to chronic lymphocytic leukemia; chloroma is a solid tumoral infiltrate of chronic myelogenous leukemia; lymphoblastic lymphoma is equivalent to acute lymphoblastic leukemia; and mycosis fungoides has a leukemic equivalent in Sézary syndrome.

187—E (Chapter 9) Sickling and thrombotic occlusion of small blood vessels causes infarcts and shrinkage of the spleen (autosplenectomy) in sickle cell anemia. All the other diseases listed are characterized by splenomegaly. In hereditary spherocytosis, there is splenic pooling and destruction of abnormal red blood cells (spherocytes). In cirrhosis, the spleen is enlarged due to portal hypertension. In myelofibrosis with myeloid metaplasia, the spleen shows extensive extramedullary hematopoiesis. In splenomegaly of Gaucher disease, fixed splenic macrophages are transformed into lipid-laden foam cells, due to the genetic defect in the gene encoding glucocerebrosidase.

188—E (Chapter 8) Smoking causes chronic bronchitis and emphysema and is considered the major risk factor for lung cancer. It is not a cause of adult respiratory distress syndrome, which may be caused by all of the other conditions listed in the question (i.e., disseminated intravascular coagulation, drug overdose, oxygen toxicity, and shock).

189—A (Chapter 10) Carcinoma develops in 3% to 5% of gastric ulcers, but it is not a recognized complication of duodenal peptic ulcer. Duodenal ulcers can bleed or perforate, leading to peritonitis or pneumoperitoneum (air in the abdominal cavity) and thus cause shock. Extensive scarring that occurs during the healing of a peptic ulcer can cause narrowing (stenosis) or complete obstruction of the duodenum.

190—E (Chapter 8) In contrast to the other conditions listed (abscess, cancer, fungal disease, and tuberculosis), viral pneumonia does not produce cavitary lesions in the lung. Instead, it causes widespread interstitial pneumonitis in which the alveolar septa are infiltrated with lymphocytes and macrophages.

191—B (Chapter 1) Depletion of adenosine triphosphate causes cellular swelling, which includes mitochondrial swelling, influx of sodium and water into the cells, and invaginations of plasma membranes. It also causes degranulation of rough endoplasmic reticulum, which results in reduced synthesis of proteins for export. On the other hand, it does not induce hyperplasia of smooth endoplasmic reticulum. This change is typically induced by drugs that are metabolized in the smooth endoplasmic reticulum.

192—E (Chapter 12) Edema of the pancreas with acute inflammation (infiltrates of neutrophils), hemorrhage, and fat necrosis are typical of acute pancreatitis. These changes can be related to the release of enzymes from the damaged pancreatic acini. Plasma cells are not found in any acute inflammation, including acute pancreatitis.

193—B (Chapter 15) Dysgerminomas are germ cell tumors of the ovary that do not secrete hormones. Sertoli-Leydig cell tumors secrete androgens, theca and granulosa cells secrete estrogens, whereas choriocarcinomas secrete hCG.

194—C (Chapter 9) Multiple myeloma produces bone lesions that are typically lytic and not osteoblastic. These lesions are composed of plasma cells and have a typical "punched out" radiographic appearance. Bone destruction leads to hypercalcemia. Neoplastic cells secrete immunoglobulins, accounting for the typical monoclonal (M) immunoglobulin spike and hypergammaglobulinemia. Deposition of light chains of immunoglobulin results in amyloidosis.

195—B (Chapter 16) Addison disease is characterized by hypotension, whereas the other conditions listed (i.e., acute glomerulonephritis, adrenal cortical tumors, adrenal medullary tumors, and chronic renal failure) cause hypertension.

196—C (Chapter 15) Multiple sex partners and promiscuity are risk factors for cervical cancer, but not for adenocarcinoma of the

uterus. Infertility, hyperestrinism (e.g., exogenous estrogens or ovarian tumors, such as thecomas and granulosa cell tumors) are associated with an increased incidence of endometrial adenocarcinomas.

