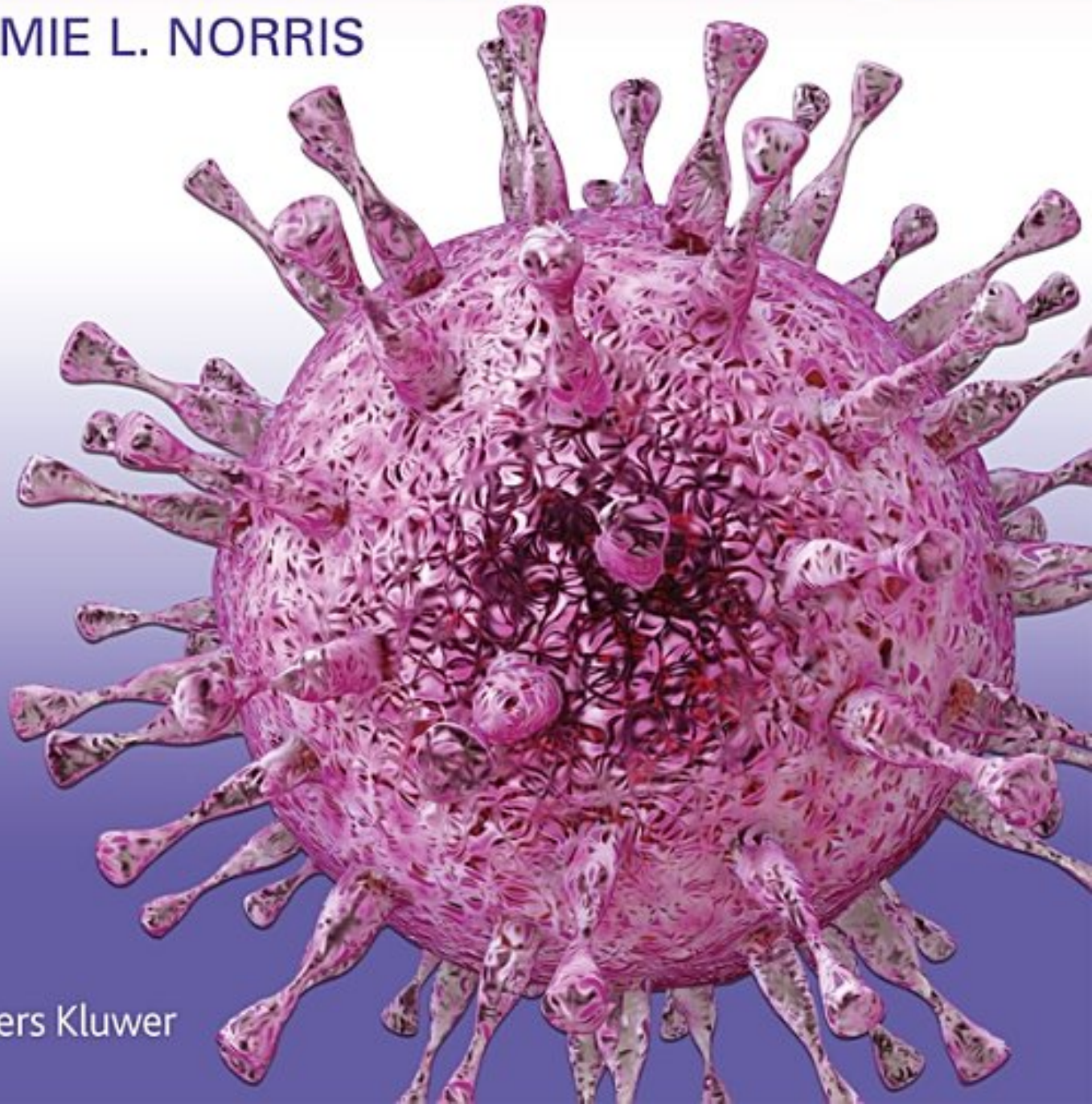
PORTH'S

Essentials of Pathophysiology

FIFTH EDITION

TOMMIE L. NORRIS



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FIFTH EDITION

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To my husband, Stephen Sr., and children—Richie, Robby,
Stephen Jr., and Rachel—who always inspire me.
To those pursuing or continuing a love for healthcare,
with a special thanks for your dedication, compassion, and selflessness.

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Preface

This book was written with the intent of presenting the subject matter of pathophysiology as the foundation for all future studies in the health sciences. The text provides necessary content for the beginning student to build upon while also serving those furthering their education by reinforcing the link between comprehending complex disease process and clinical decision-making. This text will serve as a reference long after the coursework is completed.

This edition considers the many technologic advances allowing health care providers to diagnose earlier and with more accuracy. A diverse array of contributors for *Porth's Pathophysiology*, 10th Edition (from which this *Essentials* book is derived)was selected based on subject expertise.

This text focuses on the scientific basis upon which the practice components of the health professions are based. The evidence-based information provides data for best practices, ultimately improving health care outcomes.

A holistic conceptual framework uses body systems as an organizing structure and demonstrates how the systems are interrelated. Selection of content was based on common causes of morbidity and mortality across the life span, and recent advances in the fields of genetics, epigenetics, immunology, microbiology, and molecular biology are included. Content is presented in a manner that is logical and understandable for students. One goal of the new edition is to provide critical information needed to understand complex health alterations while delivering the content in a reader-friendly format. The chapters are arranged so that fundamental concepts such as cellular adaptation, inflammation and repair, genetic control of cell function and inheritance, and immunologic processes appear in the early chapters before the specific discussions of particular disease states.

Strengths of the text include the expanded chapters on health and disease; nutrition; sleep and sleep disorders; and thought, emotion, and mood disorders. Advances in health care are presented through the inclusion of international studies, World Health Organization guidelines, updated standards, and the health variants of diverse populations.

Organization

Many of the units have an introductory chapter that contains essential information about the structure and function of the body systems that are being discussed in the unit. Each such chapter provides the foundation for understanding the pathophysiology content presented in

the subsequent chapters. The chapter outline that appears at the beginning of each chapter provides an overall view of the chapter content and organization.

Features of This Book

This book includes the following special features to help you master the essential content.

Objectives

Objectives appear at the beginning of each chapter to provide a focus for your study. After you have finished each of these areas of content, you may want to go back and make sure that you have met each of the objectives.

Learning Objectives

After completing this chapter, the learner will be able to meet the following objectives:

1. Contrast disorders due to multifactorial inheritance with those caused by single-gene inheritance.
2. Cite the most susceptible period of intrauterine life for development of defects because of teratogenic agents.
3. State the cautions that should be observed when considering use of drugs during pregnancy, including the possible effects of alcohol abuse, vitamin A derivatives, and folic acid deficiency on fetal development.
4. Describe the process of genetic assessment.
5. Describe screening methods used for prenatal diagnosis including specificity and risks.

Key Terms and Glossary

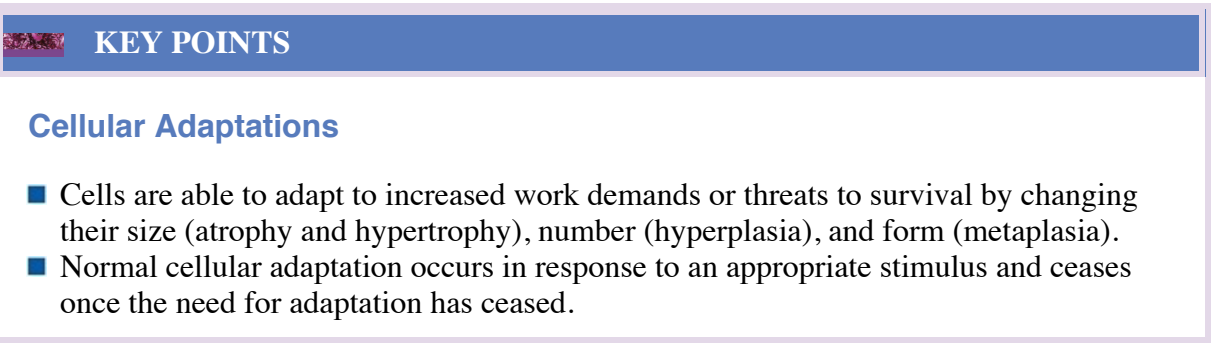
To enable you to better use and understand the vocabulary of your profession, throughout the text you will encounter key terms in bold purple. This is a signal that a word and the ideas associated with it are important to learn. In addition, a glossary is provided to help you expand your vocabulary and improve your comprehension of what you are reading. The glossary contains concise definitions of the key terms. If you are unsure of the meaning of a term you encounter in your reading, check the glossary in the back of the book before proceeding.

Lysosomes play an important role in the normal metabolism of certain substances in the body. In some inherited diseases known as **lysosomal storage disorders**, a specific lysosomal enzyme is absent or inactive, preventing digestion of certain cellular substances and allowing them to build up in cells.[6] There are approximately 50 lysosomal storage disorders, each caused by a lack of activity of one or more lysosomal enzymes, and each disorder is rare.

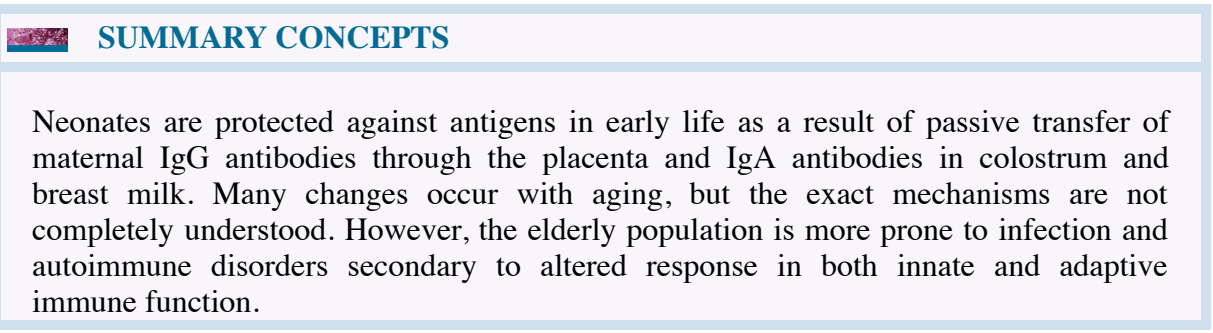
Boxes

Boxes are used throughout the text to summarize and highlight key information.

"Key Points" Boxes
One of the ways to approach learning is to focus on the major ideas or concepts. Because health care is an applied science, it is imperative that rather than trying to memorize a list of related and unrelated bits of information, you understand the content and relate it to cases you encounter. Health care providers must apply these concepts in the clinical setting, which requires an understanding of the underlying etiology, histology, symptoms, risk factors, and hallmark features of a particular disease. As you have probably already discovered, it is impossible to memorize everything that is in a particular section or chapter of the book. It has been said that pathophysiology is a new language for many students. So not only does your brain have to figure out where to store all the information, it must also be able to retrieve the information when you need it. This is best accomplished by understanding rather than memorizing information. Most important of all, memorized lists of content can seldom, if ever, be applied directly to an actual clinical situation. The "Key Points" boxes guide you in identifying the major ideas or concepts that form the foundation for truly understanding the major areas of content. When you understand the concepts in the "Key Points" boxes, you will have a framework for remembering and using the facts given in the text.



