



***CROWLEY'S***

AN INTRODUCTION TO

# HUMAN DISEASE

Pathology and Pathophysiology Correlations

***TENTH EDITION***

**Emily Reisner  
Howard Reisner**

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World Headquarters  
Jones & Bartlett Learning  
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Burlington, MA 01803  
978-443-5000  
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09938-6

#### Production Credits

General Manager: Eduardo Moura  
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Director of Marketing: Andrea DeFronzo  
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Composition: Cenveo® Publisher Services  
Project Management: Cenveo Publisher Services  
Cover Design: Kristin E. Parker  
Rights & Media Specialist: Jamey O'Quinn  
Media Development Editor: Troy Liston  
Cover Image: © CDC/Dr. Dudman, Dr. Kaplan  
Printing and Binding: RR Donnelley  
Cover Printing: RR Donnelley

#### Library of Congress Cataloging-in-Publication Data

Names: Reisner, Emily G., author. | Reisner, Howard M., author. | Crowley, Leonard V., 1926- Introduction to human disease. Preceded by (work): Title: Crowley's an introduction to human disease: pathology and pathophysiology correlations/Emily G. Reisner, Howard M. Reisner.

Other titles: Introduction to human disease

Description: Tenth edition. | Burlington, MA: Jones & Bartlett Learning, [2017] | Preceded by An introduction to human disease/Leonard V. Crowley. 9th ed. c2013. | Includes bibliographical references and index.

Identifiers: LCCN 2016010951 | ISBN 9781284050233 (casebound: alk. paper)

Subjects: | MESH: Disease | Pathology

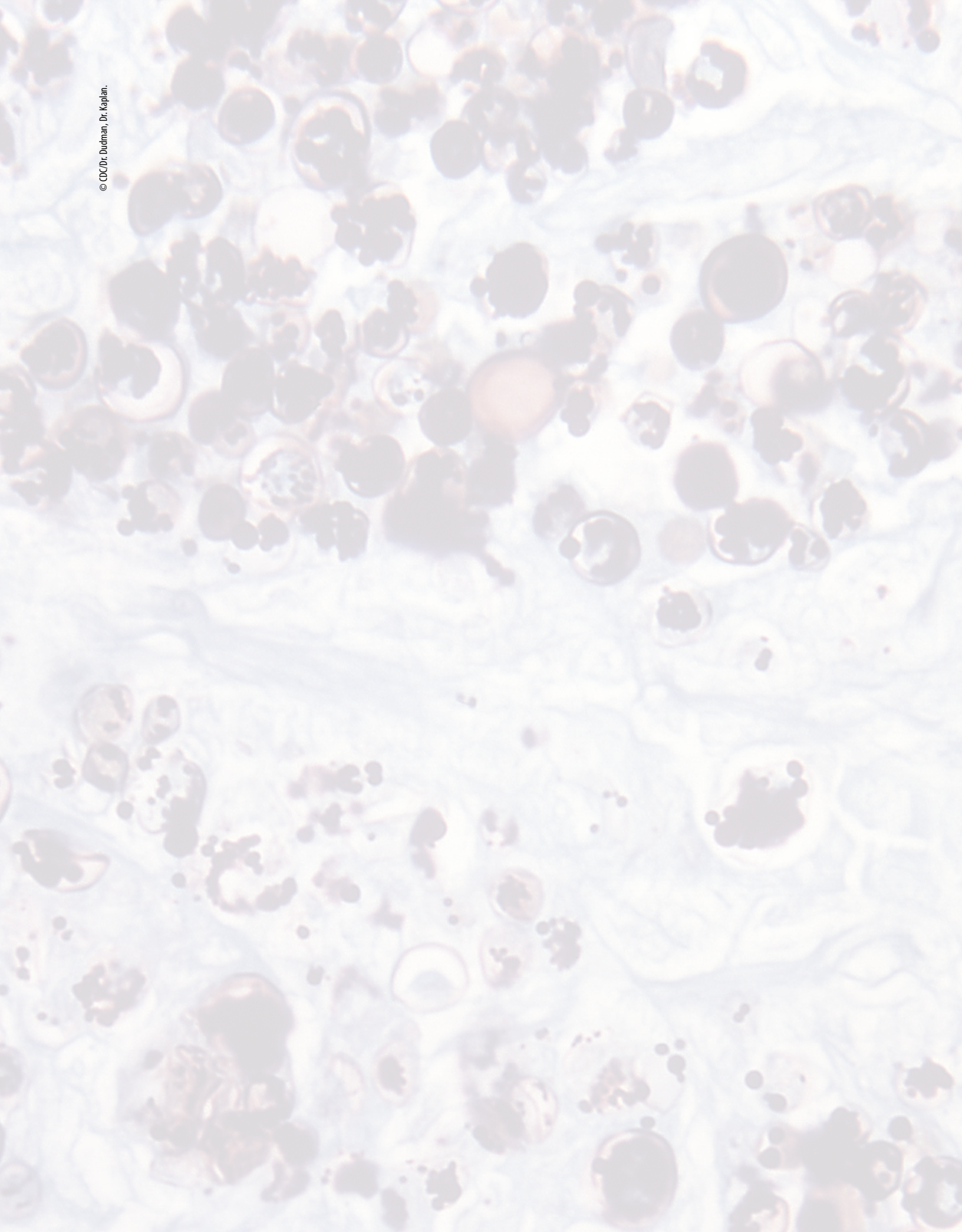
Classification: LCC RB112 | NLM QZ 4 | DDC 616.07—dc23 LC record available at <http://lcn.loc.gov/2016010951>

6048

Printed in the United States of America

20 19 18 17 16 10 9 8 7 6 5 4 3 2 1

*This Tenth Edition is dedicated to the memory of Dr. Leonard V. Crowley, without whom there would be no book.*



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# Preface

In recent years, increased emphasis has been placed on how changes in the genome are expressed as disease. This information now has a larger role in both diagnosis and therapy, which is reflected in the text for this edition. We have preserved Dr. Crowley's organization from the *Ninth Edition*, starting with six general chapters followed by chapters on organ systems and their diseases, but in this *Tenth Edition* we have provided more information on the cellular and molecular roots of disease.

## The Audience

How did we visualize the reader of this work? The authors hope that any individual interested in the health sciences who wishes to understand the nature of disease would find the text of interest. Specifically, we hope that the text would allow a beginning student of the health sciences who has a working knowledge of biology to equip themselves with the concepts and vocabulary for more specialized areas of study in any of the health related fields. To do this we have taken particular care to present recent information relating to the therapy and molecular diagnosis of disease.

## New to This Edition

Throughout this new edition, extensive updates have been made.

### Chapter 1

- Expanded principles of diagnosis, including additional material on taking a history, performing a physical diagnosis, and selecting a diagnostic test
- Updated information on clinical laboratory testing and imaging techniques
- Introduction of concepts including evidence-based and patient-centered medicine
- Addition of new testing procedures, such as virtual colonoscopy and single-photon computed tomography (SPECT)
- Updated with new figures
- Case presentation added
- Expansion of definition list
- Update of reference list

### Chapter 2

- Added information on cell–cell signaling
- Added/updated information on cell injury and cell death
- Added information on Hayflick limit for cell division
- Case presentation added
- Expansion of definition list
- Update of reference list

### Chapter 3

- Information on genes and DNA moved from previous edition Chapter 2 and integrated into presentation of genetics
- Information added on pedigree analysis and inheritance patterns



- Information on the HLA system moved to Chapter 5
- Information added regarding definition of race
- Case presentation added
- More than doubled the number of definitions
- Update of reference list

#### Chapter 4 (was Chapter 9 in the previous edition)

- Reorganized to better integrate with Chapter 3
- Presentation on fetal testing updated
- Material added on HIV infection in the mother
- Cases reviewed and updated
- New figures
- Number of definitions increased
- Update of reference list

#### Chapter 5 (was Chapter 4 in the previous edition)

- Material and terminology modernized; chapter linked to Chapter 6 on immunology
- Case presentation added
- Number of definitions more than doubled
- Figures replaced
- Update of reference list

#### Chapter 6 (was Chapter 5 in the previous edition)

- Eighty percent rewritten to focus on the most recent information on the development of adaptive immunity
- Material added on immunodeficiency
- Number of definitions increased
- New figures added
- New case added
- Update of reference list

#### Chapter 7 (was Chapter 10 in the previous edition)

- Extensively rewritten to focus on principles of neoplastic process in general rather than results of the process in specific organs; neoplasia presentations are now in the specific organ chapters
- Added two additional figures to illustrate critical points; updated other figures and tables

- Expanded presentation of oncogenes and tumor suppressor genes
- Updated presentation on immunotherapy and anticancer drugs
- Case presentation added; original short cases deleted
- Update of reference list

#### Chapter 8 (was Chapter 6 in the previous edition)

- Material added on hemorrhagic fevers, including Ebola
- Material added on molecular testing for microorganisms
- Material added on aspergillosis
- Number of definitions increased
- New figures added
- New case about measles added
- Update of reference list

#### Chapter 9 (was Chapter 7 in the previous edition)

- Chapter renamed to better reflect material
- Material added on Chagas disease, leishmaniasis, strongyloidiasis, and trichomoniasis
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

#### Chapter 10 (was Chapter 8 in the previous edition)

- Chapter renamed to better reflect material
- Chapter reorganized to improve presentation
- Material on Ebola transmission control added
- HIV material updated
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