197—B (Chapter 10) Granulomas are found in intestines affected by Crohn disease, but they are not a feature of ulcerative colitis. All the other pathologic changes noted (i.e., carcinoma of the colon, hemorrhage, megacolon, and pseudopolyps) are found in ulcerative colitis.

198—D (Chapter 18) The basic defect in scurvy is defective collagen synthesis leading to inappropriate matrix (osteoid) formation. The defective collagen is also at the root of impaired wound healing and hemorrhage. Mineralization of cartilage is normal.

199—C (Chapter 11) Gilbert disease is a familial, mild form of jaundice and does not cause any other liver disturbances.

200—D (Chapter 2) Neurons are permanent postmitotic, nondividing cells. Hematopoietic stem cells and intestinal cells (enterocytes) are labile (mitotic) cells, whereas hepatocytes and osteoblasts are stable (facultatively mitotic) cells that can enter mitosis and regenerate.

201—D (Chapter 18) Vitamin D is hydroxylated in the liver into 25-(OH)D and this compound is converted into its active form, $1,25(OH)_2D$, in the kidney.

202—B (Chapter 9) Intrinsic factor secreted by the gastric parietal cells is essential for the absorption of vitamin B_{12}. A lack of intrinsic factor in atrophic gastritis results in vitamin B_{12} deficiency and pernicious anemia.

203—C (Chapter 2) Vitamin C is essential for the synthesis of collagen.

204—C (Chapter 9) Vitamin C deficiency weakens the extracellular matrix of small blood vessels, causing scurvy. Vascular purpura is a prominent symptom of scurvy.

205—B (Chapter 20) Vitamin B_{12} deficiency may result in a loss of myelinated axons in the posterior column of the spinal cord, which affects normal proprioception and results in abnormalities in gait.

206—E (Chapter 14) Condyloma latum is a typical skin manifestation of syphilis, caused by *Treponema pallidum* infection.

207—E (Chapter 20) Dementia is a feature of tertiary syphilis, which is caused by *Treponema pallidum.*

208—A (Chapter 14) *Candida albicans* is a common cause of fungal vaginitis.

209—D (Chapter 17) Infectious arthritis is a complication of gonorrhea, which is caused by the pathogen *Neisseria gonorrhoeae.*

210—E (Chapter 14) Genital ulcers are a feature of primary syphilis, caused by *Treponema pallidum.*

211—E (Chapter 6) Thromboemboli most often originate from deep veins of lower extremities.

212—B (Chapter 6) Amniotic fluid embolism is the best known cause of postpartum disseminated intravascular coagulation.

213—B (Chapter 13) In chronic glomerulonephritis, the kidneys are symmetrically shrunken and finely granular. Loss of renal parenchyma is accompanied by signs of uremia, a term used as a synonym for end-stage kidney disease.

214—D (Chapter 13) IgA nephropathy, also known as Berger disease, has features similar to those of Henoch-Schönlein purpura. Most important, in both diseases there are deposits of IgA in the glomerular mesangium.

215—E (Chapter 13) Childhood nephrotic syndrome is a syndrome characterized by proteinuria without other pathologic urinary findings (such as hematuria and leukocyturia), hypoalbuminemia, and edema. It is most often caused by minimal change nephropathy.

216—A (Chapter 13) In most instances, acute poststreptococcal glomerulonephritis heals spontaneously without any treatment.

217—C (Chapter 13) Goodpasture syndrome is mediated by antibodies to collagen type IV in the glomerular basement membranes. It presents as a crescentic rapidly progressing glomerulonephritis.

218—D (Chapter 15) In most instances, carcinoma of the vulva is histologically classified as squamous cell carcinoma.

219—A (Chapter 13) Clear cell adenocarcinoma of the vagina is a rare tumor that has often been found in young women whose mothers were treated with diethylstilbestrol during pregnancy.