"Summary Concepts" Boxes
The "Summary Concepts" boxes at the end of each main section provide a review and a reinforcement of the important content that has been covered. Use the summaries to ensure that you have covered and understood what you have read.



"Understanding" Boxes
"Understanding" boxes focus on the physiologic processes and phenomena that form the basis for understanding disorders presented in the text. This feature breaks a process or phenomenon

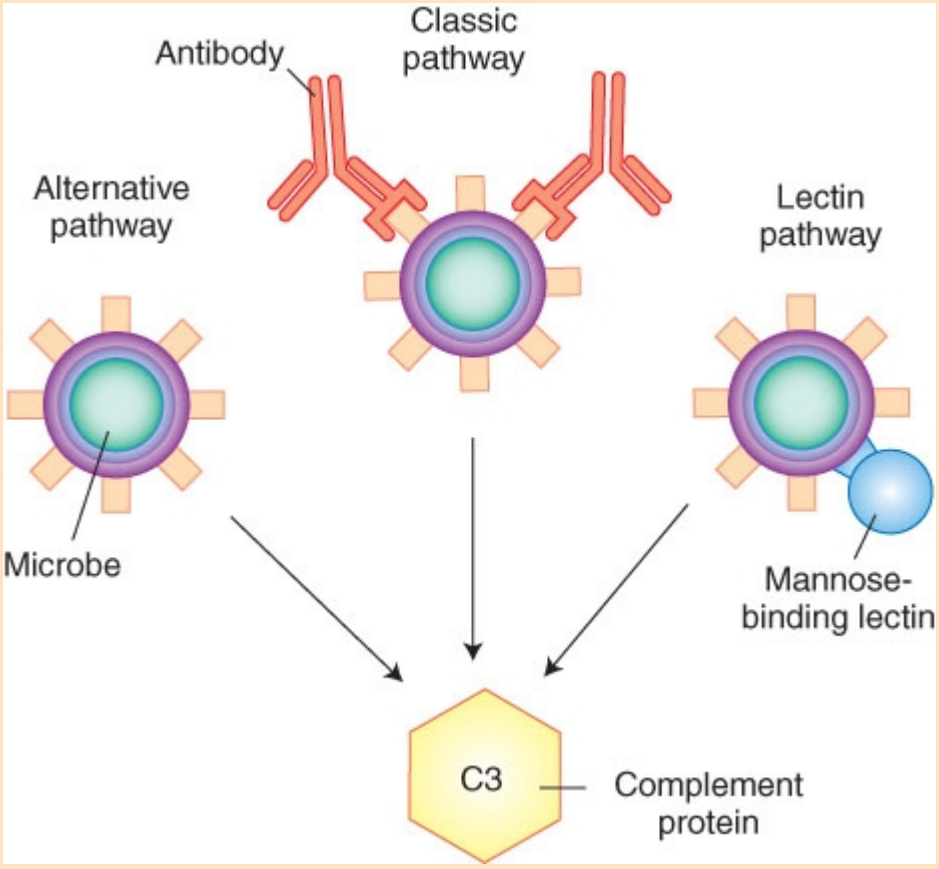
down into its component parts and presents it in a sequential manner, providing an insight into the many opportunities for disease processes to disrupt the sequence.

UNDERSTANDING → The Complement System

The complement system provides one of the major effector mechanisms of both humoral and innate immunity. The system consists of a group of proteins (complement proteins C1 through C9) that are normally present in the plasma in an inactive form. Activation of the complement system is a highly regulated process, involving the sequential breakdown of the complement proteins to generate a cascade of cleavage products capable of proteolytic enzyme activity. This allows for tremendous amplification because each enzyme molecule activated by one step can generate multiple activated enzyme molecules at the next step. Complement activation is inhibited by proteins that are present on normal host cells; thus, its actions are limited to microbes and other antigens that lack these inhibitory proteins.

The reactions of the complement system can be divided into three phases: **(1)** the initial activation phase, **(2)** the early-step inflammatory responses, and **(3)** the late-step membrane attack responses.

1 Initial Activation Phase



There are three pathways for recognizing microbes and activating the complement system: (1) the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody and is a component of innate immunity; (2) the classical pathway, which is activated by certain types of antibodies bound to antigen and is part of humoral immunity; and (3) the lectin pathway, which is activated by a plasma lectin that binds to mannose on microbes and activates the classical system pathway in the absence of antibody.

Tables and Charts

Tables and charts are designed to present complex information in a format that makes it more meaningful and facilitates recall of the information. Tables, which have two or more columns, are often used for the purpose of comparing or contrasting information. Charts, which have one column, are used to summarize information.

TABLE 20-1 Common Disorders Affecting the Vestibular System

Type of Disorder	Pathology
Acoustic neuroma	A noncancerous growth or tumor on the vestibulocochlear nerve
Benign paroxysmal positional vertigo	Disorder of otoliths
Ménière disease	Dislodgement of otoliths that participate in the receptor function of the vestibular system
Motion sickness	Repeated stimulation of the vestibular system such as during car, air, and boat travel
Labyrinthitis	Acute viral or bacterial infection of the vestibular pathways
Vestibular migraine	Dizziness or vertigo occurs with or without headache; related to the neurotransmitter serotonin

Illustrations and Photos

The detailed, full-color illustrations will help you to build your own mental image of the content that is being presented. Each drawing has been developed to fully support and build upon the ideas in the text. Some illustrations are used to help you picture the complex interactions of the multiple phenomena that are involved in the development of a particular disease; others can help you to visualize normal function or understand the mechanisms that enable the disease processes to exert their effects. In addition, photographs provide a realistic view of selected pathologic processes and lesions.

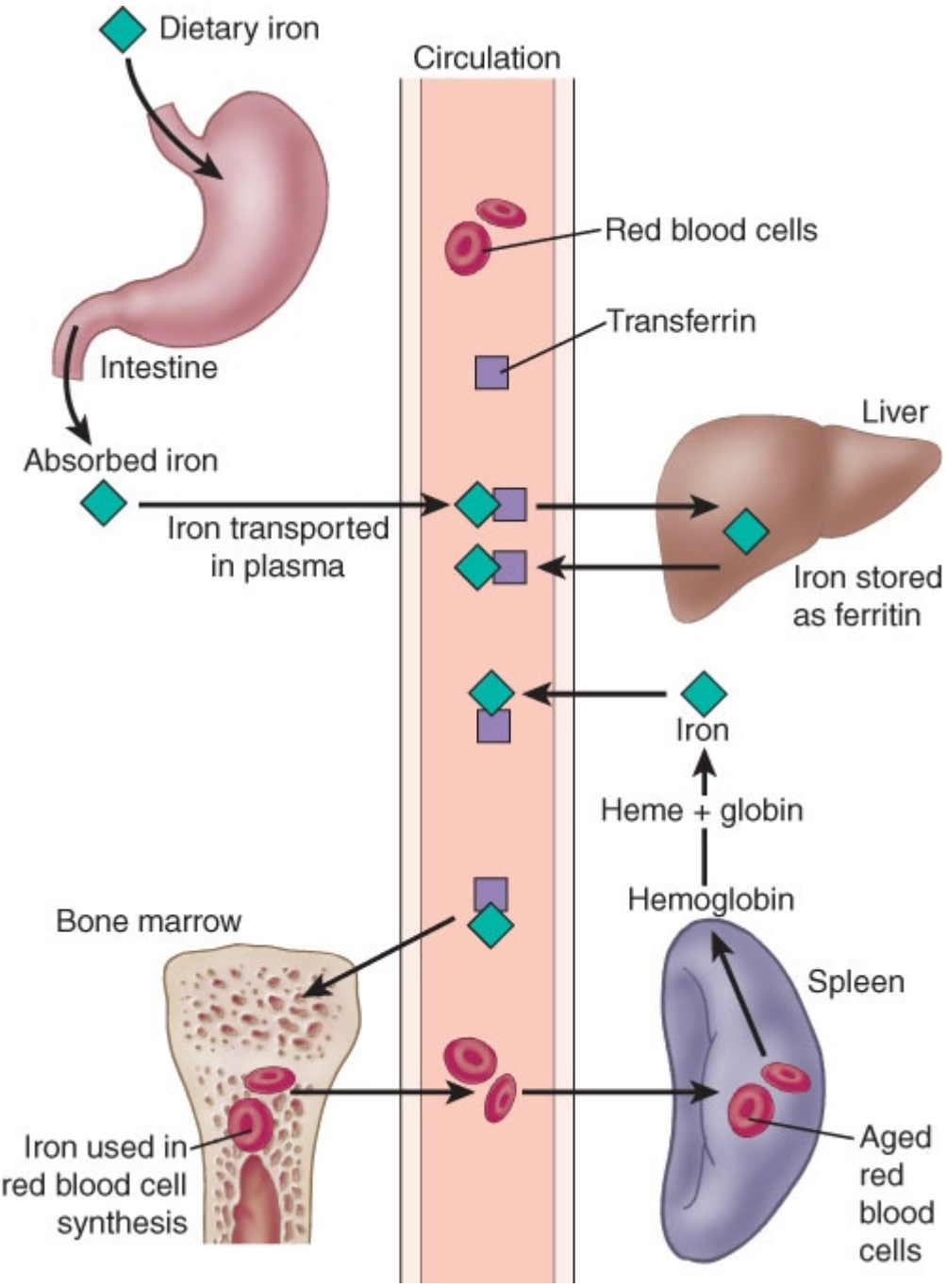


FIGURE 23-3 Diagrammatic representation of the iron cycle, including its absorption from the gastrointestinal tract, transport in the circulation, storage in the liver, recycling from aged red cells destroyed in the spleen, and use in the bone marrow synthesis of red blood cells.

Concept Mastery Alerts

Concept Mastery Alerts clarify fundamental nursing concepts to improve the reader's understanding of potentially confusing topics, as identified by Misconception Alerts in Lippincott's Adaptive Learning Powered by prepU.

Concept Mastery Alert

Smoking is an independent risk factor for the development of coronary artery disease and should be avoided, but it has not been identified as a direct cause of hypertension.

Interactive Learning Resources

Interactive learning tools available online enrich learning and are identified with icons in the text.

- **Concepts in Action Animations** bring physiologic and pathophysiologic concepts to life, explaining concepts that are difficult to understand.
- **Interactive Tutorials** include graphics and animations and provide interactive review exercises.