#### Chapter 11 (was Chapter 13 in the previous edition)

- Completely rewritten; now focused on the heart and associated diseases
- Material on vascular disease moved to Chapter 12

- Updated terminology
- Expanded definition list
- Replaced figures
- New case
- Update of reference list

### Chapter 12 (was Chapter 13 in the previous edition)

- Completely rewritten; now focused on the vasculature and associated diseases
- Section on risks for atherosclerosis updated and completely rewritten
- Updated terminology
- Expanded definition list
- Replaced figures
- New case
- Update of reference list

### Chapter 13

- Material on leukemia and lymphoma added and updated (This chapter contains all information on these systems, including neoplasms, which were previously split between Chapters 10 and Chapter 14.)
- Material on thalassemia was expanded
- Consolidation of all material on diseases of hematopoietic tissue
- Presentation on stem cell therapy updated
- Case presentation added; original short case deleted
- Update of definitions
- Update of reference list

### Chapter 14

- Major rewrite of primary and secondary hemostasis to bring up-to-date with current concepts
- Material added on molecular mechanisms of Coumadin
- Enhanced presentation of coagulation diagnostic tests
- Case presentation added; original short cases deleted
- Update of definitions
- Figures replaced
- Update of reference list

### Chapter 15

- Tuberculosis information updated
- Lung cancer information updated

- Information on MERS added
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

### Chapter 16

- Material added on molecular diagnosis of breast cancer
- Material updated to reflect most recent American Cancer Society diagnosis and treatment guidelines
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

### Chapter 17

- Material added on the anatomy of the female reproductive tract and the menstrual cycle
- Material added on polycystic ovary disease (PCOS)
- Expanded presentation of uterine cancer
- Terminology updated for presentation of HPV and cancer
- Case presentation added; original short cases deleted
- Update of reference list

### Chapter 18

- Condensed and updated presentation of red cell system incompatibilities
- Updated presentation of preeclampsia and eclampsia
- New case
- Additional definitions
- Revised figures
- Update of reference list

### Chapter 19 (incorporates material from previous edition Chapters 19 and 24)

- Material on body water management integrated from Chapter 24
- Expanded and revised section on glomerular injury
- Material on transplantation updated
- New case added with two diagnoses
- Update of definitions
- Update of illustrations
- Update of reference list

**Chapter 20**

- Material added on developmental abnormalities of the ureter and penis
- Material updated on adenocarcinoma of the prostate
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

**Chapter 21**

- Chapter reorganized
- Material updated
- Case presentation added; original short cases deleted
- Figures replaced
- Update of reference list

**Chapter 22**

- Chapter reorganized
- Material updated, especially in regard to genetics of diabetes and metabolic syndrome
- Two case presentations added; original cases deleted
- Figures added
- Update of reference list

**Chapter 23**

- Chapter reorganized
- Material updated, especially in regard to addition of discussions of cholera and colorectal cancer
- Case presentation added on gluten sensitivity; original cases deleted
- Figures reviewed and replaced
- Update of reference list

**Chapter 24 (was Chapter 25 in the previous edition)**

- Material added on multiple endocrine neoplasia (MEN)
- Thyroid neoplasia presentation updated
- Case presentation added on short stature and growth hormone deficiency; original cases deleted
- Figures reviewed and replaced
- Update of reference list

**Chapter 25**

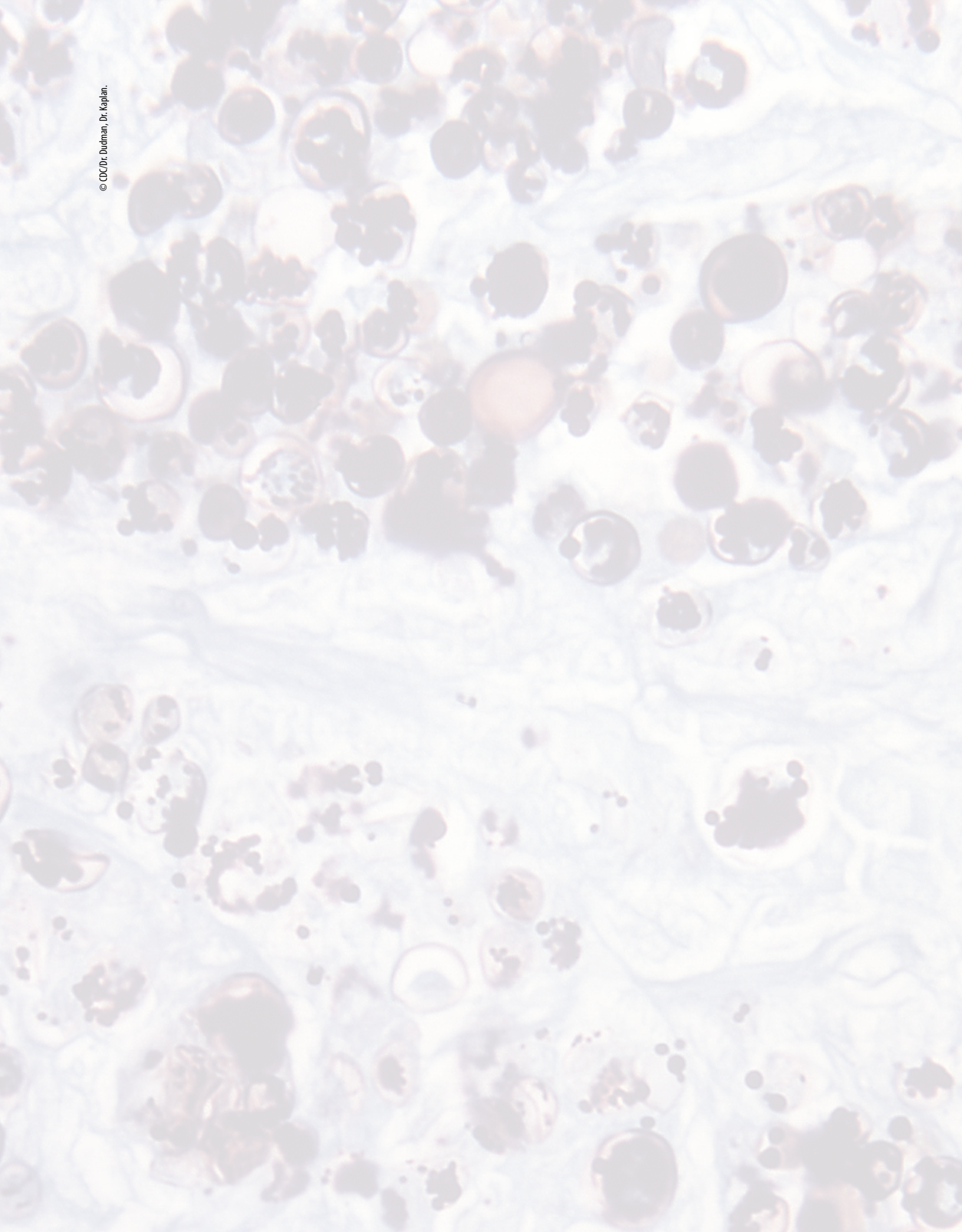
- Material added on rabies and brain cancer
- Peripheral neuritis presentation updated
- Material on Creutzfeldt-Jakob syndrome corrected
- Presentation on structure and function condensed
- Case presentation added; original cases deleted
- Update of definition list
- Figures reviewed and replaced
- Update of reference list

**Chapter 26**

- Discussion of rheumatoid arthritis updated
- Presentation of tumors of bone added
- Case presentation added
- Figures reviewed and replaced; figures describing skeleton and muscle structure added, along with others
- Definition list expanded
- Update of reference list

