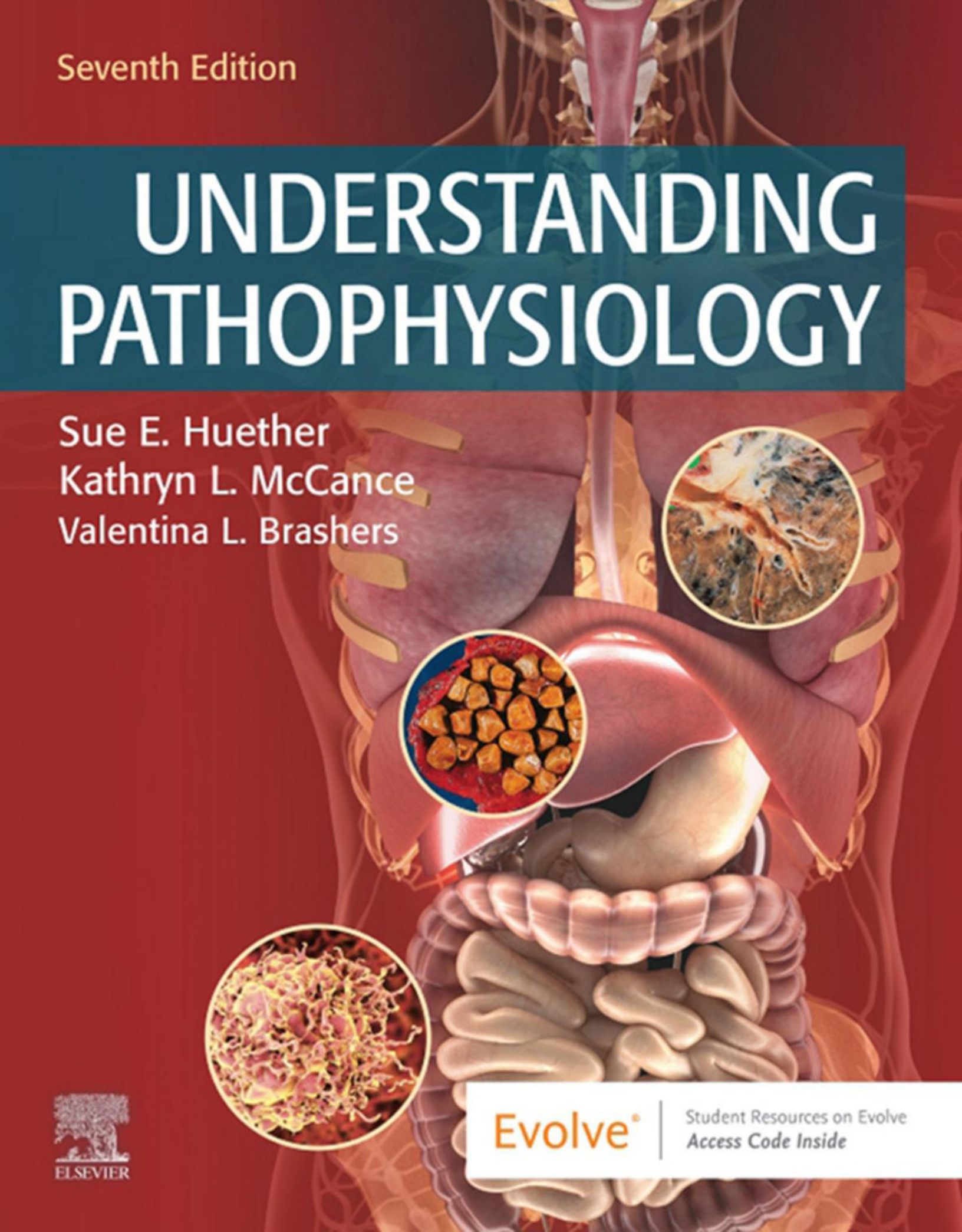
Seventh Edition

UNDERSTANDING PATHOPHYSIOLOGY

Sue E. Huether
Kathryn L. McCance
Valentina L. Brashers



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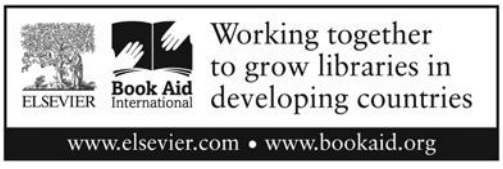

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PREFACE

The updates for the seventh edition of *Understanding Pathophysiology,* include a simplification of the content to make it less complex and easier for student comprehension. The primary focus of the text is the pathophysiology associated with the most common diseases. Some of the molecular and cellular content has been rewritten into more general explanations of disease processes. The text has also been written to assist students with the translation of the concepts and processes of pathophysiology into clinical practice and to promote lifelong learning. For preparatory knowledge, students need to have a good understanding of human organ system anatomy and physiology. Because of the rapidly evolving discovery of disease mechanisms and treatment at the molecular and cellular level, students also need to have a working understanding of cell structure and function. We continue to include discussions of the following interconnected topics to highlight their importance for clinical practice:

- Pathophysiologic alterations of organ and cell function related to mechanisms of disease
- A life-span approach that includes special sections on aging and separate chapters on children
- Epidemiology and incidence rates showing regional and worldwide differences that reflect the importance of environmental and lifestyle factors on disease initiation and progression
- Sex differences that affect epidemiology and pathophysiology
- Clinical manifestations, summaries of treatment, and health promotion/risk reduction strategies

ORGANIZATION AND CONTENT FOR THE SEVENTH EDITION

The book is organized into two parts: Part One, Basic Concepts of Pathophysiology, and Part Two, Body Systems and Diseases. All content has been updated and includes the most common content related to mechanisms of disease.

Part One: Basic Concepts of Pathophysiology

Part One introduces basic principles and processes that are important for a contemporary understanding of the pathophysiology of common diseases. The concepts include descriptions of cell structure, cellular transport and communication; forms of cell injury; genes and genetic disease; epigenetics; fluid and electrolytes and acid and base balance; immunity, inflammation and wound healing; mechanisms of infection; stress, coping, and illness; tumor biology and cancer epidemiology. We separated the content on infection into a new chapter, Chapter 9.

Part Two: Body Systems and Diseases

Part Two presents the pathophysiology of the most common alterations according to body system. To promote readability and comprehension, we have used a logical sequence and uniform approach in presenting the content of the units and chapters. Each unit focuses on a specific organ system and contains chapters related to anatomy and physiology, the pathophysiology of the most common diseases, and common alterations in children. The anatomy and physiology content is presented as a review to enhance the learner's understanding of the structural and functional changes inherent in pathophysiology. A brief summary of normal aging effects is included at the end of these review chapters. The general organization of each disease/disorder discussion includes an introductory paragraph on relevant risk factors and epidemiology, a significant focus on pathophysiology and clinical manifestations, and then a brief review of evaluation and treatment. A new chapter was added with content related to obesity, starvation, and anorexia of aging, Chapter 21.

FEATURES TO PROMOTE LEARNING

A number of features are incorporated into this text that guide and support learning and understanding, including:

- *Chapter Outlines* including page numbers for easy reference
- *Quick Check* questions strategically placed throughout each chapter to help readers confirm their understanding of the material; answers are included on the textbook's Evolve website
- *Risk Factors* boxes for selected diseases
- *Did You Know* boxes
- End-of-chapter *Summary Reviews* that condense the major concepts of each chapter into an easy-to-review list format; printable versions of these are available on the textbook's Evolve website
- *Key Terms* set in blue boldface in text and listed, with page numbers, at the end of each chapter
- Special boxes for *Aging* and *Pediatrics* content that highlight discussions of life-span alterations

ART PROGRAM

All of the figures and photographs have been carefully reviewed, revised, or updated. This edition features approximately 100 new or heavily revised illustrations and photographs with a total of approximately 1000 images. The figures and algorithms are designed to help students visually understand sometimes difficult and complex material. High-quality photographs show actual pathologic features of disease. Micrographs show normal and abnormal cellular structure. The combination of illustrations, algorithms, photographs, and use of color for tables and boxes allows a more complete understanding of essential information.

TEACHING/LEARNING PACKAGE

For Students

The free electronic **Student Resources** on Evolve include review questions and answers, numerous animations, answers to the Quick Check questions in the book, chapter summary reviews, and bonus case studies with questions and answers. These electronic resources enhance learning options for students. Go to http://evolve.elsevier.com/Huether.

The newly rewritten **Study Guide** includes many different question types, aiming to help the broad spectrum of student learners. Question types include the following:
Choose the Correct Words
Complete These Sentences
Categorize These Clinical Examples
Explain the Pictures
Teach These People about Pathophysiology
Plus many more…

Answers are found in the back of the **Study Guide** for easy reference for students.

For Instructors

The electronic **Instructor Resources** on Evolve are available free to instructors with qualified adoptions of the textbook and include the following: TEACH Lesson Plans with case studies to assist with clinical

application; a Test Bank of more than 1200 items; PowerPoint Presentations for each chapter, with integrated images, audience response questions, and case studies; and an Image Collection of approximately 1000 key figures from the text. All of these teaching resources are also available to instructors on the book's Evolve site. Plus the *Evolve Learning System* provides a comprehensive suite of course communication and organization tools that allow you to upload your class calendar and syllabus, post scores and announcements, and more. Go to http://evolve.elsevier.com/Huether.

The most exciting part of the learning support package is **Pathophysiology Online,** a complete set of online modules that provide thoroughly developed lessons on the most important and difficult topics in pathophysiology supplemented with illustrations, animations, interactive activities, interactive algorithms, self-assessment reviews, and exams. Instructors can use it to enhance traditional classroom lecture courses or for distance and online-only courses. Students can use it as a self-guided study tool.

ACKNOWLEDGMENTS

This book would not be possible without the knowledge and collaboration of our contributing authors, both those who have worked with us through previous editions and the new members of our team. Their reviews and synthesis of the evidence and clear concise presentation of information is a strength of the text. We thank them.

The reviewers for this edition provided excellent recommendations for focus of content and revisions. We appreciate their insightful work.

Tina Brashers, MD, is our section editor and a contributing author. Tina is a distinguished teacher and has received numerous awards for her teaching and work with nursing and medical students and faculty. She is nationally known for her leadership and development in promoting and teaching interprofessional collaboration and is the founder of the Center for Academic Strategic Partnerships for Interprofessional Research and Education (ASPIRE) at the University of Virginia. Tina brings innovation and clarity to the subject of pathophysiology. Her contributions to the online course continue to be intensive and creative, and a significant learning enhancement for students. Thank you, Tina, for the outstanding quality of your work.

Karen Turner joined our team with a new role for this edition. She assisted with the editing of several chapters, managed the revision of artwork, and organized the flow of content for the Summary Reviews. She is an experienced and dedicated editor and made significant contributions to this edition. Thank you, Karen.

Kellie White was our Executive Content Strategist for the first year of the revision until she was promoted to another position. We appreciate her helpful leadership and guidance not only for this edition but, for the past years that she has worked with us. Thank you, Kellie. Jennifer Wade was our Content Development Specialist. Jennifer kept us on track and managed the multiple tasks of acquiring images and getting the manuscript ready for copy editing and page proofs. Thank you, Jennifer.

We are particularly grateful to Cassie Carey who jumped into the copy edit process and kept us going when Beth Welch, our long time copy editor, had to take medical leave. We appreciate the work you both contributed to this edition.

The internal layout, selection of colors, and design of the cover were done by our Designer, Maggie Reid. Great work, Maggie! Thanks to the team from Graphic World, who created many new images and managed the cleanup and scanning of artwork obtained from many resources.

Rich Barber was our Senior Project Manager and brought us into the home stretch and took us through copy edit to final page proofs. Thank you, Rich.

Tamara Meyers, Director of Traditional Nursing Programs, provided the oversight for the entire 7th edition revision. We are thankful for her exceptional leadership, coordination and problem solving in bringing this project to completion.