Review Exercises

The Review Exercises at the end of each chapter are designed to help you integrate and synthesize material and to help you verify your understanding of the material presented. If you are unable to answer a question, reread the relevant section in the chapter. (Answers are available for instructors at http://thepoint.lww.com/PorthEssentials5e.)

Review Exercises

1. A 32-year-old woman with diabetes is found to have a positive result on a urine dipstick test for microalbuminuria. A subsequent 24-hour urine specimen reveals an albumin excretion of 50 mg (an albumin excretion >30 mg/day is abnormal).
   - **A.** Use the structures of the glomerulus in Figure 32-5 to provide a possible explanation for this finding. Why specifically test for the albumin rather than the globulins or other plasma proteins?
   - **B.** Strict control of blood sugars and treatment of hypertension have been shown to decrease the progression of kidney disease in person with diabetes. Explain the physiologic rationale for these two types of treatments.
2. A 54-year-old man, seen by his physician for an elevated blood pressure, was found to have a serum creatinine of 2.5 and BUN of 30. He complains that he has been urinating more frequently than usual, and his first morning urine specimen reveals dilute urine with a specific gravity of 1.010.
   - **A.** Explain the elevation of serum creatinine in terms of renal function.
   - **B.** Explain the inability of people with early renal failure to produce concentrated urine as evidenced by the frequency of urination and the low specific gravity of his first morning urine specimen.

Appendix

The appendix "Lab Values" provides rapid access to normal values for many laboratory tests, as well as a description of the prefixes, symbols, and factors (*e.g.*, micro, μ, 10^{-6}) used for describing these values. Knowledge of normal values can help you to put abnormal values in context.

A Comprehensive Package for Teaching and Learning

To further facilitate teaching and learning, a carefully designed ancillary package has been developed to assist faculty and students.

Instructor Resources

Tools to assist you with teaching your course are available upon adoption of this text on thePoint at http://thepoint.lww.com/PorthEssentials5e.

- A **Test Generator** features NCLEX-style questions mapped to chapter learning objectives.
- An extensive collection of materials is provided for each book chapter:
  - **Pre-lecture Quizzes** (and answers) allow you to check students' reading.
  - **PowerPoint Presentations** provide an easy way to integrate the textbook with your students' classroom experience; multiple-choice and true/false questions are included to promote class participation.
  - **Guided Lecture Notes** walk you through the chapter, learning objective by learning objective, with integrated references to the PowerPoint presentations.
  - **Discussion Topics** (and suggested answers) can be used in the classroom or in online discussion boards to facilitate interaction with your students.
  - **Assignments** (and suggested answers) include group, written, clinical, and Web assignments to engage students in varied activities and assess their learning.
  - **Case Studies** with related questions (and suggested answers) give students an opportunity to apply their knowledge to a client case similar to one they might encounter in practice.
  - **Answers to the Review Exercises** in the book facilitate review of student responses to these exercises.
- Sample **Syllabi** are provided for 14-week and 28-week courses.
- An **Image Bank** lets you use the photographs and illustrations from this textbook in your course materials.
- An **ebook** serves as a handy resource.
- **Strategies for Effective Teaching** provide general tips for instructors related to preparing course materials and meeting student needs.
- **Dosage Calculation Quizzes** and **Drug Monographs** are convenient references.
- Access to all **Student Resources** is provided so that you can understand the student experience and use these resources in your course as well.

Student Resources

An exciting set of free learning resources is available on thePoint to help students review and apply vital concepts. Multimedia engines have been optimized so that students can access many of these resources on mobile devices. Students can access all these resources at

http://thepoint.lww.com/PorthEssentials5e using the codes printed in the front of their textbooks.

- **NCLEX-Style Review Questions** for each chapter help students review important concepts and practice for NCLEX.
- **Interactive learning resources** appeal to a variety of learning styles. As mentioned previously in this preface, icons in the text direct readers to relevant resources:
  - **Concepts in Action Animations** bring physiologic and pathophysiologic concepts to life, explaining concepts that are difficult to understand.
  - **Interactive Tutorials** include graphics and animations and provide interactive review exercises.
- **Journal Articles** offer access to current articles relevant to each chapter and available in Wolters Kluwer journals to familiarize students with nursing literature.
- **Learning Objectives** from the book.
- **A Spanish–English Audio Glossary** provides helpful terms and phrases for communicating with patients who speak Spanish.

Adaptive Learning Powered by PrepU

Lippincott's Adaptive Learning Powered by prepU helps every student learn more, while giving instructors the data they need to monitor each student's progress, strengths, and weaknesses. The adaptive learning system allows instructors to assign quizzes or students to take quizzes on their own that adapt to each student's individual mastery level. Visit http://thePoint.lww.com/prepU to learn more.

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The same trusted solution, innovation, and unmatched support that you have come to expect from *Lippincott CoursePoint* is now enhanced with more engaging learning tools and deeper analytics to help prepare students for practice. This powerfully integrated digital learning solution combines learning tools, case studies, real-time data, and the most trusted nursing education content on the market to make curriculum-wide learning more efficient and to meet students where they are at in their learning. And now, it is easier than ever for instructors and students to use, giving them everything they need for course and curriculum success!

Lippincott CoursePoint includes:

- Engaging course content provides a variety of learning tools to engage students of all learning styles.
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- Powerful tools, including varying levels of case studies, interactive learning activities, and adaptive learning powered by PrepU, help students learn the critical thinking and clinical judgment skills to help them become practice-ready nurses.
- Unparalleled reporting provides in-depth dashboards with several data points to track student progress and help identify strengths and weaknesses.
- Unmatched support includes training coaches, product trainers, and nursing education consultants to help educators and students implement CoursePoint with ease.

Acknowledgments

The expertise of the contributors for *Porth's Pathophysiology*, 10th Edition (from which this *Essentials* book is derived) keeps the book at the forefront of advances in science and medicine. Their attention to detail and desire to share current, relevant, and essential information with learners are primary strengths of the text. For the fifth edition, several chapters were merged to improve flow of content, and chapters that include new discoveries were added. Thanks also to Dr. Rupa Lalchandani Tuan for her time and talent in helping to ensure the accuracy of the information and assisting in condensing it to reflect only essential content needed to understand disease processes.

I would like to thank Jonathan Joyce, senior acquisitions editor, for keeping us on task so the project remained on track. Many thanks go to Meredith Brittain, senior development editor, for her edits and comments that kept the focus of this book consistent. I also want to thank Jennifer Forestieri, director of product development, who stepped in to help, and especially for all her encouragement. Thanks also to Tim Rinehart, who provided the chapter tracking updates.

Lastly, I want to thank my family for their inspiration during this difficult time of transition in my life. I also want to thank all the professors who have kept in touch with me throughout this project, cheering me forward to produce a text that is understandable yet concise and that meets the learning needs of today's health care professional.

Contents

UNIT 1

Concepts of Health and Disease

CHAPTER 1

Concepts of Health and Disease

Concepts of Health and Disease

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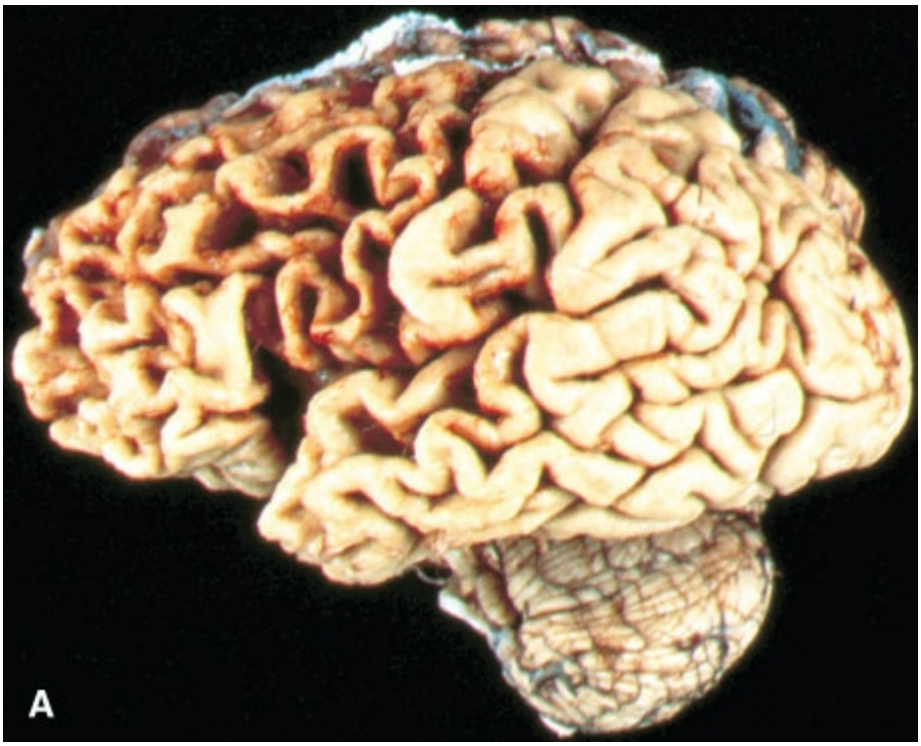
Learning Objectives

After completing this chapter, the learner will be able to meet the following objectives:

1. Compare the World Health Organization definition of health to the *Healthy People 2020* definition.
2. Define *pathophysiology*.

3. Describe the process of disease to include etiology, pathogenesis, morphologic changes, clinical manifestations, diagnosis, and clinical course.
4. Define the term *epidemiology*.
5. Compare the meaning of the terms *incidence* and *prevalence* as they relate to measures of disease frequency.
6. Differentiate primary, secondary, and tertiary levels of prevention.
7. Compare morbidity and mortality.

The term *pathophysiology*, which is the focus of this book, may be defined as the physiology of altered health. The term combines the words *pathology* and *physiology*. Pathology (from the Greek *pathos*, meaning "disease") deals with the study of the structural and functional changes in cells, tissues, and organs of the body that cause or are caused by disease. Physiology deals with the functions of the human body. Thus, pathophysiology deals not only with the cellular and organ changes that occur with disease but also with the effects that these changes have on total body function (Fig. 1-1). Examples of atrophy of the brain (Fig. 1-1A) and hypertrophy of the myocardium (Fig. 1-1B) illustrate pathophysiologic changes from a cerebrovascular accident to long-standing unmanaged hypertension and how this impacts the myocardium. Pathophysiology also focuses on the mechanisms of the underlying disease and provides information to assist with planning preventive as well as therapeutic health care measures and practices such as following a healthy diet, exercising, and being compliant with prescribed medications. This chapter is intended to orient the reader to the concepts of health and disease, various terms that are used throughout the book, the sources of data and what they mean, and the broader aspects of pathophysiology in terms of the health and well-being of populations.