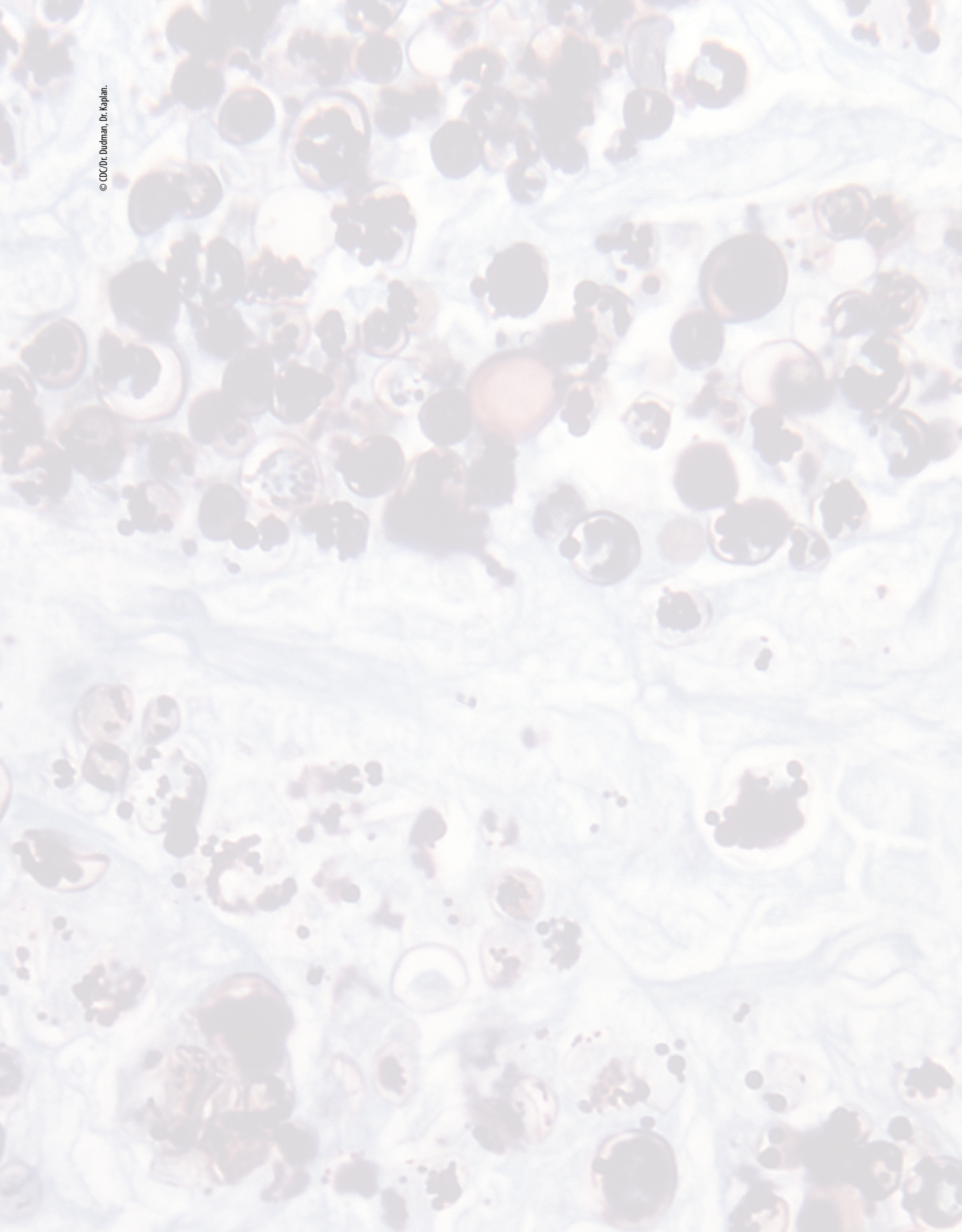
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# Acknowledgments

The authors would like to thank the team at Jones & Bartlett Learning for their support throughout this project: Cathy Esperti, publisher; Carter McAlister, editorial assistant; Leah Corrigan, senior production editor; Troy Liston, media development editor; and Jamey O'Quinn, rights and media specialist. We would also like to thank Apoorva Goel, project manager at Cenveo Publisher Services.



# Reviewers

Jones & Bartlett Learning and the authors would like to thank the following people for reviewing the *Ninth Edition* and providing feedback for updating this edition.

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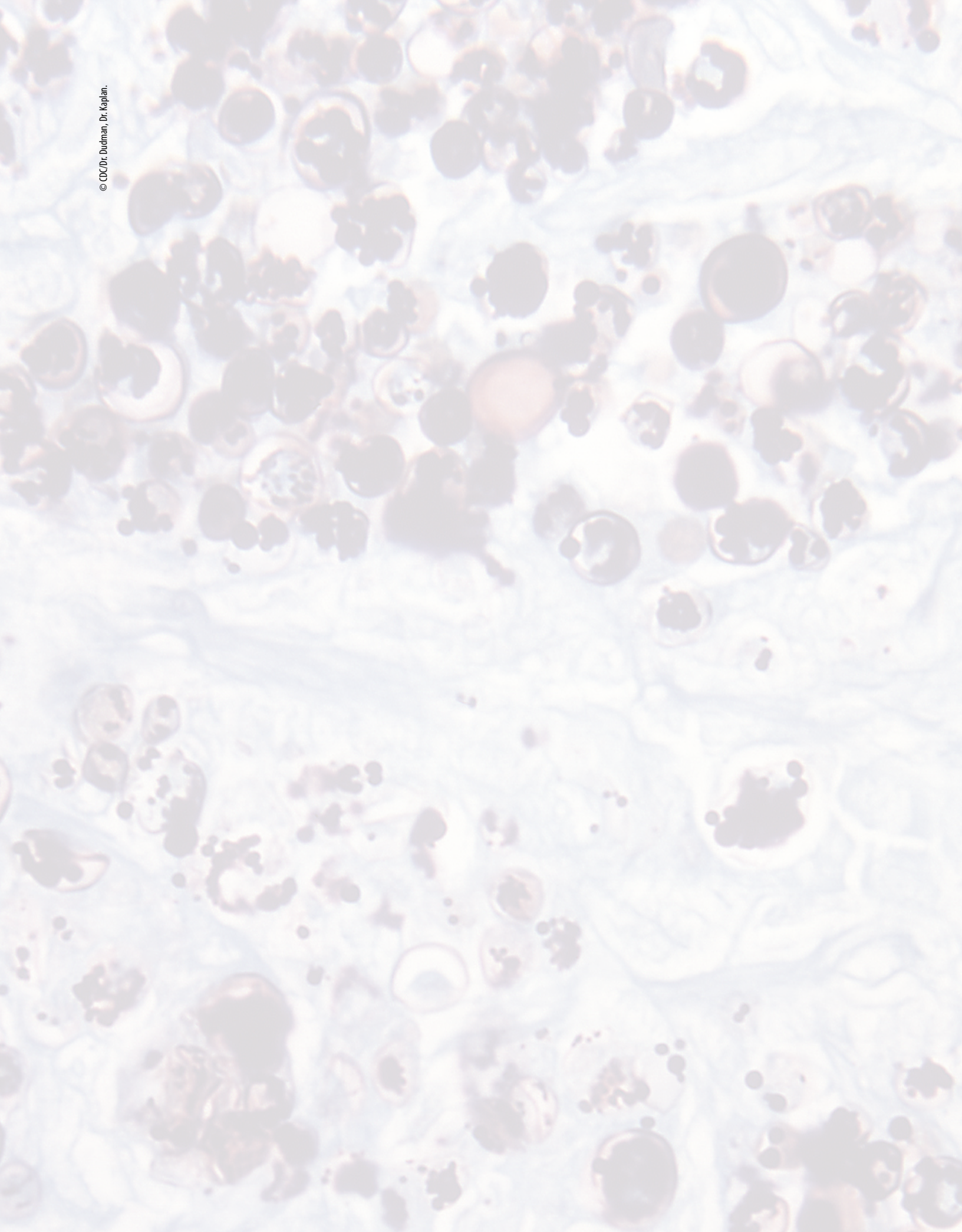
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# A Visual Walkthrough

Various learning features are included to enhance the usefulness of this product.

## LEARNING OBJECTIVES

Learning objectives provide students with expected outcomes for each chapter as well as a checklist for measuring comprehension.

**LEARNING OBJECTIVES**

1. Explain the basic anatomic and physiologic principles of ventilation and gas exchange.
2. Describe the physiological basis and use of pulmonary function tests.
3. Describe the causes, clinical effects, complications, and treatment of pneumothorax and atelectasis.
4. Describe the clinical symptoms, complications, and treatment of pneumonia.
5. Describe the histologic characteristics of a tuberculous infection. Explain the possible outcome of an infection. Describe methods of diagnosis and treatment.
6. Differentiate between bronchitis and bronchiectasis.
7. List the anatomic and physiologic derangements in obstructive lung disease. Explain its pathogenesis. Describe clinical manifestations and methods of treatment.
8. Describe the pathogenesis and manifestations of bronchial asthma and respiratory distress syndrome.
9. Explain the causes and effects of pulmonary fibrosis. Describe the special problems associated with asbestosis.
10. List the major types of lung carcinoma. Describe the clinical manifestations of lung carcinoma and explain the principles of treatment.

## EXTENSIVE GLOSSARY

The extensive glossary proves useful to students who may not have had a course in medical terminology. It also serves as a convenient reference for students who want to quickly review a particular term. Words appearing in the glossary are set in boldface type in the text and set off in the margin for easy reference.