We thank the Department of Dermatology at the University of Utah School of Medicine, which provided numerous photos of skin lesions. Thank you to our many colleagues and friends at the University of Utah College of Nursing and Health Sciences Center for their suggestions and content critiques.

We extend gratitude to those who contributed to the book supplements**.** Linda Felver has created an all new inventive and resourceful Study Guide. Thank you, Linda, for your very astute edits. A special thanks to Amber Ballard and Karen Turner for their thorough approach in preparing the materials for the Evolve website. Tina Brashers, Amber Ballard, and Linda Turchin also updated the interactive online lessons and activities for *Pathophysiology Online*.

Sincerely and with great affection we thank our families, especially Mae and John. Always supportive, you make the work possible!

Sue E. Huether
Kathryn L. McCance

We dedicate this book to Sue Anne Meeks, who has been our manuscript manager since the first edition of *Understanding Pathophysiology* and for all of the editions of our more extensive book, *Pathophysiology: The Biologic Basis of Disease in Adults and Children*. The behind-the-scene processes for the development and revision of a major textbook is extensive and requires coordination, attention to detail, organizational skills, good communication, and lots of laughter. Sue is prodigious; she has been a tireless, dedicated, and exceptionally fun person. She is now ready for retirement. We will forever be grateful for her colossal work. We could not have done it without her at our side for the past 30 years. We wish her continuing joy and happiness as she begins her next life adventure.

INTRODUCTION TO PATHOPHYSIOLOGY

The word root *"patho"* is derived from the Greek word *pathos,* which means suffering. The Greek word root *"logos"* means discourse or, more simply, system of formal study, and *"physio"* refers to functions of an organism. Altogether, pathophysiology is the study of the underlying changes in body physiology (molecular, cellular, and organ systems) that result from disease or injury. Important, however, is the inextricable component of suffering and the psychological, spiritual, social, cultural, and economic implications of disease.

The science of pathophysiology seeks to provide an understanding of the mechanisms of disease and to explain how and why alterations in body structure and function lead to the signs and symptoms of disease. Understanding pathophysiology guides healthcare professionals in the planning, selection, and evaluation of therapies and treatments.

Knowledge of human anatomy and physiology and the interrelationship among the various cells and organ systems of the body is an essential foundation for the study of pathophysiology. Review of this subject matter enhances comprehension of pathophysiologic events and processes. Understanding pathophysiology also entails the utilization of principles, concepts, and basic knowledge from other fields of study including pathology, genetics, epigenetics, immunology, and epidemiology. A number of terms are used to focus the discussion of pathophysiology; they may be used interchangeably at times, but that does not necessarily indicate that they have the same meaning. Those terms are reviewed here for the purpose of clarification.

Pathology is the investigation of structural alterations in cells, tissues, and organs, which can help identify the cause of a particular disease. Pathology differs from **pathogenesis**, which is the pattern of tissue changes associated with the *development* of disease. **Etiology** refers to the study of the *cause* of disease. Diseases may be caused by infection, heredity, gene–environment interactions, alterations in immunity, malignancy, malnutrition, degeneration, or trauma. Diseases that have no identifiable cause are termed **idiopathic**. Diseases that occur as a result of medical treatment are termed **iatrogenic** (for example, some antibiotics can injure the kidney and cause renal failure). Diseases that are acquired as a consequence of being in a hospital environment are called **nosocomial**. An infection that develops as a result of a person's immune system being depressed after receiving cancer treatment during a hospital stay would be defined as a nosocomial infection.

Diagnosis is the naming or identification of a disease. A diagnosis is made from an evaluation of the evidence accumulated from the presenting signs and symptoms, health and medical history, physical examination, laboratory tests, and imaging. A **prognosis** is the expected outcome of a disease. **Acute disease** is the sudden appearance of signs and symptoms that last only a short time. **Chronic disease** develops more slowly and the signs and symptoms last for a long time, perhaps for a lifetime. Chronic diseases may have a pattern of remission and exacerbation. **Remissions** are periods when symptoms disappear or diminish significantly. **Exacerbations** are periods when the symptoms become worse or more severe. A **complication** is the onset of a disease in a person who is already coping with another existing disease (for example, a person who has undergone surgery to remove a diseased appendix may develop the complication of a wound infection or pneumonia). **Sequelae** are unwanted outcomes of having a disease or are the result of trauma, such as paralysis resulting from a stroke or severe scarring resulting from a burn.

Clinical manifestations are the signs and symptoms or *evidence* of disease. **Signs** are objective alterations that can be observed or measured by another person, measures of bodily functions such as pulse rate, blood pressure, body temperature, or white blood cell count. Some signs are **local**, such as redness or swelling, and other signs are **systemic**, such as fever. **Symptoms** are subjective experiences reported by the person with disease, such as pain, nausea, or shortness of breath; and they vary from person to person. The **prodromal period** of a disease is the time during which a person experiences vague symptoms such as fatigue or loss of appetite before the onset of specific signs and symptoms. The term **insidious symptoms** describes vague or nonspecific feelings and an awareness that there is a change within the body. Some diseases have a **latent period**, a time during which no symptoms are readily apparent in the affected person, but the disease is nevertheless present in the body; an example is the incubation phase of an infection or the early growth phase of a tumor. A **syndrome** is a group of symptoms that occur together and may be caused by several interrelated problems or a specific disease; severe acute respiratory syndrome (SARS), for example, presents with a set of symptoms that include headache, fever, body aches, an overall feeling of discomfort, and sometimes dry cough and difficulty breathing. A **disorder** is an abnormality of function; this term also can refer to an illness or a particular problem such as a bleeding disorder.

Epidemiology is the study of tracking patterns or disease occurrence and transmission among populations and by geographic areas. **Incidence** of a disease is the number of new cases occurring in a specific time period. **Prevalence** of a disease is the number of existing cases within a population during a specific time period.

Risk factors, also known as **predisposing factors**, increase the probability that disease will occur, but these factors are not the *cause* of disease. Risk factors include heredity, age, gender, race, environment, and lifestyle. A **precipitating factor** is a condition or event that *does* cause a pathologic event or disorder. For example, asthma is precipitated by exposure to an allergen, or angina (pain) is precipitated by exertion.

Pathophysiology is an exciting field of study that is ever-changing as new discoveries are made. Understanding pathophysiology empowers healthcare professionals with the knowledge of how and why disease develops and informs their decision making to ensure optimal healthcare outcomes. Embedded in the study of pathophysiology is understanding that suffering is a personal, individual experience and a major component of disease.

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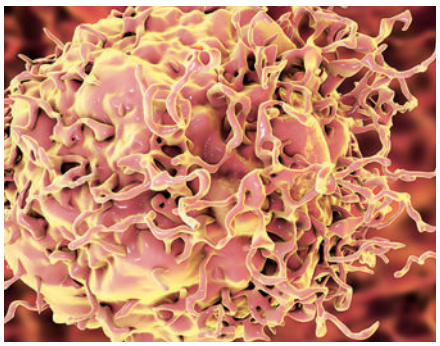
UNIT 3 Cellular Proliferation: Cancer

PART 2 Body Systems and Diseases

UNIT 4 The Neurologic System



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Cellular Biology

Kathryn L. McCance

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CHAPTER OUTLINE

All body functions depend on the integrity of cells. Therefore an understanding of cellular biology is increasingly necessary to comprehend disease processes. An overwhelming amount of information reveals how cells behave as a multicellular "social" organism. At the heart of it all is cellular communication (cellular "crosstalk")—how messages originate and are transmitted, received, interpreted, and used by the cell. Streamlined conversation between, among, and within cells maintains cellular function and specialization. Cells must demonstrate a "chemical fondness" for other cells to maintain the integrity of the entire organism. When they no longer tolerate this fondness, the conversation breaks down, and cells either adapt (sometimes altering function) or become vulnerable to isolation, injury, or disease.

PROKARYOTES AND EUKARYOTES

Living cells generally are divided into eukaryotes and prokaryotes. The cells of higher animals and plants are eukaryotes, as are the single-celled organisms, fungi, protozoa, and most algae. Prokaryotes include cyanobacteria (blue-green algae), bacteria, and rickettsiae. Prokaryotes traditionally were studied as core subjects of molecular biology. Today emphasis is on the eukaryotic cell; much of its structure and function have no counterpart in bacterial cells.

Eukaryotes (*eu* = good; *karyon* = nucleus; also spelled "eucaryotes") are larger and have more extensive intracellular anatomy and organization than prokaryotes. Eukaryotic cells have a characteristic set of membrane-bound intracellular compartments, called *organelles,* that includes a well-defined nucleus. The **prokaryotes** contain no organelles, and their nuclear material is not encased by a nuclear membrane. Prokaryotic cells are characterized by lack of a distinct nucleus.

Besides having structural differences, prokaryotic and eukaryotic cells differ in chemical composition and biochemical activity. The *nuclei* of prokaryotic cells carry genetic information in a single circular chromosome, and they lack a class of proteins called *histones,* which in eukaryotic cells bind with deoxyribonucleic acid (DNA) and are involved in the supercoiling of DNA. Eukaryotic cells have several or many chromosomes. Protein production, or synthesis, in the two classes of cells also differs because of major structural differences in ribonucleic acid (RNA)–protein complexes. Other distinctions include differences in mechanisms of transport across the outer cellular membrane and in enzyme content.

CELLULAR FUNCTIONS

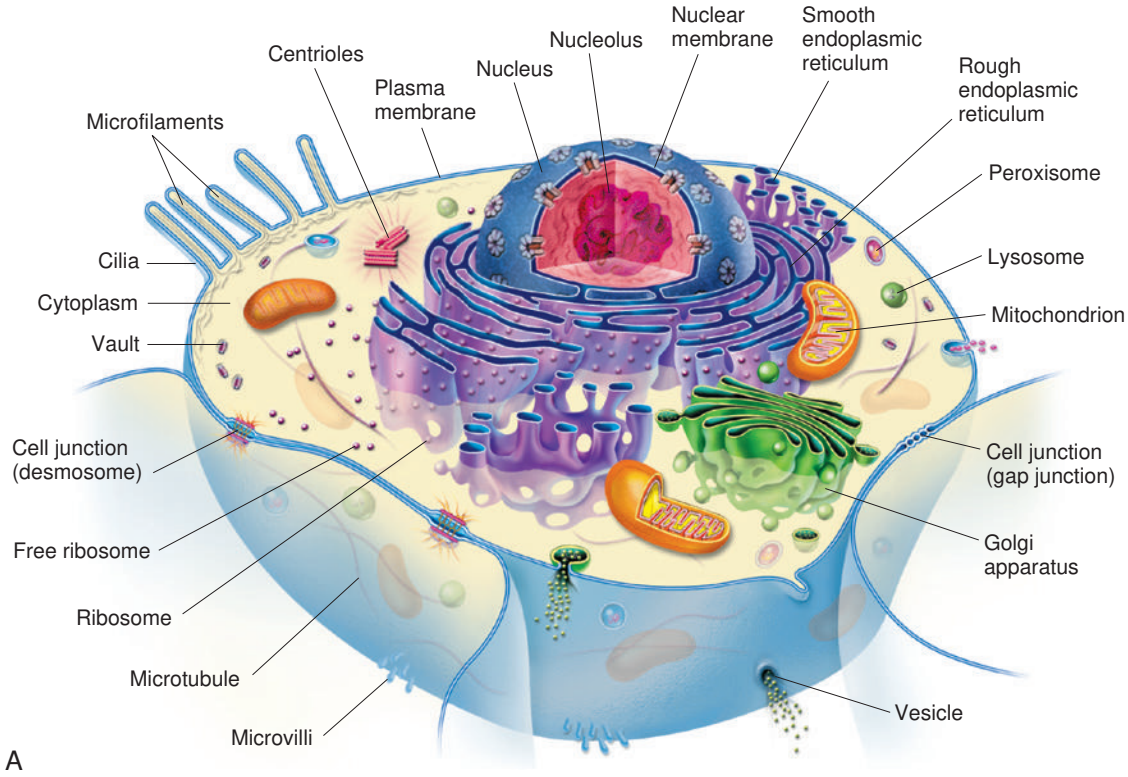
Cells become specialized through the process of **differentiation**, or maturation, so that some cells eventually perform one kind of function and other cells perform other functions. Cells with a highly developed function, such as movement, often lack some other property, such as hormone production, which is more highly developed in other cells.