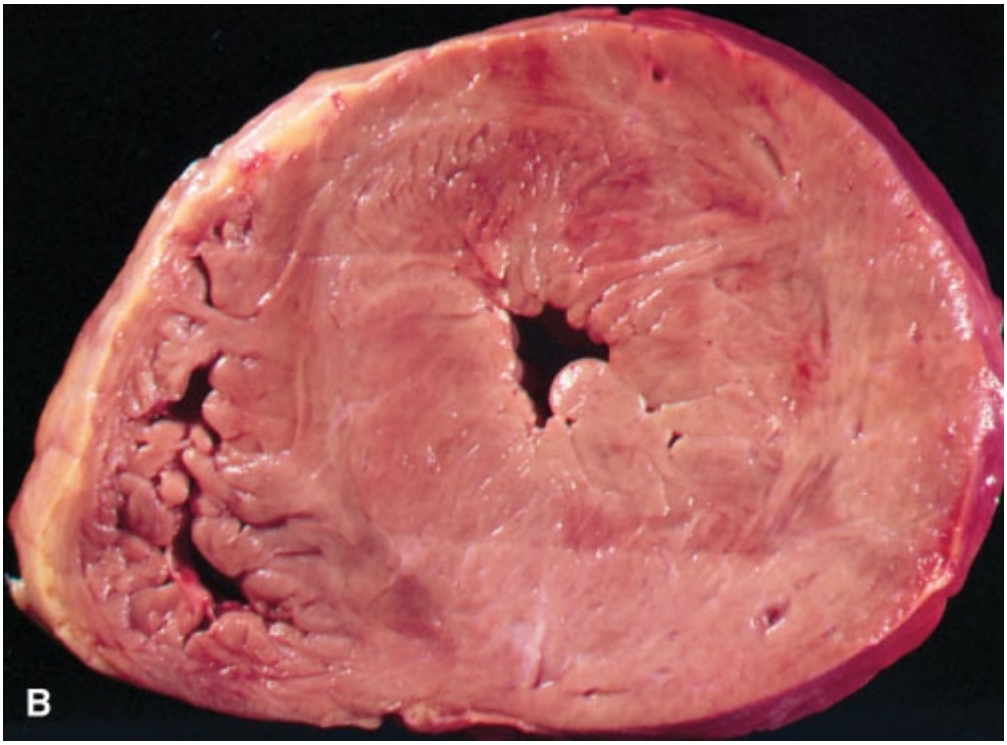


FIGURE 1-1 **(A)** Atrophy of the frontal lobe of the brain. The gyri are thin and the sulci are extremely wide. **(B)** Myocardial hypertrophy. This cross section of the heart illustrates left ventricular hypertrophy because of long-standing hypertension. (From Strayer D. S., Rubin R. (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., p. 16). Philadelphia, PA: Lippincott Williams & Wilkins.)

Concepts of Health and Disease

What constitutes health and disease often is difficult to determine because of the way different people view the topic. What is defined as health is determined by many factors, including genetics, age, gender, cultural, and ethnic differences, as well as individual, group, and governmental expectations. Most importantly, health is what the individual perceives it to be, which may vary across time and the factors mentioned.

Health

In 1948, the Preamble to the Constitution of the World Health Organization (WHO) defined health as a "state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity," a definition that has not been amended since that time.[1] Although ideal for many people, this was an unrealistic goal. The U.S. Department of Health and Human Services in *Healthy People 2020* describes the determinants of health as

1. Attain lives free of preventable disease, disability, injury, and premature death.
2. Achieve health equity and eliminate disparities.
3. Promote good health for all.
4. Promote healthy behaviors across the life span.[2]

Every decade, the U.S. Department of Health and Human Services leads initiatives to facilitate the goals of the new decade in their report such as the current *Healthy People 2020*. These consensus reports are developed to specifically assist in preventing some health problems and to offer advice to promote health as defined by the WHO.

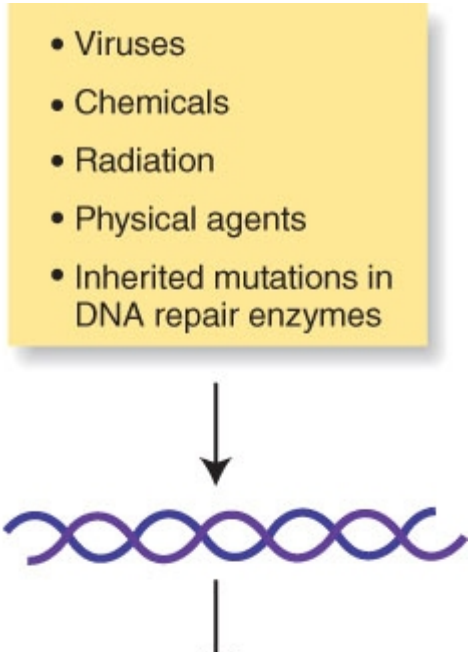
Disease

A disease is an acute or chronic illness that one acquires or is born with and that causes physiologic dysfunction in one or more body systems. Each disease generally has specific signs and symptoms that characterize its pathology and identifiable **etiology**. The aspects of the disease process include etiology, pathogenesis, morphologic changes, clinical manifestations, diagnosis, and clinical course.

Etiology

The causes of disease are known as *etiologic factors*. Among the recognized etiologic agents are biologic agents (*e.g.*, bacteria, viruses), physical forces (*e.g.*, trauma, burns, radiation), chemical agents (*e.g.*, poisons, alcohol), one's genetic inheritance, and nutritional excesses or deficits.

Most disease-causing agents are nonspecific, and many different agents can cause disease of a single organ. On the other hand, a single agent or traumatic event can lead to disease of a number of organs or systems. For example, in **cystic fibrosis**, sickle cell anemia, and familial hypercholesterolemia, a single amino acid, transporter **molecule**, or receptor protein produces widespread pathology. Although a disease agent can affect more than a single organ and a number of disease agents can affect the same organ, most disease states do not have a single cause. Instead, the majority of diseases are multifactorial in origin. This is particularly true of diseases such as cancer, heart disease, and diabetes. This is illustrated in Figure 1-2, which traces the five causes of cancer and the pathophysiology that evolves from the disease mechanisms triggered by the causes. The multiple factors that predispose to a particular disease often are referred to as *risk factors*.



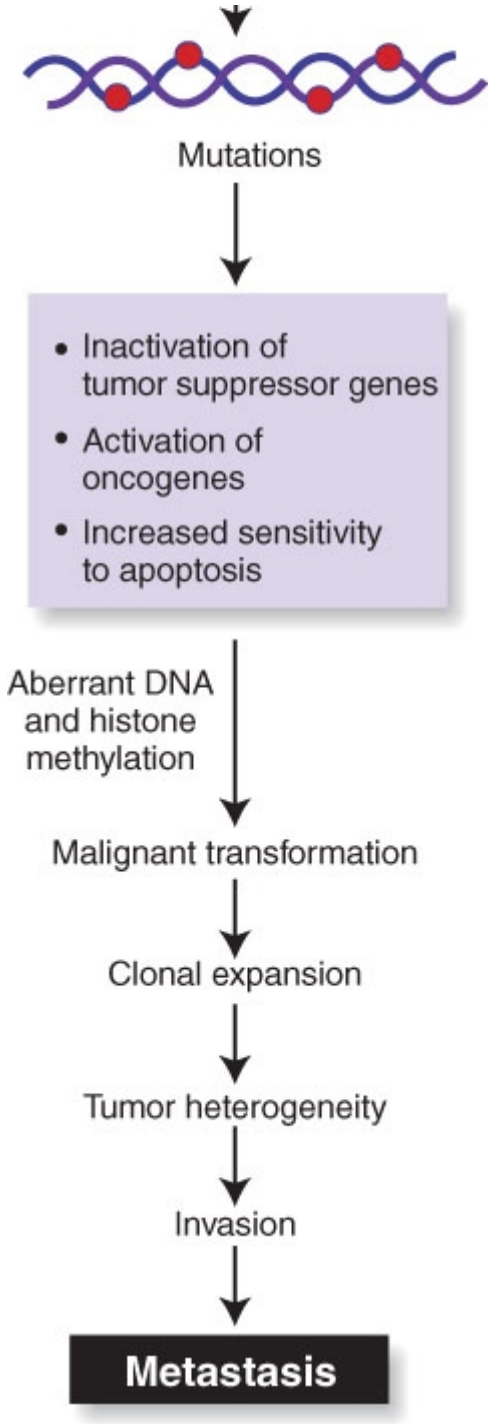


FIGURE 1-2 Summary of the general mechanisms of cancer. DNA, deoxyribonucleic acid. (From Strayer D. S., Rubin R. (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., p. 231). Philadelphia, PA: Lippincott Williams & Wilkins.)

One way to view the factors that cause disease is to group them into categories according to whether they were present at birth or acquired later in life. **Congenital** *conditions* are defects that are present at birth, although they may not be evident until later in life or may never

manifest. Congenital conditions may be caused by genetic influences, environmental factors (*e.g.*, viral infections in the mother, maternal drug use, irradiation, or gestational position in utero), or a combination of genetic and environmental factors. *Acquired defects* are those that are caused by events that occur after birth. These include injury, exposure to infectious agents, inadequate nutrition, lack of oxygen, inappropriate immune responses, and neoplasia. Many diseases are thought to be the result of a genetic predisposition and an environmental event or events that serve as a trigger to initiate disease development. There are 35,000 genes in the human genome, 1 to 10 million proteins, and 2 to 3000 metabolites of the human metabolome.[3] Huge advances in molecular biology and the wide variability of people have led to evolution in systems biology and personalized medicine. This will assist in identifying the etiology of disease and in the development of individualized interventions.[3]

Pathogenesis

Although etiology describes what sets the disease process in motion, *pathogenesis* explains how the disease process evolves. In other words, pathogenesis is the sequence of cellular and **tissue** events that take place from the time of initial contact with an etiologic agent until the ultimate expression of a disease. Although etiology and pathogenesis are two terms often used interchangeably, their meanings are quite different. For example, atherosclerosis often is cited as the etiology (or cause) of coronary artery disease. In reality, the progression of the inflammatory process from a fatty streak to the occlusive vessel **lesion** seen in people with coronary artery disease represents the pathogenesis of the disorder. The true etiology of atherosclerosis remains largely uncertain.