220—C (Chapter 13) Leiomyoma is the most common tumor of the uterus.

Pathology
Must-Know Topics

The following are must-know topics discussed in this review. It would be useful for you to formulate outlines of these subjects because knowledge of the related material will be key to your understanding of the subject and material and for passing the examination.

Cell Pathology

- Clinical examples of atrophy, hypertrophy, hyperplasia, and metaplasia
- Five forms of necrosis
- Response of the cell to injury

Inflammation and Repair

- Functions of inflammatory cells, especially polymorphonuclear leukocytes and macrophages
- Mediators of inflammation
- Sequence of events in acute inflammation
- Wound healing and causes of delayed wound healing

(continued)

Immunopathology

- Acquired immunodeficiency syndrome
- Cells of the immune system and their functions
- Hypersensitivity reactions
- Important autoimmune diseases: systemic lupus erythematosus, scleroderma, dermatomyositis, Sjögren disease, and amyloidosis

Neoplasia

- Examples of carcinogens and tumor-suppressor genes
- Nomenclature of tumors
- Paraneoplastic syndromes
- Tumor markers

Developmental and Genetic Disorders

- Common chromosomal abnormalities: Down, Klinefelter, and Turner syndromes
- Common mendelian diseases
- Cystic fibrosis

Circulatory Disturbances

- Edema
- Shock
- Thrombosis and embolism

Cardiovascular System

- Aneurysms
- Atherosclerosis and its complications
- Common congenital heart diseases
- Coronary heart disease
- Endocarditis
- Hypertension
- Vasculitis

Respiratory System

- Adult respiratory distress syndrome
- Chronic obstructive pulmonary disease
- Lung cancer
- Pneumoconioses
- Pneumonia

(continued)

Hematopoietic and Lymphoid System

- Anemia
- Bleeding disorders, especially hemophilia and disseminated intravascular coagulation
- Leukemia
- Lymphoma and Hodgkin disease
- Multiple myeloma

Gastrointestinal System

- Inflammation of the mouth, esophagus, and stomach
- Inflammatory bowel disease: ulcerative colitis and Crohn disease
- Malabsorption
- Peptic ulcer disease
- Tumors of the gastrointestinal tract

Liver and Biliary System

- Cirrhosis
- Gallstones
- Hepatitis
- Jaundice
- Tumors of the liver and biliary tract

Pancreas

- Diabetes mellitus
- Pancreatitis, acute and chronic
- Tumors of the pancreas

Kidneys and Urinary Tract

- Cystitis
- Glomerulonephritis
- Nephrotic syndrome
- Polycystic kidney disease
- Pyelonephritis
- Tumors of the kidney and urinary bladder

Male Reproductive System

- Benign prostatic hyperplasia
- Testicular tumors
- Tumors of the prostate

Female Reproductive System

- Breast carcinoma
- Infections of the female genital system
- Tumors of the cervix, uterus, and ovary

(continued)

Endocrine System

- Hyperfunction and hypofunction of the pituitary, thyroid, parathyroid, and adrenals
- Tumors of the endocrine glands

Skin

- Infectious dermatitis
- Immune skin diseases
- Melanoma and pigmented skin lesions
- Skin carcinoma

Bones and Joints

- Bone tumors
- Gout
- Metabolic bone diseases: osteoporosis and osteomalacia
- Osteoarthritis
- Renal osteodystrophy
- Rheumatoid arthritis

Skeletal Muscles

- Muscular dystrophy
- Myasthenia gravis
- Myositis
- Neurogenic muscle disease

Nervous System

- Dysraphic CNS disorders: anencephaly and spina bifida
- Infections of the CNS
- Multiple sclerosis
- Neurodegenerative diseases: Alzheimer, Parkinson, and Huntington diseases
- Stroke

Sensory Organs

- Deafness
- Eye infections
- Glaucoma
- Tumors: melanoma and retinoblastoma

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