The eight chief cellular functions are as follows:

1. *Movement.* Muscle cells can generate forces that produce motion. Muscles that are attached to bones produce limb movements, whereas those muscles that enclose hollow tubes or cavities move or empty contents when they contract (e.g., the colon).
2. *Conductivity.* Conduction as a response to a stimulus is manifested by a wave of excitation, an electrical potential that passes along the surface of the cell to reach its other parts. Conductivity is the chief function of nerve cells.
3. *Metabolic absorption.* All cells can take in and use nutrients and other substances from their surroundings.
4. *Secretion.* Certain cells, such as mucous gland cells, can synthesize new substances from substances they absorb and then secrete the new substances to serve, as needed, elsewhere.
5. *Excretion.* All cells can rid themselves of waste products resulting from the metabolic breakdown of nutrients. Membrane-bound sacs (lysosomes) within cells contain enzymes that break down, or digest, large molecules, turning them into waste products that are released from the cell.
6. *Respiration.* Cells absorb oxygen, which is used to transform nutrients into energy in the form of adenosine triphosphate (ATP). Cellular respiration, or oxidation, occurs in organelles called *mitochondria.*
7. *Reproduction.* Tissue growth occurs as cells enlarge and reproduce themselves. Even without growth, tissue maintenance requires that new cells be produced to replace cells that are lost normally through cellular death. Not all cells are capable of continuous division. (see Chapter 4).
8. *Communication.* Communication is vital for cells to survive as a society of cells. Appropriate communication allows the maintenance of a dynamic steady state.

STRUCTURE AND FUNCTION OF CELLULAR COMPONENTS

Fig. 1.1, *A*, shows a "typical" eukaryotic cell, which consists of three components: an outer membrane called the **plasma membrane**, or **plasmalemma**; a fluid "filling" called **cytoplasm** (see Fig. 1.1, *B*); and



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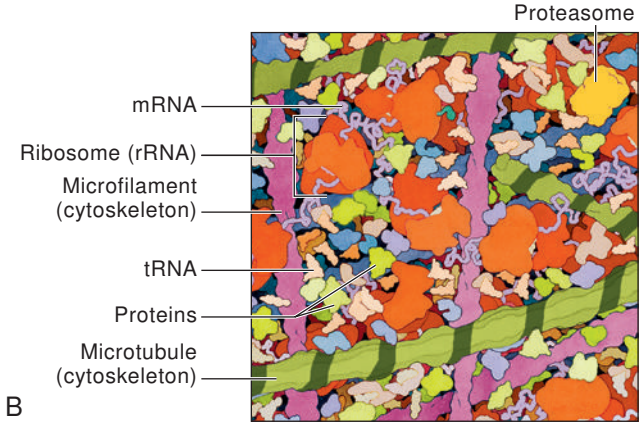


B

FIGURE 1.1 Typical Components of a Eukaryotic Cell and Structure of the Cytoplasm. A, Artist's interpretation of cell structure. Note the many mitochondria known as the "power plants" of the cell. Note, too, the innumerable dots bordering the endoplasmic reticulum. These are ribosomes, the cell's "protein factories." **B,** Color-enhanced electron micrograph of a cell showing the cell is crowded. (**B,** from Patton KT, Thibodeau GA: *Anatomy & physiology,* ed 8, St Louis, 2013, Mosby.)

the "organs" of the cell—the membrane-bound intracellular **organelles**, among them the nucleus.

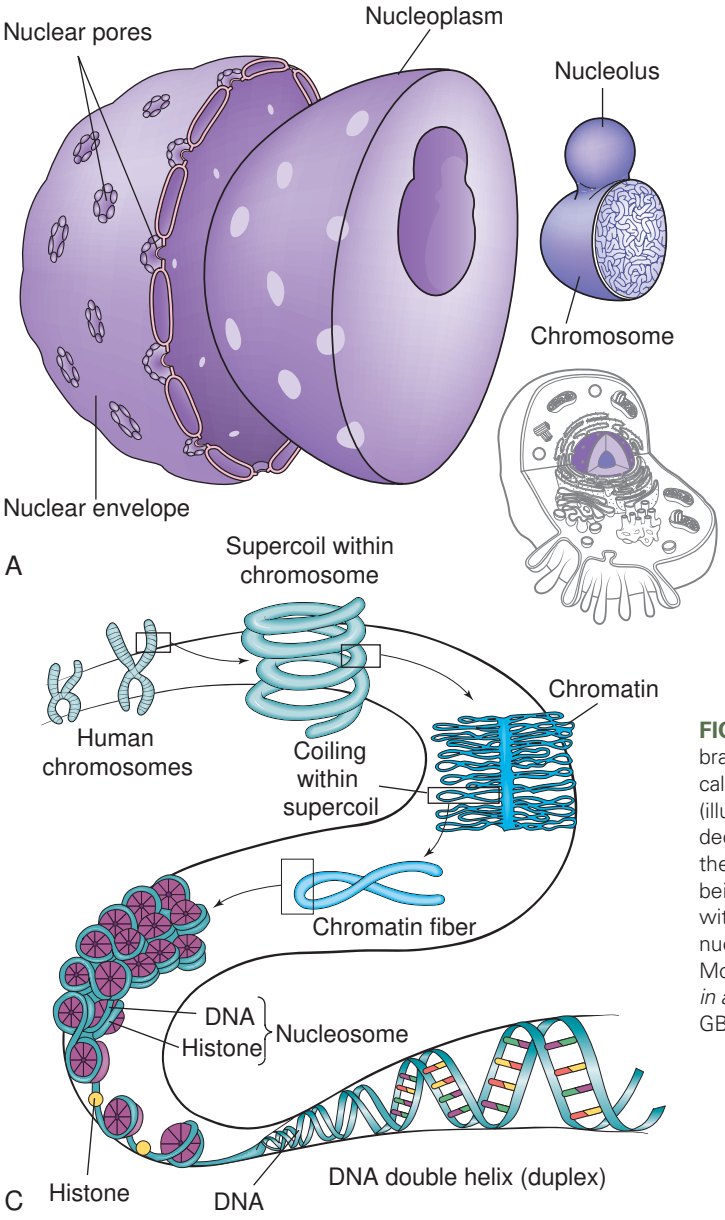
Nucleus

The **nucleus**, which is surrounded by the cytoplasm and generally is located in the center of the cell, is the largest membrane-bound organelle. Two pliable membranes compose the **nuclear envelope** (Fig. 1.2, *A*). The nuclear envelope is pockmarked with pits, called **nuclear pores**, which allow chemical messages to exit and enter the nucleus (see Fig. 1.2, B). The outer membrane is continuous with membranes of the endoplasmic reticulum (see Fig. 1.1). The nucleus contains the **nucleolus** (a small dense structure composed largely of RNA), most of the cellular DNA, and the DNA-binding proteins (i.e., the histones) that regulate its activity. The DNA "chain" in eukaryotic cells is so long that it is easily broken. Therefore the histones that bind to DNA cause DNA to fold into chromosomes (see Fig. 1.2, *C*), which decreases the risk of breakage and is essential for cell division in eukaryotes.

The primary functions of the nucleus are cell division and control of genetic information. Other functions include the replication and repair of DNA and the transcription of the information stored in DNA. Genetic information is transcribed into RNA, which can be processed into messenger, transport, and ribosomal RNAs and introduced into the cytoplasm, where it directs cellular activities. Most of the processing of RNA occurs in the nucleolus. (The roles of DNA and RNA in protein synthesis are discussed in Chapter 2.)

Cytoplasmic Organelles

Cytoplasm is an aqueous solution (**cytosol**) that fills the **cytoplasmic matrix**—the space between the nuclear envelope and the plasma membrane. The cytosol represents about half the volume of a eukaryotic cell. It contains thousands of enzymes involved in intermediate metabolism and is *crowded* with ribosomes making proteins (see Fig. 1.1, *B*). Newly synthesized proteins remain in the cytosol if they lack a signal for transport to a cell organelle.[1] The organelles suspended in the cytoplasm are enclosed in biologic membranes, so they can simultaneously carry out functions requiring different biochemical environments. Many of these functions are directed by coded messages carried from the nucleus by RNA. The functions include synthesis of proteins and hormones and their transport out of the cell, isolation and elimination of waste products from the cell, performance of metabolic processes,



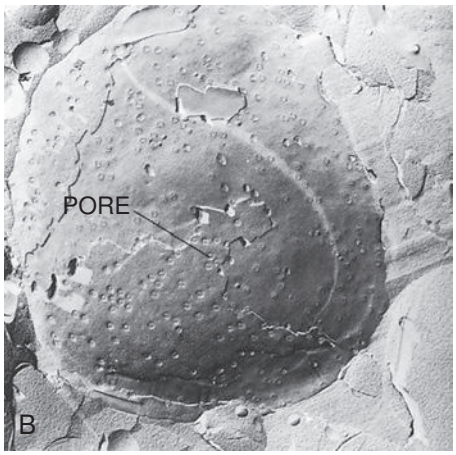


FIGURE 1.2 The Nucleus. The nucleus is composed of a double membrane, called a nuclear envelope, which encloses the fluid-filled interior, called *nucleoplasm*. The chromosomes are suspended in the nucleoplasm (illustrated here much larger than actual size to show the tightly packed deoxyribonucleic acid [DNA] strands). Swelling at one or more points of the chromosome, shown in **A,** occurs at a nucleolus where genes are being copied into ribonucleic acid (RNA). The nuclear envelope is studded with pores. **B,** The pores are visible as dimples in this freeze-etch of a nuclear envelope. **C,** Histone-folding DNA in chromosomes. (**A, C,** from McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier. **B,** from Raven PH, Johnson GB: *Biology,* St Louis, 1992, Mosby.)

breakdown and disposal of cellular debris and foreign proteins (antigens), and maintenance of cellular structure and motility. The cytosol is a storage unit for fat, carbohydrates, and secretory vesicles. Table 1.1 lists the principal cytoplasmic organelles.

QUICK CHECK 1.1

1. Why is the process of differentiation essential to specialization? Give an example.
2. Describe at least two cellular functions.

Plasma Membranes

Every cell is contained within a membrane with gates, channels, and pumps. Membranes surround the cell or enclose an intracellular organelle and are exceedingly important to normal physiologic function because they control the composition of the space, or compartment, they enclose. Membranes can allow or exclude various molecules, and because of selective transport systems, they can move molecules in or out of the space (Fig. 1.3). By controlling the movement of substances from one compartment to another, membranes exert a powerful influence on metabolic pathways. Directional transport is facilitated by polarized domains, distinct apical and basolateral domains. **Cell polarity**, the direction of cellular transport, maintains normal cell and tissue structure for numerous functions (e.g., movement of nutrients in and out of the cell) and becomes altered with diseases (Fig. 1.4). The plasma membrane also has an important role in cell-to-cell recognition. Other functions of the plasma membrane include cellular mobility and the maintenance of cellular shape (Table 1.2).