Morphology and Histology

Morphology refers to the fundamental structure or form of **cells** or tissues. *Morphologic changes* are concerned with both the gross anatomic and microscopic changes that are characteristic of a disease. **Histology** deals with the study of the cells and extracellular **matrix** of body tissues. The most common method used in the study of tissues is the preparation of histologic sections—thin, translucent sections of human tissues and organs—that can be examined with the aid of a microscope. Histologic sections play an important role in the diagnosis of many types of cancer. Diagnostic pathology has evolved greatly in the last few years to include immunologic and molecular biologic tools for studying disease states (Fig. 1-3).[4]

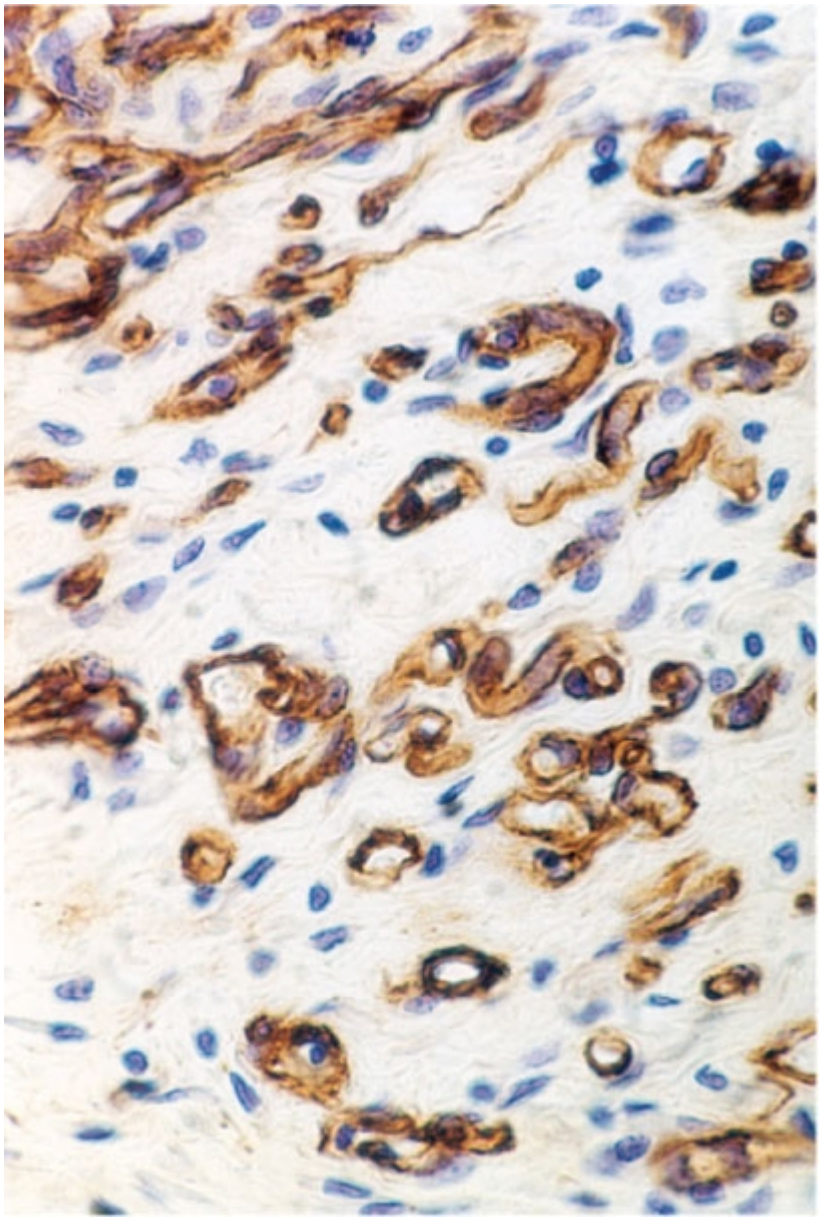


FIGURE 1-3 Granulation tissue. A photomicrograph of granulation tissue shows thin-walled capillary sprouts immunostained to highlight the basement membrane collagens. The infiltrating capillaries penetrate a loose connective tissue matrix containing mesenchymal cells and occasional inflammatory cells. (From Rubin R., Strayer D. S. (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., p. 113. Figure 3–9). Philadelphia, PA: Lippincott Williams & Wilkins.)

Clinical Manifestations

Diseases can manifest in a number of ways. Sometimes, the condition produces manifestations, such as fever, that make it evident that the person is sick. In other cases, the condition is silent at the onset and is detected during examination for other purposes or after the disease is far advanced.

Signs and *symptoms* are terms used to describe the structural and functional changes that accompany a disease. A *symptom* is a subjective complaint that is noted by the person with a disorder, whereas a *sign* is a manifestation that is noted by an observer. Pain, difficulty in breathing, and dizziness are symptoms of a disease. An elevated temperature, a swollen extremity, and changes in pupil size are objective signs that can be observed by someone other than the person with the disease. Signs and symptoms may be related to the primary disorder, or they may represent the body's attempt to compensate for the altered function caused by the pathologic condition. A **syndrome** is a compilation of signs and symptoms (*e.g.*, chronic fatigue syndrome) that are characteristic of a specific disease state. *Complications* are possible adverse **extensions** of a disease or outcomes from treatment. *Sequelae* are lesions or impairments that follow or are caused by a disease.

Diagnosis

A *diagnosis* is the designation as to the nature or cause of a health problem (*e.g.*, bacterial pneumonia or hemorrhagic stroke). The diagnostic process requires a careful history, physical examination (PE), and diagnostic tests. The history is used to obtain a person's account of his or her symptoms and their progression and the factors that contribute to a diagnosis. The PE is done to observe for signs of altered body structure or function. Diagnostic tests are ordered to validate what is thought to be the problem. They are also performed to determine other possible health problems that were not obtained from the history and PE, but may be present given the signs and symptoms identified.

The development of a diagnosis involves weighing competing possibilities and selecting the most likely one from among the conditions that might be responsible for the person's clinical presentation. The clinical probability of a given disease in a person of a given age, gender, race, lifestyle, genetic background, and locality often is influential in arrival at a presumptive diagnosis. Laboratory tests and imaging are used to confirm a diagnosis.

An important factor when interpreting diagnostic test results is the determination of whether they are normal or abnormal. Is a blood count above normal, within the normal range, or below normal? What is termed a *normal* value for a laboratory test is established statistically from test results obtained from a selected sample of people. A normal value represents the test results that fall within the bell curve or the 95% distribution. Thus, the normal levels for serum sodium (136 to 145 mEq/L) represent the mean serum level for the reference population ±2 standard deviations. The normal values for some laboratory tests are adjusted for gender, other comorbidities, or age. For example, the normal hemoglobin range for women is 12.0 to 16.0 g/dL and for men, 14.0 to 17.4 g/dL.[5] Serum creatinine level often is adjusted for age in the elderly, and normal values for serum phosphate differ between adults and children.

Laboratory parameters are interpreted based on the reliability, validity, sensitivity, and specificity of the measurement.[5,6] *Validity* refers to the extent to which a measurement tool measures what it is intended to measure. For example, the validity of blood pressure measurements obtained by a sphygmomanometer might be compared with those obtained by intraarterial findings, which are measurements obtained from invasive arterial catheters inserted into radial arteries of acutely ill people. *Reliability* refers to the extent to which an observation, if repeated, gives the same result. A poorly calibrated blood pressure machine may give inconsistent measurements of blood pressure, particularly of pressures in either the high or low range. Reliability also depends on the person's skill in taking the measurements. For example, blood pressure measurements may vary from one person to another because of the technique that is used (*e.g.*, different observers may deflate the cuff at a different rate, thus

obtaining different values), the way the numbers on the manometer are read, or differences in hearing **acuity**.

In the field of clinical laboratory measurements, *standardization* is aimed at increasing the trueness and reliability of measured values. Standardization relies on the use of written standards, reference measurement procedures, and reference materials.[7] In the United States, the Food and Drug Administration reviews information to decide whether a product may be marketed in the United States.

Measures of sensitivity and specificity are concerned with determining how likely or how well the test or observation will identify people with the disease and people without the disease (Fig. 1-4).[5,6] *Sensitivity* refers to the proportion of people with a disease who are positive for that disease on a given test or observation (called a *true-positive* result). If the result of a very sensitive test is negative, it tells us the person does not have the disease and the disease has been excluded or "ruled out." *Specificity* refers to the proportion of people without the disease who are negative on a given test or observation (called a *true-negative* result). Specificity can be calculated only from among people who do not have the disease. A test that is 95% specific correctly identifies 95 of 100 normal people. The other 5% are *false-positive* results. A false-positive test result can be unduly stressful for the person being tested, whereas a *false-negative* test result can delay diagnosis and jeopardize the outcome of treatment.

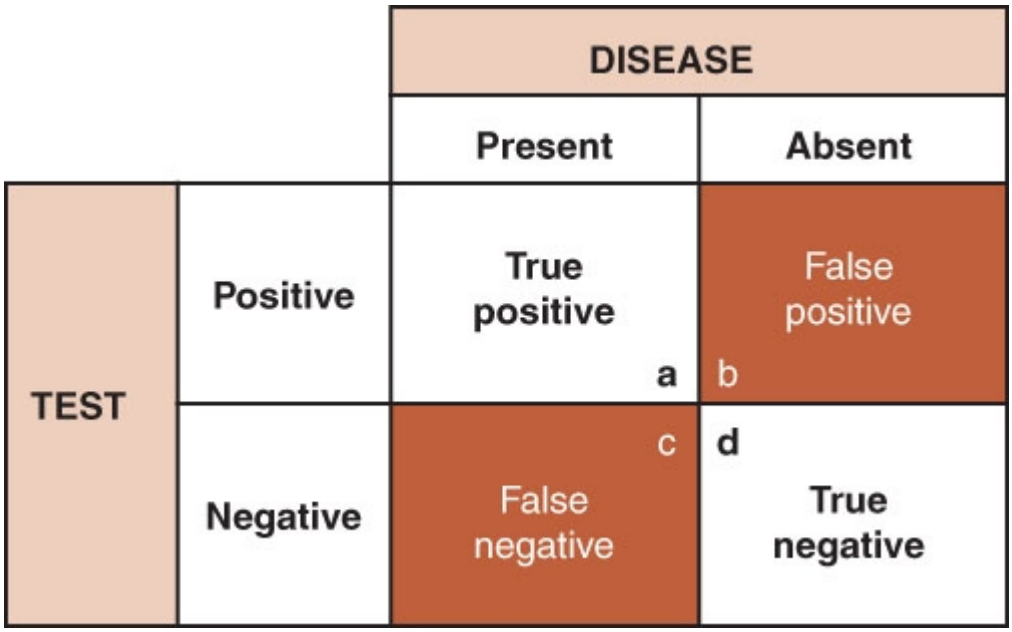


FIGURE 1-4 The relationship between a diagnostic test result and the occurrence of disease. There are two possibilities for the test result to be correct (true positive and true negative) and two possibilities for the result to be incorrect (false positive and false negative). (From Fletcher R. H., Fletcher S. W. (2014). *Clinical epidemiology: The essentials* (5th ed., p. 109). Philadelphia, PA: Lippincott Williams & Wilkins.)