**Introduction**

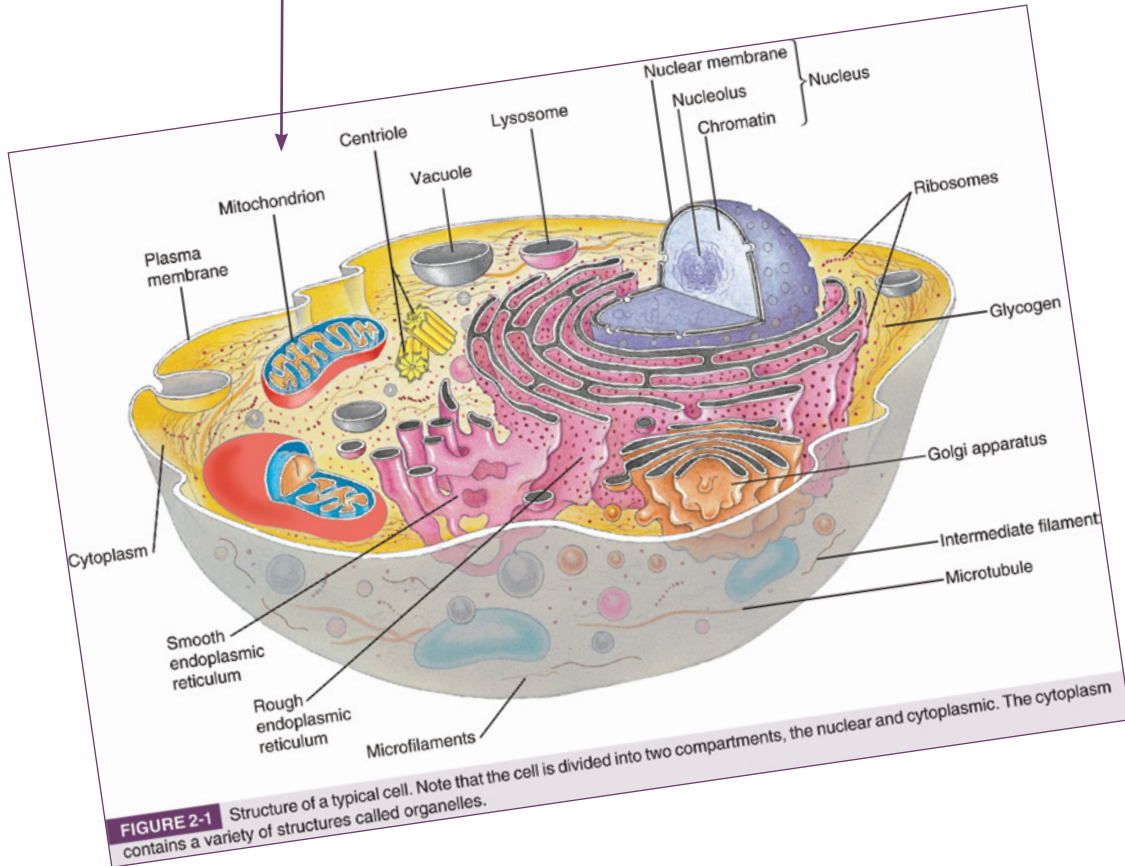
Transmission of genetic information was initially studied through the analysis of the inheritance of detectable traits (**phenotypic traits**) from parent through successive generations of offspring using **patterns of inheritance**. These phenotypic traits are now understood as the expression of the **genotype** of the individual; that is, the genes that are the functional manifestation of the chemical code of the **DNA** organized in **chromosomes** in the nucleus of the cell. The human **genome** contains about

**Phenotype** Collection of inherited/phenotypic traits detectable in an individual.

**Phenotypic traits** Characteristics apparent in the individual.

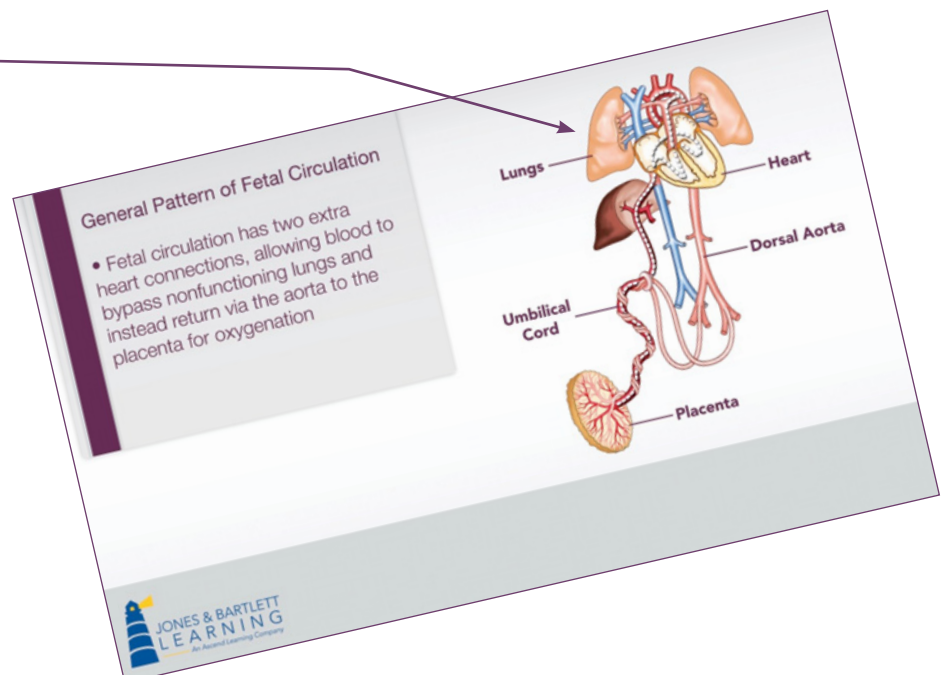
## EXTENSIVE ART PROGRAM

The extensive art program with a number of new photos and revised illustrations has been updated and enhanced to support the new focus on the cellular and molecular roots of disease, as well as to provide additional visual support for student comprehension.



## ANIMATIONS

Animations come with new, unused purchases of this book. Animations add visual clarity to key concepts and competencies.



## CASE STUDIES

Case studies in each chapter provide an opportunity for the student to apply the concepts presented in the text to a medical setting. The cases range from common diseases likely to be encountered by the student to more uncommon conditions, both of which serve to teach specific information that expands on what is presented in the chapter. For this reason, the cases are integral to the information we hope to impart.

### CASE 10-1

The patient, an eighteen-year-old female, is seen at the emergency room of a local hospital complaining of severe abdominal pain, vaginal bleeding, and delay in her expected menstrual period. She notes that she had unprotected vaginal intercourse about seven weeks prior and is concerned about a sexually transmitted disease. She experienced coitarche (initial sexual intercourse) at age fifteen and has been sexually active since that time with a variety of partners. She states that usually barrier protection was used by the male (condoms) but they did sometimes "forget." She notes that she has been seen in a venereal disease clinic several times in the past and was diagnosed with both gonorrhea and chlamydia infections for which she received antibiotic therapy "several times." A rapid pregnancy test is ordered, which is positive. Transvaginal ultrasound detects signs of an ectopic pregnancy (the fetus is implanted in a site other than the uterus) located in the fallopian tube (oviduct), a so-called tubal pregnancy. She suffers a decrease in blood pressure with hemorrhage (hemorrhagic shock) and is rushed to surgery. At surgery blood is found in the abdominal cavity (hemoperitoneum) and an 8 cm left mass was found that encompassed both the left fallopian tube and ovary. The mass contained a nonviable fetus judged to be of eight weeks gestational age (FIGURE 10-10). Both the left ovary and fallopian tube were removed (salpingo-oophorectomy). The contralateral fallopian tube and ovary showed numerous adhesions that distorted their anatomy and were considered to be consistent with long-standing pelvic inflammatory disease. Recovery was complicated by ongoing infections, but she eventually recovered.

## REVIEW QUESTIONS AND A DETAILED OUTLINE SUMMARY

Review questions and a detailed outline summary are provided for each chapter and provide students with a means to measure their learning.

### QUESTIONS FOR REVIEW

1. Why do spontaneous abortions occur? What are the consequences of prolonged retention of a dead fetus within the uterine cavity?
2. What is an ectopic pregnancy? What factors predispose to development of an ectopic pregnancy in the fallopian tube? What are the consequences of a tubal pregnancy?
3. What is the difference between a hydatidiform mole and a choriocarcinoma?
4. In infants with hemolytic disease, why does jaundice increase after delivery? Why does anemia become more severe after delivery?
5. How does the physician make a diagnosis of hemolytic disease? How is the disease treated?
6. What structures contribute to the formation of the placenta? What are the main functions of the placenta?
7. Describe some of the important abnormalities of the placenta and umbilical cord that may have an unfavorable effect on pregnancy.
8. What is the source of amniotic fluid? What factors regulate the total volume of amniotic fluid?
9. What are the possible causes and the significance of polyhydramnios? of oligohydramnios?

## SUPPLEMENTARY READINGS

Supplementary readings were selected to provide an opportunity for the student to dig deeper. We have tried to emphasize information sources that review and expand on the text although in some cases we have suggested more research-based material that we think is of specific interest. Such papers may be a challenge to some readers, but we hope they will encourage the learner. When possible we have tried to include authoritative sources and freely available material, much of which is web-based. We hope this text will interest and encourage anyone interested in pursuing a health-related career to continue in what is an area of critical importance to our society.

### SUPPLEMENTARY READINGS

Loeffler, A. G., and Hart, M. N. 2015. *Introduction to Human Disease*. 6th ed. Burlington, MA: Jones & Bartlett Learning.

- ▶ Those interested in the detailed study of male reproductive disease should consult a work on human pathology aimed at the undergraduate medical curriculum. However, a good place to start at a less advanced level is by reading Chapter 16 in this book.

Simmons, M. N., Berglund, R. K., and Jones, S. J. 2011. A practical guide to prostate cancer diagnosis and management. *Cleveland Clinic Journal of Medicine* 78:321–31.