Membrane Composition

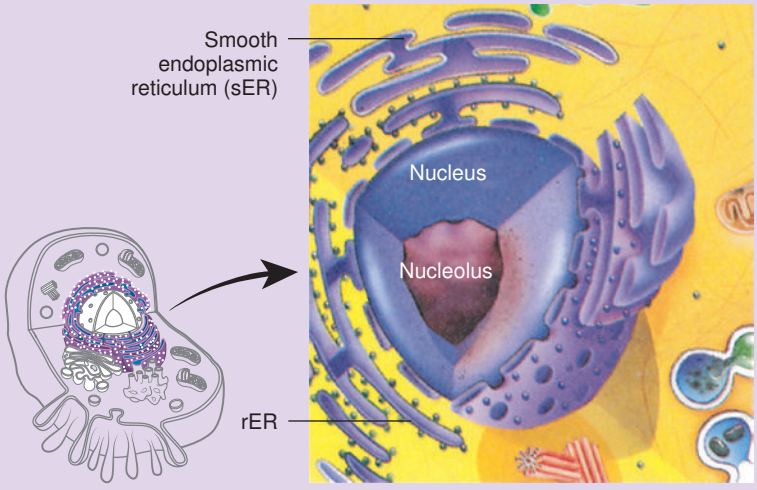
The basic structure of cell membranes is the **lipid bilayer**, composed of two apposing leaflets and proteins that span the bilayer or interact with the lipids on either side of the two leaflets (Fig. 1.5). Lipid research is growing and principles of membrane organization are being overhauled. In short, the main constituents of cell membranes are lipids and proteins. Historically, the plasma membrane was described as a fluid lipid bilayer (fluid mosaic model) composed of a *uniform* lipid distribution with inserted moving proteins. Although the notion is controversial, it now appears that the lipid bilayer is a much more complex structure where lipids and proteins are not uniformly distributed but may separate into discrete units called *microdomains,* differing in their protein and lipid compositions. Different membranes have varying percentages of lipids and proteins. Intracellular membranes may have a higher percentage of proteins than do plasma membranes, presumably because most enzymatic activity occurs within organelles. The membrane organization is achieved through noncovalent bonds that allow different physical states called phases (solid gel, fluid liquid–crystalline, and liquid ordered). These phases can change under physiologic factors, such as temperature and pressure fluctuations. Carbohydrates are mainly associated with plasma membranes, in which they are chemically combined with lipids, forming **glycolipids**, and with proteins, forming **glycoproteins** (see Fig. 1.5).

The outer surface of the plasma membrane in many types of cells, especially endothelial cells and adipocytes, is not smooth but dimpled with flask-shaped invaginations known as *caveolae* ("tiny caves"). Caveolae are thought to serve as a storage site for many receptors, provide a route for transport into the cell and may act as the initiator for relaying signals from several extracellular chemical messengers into the cell's interior.

Lipids. Each lipid molecule is said to be polar, or **amphipathic**, which means that one part is hydrophobic (uncharged, or "water hating") and another part is hydrophilic (charged, or "water loving") (see Fig. 1.5, *B*). The membrane spontaneously organizes itself into two layers because of these two incompatible solubilities. The hydrophobic region (hydrophobic tail) of each lipid molecule is protected from water, whereas the hydrophilic region (hydrophilic head) is immersed in it. The bilayer

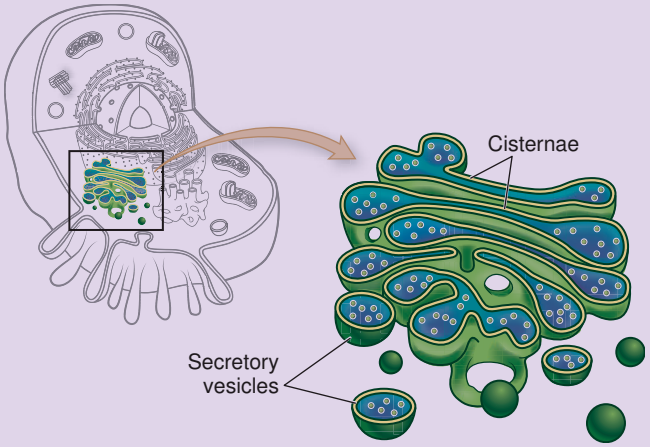
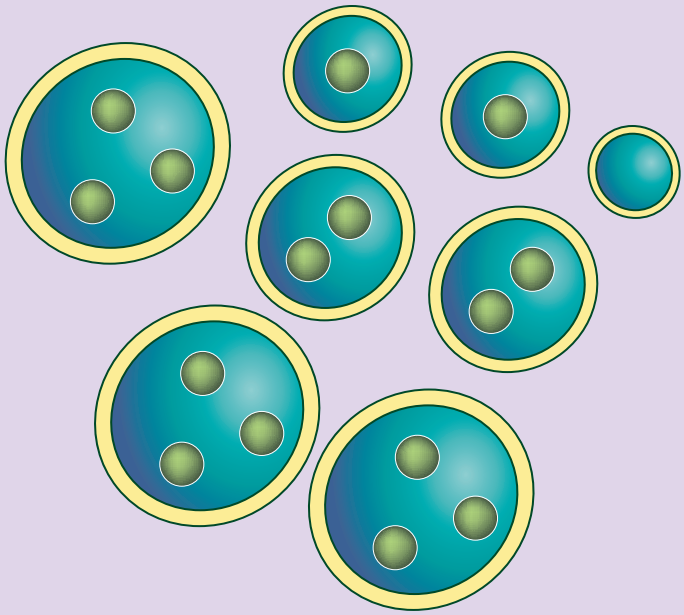
TABLE 1.1 Principal Cytoplasmic Organelles

Organelle	Characteristics and Description
Ribosomes	Ribonucleic acid (RNA)–protein complexes (nucleoproteins) synthesized in nucleolus and secreted into cytoplasm. Provide sites for cellular protein synthesis.
Endoplasmic reticulum	Network of tubular channels (cisternae) that extend throughout outer nuclear membrane. Specializes in synthesis, folding, and transport of protein and lipid components of most organelles. A new role is sensing cellular stress.



(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)

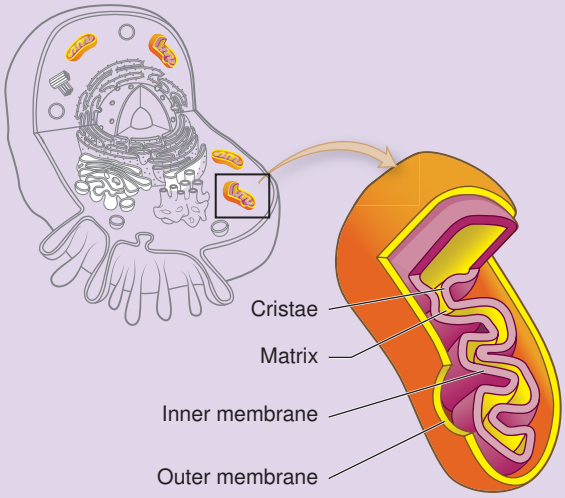
TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Organelle	Characteristics and Description
Golgi complex	Network of smooth membranes and vesicles located near nucleus. Responsible for processing and packaging proteins onto secretory vesicles that break away from the complex and migrate to various intracellular and extracellular destinations, including plasma membrane. Best-known vesicles are those that have coats largely made of the protein *clathrin.* Proteins in the complex bind to the cytoskeleton, generating tension that helps organelle function and keep its stretched shape intact. The complex is a refining plant and directs traffic.  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)
Lysosomes	Sac-like structures that contain enzymes for digesting most cellular substances to their basic form, such as amino acids, fatty acids, and carbohydrates (sugars). Cellular injury leads to release of lysosomal enzymes that cause cellular self-destruction. A new function of lysosomes is signaling hubs of a sophisticated network for cellular adaptation.  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)
Peroxisomes	Similar to lysosomes in appearance but contain several oxidative enzymes (e.g., catalase, urate oxidase) that produce hydrogen peroxide; reactions detoxify various wastes (see Fig. 1.1, *A*).

Continued

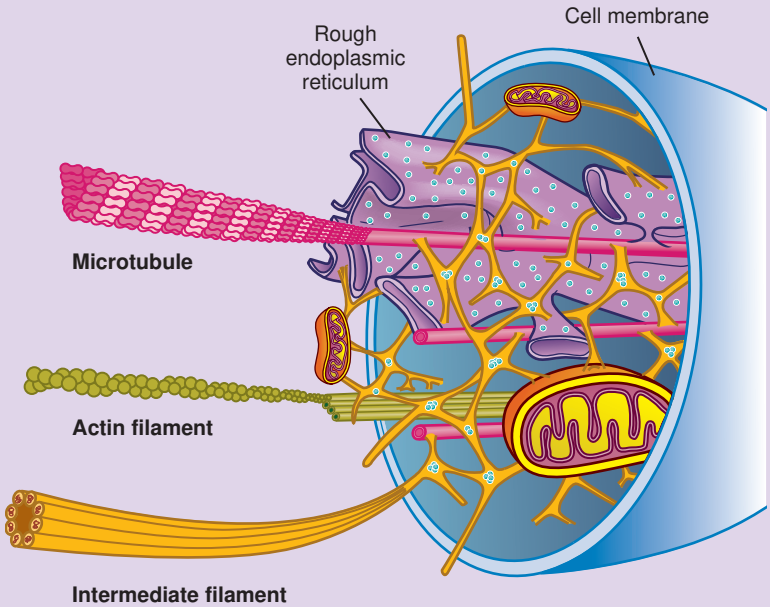
TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Organelle	Characteristics and Description
Mitochondria	Contain metabolic machinery needed for cellular energy metabolism. Enzymes of respiratory chain (electron-transport chain), found in inner membrane of mitochondria, generate most of cell's adenosine triphosphate (ATP) (oxidative phosphorylation). Have a role in osmotic regulation, pH control, calcium homeostasis, and cell signaling.



(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)

Cytoskeleton	"Bone and muscle" of cell. Composed of a network of protein filaments, including microtubules and actin filaments (microfilaments); forms cell extensions (microvilli, cilia, flagella). Intermediate filaments bridge the cytoplasm from one cell junction to another strengthening and supporting the sheet of epithelium.



(From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)

serves as a barrier to the diffusion of water and hydrophilic substances, while allowing lipid-soluble molecules, such as oxygen (O_2) and carbon dioxide (CO_2), to diffuse through the membrane readily.

A major component of the plasma membrane is a bilayer of lipid molecules—glycerophospholipids, sphingolipids, and sterols (e.g., cholesterol). The most abundant lipids are phospholipids. **Phospholipids** have a phosphate-containing hydrophilic head connected to a hydrophobic tail. Phospholipids and glycolipids form self-sealing lipid bilayers. Lipids along with protein assemblies act as "molecular glue" for the structural integrity of the membrane. Investigators are studying the concept of *lipid rafts,* which may be structurally and functionally distinct regions of the plasma membrane.

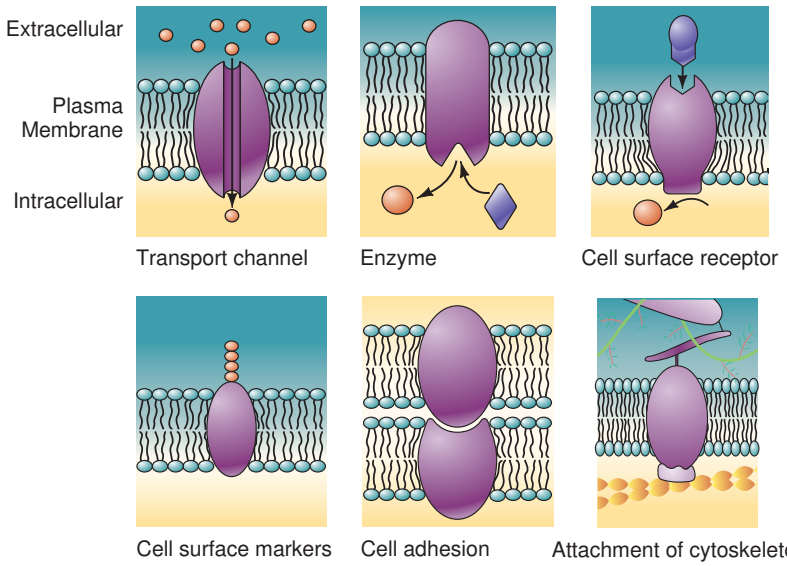


FIGURE 1.3 Functions of Plasma Membrane Proteins. The plasma membrane proteins illustrated here show a variety of functions performed by the different types of plasma membranes. (From Raven PH, Johnson GB: *Understanding biology,* ed 3, Dubuque, IA, 1995, Brown.)