Predictive value is the extent to which an observation or test result is able to predict the presence of a given disease or condition.[8] A *positive predictive value* refers to the proportion of true-positive results that occurs in a given population. In a group of women found to have "suspect breast nodules" in a cancer screening program, the proportion later determined to have breast cancer would constitute the positive predictive value. A *negative predictive value*

refers to the true-negative observations in a population. In a screening test for breast cancer, the negative predictive value represents the proportion of women without suspect nodules who do not have breast cancer. Despite unchanging sensitivity and specificity, the positive predictive value of an observation rises with **prevalence**, whereas the negative predictive value falls.

Clinical Course

The clinical course describes the evolution of a disease. A disease can have an acute, subacute, or chronic course. An *acute disorder* is one that is relatively severe, but self-limiting. *Chronic disease* implies a continuous, long-term process. A chronic disease can run a continuous course or can present with **exacerbations** (aggravation of symptoms and severity of the disease) and **remissions** (a period during which there is a decrease in severity and symptoms). *Subacute disease* is intermediate or between acute and chronic. It is not as severe as an acute disease and not as prolonged as a chronic disease.

The spectrum of disease severity for infectious diseases, such as hepatitis B, can range from preclinical to persistent chronic infection. During the *preclinical stage*, the disease is not clinically evident but is destined to progress to clinical disease. As with hepatitis B, it is possible to transmit a virus during the preclinical stage. *Subclinical disease* is not clinically apparent and is not destined to become clinically apparent. It is diagnosed with antibody or culture tests. Most cases of tuberculosis are not clinically apparent, and evidence of their presence is established by skin tests. *Clinical disease* is manifested by signs and symptoms. A persistent chronic infectious disease persists for years, sometimes for life. *Carrier status* refers to a person who harbors an organism but is not infected, as evidenced by antibody response or clinical manifestations. This person still can infect others. Carrier status may be of limited duration or it may be chronic, lasting for months or years.

SUMMARY CONCEPTS

The term *pathophysiology* may be defined as the physiology of altered health. A *disease* has been defined as any deviation from or interruption of the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms or signs and whose etiology, pathology, and prognosis may be known or unknown. The causes of disease are known as *etiologic factors*. *Pathogenesis* describes how the disease process evolves. *Morphology* refers to the structure or form of cells or tissues; *morphologic changes* are changes in structure or form that are characteristic of a disease.

A disease can manifest in a number of ways. A *symptom* is a subjective complaint, such as pain or dizziness, whereas a *sign* is an observable manifestation, such as an elevated temperature or a reddened, sore throat. A *syndrome* is a compilation of signs and symptoms that are characteristic of a specific disease state.

A *diagnosis* is the designation as to the nature and cause of a health problem. Having a comprehensive understanding of pathophysiology will assist the health care provider to best identify problems during the history and PE and to use laboratory data as further validation.[5]

The *clinical course* of a disease describes its evolution. It can be acute (relatively severe, but self-limiting), chronic (continuous or episodic, but taking place over a long

period), or subacute (not as severe as acute or as prolonged as chronic). Within the disease spectrum, a disease can be designated preclinical, not clinically evident; subclinical, not clinically apparent and not destined to become clinically apparent; or clinical, characterized by signs and symptoms.

Health and Disease in Populations

The health of people is closely linked to the health of the community and to the population it encompasses. The ability to traverse continents in a matter of hours has opened the world to issues of populations at a global level. Diseases that once were confined to local areas of the world now pose a threat to populations throughout the world. The focus of health care also has begun to emerge as a partnership in which people are asked to assume greater responsibility for their own health.

Epidemiology and Patterns of Disease

Epidemiology is the study of disease occurrence in human populations.[8] It was initially developed to explain the spread of infectious diseases during epidemics and has emerged as a science to study the risk factors for multifactorial diseases, such as heart disease and cancer. Epidemiology looks for patterns of people affected with a particular disorder, such as age, race, dietary habits, lifestyle, or geographic location. The epidemiologist is more concerned with whether smoking itself is related to cardiovascular disease and whether the risk of heart disease decreases when smoking ceases. Much of our knowledge about disease comes from epidemiologic studies. Epidemiologic methods are used to determine how a disease is spread, how to control it, how to prevent it, and how to eliminate it. Epidemiologic methods also are used to study the natural history of disease, to evaluate new preventive and treatment strategies, to explore the impact of different patterns of health care delivery, and to predict future health care needs. As such, epidemiologic studies serve as a basis for clinical decision making, allocation of health care dollars, and development of policies related to public health issues.

Incidence and Prevalence

Measures of disease frequency are an important aspect of epidemiology. They establish a means for predicting what diseases are present in a population and provide an indication of the rate at which they are increasing or decreasing. A *disease case* can be either an existing case or the number of new episodes of a particular illness that is diagnosed within a given period. **Incidence** reflects the number of new cases arising in a population at risk during a specified time. The population at risk is considered to be people without the disease but who are at risk for developing it. It is determined by dividing the number of new cases of a disease by the population at risk for development of the disease during the same period (*e.g.*, new cases per 1000 or 100,000 people in the population who are at risk). The cumulative incidence estimates the risk of developing the disease during that period of time. Prevalence is a measure of existing disease in a population at a given point in time (*e.g.*, number of existing cases divided by the current population).[8] The prevalence is not an estimate of risk of developing a disease

because it is a function of both new cases and how long the cases remain in the population. Incidence and prevalence are always reported as rates (*e.g.*, cases per 100 or cases per 100,000).

Morbidity and Mortality

Morbidity and mortality statistics provide information about the functional effects (morbidity) and death-producing (mortality) characteristics of a disease. These statistics are useful in terms of anticipating health care needs, planning of public education programs, directing health research efforts, and allocating health care dollars.

Morbidity describes the effects an illness has on a person's life. Many diseases, such as arthritis, have low death rates but a significant impact on a person's quality of life. Morbidity is concerned with persistence and the long-term consequences of the disease.

Mortality statistics provide information about the causes of death in a given population. In most countries, people are legally required to record certain facts such as age, gender, and cause of death on a death certificate. Internationally agreed classification procedures (the International Classification of Diseases by the WHO) are used for coding the cause of death, and the data are expressed as death rates.[1] Crude mortality rates (*i.e.*, number of deaths in a given period) do not account for age, gender, race, socioeconomic status, and other factors. For this reason, mortality often is expressed as death rates for a specific population, such as the infant mortality rate. Mortality also can be described in terms of the leading causes of death according to age, gender, race, and ethnicity. For example, among all people 65 years of age and older, leading causes of death in the United States are heart disease, cancer, chronic lower respiratory disease, and cerebrovascular diseases.[9]

Determination of Risk Factors

Conditions suspected of contributing to the development of a disease are called *risk factors*. They may be inherent to the person (high blood pressure or overweight) or external (smoking or drinking alcohol). There are different types of studies used to determine risk factors, including cross-sectional studies, case–control studies, and cohort studies.

Cross-Sectional and Case–Control Studies

Cross-sectional studies use the simultaneous collection of information necessary for classification of exposure and outcome status. They can be used to compare the prevalence of a disease in those with the factor (or exposure) with the prevalence of a disease in those who are unexposed to the factor, for example, by comparing the prevalence of coronary heart disease in smokers and nonsmokers. *Case–control studies* are designed to compare people known to have the outcome of interest (*cases*) and those known not to have the outcome of interest (*controls*).[8] Information on exposures or characteristics of interest is then collected from people in both groups. For example, the characteristics of maternal alcohol consumption in infants born with fetal alcohol syndrome (cases) can be compared with those in infants born without the syndrome (controls).

Cohort Studies

A *cohort* is a group of people who were born at approximately the same time or share some characteristics of interest.[8] People enrolled in a cohort study (also called a *longitudinal study*) are followed over a period of time to observe a specific health outcome.

Framingham Study

One of the best-known examples of a cohort study is the Framingham Study, which was carried out in Framingham, MA.[10] This longitudinal study, which began in 1950, was set up by the U.S. Public Health Service to study the characteristics of people who would later develop coronary heart disease. The study consisted of 5000 persons, between 30 and 59 years of age, selected at random and followed for an initial period of 20 years. During this time, it was predicted that 1500 of them would develop coronary heart disease. The advantage of such a study is that it can explore a number of risk factors at the same time and determine the relative importance of each. Another advantage is that the risk factors can be related later to other diseases such as stroke.

Nurses' Health Study

Another well-known cohort study is the Nurses' Health Study, which was developed by Harvard University and Brigham and Women's Hospital. The study began in 1976 with a cohort of 121,700 female caregivers, 30 to 55 years of age, living in the United States.[11] The study expanded in 1989 to include a group of 238,000 female caregiver participants.[11] Initially designed to explore the relationship between oral contraceptives and breast cancer, caregivers in the study have provided answers to detailed questions about their menstrual cycle, smoking habits, diet, weight and waist measurements, activity patterns, health problems, and medication use. They have collected urine and blood samples and even provided researchers with their toenail clippings. In selecting the cohort, it was reasoned that caregivers would be well organized, accurate, and observant in their responses and that physiologically they would be no different from other groups of women. It also was anticipated that their child-bearing, eating, and smoking patterns would be similar to those of other working women.

Natural History

The *natural history* of a disease refers to the progression and projected outcome of the disease without medical intervention. By studying the patterns of a disease over time in populations, epidemiologists can better understand its natural history. Knowledge of the natural history can be used to determine disease outcome, establish priorities for health care services, determine the effects of screening and early detection programs on disease outcome, and compare the results of new treatments with the expected outcome without treatment.

There are some diseases for which there are no effective treatment methods available, or the current treatment measures are effective only in certain people. In this case, the natural history of the disease can be used as a predictor of outcome. For example, the natural history of hepatitis C indicates that 75% to 85% of people who become infected with the virus fail to clear the virus and progress to chronic infection.[12] Information about the natural history of a disease and the availability of effective treatment methods provides directions for preventive measures. In the case of hepatitis C, careful screening of blood donations and education of intravenous drug abusers can be used to prevent transfer of the virus.

Prognosis refers to the probable outcome and prospect of recovery from a disease. It can be designated as chances for full recovery, possibility of complications, or anticipated survival time. Prognosis often is presented in relation to treatment options, that is, the expected

outcomes or chances for survival with or without a certain type of treatment. The prognosis associated with a given type of treatment usually is presented along with the risk associated with the treatment.