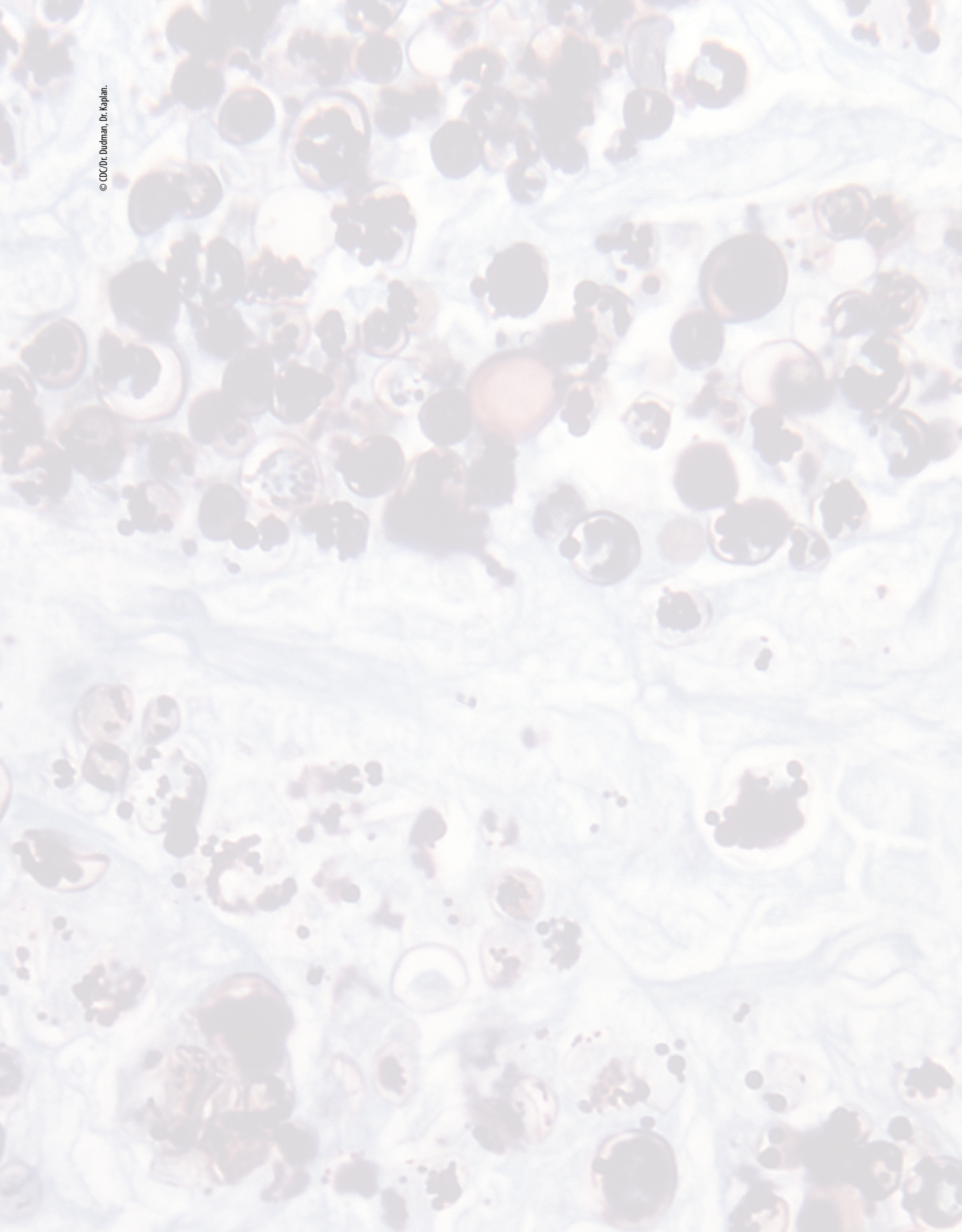
Ilic, D., Neuberger, I. D., Djulbegovic, M., and Dahm, P. 2013. Screening for prostate cancer (Review). Wiley Online Library. The Cochrane Collaboration. doi: 10.1002/14651858.CD004720.pub3

Hayes, J. H., and Barry, M. J. 2014. Screening for prostate cancer with prostate-specific antigen test. A review of current literature. *JAMA* 311:1143–49.

- ▶ One of the more controversial areas in urology is the appropriate role of prostate cancer screening. The first reference represents a conservative point of view for both diagnosis and therapy. The second entry provides a book-length review (see pages 1–9 for a brief review aimed at nontechnical readers). Both the second and third entries provide exhaustive of the literature with results that suggest little or no benefit for most groups of men (as measured in reduced deaths as a result of prostate cancer) using current approaches to screening.

# Case Studies

Chapter	Case Study
1	Appendicitis
2	Steatosis or Alcoholic Fatty Liver Disease
3	Hemophilia B
4	Congenital Cytomegalovirus Infection
5	Wound Infection
6	IgA Deficiency
7	Colon Cancer
8	Measles
9	Chagas Disease
10	Tubal Pregnancy
11	Sudden Cardiac Death
12	Kawasaki Disease
13	Acute Lymphoblastic Leukemia
14	Hemolytic Uremic Syndrome
15	Childhood Asthma
16	Fat Necrosis
17	Polycystic Ovary Syndrome
18	Potter Sequence
19	Minimal Change Disease
20	Testicular Cancer
21	Tylenol Overdose
22	Diabetes Cases (2)
23	Celiac Disease
24	Isolated GH Deficiency
25	Meningitis
26	Duchenne Muscular Dystrophy



# Teaching and Learning Aids

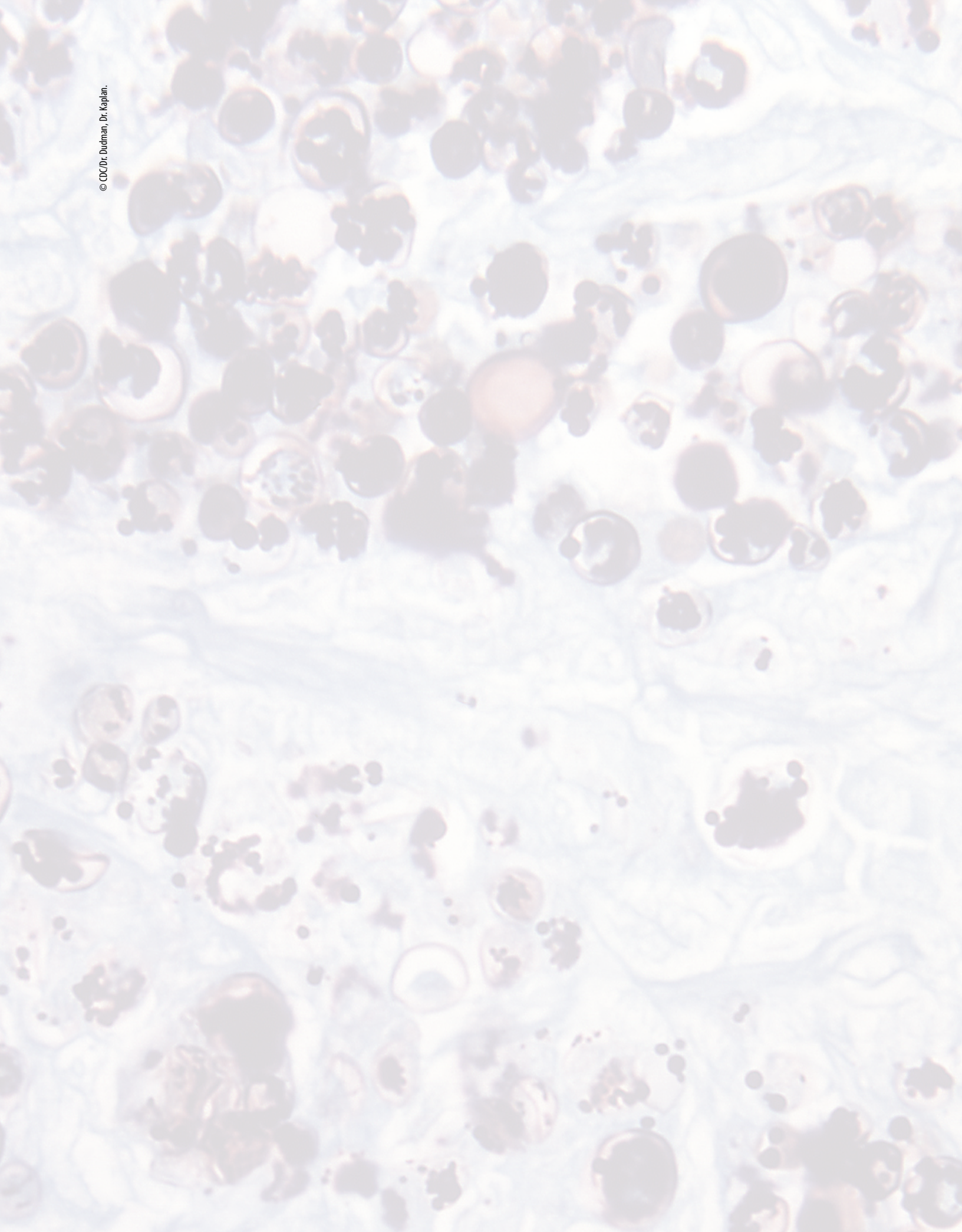
## Instructor Resources Include:

- Testbank
- Slides in PowerPoint Format
- Answers to Student Workbook
- Animations
  - Chromosomes -> DNA
  - Mitosis Stages A–F
  - Meiosis
  - Gametogenesis
  - Phagocytosis
  - Formation of Antigen Binding Regions in T and B Cells
  - How Antibodies Work in Host Defense
  - Pathogenesis of an Allergy
  - Replication Cycle of HIV
  - Blood Flow in the Heart
  - Fetal Circulation
  - Development of Gametes and Fertilization
  - Maturation of Ovum
  - TIPS Procedure
  - Rotary Twist of Sigmoid Colon

## Student Resources Include:

- Writable workbook exercises
- Student practice activities and assessments





# General Concepts of Disease: Principles of Diagnosis

## LEARNING OBJECTIVES

1. Define the common terms used to describe disease including, but not limited to, lesions, symptomatic and asymptomatic disease, etiology, and pathogenesis.
2. List the major categories of human disease.
3. Outline the approach a practitioner uses to make a diagnosis and decide on a patient's treatment.
4. Describe the various types of diagnostic tests and procedures that can help the practitioner make a diagnosis.
5. Compare and contrast the different imaging techniques described.