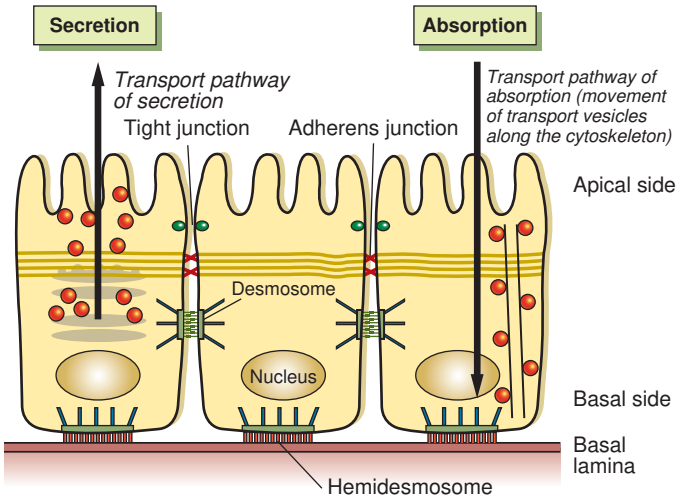


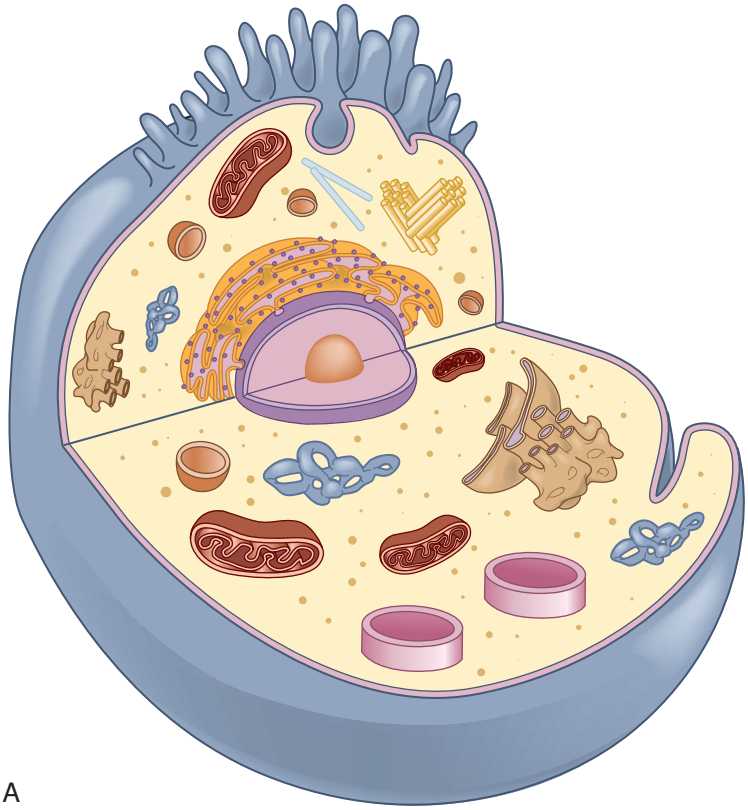
FIGURE 1.4 Cell Polarity of Epithelial Cells. Schematic of cell polarity (cell direction) of epithelial cells. Shown are the directions of the basal side and the apical side. Organelles and cytoskeleton are also arranged directionally to enable, for example, intestinal cell secretion and absorption. (Adapted from *Life science web textbook,* The University of Tokyo.)

Proteins. Proteins perform most of the plasma membrane's tasks. A **protein** is made from a chain of amino acids, known as **polypeptides**. There are 20 types of amino acids in proteins and each type of protein has a unique sequence of amino acids. After translation (the synthesis of protein from RNA, see Chapter 2) of a protein, **posttranslational modifications (PTMs)** are the methods used to diversify the limited numbers of proteins generated. These modifications alter the activity and functions of proteins and have become very important in understanding diseases. Researchers have known for decades that pathogens interfere with the host's PTMs. New approaches are being used to understand changes in proteins—a field called **proteomics** is the study of the **proteome**, or entire set of proteins expressed by a genome from synthesis, translocation, and modification (e.g., folding), and the analysis of the roles of proteomes in a staggering number of diseases.

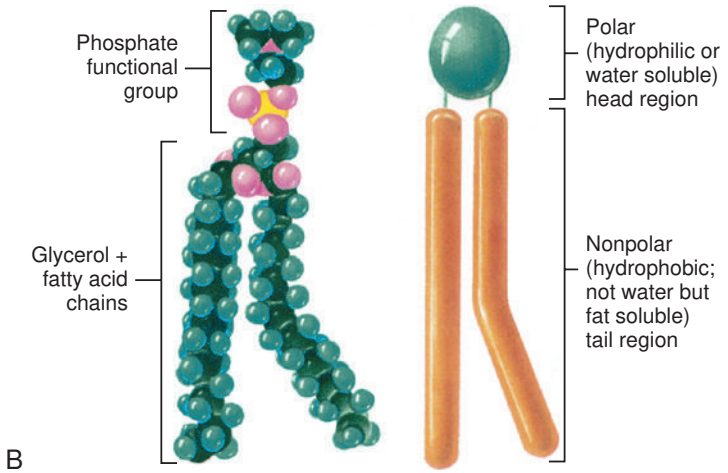
TABLE 1.2 Plasma Membrane Functions

Cellular Mechanism	Membrane Functions
Structure	Usually thicker than membranes of intracellular organelles Containment of cellular organelles Maintenance of relationship with cytoskeleton, endoplasmic reticulum, and other organelles Maintenance of fluid and electrolyte balance (ion channels) Outer surfaces of plasma membranes in many cells are not smooth but are dimpled with cave-like indentations called *caveolae;* they are also studded with cilia or even smaller cylindrical projections called *microvilli;* both are capable of movement
Protection	Barrier to toxic molecules and macromolecules (proteins, nucleic acids, polysaccharides) Barrier to foreign organisms and cells
Activation of cell	Hormones (regulation of cellular activity) Mitogens (cellular division; see Chapter 2) Antigens (antibody synthesis; see Chapter 7) Growth factors (proliferation and differentiation; see Chapter 11)
Storage	Storage site for many receptors Transport (e.g., sodium [Na^+] pump) Diffusion and exchange diffusion Endocytosis (pinocytosis, phagocytosis) Exocytosis (secretion) Active transport
Cell-to-cell interaction	Communication, anchors (integrins), and attachment at junctional complexes Symbiotic nutritive relationships Release of enzymes and antibodies to extracellular environment Relationships with extracellular matrix

Modified from King DW, Fenoglio CM, Lefkowitch JH: *General pathology: principles and dynamics,* Philadelphia, 1983, Lea & Febiger.



A



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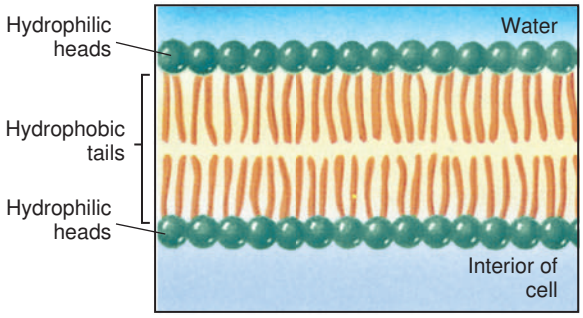

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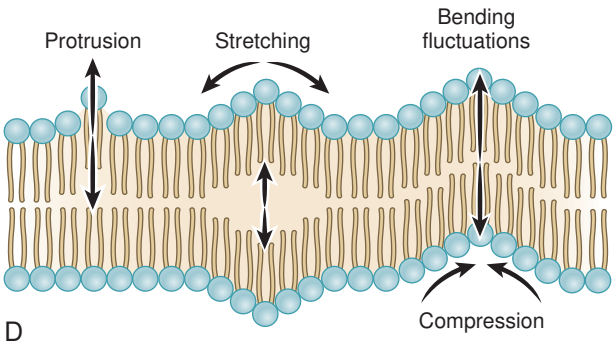


D

FIGURE 1.5 **Lipid Bilayer Membranes. A,** Concepts of biologic membranes have markedly changed in the last two decades, from the classic fluid mosaic model to the current model that lipids and proteins are not evenly distributed but can isolate into microdomains, differing in their protein and lipid composition. Important for pathophysiology is the proposal that protein–lipid interactions can be critical for correct insertion, folding, and orientation of membrane proteins. For example, diseases related to lipids that interfere with protein folding are becoming more prevalent. **B,** Each phospholipid molecule consists of a phosphate functional group and two fatty acid chains attached to a glycerol molecule. **C,** The fatty acid chains and glycerol form nonpolar, hydrophobic "tails," and the phosphate functional group forms the polar, hydrophilic "head" of the phospholipid molecule. When placed in water, the hydrophobic tails of the molecule face inward, away from the water, and the hydrophilic head faces outward, toward the water. **D,** The cell membrane is not static but is always moving. Observed for the first time from measurements taken at the National Institute of Standards and Technology (NIST) and France's Institute Laue-Langevin (ILL). (A & D, adapted from Bagatolli LA et al: An outlook on organization of lipids in membranes: searching for a realistic connection with the organization of biological membranes, *Prog Lipid Res* 49[4]:378–389, 2010; Contreras FX et al: Specificity of intramembrane protein-lipid interactions, *Cold Spring Harb Perspect Biol* 3[6]:pii a004705, 2011; Cooper GM: *The cell—a molecular approach,* ed 2, Sunderland, MA, 2000, Sinauer Associates; Defamie N, Mesnil M: *Biochim Biophys Acta* 1818(8):1866–1869, 2012; Woodka AC et al: *Phys Rev Lett* 9(5):058102, 2012. B & C, from Raven PH, Johnson GB: *Understanding biology,* ed 3, Dubuque, IA, 1995, Brown.)

Membrane proteins associate with the lipid bilayer in different ways (Fig. 1.6), including:

1. **Transmembrane proteins** that extend across the bilayer and exposed to an aqueous environment on both sides of the membrane (see Fig. 1.6, *A*)
2. Proteins located almost entirely in the cytosol and associated with the cytosolic half of the lipid bilayer by an α helix exposed on the surface of the protein (see Fig. 1.6, *B*)
3. Proteins that exist outside the bilayer, on one side or the other, and attached to the membrane by one or more covalently attached lipid groups (see Fig. 1.6, *C*)
4. Proteins bound indirectly to one or the other bilayer membrane face and held in place by their interactions with other proteins (see Fig. 1.6, *D*).[1].

Proteins directly attached to the membrane bilayer can be removed by dissolving the bilayer with detergents called **integral membrane proteins**. The remaining proteins that can be removed by gentler procedures that interfere with protein–protein interactions but do not dissolve the bilayer are known as **peripheral membrane proteins**.

Proteins exist in densely folded molecular configurations rather than straight chains; thus most hydrophilic units are at the surface of the molecule, and most hydrophobic units are inside. Membrane proteins, like other proteins, are synthesized by the ribosome and translocate, called *trafficking,* to different membrane locations of a cell. Trafficking puts unique demands on membrane proteins for folding, translocation, and stability. Therefore much research is now being done to understand misfolded proteins (e.g., as a cause of disease; Box 1.1).