Preventing Disease

There are three fundamental types of prevention—primary prevention, secondary prevention, and tertiary prevention (Fig. 1-5).[8]

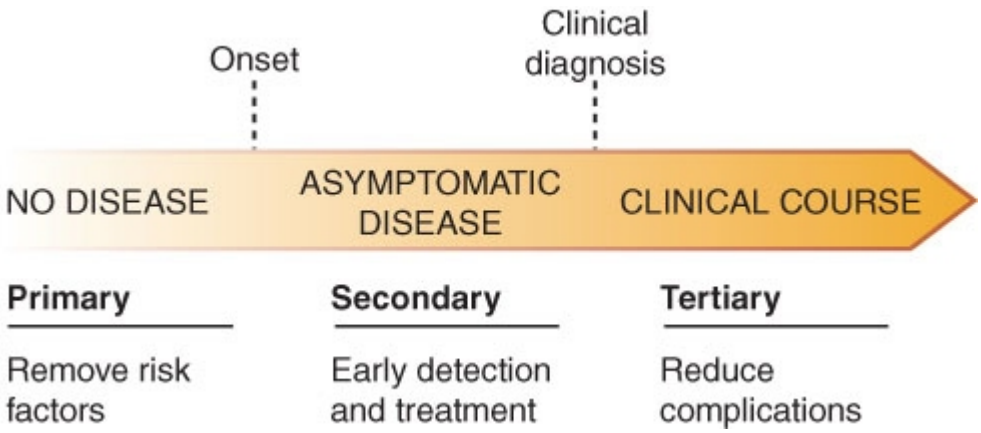


FIGURE 1-5 Levels of prevention. Primary prevention prevents disease from occurring. Secondary prevention detects and cures disease in the asymptomatic phase. Tertiary prevention reduces complications of disease. (From Fletcher R. H., Fletcher S. W. (2014). *Clinical epidemiology: The essentials* (5th ed., p. 153). Philadelphia, PA: Lippincott Williams & Wilkins.)

Primary prevention is directed at keeping disease from occurring by removing risk factors. Examples of primary prevention include the administration of folic acid to pregnant women and women who may become pregnant to prevent fetal neural tube defects, giving immunizations to children to prevent communicable disease, and counseling people to adopt healthy lifestyles as a means of preventing heart disease.[8]

Secondary prevention detects disease early when it is still asymptomatic and treatment measures can effect a cure or stop the disease from progressing. The use of a Papanicolaou (Pap) smear for early detection of cervical cancer is an example of secondary prevention. Screening also includes history taking, blood pressure measurement, laboratory tests, and other procedures such as a colonoscopy that can be "applied reasonably rapidly to asymptomatic people."[8] *Tertiary prevention* is directed at clinical interventions that prevent further deterioration or reduce the complications of a disease that is already present. An example is the use of β-**adrenergic** drugs to reduce the risk of death in people who have had a heart attack.[8] Another example is support groups for people with alcohol addiction.

Evidence-Based Practice and Practice Guidelines

Evidence-based practice and evidence-based practice guidelines have gained popularity with providers and the public as a means of improving the quality and efficiency of health care.[13] Their development has been prompted by more educated consumers who are fueled by published information about diagnostic and treatment measures for various disease conditions as well as demands for better and more cost-effective health care.

Evidence-based practice refers to making decisions in health care based on scientific data that have shown a specific way of managing a disease, patient symptoms, and complaints. Using evidence-based practice mandates that health care providers cannot practice according to only "their" way or according to "how it has always been done before."[13]

Clinical practice guidelines are systematically developed statements intended to inform practitioners and people in making decisions about health care for specific clinical circumstances.[6,13] Providers must consider benefits versus risks or impact on quality of life when applying these guidelines. The development of evidence-based practice guidelines often uses methods such as meta-analysis to combine evidence from different studies to produce a more precise estimate of the accuracy of a diagnostic method or the effects of an intervention method.[14] Practitioners with expertise in clinical content, experts in guideline development, and potential users of the guideline are best at evaluating the guidelines.[13]

Once developed, practice guidelines must be continually reviewed and changed to keep pace with new research findings and new diagnostic and treatment methods. For example, both the Guidelines for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, first developed in 1972 by the Joint National Committee, and the Guidelines for the Diagnosis and Management of Asthma,[15] first developed in 1991 by the Expert Panel, have undergone multiple revisions as new evidence from research has evolved.

SUMMARY CONCEPTS

Epidemiology refers to the study of disease in populations. It looks for patterns such as age, race, and dietary habits of people who are affected with a particular disorder. These patterns are used to determine under what circumstances the particular disorder will occur. *Incidence* is the number of new cases arising in a given population during a specified time. *Prevalence* is the number of people in a population who have a particular disease at a given point in time or period. Incidence and prevalence are reported as proportions or rates (*e.g.*, cases per 100 or 100,000 population). *Morbidity* describes the effects an illness has on a person's life. It is concerned with the incidence of disease as well as its persistence and long-term consequences. *Mortality*, or death, statistics provide information about the causes of death in a given population.

Conditions suspected of contributing to the development of a disease are called *risk factors*. Studies used to determine risk factors include cross-sectional studies, case–control studies, and cohort studies. The *natural history* refers to the progression and projected outcome of a disease without medical intervention. *Prognosis* is the term used to designate the probable outcome and prospect of recovery from a disease.

The three fundamental types of prevention are primary prevention, secondary prevention, and tertiary prevention. *Primary prevention*, such as immunizations, is directed at removing risk factors so disease does not occur. *Secondary prevention*, such as a Pap smear, detects disease when it still is asymptomatic and curable with treatment. *Tertiary prevention*, such as use of β-adrenergic drugs to reduce the risk of death in persons who have had a heart attack, focuses on clinical interventions that prevent further deterioration or reduce the complications of a disease.

Evidence-based practice and *evidence-based practice guidelines* are mechanisms that use the current best evidence to make decisions about the health of people. They are based on the expertise of the individual practitioner integrated with the best clinical

evidence from systematic review of credible research studies. Practice guidelines may take the form of algorithms, which are step-by-step methods for solving a problem, written directives, or a combination thereof.

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UNIT 2

Cell Function and Growth

CHAPTER 2

Cell and Tissue Characteristics

Functional Components of the Cell

Learning Objectives

After completing this chapter, you should be able to meet the following objectives:

1. Predict the effects of dysfunction in each cellular organelle.
2. Differentiate the four functions of the cell membrane.
3. Order the pathway for cell communication, from the receptor to the response, and explain why the process is often referred to as *signal transduction*.
4. Link the phases of the cell cycle to cell replication.
5. Predict how changes in oxygen delivery to cells change cellular respiration and levels of adenosine triphosphate and carbon dioxide.
6. Compare and contrast membrane transport mechanisms: diffusion, osmosis, active transport, endocytosis, and exocytosis.
7. Predict changes in membrane potentials based on diffusion of ions.
8. Link the process of cell differentiation to the development of organ systems in the embryo and the regeneration of tissues in postnatal life.
9. Compare and contrast the characteristics of the four different tissue types.

In most organisms, the cell is the smallest functional unit that has the characteristics necessary for life. Cells combine to form tissues based on their embryonic origin. These tissues combine to form organs. Although cells of different tissues and organs vary in structure and function, certain characteristics are common to all cells. Because most disease processes start at the cellular level, we need to understand cell function to understand disease processes. This chapter discusses the structural parts of cells, cell functions and growth, movement of substances such as ions across the cell membrane, and tissue types.

Functional Components of the Cell

Most organisms, including humans, contain **eukaryotic** cells that are made up of internal membrane-bound compartments called **organelles** ("small organs" within cells); an example of an organelle is the nucleus. This is in contrast to prokaryotes, such as bacteria, that do not contain membrane-bound organelles. When seen under a microscope, three major components of a eukaryotic cell become evident—the nucleus, the **cytoplasm**, and the cell membrane (Fig. 2-1).

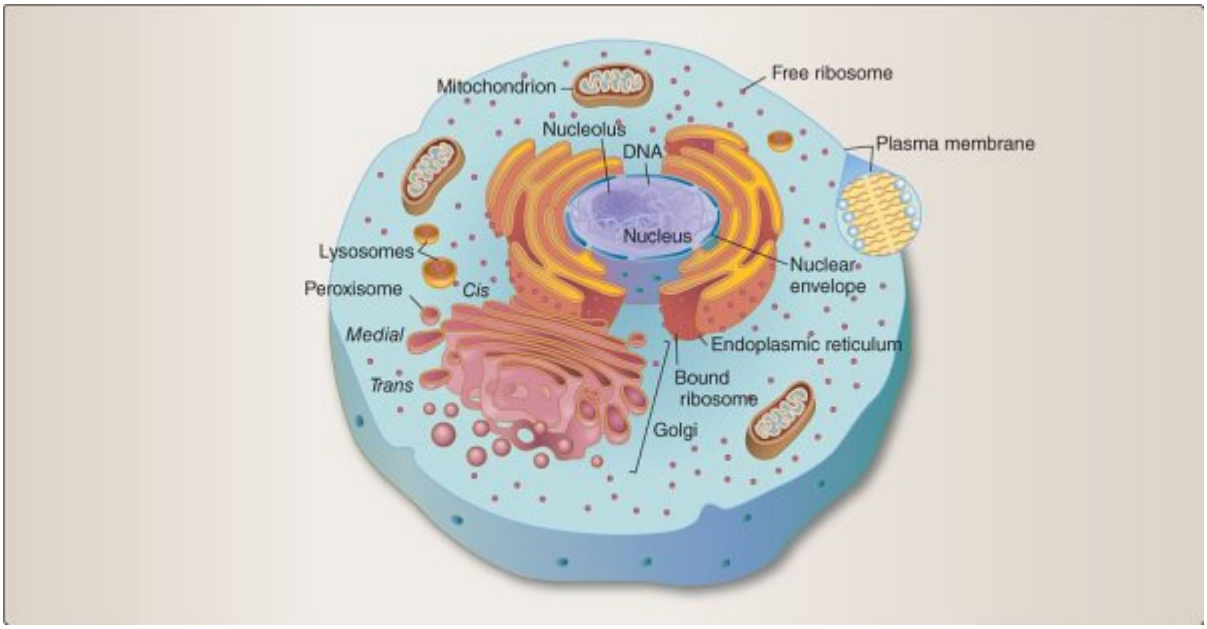

FIGURE 2-1 Cell organelles. DNA, deoxyribonucleic acid. (Reprinted from Leeper-Woodford. (2016). *Lippincott illustrated reviews: Integrated systems* (Fig. 2.1, p. 39). Philadelphia, PA: Wolters Kluwer, with permission.)

Protoplasm

Biologists call the intracellular fluid **protoplasm**. Protoplasm is composed of water, proteins, lipids, carbohydrates, and electrolytes.[1]

- Water makes up 70% to 85% of the cell's protoplasm.[1]
- Proteins make up 10% to 20% of the protoplasm. Proteins are polar and soluble in water. Examples of proteins include **enzymes** necessary for cellular reactions, structural proteins, ion channels, and receptors.[1]
- Lipids make up 2% to 3% of the protoplasm. Lipids are nonpolar and insoluble in water. They are the main parts of cell membranes surrounding the outside and inside of cells. Examples of lipids include phospholipids and cholesterol. Some cells also contain large quantities of triglycerides. In fat cells, triglycerides can make up as much as 95% of the total cell mass.[1] Carbohydrates make up approximately 1% of the protoplasm. These serve primarily as a rapid source of energy.[1]
- The major intracellular electrolytes include potassium, magnesium, phosphate, sulfate, and bicarbonate ions. Small quantities of the electrolytes sodium, chloride, and calcium ions are also present in cells. These electrolytes participate in reactions that are necessary for the cell's **metabolism**, and they help generate and send signals in neurons, muscle cells, and other cells.