## What Is Disease?

**Disease**, in its broadest sense, is any compromise to the normal function of the body and the systems of which it is composed. However, it is best to consider health and illness as two extremes of a continuum. At one extreme is severe, disabling, or life-threatening illness with corresponding effects on our physical and emotional well-being. At the other extreme is ideal, perfectly good health, a state of physical and mental well-being wished for but rarely attained. Between these two extremes are many gradations of health and disease, ranging from mild or short-term illness that limits activities to some extent to moderate good health that falls short of the ideal state. The midpoint in this continuum, one in which one is neither ill nor in ideal good health, is where most of us are likely to fall. Who does not suffer from an occasional cold, sprain, upset stomach, or headache? As we get older, our average position in the continuum begins to shift. Disease is no longer occasional but becomes chronic as we suffer from degenerative conditions, which are part of the inevitable process of aging.

**Disease** Any disturbance of the structure or function of the body.

## How Do We Know We Are Sick?

How do you know you are sick? This seems an obvious question. Sometimes you do know and sometimes you don't. The subjective manifestations of disease, called

**Symptoms** Subjective manifestations of disease.

**Lesion** Any structural abnormality or pathologic change.

**Trauma** Injury caused by a physical extrinsic agent.

**Pathogen** Causative agent of disease.

**Inflammation** An early defensive reaction by the body to insult.

**Pathologist** Person who studies the structural and functional changes in the body caused by disease.

**Etiology** The cause, especially the cause of a disease.

**Pathogenesis** Manner in which a disease develops.

**Gross examination** Study of diseased organ with the naked eye.

**Histologic examination** Study of disease using a microscope to examine tissue.

**Immunological techniques** Techniques using antibody or antigen preparations, usually with chemical labels.

**Laboratory medicine** Study of the composition of body fluids to diagnose disease.

**Mnemonics** Aides to memory.

**Idiopathic** Disease of unknown origin.

**Iatrogenic** Disease resulting from a medical intervention.

**Clinician** Physician having direct contact with patients.

**Signs** Physical findings of disease.

**Asymptomatic** Disease without symptoms.

**symptoms**, may be related to apparent **lesions** such as structural abnormalities like a broken bone or a painful swelling. Often, symptoms are the result of the body's reaction to injury, which may be the result of **trauma** or infection by **pathogens**. Symptoms such as fever, muscle aches, and pain are part of the process of **inflammation**, an early defensive reaction by the body to insult (discussed in the presentation on inflammation).

**Pathologists** study the **etiology** (cause) and **pathogenesis** (progression or “natural history”) of disease by evaluating lesions at the level of organs, the tissues that comprise the organs, the cells that form the tissues, and the molecules of which the cells are composed. The pathologist may observe the diseased tissue with the naked eye (**gross examination**) or with the aid of a microscope (**histologic examination**). Histologic examination may be supplemented by the use of special methods of identifying normal or abnormal tissue components using biochemical or **immunological techniques** (see the discussion of immunology). It is increasingly common for pathologists to study the molecules of which the tissue is composed using the techniques of molecular biology. In addition, pathologists working in the area of **laboratory medicine** study the composition of our body fluids (blood and urine, for example) to look for markers of disease.

## Classifications of Disease

Pathologists interested in etiology classify diseases into several large categories. Although these categories are broad, this helps in understanding how a disease is likely to progress and how it will affect the patient. There are several alternative systems but medical students (who appreciate **mnemonics**) often use the term VINDICATE'M as a scheme:

Vascular  
 Infectious (or Inflammatory)  
 Neoplastic  
 Degenerative (or Deficiency)  
 Idiopathic (or Iatrogenic)  
 Congenital  
 Allergic (or Autoimmune)  
 Traumatic  
 Endocrine (or Environmental)  
 Metabolic

With the exceptions of **idiopathic** (of unknown origin) and **iatrogenic** (physician caused), most of these terms will be familiar and discussed in detail in subsequent chapters. Although the above scheme is useful, many diseases fit in multiple categories or fit poorly in any.

## Principles of Diagnosis

The first physician to see the patient and to diagnose the disease is the **clinician** (the generalist physician, or specialist in a particular area of medicine or surgery) who is expert in detecting and evaluating the objective manifestations of disease, the **signs** or physical findings. However, a disease may cause the affected individual no discomfort or disability (an **asymptomatic** disease). Because disease is most often asymptomatic in its early stages, it may progress to the point where it causes subjective symptoms, abnormal physical findings, and is more difficult, impossible, or costly to treat. Therefore, early detection of disease, even before it is brought to the attention of the clinician, is of great importance to the public and is a major concern of the specialist in **public health** who might design **screening** systems for early diagnosis.

Determination of the nature and cause of a patient's illness by a physician or other health practitioner is called a **diagnosis**. It is based on the practitioner's evaluation of the patient's history, subjective symptoms, the physical findings (signs), and the results of various laboratory tests, together with other appropriate diagnostic procedures. Many diagnostic procedures are **noninvasive** (requiring no physical invasion of the body, its openings, or cavities). A common example of such noninvasive diagnostic testing is the use of imaging technology (x-rays or ultrasound, for example). Sometimes diagnosis requires an **invasive** procedure. Such procedures may be relatively minor and have little discomfort associated with them. Common examples are drawing blood, obtaining a **Pap smear** (to collect a sample of cervical cells), or sampling fluid and cells from a surface accessible lesion with a very fine needle (**fine needle aspiration**). Somewhat more invasive are a variety of endoscopic procedures in which a tube (generally flexible) is passed into a body opening such as the esophagus or anus (as is done in the case of **colonoscopy**). Laparoscopic procedures involving the introduction of devices into body cavities or obtaining samples of internal organs (liver, kidney, and lungs, for example) by the use of sampling devices guided by imaging technology are yet more invasive, but much safer and potentially less costly than a surgical procedure.

The effort to reach a diagnosis may be minimal and require nothing more than evaluation of the patient's history and a physical examination, or it may require multiple diagnostic procedures and the intervention of several diagnostic specialists and extensive testing. Whatever the case, when the clinician has reached a diagnosis, he or she can then offer a **prognosis**, an opinion concerning the eventual outcome of the disease. A course of therapy (possibly in consultation with therapeutic specialists, e.g., physical therapists) may also be instituted. The foundation for the process of obtaining a diagnosis is the history and a physical examination.

## THE HISTORY

The clinical history is a critical initial step in the evaluation. As is the case in any interaction between individuals, this requires the physician to establish a relationship with the patient that facilitates the accurate verbal transmission of information. This is a two-way street. The patient must feel enabled to present his or her history both fully and accurately. The physician must be able to elicit such information and accurately interpret it without prejudice or bias (either scientific or social). This is often called a **patient-centered approach** to the history. Acquiring such interviewing skill is an early and essential part of the training of a medical student. To facilitate obtaining and recording an accurate, organized, patient history, a standard approach is generally used on an initial encounter, although it may be modified on subsequent visits. This approach consists of several parts:

1. **Chief complaint:** This introduction to the history seeks to establish why the patient has sought medical attention. Most often this is elicited in the patient's own words. It may be followed up by a brief survey of any additional problems currently being experienced by the patient.
2. **History of the current illness:** The physician develops a chronological framework of the patient's illness from first symptoms to the present. This part of the history establishes the "when, where, and how" of the chief complaint, that is, the source of the symptoms experienced.
3. **Past medical history:** To establish the patient's general state of health, information about past illnesses and medical interventions, medications, allergies, immunizations, reproductive history, and participation in health maintenance programs is recorded.

**Public health** Area of medicine concerned with the health of populations.

**Screening** Examining a large asymptomatic population for signs of future disease.

**Diagnosis** The determination of the nature and cause of a patient's illness.

**Noninvasive testing** Diagnostic procedure requiring no physical invasion of the body.

**Invasive** Test requiring a physical invasion of the body.

**Pap smear** A study of cells from the cervix. Commonly used as a screening test for cancer.

**Fine needle aspiration** Sampling fluid and cells from a surface accessible lesion.

**Colonoscopy** Examination of the colon with an endoscopic procedure.

**Prognosis** The probable outcome of a disease or disorder, the outlook for recovery.

**Patient-centered approach** Interviewing technique empowering the patient to provide a candid and complete medical history.