Although membrane structure is determined by the lipid bilayer, membrane functions are determined largely by proteins. Proteins act as:

1. Recognition and binding units (receptors) for substances moving into and out of the cell
2. Pores or transport channels for various electrically charged particles, called **ions** or *electrolytes,* and specific carriers for amino acids and monosaccharides
3. Specific enzymes that drive active pumps to promote concentration of certain ions, particularly potassium (K^+), within the cell while keeping concentrations of other ions (e.g., sodium [Na^+]), less than concentrations found in the extracellular environment;
4. Cell surface markers, such as **glycoproteins** (proteins attached to carbohydrates), which identify a cell to its neighbor
5. **Cell adhesion molecules (CAMs)**, or proteins that allow cells to hook together and form attachments of the cytoskeleton for maintaining cellular shape
6. Catalysts of chemical reactions (e.g., conversion of lactose to glucose (see Fig. 1.3).

Membrane proteins are key components of energy transduction, converting chemical energy into electrical energy, or electrical energy into either mechanical energy or synthesis of ATP. Investigators are studying ATP enzymes and the changes in shape of biologic membranes, particularly mitochondrial membranes, and their relationship to aging and disease.

In animal cells, the plasma membrane is stabilized by a meshwork of proteins attached to the underside of the membrane called the **cell cortex**. Human red blood cells have a cell cortex that maintains their flattened biconcave shape.[1]

Protein regulation in a cell: proteostasis. The cellular protein pool is in constant change or flux. **Proteostasis** is a state of cell balance of the processes of protein synthesis, folding, and dehydration. It is vital to health. This adaptable system depends on how quickly proteins are made, how long they survive, or when they are broken down. The proteostasis network comprises ribosomes (makers); chaperones (helpers); and two protein breakdown systems or **proteolytic** systems—lysosomes and the ubiquitin–proteasome system (UPS). These systems regulate protein homeostasis under a large variety of conditions, including variations in nutrient supply, the existence of oxidative stress or cellular differentiation, changes in temperature, and the presence of heavy metal ions and other sources of stress. Malfunction or failure of the proteostasis network is associated with human (Fig. 1.7).

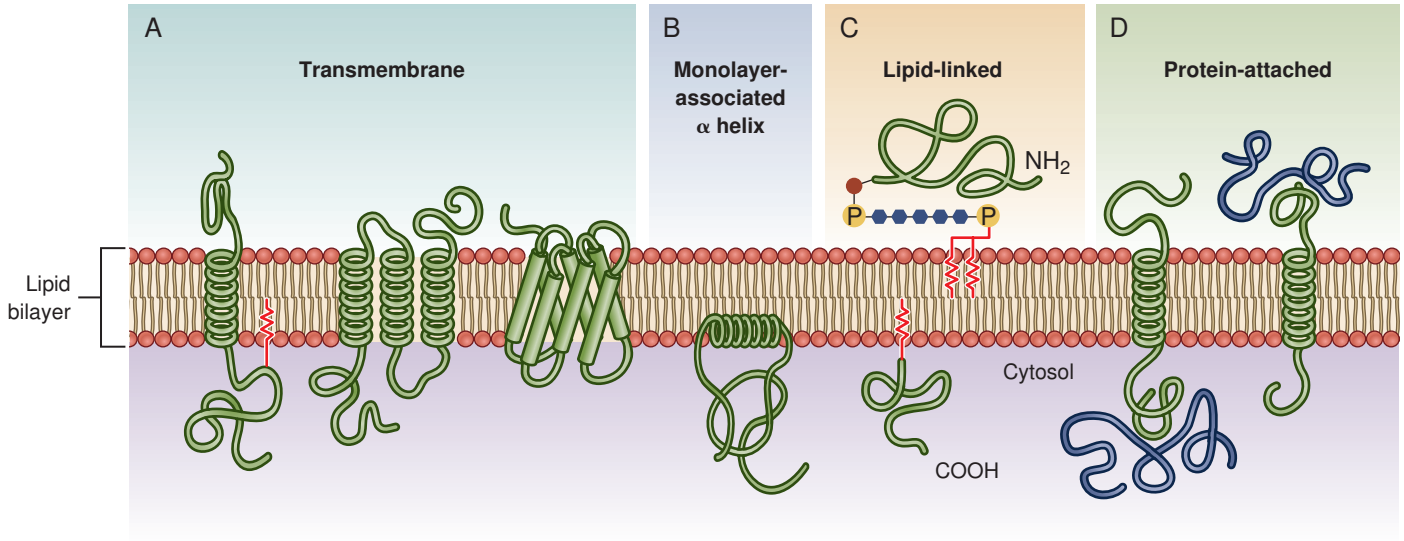
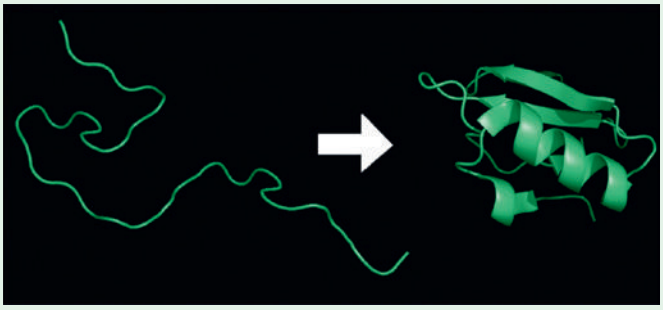


FIGURE 1.6 Proteins Attach to the Plasma Membrane in Different Ways. A, Transmembrane proteins extend through the membrane as a single α helix, as multiple α helices, or as a rolled-up barrel-like sheet called a β barrel. **B,** Some membrane proteins are anchored to the cytosolic side of the lipid bilayer by an amphipathic α helix. **C,** Some proteins are linked on either side of the membrane by a covalently attached lipid molecule. **D,** Proteins are attached by weak noncovalent interactions with other membrane proteins. (**D,** adapted from Alberts B et al: *Essential cell biology,* ed 4, New York, 2014, Garland.)

BOX 1.1 Endoplasmic Reticulum, Protein Folding, and Endoplasmic Reticulum Stress

Protein folding in the endoplasmic reticulum (ER) is critical for humans. As the biologic workhorses, proteins perform vital functions in every cell. To do these tasks, proteins must fold into complex three-dimensional structures (see figure). Most secreted proteins *fold* and are modified in an error-free manner, but ER or cell stress, mutations, or random (stochastic) errors during protein synthesis can decrease the folding amount or the rate of folding. Pathophysiologic processes, such as viral infections, environmental toxins, and mutant protein expression, can perturb the sensitive ER environment. Natural processes also can perturb the environment, such as the large protein-synthesizing load placed on the ER. These perturbations cause the accumulation of immature and abnormal proteins in cells, leading to **ER stress**. Fortunately, the ER is loaded with protective ways to help folding, for example, protein so-called *chaperones* that facilitate folding and prevent the formation of off-pathway types. Because specialized cells produce large amounts of secreted proteins, the movement or flux through the ER is tremendous. Therefore misfolded proteins not repaired in the ER are observed in some diseases and can initiate apoptosis, or cell death. It has recently been shown that the ER mediates intracellular signaling pathways in response to the accumulation of unfolded or misfolded proteins; collectively, the adaptive pathways are known as the **unfolded-protein response (UPR)**. Investigators are studying UPR-associated inflammation and how the UPR is coupled to inflammation in health and disease. Specific diseases include Alzheimer disease, Parkinson disease, prion disease, amyotrophic lateral sclerosis, diabetes mellitus, and sepsis. Additionally being studied is ER stress and how it may accelerate age-related dysfunction. Overall, ER is a major organelle for protein quality control.



Protein Folding. Each protein exists as an unfolded polypeptide *(left)* or random coil after the process of translation from a sequence of messenger ribonucleic acid (mRNA) to a linear string of amino acids. From amino acids interacting with each other they produce a three-dimensional structure called the folded protein *(right)* that is its native state.

Data from Alberts B et al: *Molecular biology of the cell,* ed 6, New York, 2015; Brodsky J, Skach WR: *Curr Opin Cell Biol* 23:464–475, 2011; Jäger R et al: *Biol Cell* 104(5):259–270, 2012; Khan MM, Yang VVL, Wang P: *Shock* 44(4):294–304, 2015; Shah SZ et al: *J Mol Neurosci* 57(4):529–537, 2015.

Carbohydrates. The short chains of sugars or carbohydrates *(oligosaccharides)* contained within the plasma membrane are mostly bound to membrane proteins (glycoproteins) and lipids (glycolipids). Long polysaccharide chains attached to membrane proteins are called *proteoglycans.* All of the carbohydrate on the glycoproteins, proteoglycans, and glycolipids is located on the outside of the plasma membrane and the carbohydrate coating is called the **glycocalyx**. The glycocalyx helps protect the cell from mechanical damage.[1] Additionally, the layer of carbohydrate gives the cell a slimy surface that assists the mobility of other cells, such as leukocytes, to squeeze through the narrow spaces.[1] Other functions of carbohydrates include specific cell-to-cell recognition and adhesion. Intercellular recognition is an important function of membrane oligosaccharides; for example, the transmembrane proteins called *lectins,* which bind to a particular oligosaccharide, recognize neutrophils at the site of bacterial infection. This recognition allows the neutrophil to adhere to the blood vessel wall and migrate from blood into the infected tissue to help eliminate the invading bacteria.[1]

Cellular Receptors

Cellular receptors are protein molecules on the plasma membrane, in the cytoplasm, or in the nucleus that can recognize and bind with specific smaller molecules called **ligands** (from the Latin *ligare,* "to bind") (Fig. 1.8). The region of a protein that associates with a ligand is called its **binding site**. Hormones, for example, are ligands. Numerous receptors are found in most cells, and ligand binding to receptors activates or inhibits the receptor's associated signaling or biochemical pathway (see the Cellular Communication and Signal Transduction section). Recognition and binding depend on the chemical configuration of the receptor and its smaller ligand, which must fit together somewhat like the pieces of a jigsaw puzzle (see Chapter 19). Binding selectively to a protein receptor with high affinity to a ligand depends on formation of weak, noncovalent interactions—hydrogen bonds, electrostatic attractions, and van der Waals attractions—and favorable hydrophobic forces.[1]

Plasma membrane receptors protrude from or are exposed at the external surface of the membrane and are important for cellular uptake of ligands (see Fig. 1.8). The ligands that bind with membrane receptors include hormones, neurotransmitters, antigens, complement components, lipoproteins, infectious agents, drugs, and metabolites. Many new discoveries concerning the specific interactions of cellular receptors with their respective ligands have provided a basis for understanding disease.

Although the chemical nature of ligands and their receptors differs, receptors are classified on the basis of their location and function. Cellular type determines overall cellular function, but plasma membrane receptors determine which ligands a cell will bind with and how the cell will respond to the binding. Specific processes also control intracellular mechanisms.

Receptors for different drugs are found on the plasma membrane, in the cytoplasm, and in the nucleus. Membrane receptors have been found for certain anesthetics, opiates, endorphins, enkephalins, antibiotics, cancer chemotherapeutic agents, digitalis, and other drugs. Membrane receptors for endorphins, which are opiate-like peptides isolated from the pituitary gland, are found in large quantities in pain pathways of the nervous system (see Chapters 14 and 15). With binding to the receptor, the endorphins (or drugs, e.g., morphine) change the cell's permeability to ions, increase the concentration of molecules that regulate intracellular protein synthesis, and initiate molecular events that modulate pain perception.

Receptors for infectious microorganisms, or antigen receptors, bind bacteria, viruses, and parasites to the cell membrane. Antigen receptors on white blood cells (lymphocytes, monocytes, macrophages, granulocytes) recognize and bind with antigenic microorganisms and activate the immune and inflammatory responses (see Chapter 6).