Two distinct regions of protoplasm exist in the cell:

- The **karyoplasm** or nucleoplasm is inside the nucleus.
- The cytoplasm is outside the nucleus. The cytosol is the fluid of the cytoplasm (cytoplasm = cytosol + organelles).

KEY POINTS

The Functional Organization of the Cell

- Organelles in the cytoplasm perform functions within cells similar to how organs in the body perform functions within the organism.
- The nucleus is the largest and most visible organelle in the cell. The nucleus is the control center for the cell. In eukaryotic cells, it contains genetic information that we inherit from our parents.[1]
- Other organelles include the mitochondria, which help to make energy molecules that cells can use, and the lysosomes and **proteasomes**, which function as the cell's digestive system. Ribosomes, which are not surrounded by membranes, are the cellular structures that make proteins; those proteins may help to make other molecules needed for cell function.

The Nucleus

The cell nucleus is a rounded or elongated structure near the center of the cell (see Fig. 2-1). All eukaryotic cells have at least one nucleus. Some cells contain more than one nucleus; osteoclasts (a type of bone cell) usually contain 12 or more nuclei.[1]

The nucleus can be thought of as the control center for the cell because it contains the instructions to make proteins, and proteins can then make other molecules needed for cellular function and survival.[1] The nucleus contains deoxyribonucleic acid (DNA), which contains genes. Genes contain the instructions for cellular function and survival. For example, the insulin gene contains instructions to make insulin protein. In addition, genes are units of inheritance that pass information from parents to their children.

The nucleus also is the site for the **synthesis** of the three main types of ribonucleic acid (RNA). These RNA molecules move from the nucleus to the cytoplasm and carry out the synthesis of proteins. These three types of RNA are as follows:

- Messenger RNA (mRNA), which is made from genetic information transcribed from the DNA in a process called transcription. mRNA travels to ribosomes in the cytoplasm so these instructions can be used to make proteins.
- Ribosomal RNA (rRNA) is the RNA component of ribosomes, the site of protein production.
- Transfer RNA (tRNA) transports amino acids to ribosomes so that mRNA can be turned into a sequence of amino acids. This process, known as translation, uses the mRNA template to link amino acids to synthesize proteins.[1]

The Cytoplasm and Its Organelles

The cytoplasm includes the fluid and organelles outside the nucleus but within the cell membrane surrounding the cell. Cytoplasm is a solution that contains water, electrolytes, proteins, fats, and carbohydrates.[1] Pigments may also accumulate in the cytoplasm. Some pigments are normal parts of cells. One example is melanin, which gives skin its color. Some pigments are not normal parts of cells. For example, when the body breaks down old red blood cells, pigments in red blood cells are changed to the pigment bilirubin, which the body can excrete. Embedded in the cytoplasm are various organelles that function as the organs of the cell. In addition to the nucleus, which was discussed in the previous section, these organelles include the ribosomes, the endoplasmic reticulum (ER), the Golgi complex, lysosomes, **peroxisomes**, proteasomes, and mitochondria.[1]

Ribosomes

The ribosomes are the sites of protein synthesis in the cell. There are two subunits of ribosomes that are made up of rRNA and proteins. During protein synthesis, the two ribosomal subunits are held together by a strand of mRNA.[1] These active ribosomes either stay within the cytoplasm (Fig. 2-2) or are attached to the membrane of the ER, depending on where the protein will be used.[1]

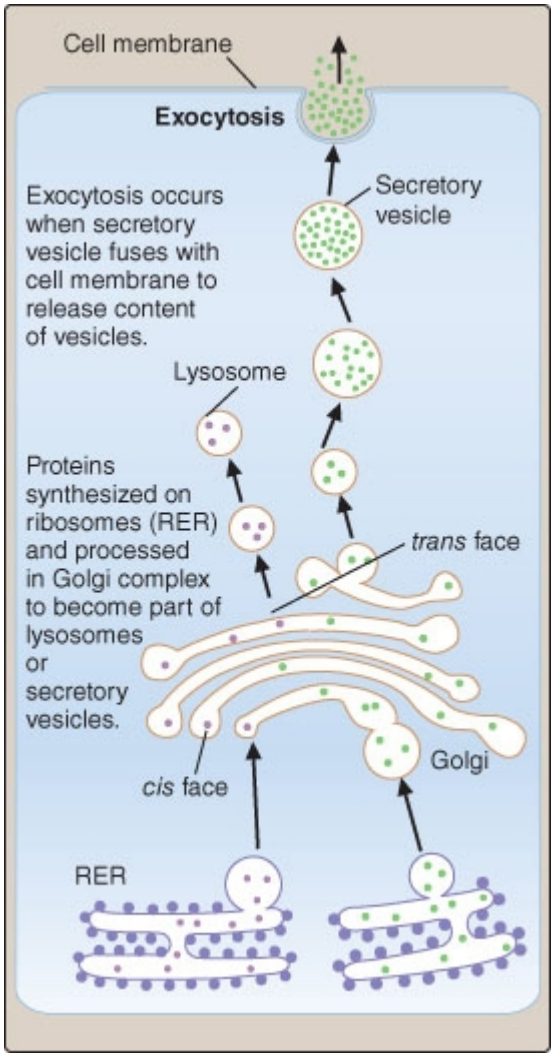

FIGURE 2-2 Endoplasmic reticulum (ER), ribosomes, and Golgi apparatus. The rough ER (RER) consists of intricately folded membranes studded with ribosomes. Ribosomes are made of protein and ribosomal ribonucleic acid organized together. Golgi apparatus processes proteins synthesized on ribosomes. (Reprinted from Leeper-Woodford. (2016). *Lippincott illustrated reviews: Integrated systems* (Fig. 2.3, p. 41). Philadelphia, PA: Wolters Kluwer, with permission.)

Endoplasmic Reticulum

The ER is an extensive system of paired membranes and flat **vesicles** that connect various parts of the inner cell (see Fig. 2-2).[1] Two forms of ER exist in cells—rough and smooth.

Rough ER has ribosomes attached, and the ribosomes appear under a microscope as "rough" structures on the ER membrane. Proteins made by the rough ER usually become parts of organelles or cell membranes, or are secreted from cells as a protein. For example, the rough ER makes (1) digestive enzymes found in lysosomes and (2) proteins that are secreted, such as the protein hormone insulin.

The smooth ER is free of ribosomes and has a smooth structure when viewed through a microscope. Because it does not have ribosomes attached, the smooth ER does not participate

in protein synthesis. Instead, the smooth ER is involved in the synthesis of lipids including steroid hormones. The smooth ER of the liver is involved in storage of extra glucose as glycogen as well as metabolism of some hormone drugs.

If proteins build up in the ER faster than they can be removed, the cell is said to experience "ER stress." The cell responds by slowing down protein synthesis and restoring homeostasis. Abnormal responses to ER stress, which can cause inflammation and even cell death, have been implicated in inflammatory bowel disease,[2] a genetic form of diabetes mellitus,[3] and a disorder of **skeletal muscle** known as myositis,[4] as well as many other diseases.

Golgi Complex

The Golgi apparatus, sometimes called the Golgi complex, consists of four or more stacks of thin, flattened vesicles or sacs (see Fig. 2-3).[1] Substances produced in the ER are carried to the Golgi complex in small, membrane-covered transfer vesicles. The Golgi complex modifies these substances and packages them into **secretory granules** or vesicles. In addition to making secretory granules, the Golgi complex is thought to make large carbohydrate molecules that combine with proteins produced in the rough ER to form glycoproteins. The Golgi apparatus can receive proteins and other substances from the cell surface by a **retrograde** transport mechanism. Several bacterial toxins, such as Shiga and cholera toxins, and plant toxins, such as ricin, that have cytoplasmic targets have exploited this retrograde pathway.[1]

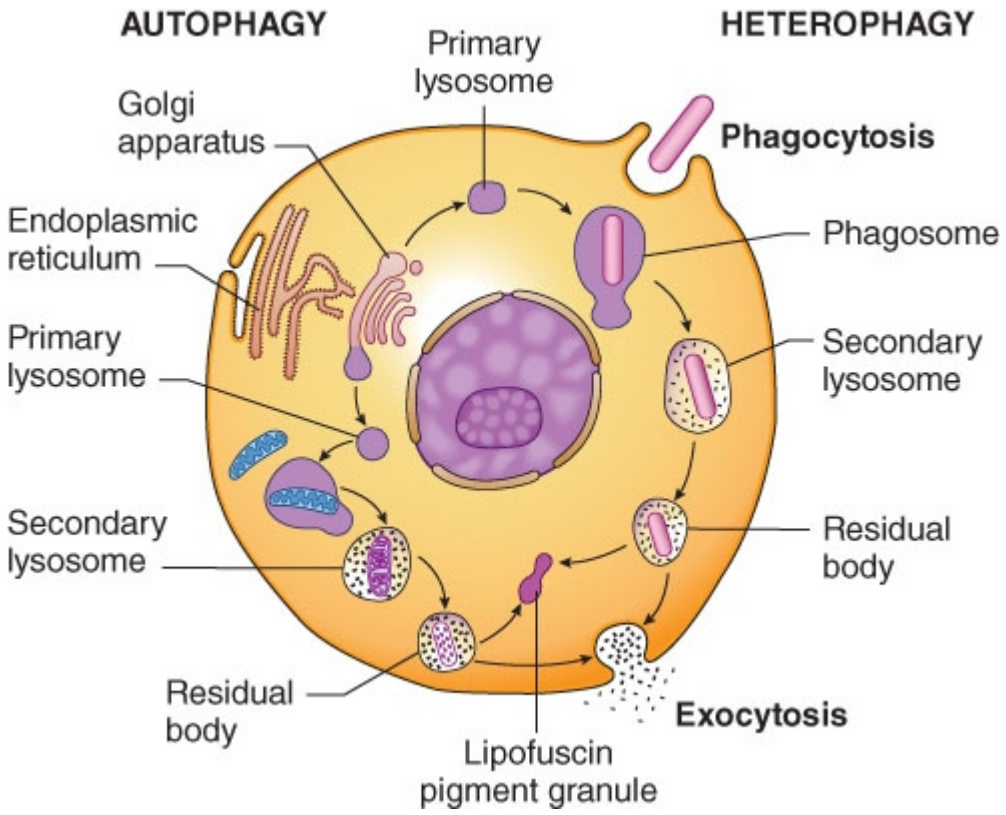

FIGURE 2-3 The processes of autophagy and heterophagy, showing the primary and secondary lysosomes, residual bodies, extrusion of residual body contents from the cell, and lipofuscin-containing residual bodies.