- 3a. *The family health history*: This part of the history provides background information about potential environmental or genetic aspects pertinent to the patient's complaint, the health status of the entire living family, and historical information about deceased relatives. Family history is important in diagnosing many common chronic diseases such as diabetes and heart disease.
- 3b. *The psychosocial and sexual history*: The patient's education and life experiences (including personal relationships, employment), and in females the gynecological/reproductive history, may provide important information to the diagnostician. Questions are asked about potentially addictive behaviors such as the use of alcohol, tobacco products, and recreational drugs.
4. *The review of systems*: This is often considered to be the center of the patient–physician encounter and consists of a body system–oriented, head to toe–review of all presenting symptoms in an organized manner. The review may disclose additional symptoms not initially reported by the patient that are important to the diagnosis. A physician investigating the presenting symptom of back pain may elicit the additional symptom of pain on urination during the review, which suggests potential urinary tract disease. The experienced physician often will undertake this review as part of the physical examination.

## THE PHYSICAL EXAMINATION

The physical examination is a system-based examination of the patient in an ordered manner. The practitioner places particular emphasis on the part of the body affected by the illness, such as the ears, throat, chest, and lungs in the case of a potential respiratory infection. However, particularly in a first encounter, all body systems are examined. For example, respiratory symptoms may be associated with a range of etiologies affecting multiple body systems (e.g., allergic diseases). Any abnormalities detected on the physical examination are correlated with the clinical history. At this point, the practitioner begins to construct a hypothesis regarding diseases or conditions that best fit with the clinical findings. Often, more than one diagnosis must be considered, and such consideration is likely to be altered by the results of laboratory and other diagnostic tests. In a **differential diagnosis**, the practitioner must consider a number of diseases that are characterized by the patient's symptoms. For example, respiratory symptoms might, based on patient history, suggest a seasonal allergy. Simple blood-based tests can aid in establishing such a diagnosis. A suggestion of renal problems in the patient could point to a serious, multisystem disease involving blood vessels (a vascular disease). Additional laboratory tests and potentially invasive procedures to sample patient tissue would be needed to support such a diagnosis.

In difficult cases, the clinician may also obtain the opinion of a medical consultant (a physician with special training and experience in the type of medical problem presented by the patient). For a respiratory disease, a pathologist experienced in tissue-based diagnosis or a **radiologist** expert in the analysis of x-ray and other visualization data produced by physical methods might be consulted. The wise physician always maintains a probabilistic approach in constructing the diagnosis. Given the patient's history, the most likely diagnosis is considered first (a respiratory infection) followed by alternatives (a seasonal allergy) and far less likely (but potentially life-threatening) multisystem vascular disease. In testing the diagnostic hypothesis, the clinician uses a variety of tests and procedures and considers the usefulness of possible results of the tests in the clinical reasoning process.

### Differential diagnosis

Consideration of the different diseases possible given the patient's symptoms.

**Radiologist** Physician expert in the use and analysis of imaging techniques and results.

## Diagnostic Tests and Procedures

Today a huge number of tests and procedures are available to the physician, with more than 60,000 medical and surgical procedures recognized in the standard coding system used in the United States (ICD-10-PCS). One major medical center lists more than 1,300 laboratory tests that are available to its staff. How does the clinician choose from this massive array? Medical procedures carry a degree of risk, ranging from trivial to potentially serious. Diagnostic tests and procedures also vary in the amount of information they provide in relation to a potential diagnosis. For example, colonoscopy provides no information in the case of respiratory symptoms, but it may lead to a definitive diagnosis in the case of possible bleeding from the rectum. Tests and procedures differ in complexity and cost. Colonoscopy costs thousands of dollars at a major medical center, whereas determination of fecal blood (i.e., blood in stool) is trivial in cost. In a period of increased concern about the economic aspects of health care, cost must also be considered.

## Choosing a Diagnostic Test

A diagnostic test can be defined in terms of a set of characteristics that help the clinician judge the usefulness of the procedure in diagnosing a specific disease. A perfect test would always be positive in a patient who has the disease in question and always negative in one who does not. Such a test does not exist. Instead, tests are classified by the terms *sensitivity* and *specificity*. **Sensitivity** refers to the percentage of patients classified as positive by a test who *do* have the disease. A test with a high sensitivity will miss few people with the disease (have a low rate of **false negatives**). The obverse of sensitivity is **specificity**. Specificity refers to the percentage of patients without the disease who are classified as negative by the test. Tests with a high specificity will have a low rate of **false positives**. The clinician attempts to choose a test with as high a sensitivity and specificity as possible for the diagnosis in question. Unfortunately, highly sensitive tests tend to have lower specificity (misdiagnosing people as having a disease they do not have; i.e., having a higher rate of false positives). “Missing” a disease is obviously harmful, leading to a delay in therapy and potentially a more severe illness. However, a false positive result, assuming a patient has a disease he or she does not, may also lead to anxiety, discomfort, and unneeded therapy.

Choice of tests also depends on the patient population. For example, a patient in a clinic who is suspected of having a disease (based on prior clinical information) is much less likely to yield a false negative result than an individual chosen at random off the street. A physician who is considering an invasive, painful, or costly mode of therapy might choose to use a test with high specificity to exclude a false positive result. However, the case is different when choosing screening assays to be applied to a population in which the diagnostic target is a relatively uncommon but potentially serious (possibly fatal) illness where early diagnosis might effect a cure. If we choose a highly sensitive test (so as not to miss the uncommon affected person), the test is likely to lack specificity, increasing the number of individuals incorrectly suspected of having the disease. If there is an acceptable confirmatory test, or if the therapy is relatively harmless, such a test might be considered for use in screening. However, if the only confirmatory test (or therapy) requires a risky procedure (such a surgery), the test would be unacceptable. This is a very real problem. For example, a number of noninvasive tests have been proposed to screen for ovarian cancer because undiagnosed and untreated ovarian cancer is fatal. However, the currently available tests lack specificity and would expose an appreciable number of nonaffected women to invasive diagnostic procedures (although undoubtedly the test would lead to

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**Sensitivity** Classification of diagnostic tests in regard to percentage of patients classified as positive by a test who do have the disease.

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**False negative** Negative test result which should be positive.

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**Specificity** Classification of diagnostic tests in regard to the percentage of patients without the disease who are classified as negative by the test.

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**False positive** Positive test result which should be negative.

---

early diagnosis in some). So decisions in screening assay use are difficult and often lead to controversy—even among experts. The recent discussion about the utility of mammography as a screening test for breast cancer (discussed in greater detail in the presentation of breast tissue) is an example of how complex such decisions are.

In summary, the clinician makes a risk/benefit/cost determination in choosing diagnostic procedures. What set of tests will yield the greatest information with the least risk and cost to the patient? At times this can be a very difficult determination in which the clinician is guided by the findings of the clinical epidemiologist. Such determinations are part of **evidence-based medicine**, which seeks to define risk/benefit/cost ratios based on prior rigorous investigations. Going hand in hand with evidence-based medicine is **patient-centered medicine**, in which patients have a central role in decisions about their care. Patients are fully informed about the possible risks and benefits so that they can make informed decisions as to whether or not to consent to the procedure or ask to consider alternative approaches.

#### Evidence-based medicine

Definition of treatment plan, risks/benefits/costs based on prior rigorous investigation.

#### Patient-centered medicine

Practice of medicine encouraging patients to have a role in decision making.

## Classification of Diagnostic Tests and Procedures

Diagnostic tests and procedures can be classified into several major categories:

1. Clinical laboratory tests: including biochemical, immunological, and molecular-based tests; determination of gases in the blood; analysis of blood cells; and microbiological analysis.
2. Imaging techniques including x-ray, ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET scans), and measurement of the distribution of radioisotopes (also called radionuclides).
3. Cytologic and histologic examination of cells and tissues removed from the patient.
4. Endoscopy.
5. Tests that measure the electrical activity in portions of the body.

There is often overlap among these categories. For example, endoscopy may provide a sample that will be examined histologically or cultured in the clinical laboratory to detect an infectious agent. Some endoscopic procedures are done using radiographic guidance. Another way of classifying tests is by the medical specialty responsible for providing them. Clinical laboratory medicine, a division of pathology, is responsible for the broad range of clinical laboratory tests. Anatomic pathology provides tissue and cell-based analysis and the autopsy service. Radiology is responsible for essentially all image-based techniques but also provides a number of therapeutic procedures. Endoscopy covers a broad range of procedures that may be performed by specific medical specialists (gastroenterologists perform colonoscopy, e.g., cardiologists are responsible for a number of intravascular procedures such as placing stents to open blocked blood vessels supplying the heart). Other endoscopic procedures are performed by the surgical specialties. For example, examination of the urinary tract is the purview of urologists.

### CLINICAL LABORATORY TESTS

Laboratory medicine is the area of pathology that provides and interprets diagnostic testing related to patient care. Clinical laboratory tests serve not only to aid in diagnosing disease but also in searching for occult (unrecognized) disease, establishing

the severity of disease, and monitoring its progression and treatment. In laboratory medicine, basic analytical science meets medical science, and it is often the place where a new aspect of biomedicine is “translated” into patient care. Hence, analytical aspects of biochemistry, immunology, microbiology, physiology, and molecular biology are used in the clinical laboratory.

The role of the clinical laboratory and the tests it provides often are not obvious to the patient, who might simply donate several tubes of blood or a urine sample as part of a visit to the physician. However, it has been estimated that 60 to 70 percent of medical diagnoses rely on clinical tests. Almost 7 billion clinical tests are performed each year in the United States, and a major medical center may perform more than 6 million tests a year. In general, such tests are a “good buy.” Less than 5 percent of health care dollars are spent on laboratory tests.

Given the large number of available tests it is difficult to summarize the many uses of clinical tests. **FIGURE 1-1** provides an example of a standard set of laboratory tests along with normal ranges for the results.