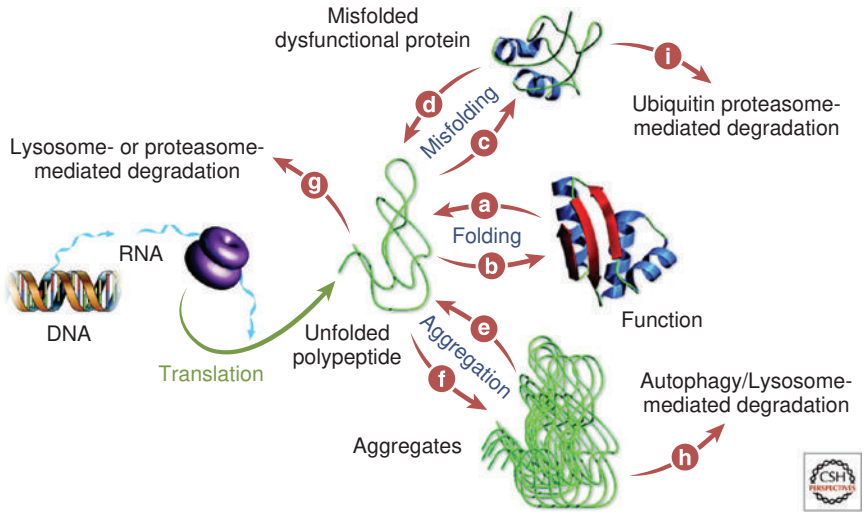


FIGURE 1.7 Protein Homeostasis System and Outcomes. A main role of the protein homeostasis network *(proteostasis)* is to minimize protein misfolding and protein aggregation. The network includes ribosome-mediated protein synthesis, chaperone (folding helpers in the ER) and enzyme mediated folding, breakdown systems of lysosome and proteasome-mediated protein degradation, and vesicular trafficking. The network integrates biologic pathways that balance folding, trafficking, and protein degradation depicted by arrows *a, b,* c, *d, e, f, g, h,* and *i. ER,* Endoplasmic reticulum. (Adapted from Lindquist SL, Kelly JW: *Cold Spring Harb Perspect Biol* 3[12]:pii: a004507, 2011.)

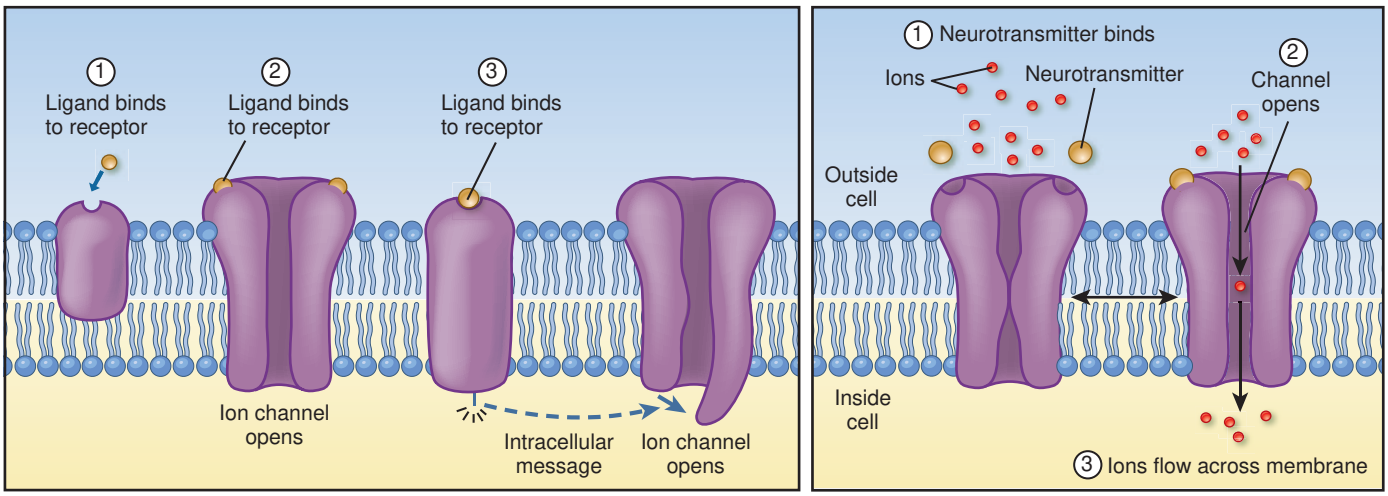


FIGURE 1.8 Cellular Receptors. A, 1. Plasma membrane receptor for a ligand (here, a hormone molecule) on the surface of an integral protein. A neurotransmitter can exert its effect on a postsynaptic cell by means of two fundamentally different types of receptor proteins. **2.** Channel-linked receptors. **3.** Non–channel-linked receptors. Channel-linked receptors are also known as *ligand-gated channels.* **B,** Example of ligand-gated ion channels. The channel structure is changed when, for example, a neurotransmitter binds and ions can now enter.

CELL-TO-CELL ADHESIONS

Cells are small and squishy, *not* like bricks. They are enclosed only by a flimsy membrane, yet the cell depends on the integrity of this membrane for its survival. How can cells be connected strongly, with their membranes intact, to form a muscle that can lift this textbook? Plasma membranes not only serve as the outer boundaries of all cells but also allow groups of cells to be held together robustly, in **cell-to-cell adhesions**, to form tissues and organs (Box 1.2). Once arranged, cells are linked by three different means: (1) cell adhesion molecules in the cell's plasma membrane, (2) the extracellular matrix (ECM), and (3) specialized cell junctions.

BOX 1.2 Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins that bind the cell to an adjacent cell and to components of the extracellular matrix (ECM). CAMs include four protein families: (1) the integrins, (2) the cadherins, (3) the selectins, and (4) the **immunoglobulin superfamily CAMs** (IgSF CAMs). **Integrins** are receptors within the ECM and regulate cell-ECM interactions with collagen. **Cadherins** are calcium (Ca^{++})–dependent glycoproteins throughout tissue, for example, epithelial (E-cadherin). **Selectins** are proteins that bind some carbohydrates, for example, mucins. The IgSF CAMs bind integrins and other IgSF CAMs.

Extracellular Matrix and Basement Membrane

Cells can be united by attachment to one another or through the ECM (including the basement membrane), which the cells secrete around themselves. The **extracellular matrix (ECM)** is an intricate meshwork of fibrous proteins embedded in a watery, gel-like substance composed of complex carbohydrates (Fig. 1.9). The **basement membrane (BM)** (also known as **basal lamina**) is a specialized type of ECM. This sheet of matrix is very thin, tough, and flexible; lies beneath epithelial cells; occurs between two cell sheets (kidney glomerulus); and surrounds individual muscle cells, fat cells, and Schwann cells (which wrap around peripheral nerve cell axons) (Fig. 1.10). The ECM is similar to glue; however it provides a pathway for diffusion of nutrients, wastes, and other water-soluble substances between the blood and tissue cells. Interwoven within the matrix are three groups of large molecules or **macromolecules**: (1) fibrous structural proteins, including collagen and elastin; (2) adhesive glycoproteins, such as fibronectin; and (3) proteoglycans and hyaluronic acid.

1. **Collagen** forms cable-like fibers or sheets that provide tensile strength or resistance to longitudinal stress. Collagen breakdown, such as occurs in osteoarthritis, destroys the fibrils that give cartilage its tensile strength.
2. **Elastin** is a rubber-like protein fiber most abundant in tissues that must be capable of stretching and recoiling, such as found in the lungs.
3. **Fibronectin**, a large glycoprotein, promotes cell adhesion and cell anchorage. Reduced amounts have been found in certain types of cancerous cells; this allows cancer cells to travel, or metastasize, to other parts of the body. All of these macromolecules occur in intercellular junctions and cell surfaces and may assemble into two different components: interstitial matrix and BM (see Fig. 1.9).

The ECM is secreted by **fibroblasts** ("fiber formers") (Fig. 1.11), local cells that are present in the matrix. The matrix and the cells within it are known collectively as *connective tissue* because they interconnect cells to form tissues and organs. Human connective tissues are enormously varied. They can be hard and dense, for example, bone; flexible, for example, tendons or the dermis of the skin; resilient and shock absorbing, for example, cartilage; or soft and transparent, similar to the jelly-like substance that fills the eye. In all these examples, the majority of the tissue is composed of ECM, and the cells that produce the matrix are scattered within it like raisins in a pudding (see Fig. 1.11).

The matrix is not just passive scaffolding for cellular attachment but also helps regulate the function of the cells with which it interacts. The matrix helps regulate important functions, such as cell growth and differentiation.

Specialized Cell Junctions

Cells in direct physical contact with neighboring cells are often interconnected at specialized plasma membrane regions called **cell junctions**. Cell junctions are classified by their function:

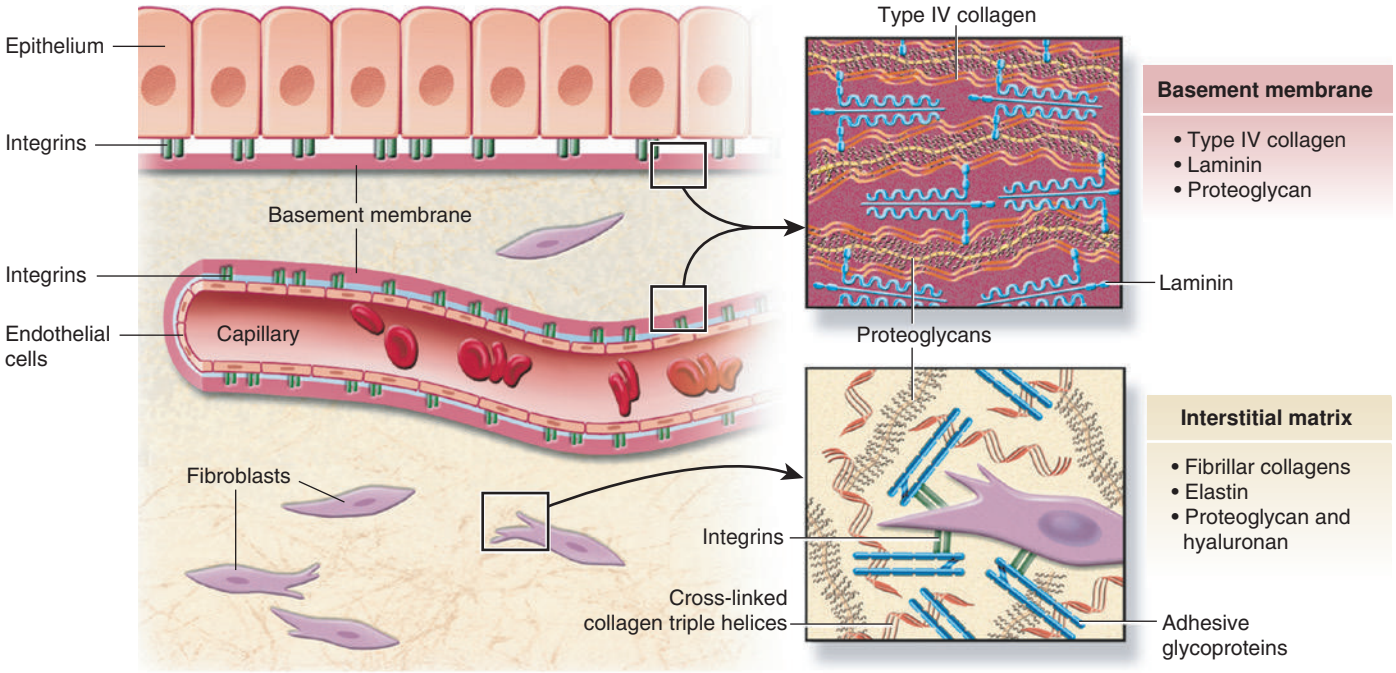


FIGURE 1.9 Extracellular Matrix. Tissues are not just cells but also extracellular space. The extracellular space is an intricate network of macromolecules called the *extracellular matrix (ECM).* The macromolecules that constitute the ECM are secreted locally (by mostly fibroblasts) and assembled into a meshwork in close association with the surface of the cell that produced them. Two main classes of macromolecules include proteoglycans, which are bound to polysaccharide chains called *glycosaminoglycans;* and fibrous proteins (e.g., collagen, elastin, fibronectin, and laminin), which have structural and adhesive properties. Together the proteoglycan molecules form a gel-like ground substance in which the fibrous proteins are embedded. The gel permits rapid diffusion of nutrients, metabolites, and hormones between blood and the tissue cells. Matrix proteins modulate cell–matrix interactions, including normal tissue remodeling (which can become abnormal, for example, with chronic inflammation). Disruptions of this balance result in serious diseases such as arthritis, tumor growth, and other pathologic conditions. (Adapted from Kumar V et al: *Robbins and Cotran pathologic basis of disease,* ed 9, Philadelphia, 2015, Saunders.)