Results that are “out of range” are flagged as either low or high, and it is up to the physician to determine the significance of the results. Determining the concentration of various constituents in the blood and urine is of major importance in evaluating the function of organ systems. For example, the concentration of a substance in the

Patient Name: DOE, MARY

Patient MRNO: 0000012345

Order Number: C6140101

Collection Date: 2009-06-14 at 0400

Source:

Site:

Date Completed	Test Name	Result	Flag	Units	Range
<b>Individual Test(s)</b>					
2009-06-14	SODIUM	129	L	MMOL/L	135-145
2009-06-14	POTASSIUM	4.2		MMOL/L	3.5-5.0
2009-06-14	CHLORIDE	97	L	MMOL/L	98-107
2009-06-14	CO <sub>2</sub>	25		MMOL/L	22-30
2009-06-14	UREA NITROGEN	26	H	MG/DL	7-21
2009-06-14	CREATININE	0.82		MG/DL	0.60-1.00
2009-06-14	EST. GFR (MDRD)	>= 60		mL/min/1.73m <sup>2</sup>	>=60
2009-06-14	ANION GAP	7	L	MMOL/L	9-15
2009-06-14	BUN/CREAT RATIO	32			UNDEFINED
2009-06-14	GLUCOSE, RANDOM	108		MG/DL	65-179
2009-06-14	MAGNESIUM	1.7		MG/DL	1.6-2.2
2009-06-14	PHOSPHORUS	3.5		MG/DL	2.4-4.5
<b>CBC+PLATELETS</b>					
2009-06-14	CBC+PLATELETS	:			
2009-06-14	WBC	11.7	H	×10 <sup>9</sup> th/L	4.5-11.0
2009-06-14	RBC	3.80	L	×10 <sup>12</sup> th/L	4.00-5.20
2009-06-14	HGB	11.9	L	G/DL	12.0-16.0
2009-06-14	HCT	33.1	L	%	36.0-46.0
2009-06-14	MCV	87		FL	80-100
2009-06-14	MCH	31		PG	26-34
2009-06-14	MCHC	36		G/DL	31-37
2009-06-14	RDW	13.1		%	12.0-15.0
2009-06-14	MPV	7.2		FL	7.0-10.0
2009-06-14	PLATELET COUNT	247		×10 <sup>9</sup> th/L	150-440

**FIGURE 1-1** Example of a laboratory report.

Courtesy of Dr. Catherine Hammett-Stabler, Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill.



blood called urea is elevated if the kidneys are not functioning properly because this constituent is normally excreted by the kidneys. The concentrations of hemoglobin and the quantity of red cells are reduced in patients with anemia. Sometimes the enzyme level in the blood is elevated because (a) enzymes are leaking from damaged cells in the diseased or injured organs (“liver function tests” are an example), (b) enzyme synthesis is increased as a result of disease, or (c) excretion of enzymes is impaired because disease has caused failure of normal excretory pathways.

Clinical laboratory tests also are used to evaluate the specific functions of organs. Pulmonary function tests measure the rate and efficiency with which air moves in and out of the lungs. Determinations of the concentration of oxygen and carbon dioxide in the blood also can indicate pulmonary function by evaluating how efficiently the lungs oxygenate the blood and eliminate carbon dioxide. A simple device (pulse oximeter) applied to the finger can determine the amount of oxygen carried by hemoglobin in circulating blood as another measure of pulmonary function. This is an example of a **point-of-care test**, which can be performed outside of the laboratory in the physician’s office or at a patient’s bedside. Of increasing importance are tests to detect and measure concentrations of substances that are likely to be produced by tumors growing within the body. Serial analyses of these substances can be used to monitor the response of certain tumors to treatment. Microbiologic tests detect the presence of disease-producing organisms in urine, blood, bronchial secretions, and feces. These tests also can determine the responsiveness of the organisms to antibiotics. Serologic tests detect and measure the presence of antibodies as an indication of response to infectious agents and can evaluate the suitability of blood for transfusion or organs for transplantation into a patient.

#### Point-of-care test

Laboratory test that can be performed at the patient’s bedside or in the physician’s office.

**Radiograph/x-ray** An image taken with x-rays.

#### Computed tomographic (CT) scan

An x-ray technique producing detailed cross-sectional images of the body by means of x-ray tube and detectors connected to a computer. Sometimes called a CAT scan.

#### Magnetic resonance imaging (MRI)

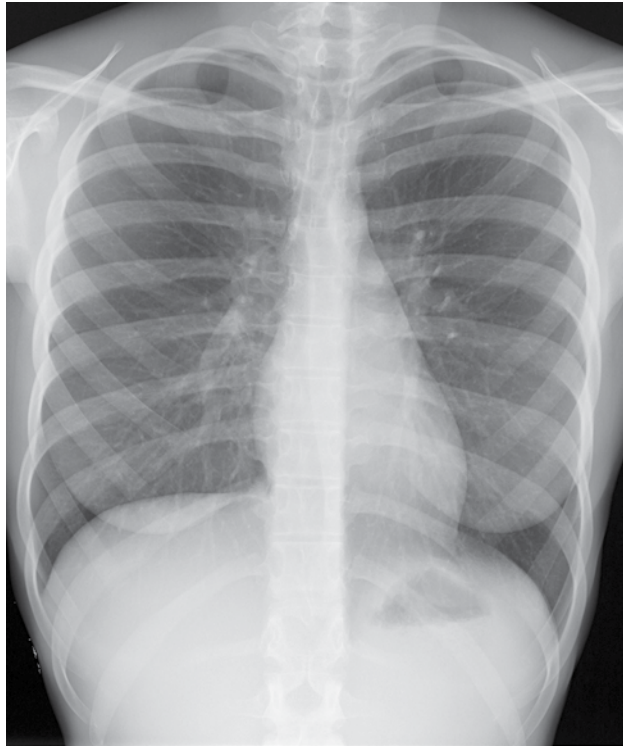
A diagnostic procedure that yields computer-generated images based on the movement of hydrogen atoms in tissues subjected to a strong magnetic field.

## IMAGING TECHNIQUES

Imaging technology enables the physician (and specifically the radiologist, the expert in obtaining and interpreting the results of imaging studies) to produce a view of the body and its organ systems previously available only to the surgeon (or to the anatomist or pathologist postmortem). Imaging technology permits anatomic investigation of the living patient, most often with little or no risk and minimal discomfort. The earliest and still an important use of imaging technology is the production of two-dimensional projected images of interior organ systems, **x-rays** or **radiographs**. However, modern computer technology now allows three-dimensional reconstruction of body systems (tomography) either using x-rays as an imaging source (**computed tomographic [CT] scans**) or by using the magnetic properties of certain body constituents (most often  $^1\text{H}$  in body water). To the physicist this property is called nuclear magnetic resonance; to the physician such studies are termed **magnetic resonance imaging (MRI)**. Of growing importance is the use of ultrasound to image accessible areas of the body. The technique depends on the differences in acoustical properties of tissue, so the movement and velocity of blood in vessels (Doppler ultrasound) is easily studied; images of the developing fetus can also safely be produced.

### X-Ray Examination

X-ray examinations are conducted in many ways, but the basic principle is the same. X-rays (electromagnetic radiation akin to visible light or radio waves, but much higher in energy) are produced in a vacuum tube by the impact of electrons on a tungsten target. The x-rays pass through the area of interest and are detected most commonly by a digital detecting device (formerly photographic film). X-rays are absorbed to a variable degree depending on the density of the tissue they pass through. Tissues



**FIGURE 1-2** Chest x-ray (normal). Normal chest x-ray shows white bones and dark lung fields. The heart (*center of image*) and organs below the diaphragm (*bottom third of image*) are also white because of the density of the soft tissue through which the x-rays pass.

Courtesy of Dr. Donald Yandow, Department of Radiology, University of Wisconsin School of Medicine and Public Health.

of low density, such as the air-filled lungs, transmit most of the x-rays and appear black on the image. Tissues of high density, such as bone, absorb most of the rays and appear white on the image. Tissues of intermediate densities appear in varying shades of gray. The two-dimensional image produced is called a radiograph, or sometimes a “plain film” (**FIGURE 1-2**).

Special terminology is used for particular radiographic studies. For example, a specialized radiographic study of the breast is called a mammogram.

The lining of some internal organ systems, such as the digestive and urinary tract, have little contrast. To aid in their examination, a nontoxic radiopaque substance (a contrast medium) designed to coat the lining (mucosa) of the organ systems may be used to outline the area of interest. For example, barium contrast media may be swallowed or given as an enema to outline portions of the gastrointestinal tract. Irregularities in the column of barium may represent constrictions in a portion of the GI tract. After the bulk of contrast material either passes through or is expelled from the tract, the remainder coats the surface of the tract and outlines details of the internal surface such as tumors, erosions, or ulcers for detection (**FIGURE 1-3**).

Other soluble radiopaque substances can be injected into the circulation to aid in detecting irregularities or blockages in the vascular system and to study the renal and urinary system as the material is excreted from the kidney and passes through the bladder and remainder of the urinary tract (an intravenous pyelogram [IVP]) (**FIGURE 1-4**). The movement of contrast agents in portions of the body also can be studied in “real time” or be recorded as a movie using a technique known as fluoroscopy.