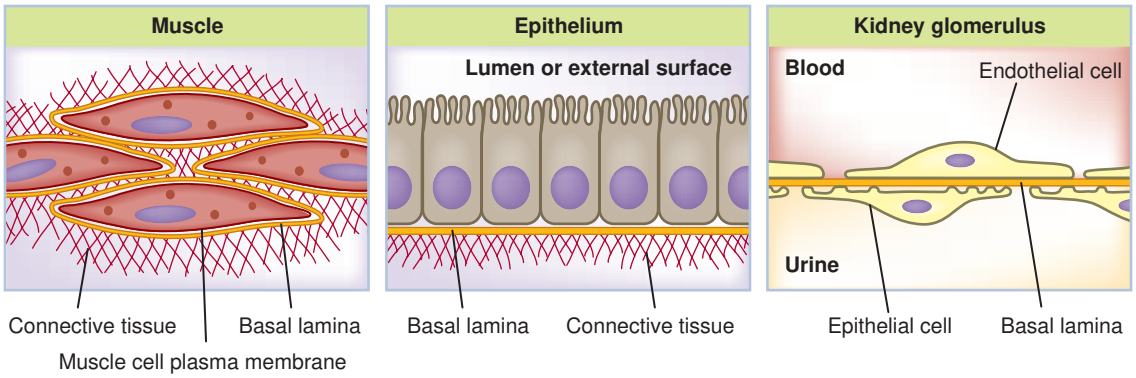


FIGURE 1.10 Three Ways Basement Membranes (Basal Laminae) Are Organized. Basal laminae (yellow) surround certain cells like skeletal cells, underlie epithelia, and occur between two cell sheets (kidney glomerulus). (Adapted from Alberts B et al: *Essential cell biology,* ed 4, New York, 2014, Garland.)

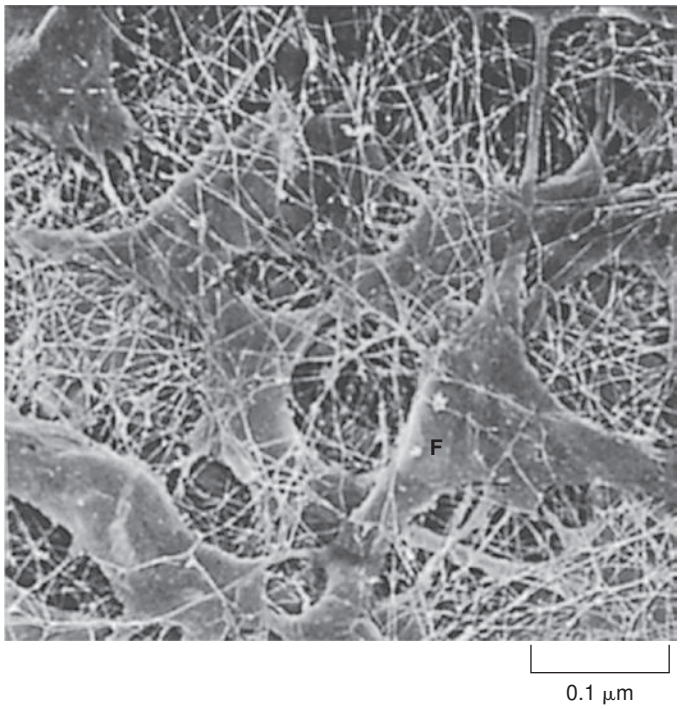


FIGURE 1.11 Fibroblasts in Connective Tissue. This micrograph shows tissue from the cornea of a rat. The extracellular matrix surrounds the fibroblasts *(F).* (From Nishida T et al: The extracellular matrix of animal connective tissues, *Invest Ophthalmol Vis Sci* 29:1887–1880, 1998.)

1. To hold cells together and form a tight seal (tight junctions)
2 To provide strong mechanical attachments (adherens junctions, desmosomes, hemidesmosomes)
3 To provide a special type of chemical communication (e.g., inorganic ions and small water-soluble molecules to move from the cytosol of one cell to the cytosol of another cell), such as those causing an electrical wave (gap junctions)
4 To maintain apico-basal polarity of individual epithelial cells (tight junctions) (Fig. 1.12)

In summary, cell junctions make the epithelium leak-proof and mediate mechanical attachment of one cell to another, allow communicating tunnels and maintaining cell polarity.

Cell junctions can be classified as symmetric and asymmetric. Symmetric junctions include tight junctions (zonula occludens), the belt desmosome (zonula adherens), desmosomes (macula adherens), and gap junctions (also called *intercellular channel* or *communicating junctions*). An asymmetric junction is the hemidesmosome (see Fig. 1.12, *A*). Together they form the **junctional complex**. **Desmosomes** unite cells either by forming continuous bands or belts of epithelial sheets or by developing button-like points of contact. Desmosomes also act as a system of braces to maintain structural stability. **Tight junctions** are barriers to diffusion, prevent the movement of substances through transport proteins in the plasma membrane, and prevent the leakage of small molecules between the plasma membranes of adjacent cells. **Gap junctions** are clusters of communicating tunnels or connexons that allow small ions and molecules to pass directly from the inside of one cell to the inside of another. **Connexons** are hemichannels that extend outward from each of the adjacent plasma membranes (see Fig. 1.12, *C*).

Multiple factors regulate gap junction intercellular communication, including voltage across the junction, intracellular pH, intracellular calcium (Ca^{++}) concentration, and protein phosphorylation.

The junctional complex is a highly permeable part of the plasma membrane where permeability is controlled by a process called **gating**. Increased levels of cytoplasmic calcium cause decreased permeability at the junctional complex. Gating enables uninjured cells to protect themselves from injured neighbors. Calcium is released from injured cells.

CELLULAR COMMUNICATION AND SIGNAL TRANSDUCTION

Cells need to communicate with each other to maintain a stable internal environment, or **homeostasis**; to regulate their growth and division; to oversee their development and organization into tissues; and to coordinate their functions. Cells communicate by using hundreds of kinds of signal molecules, for example, insulin-like growth factor 1. Cells communicate in three main ways:

1. They display plasma membrane–bound signaling molecules (receptors) that affect the cell itself and other cells in direct physical contact (Fig. 1.13, *A*).
2. They affect receptor proteins *inside* the target cell and the signal molecule has to enter the cell to bind to them (see Fig. 1.13, *B*).
3. They form protein channels (gap junctions) that directly coordinate the activities of adjacent cells (see Fig. 1.13, *C*). Alterations in cellular communication affect disease onset and progression. In fact, if a cell cannot perform gap junctional intercellular communication, normal growth control and cell differentiation is compromised, thereby favoring cancerous tumor development (see Chapter 11).

Secreted chemical signals involve communication locally and at a distance. Primary modes of intercellular signaling are contact-dependent, paracrine,

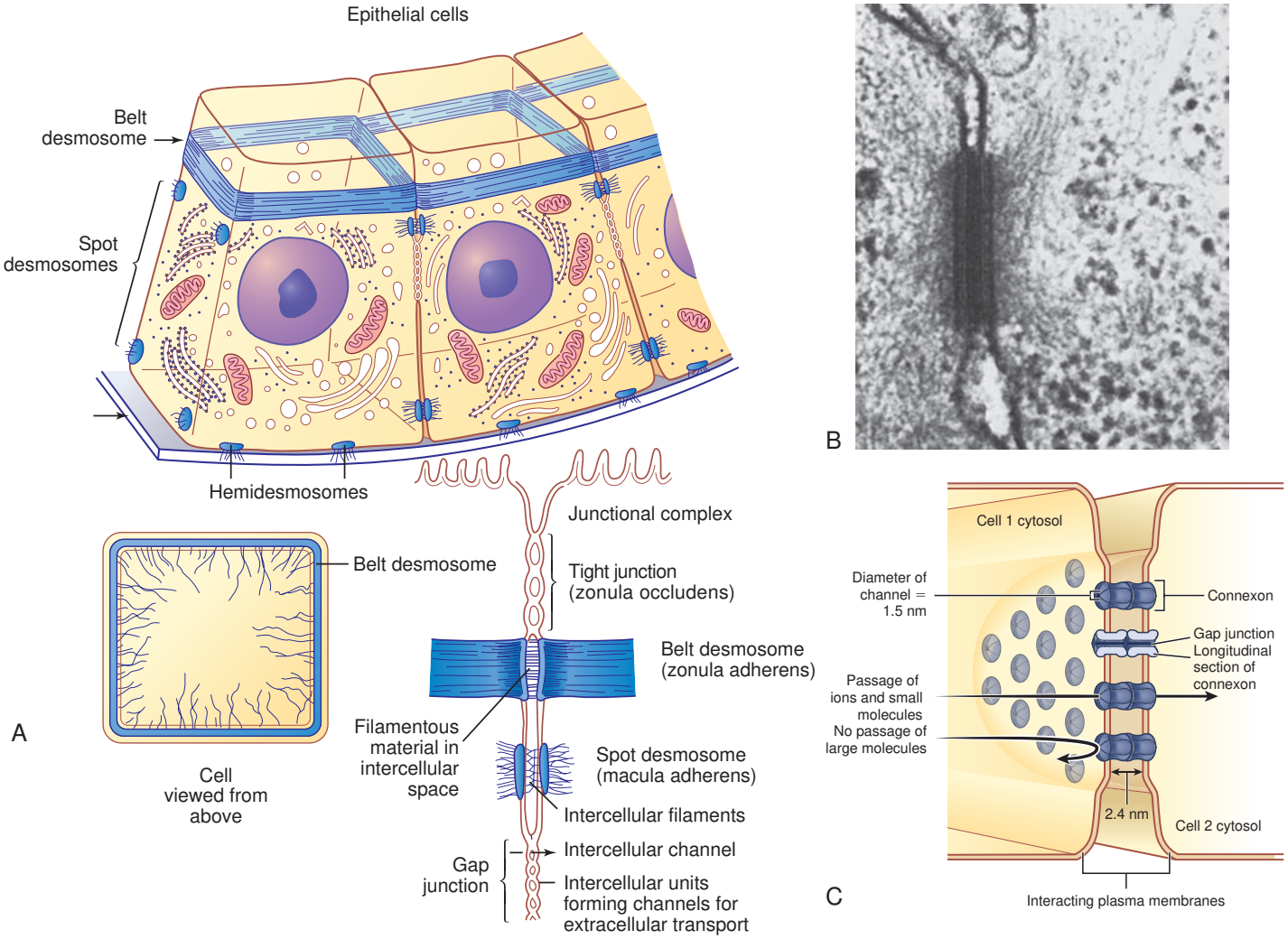


FIGURE 1.12 Junctional Complex. A, Schematic drawing of a belt desmosome between epithelial cells. This junction, also called *zonula adherens,* encircles each interacting cell. The spot desmosomes and hemidesmosomes, like the belt desmosomes, are adhering junctions. The tight junction is an impermeable junction that holds cells together but seals them in such a way that molecules cannot leak between them. The gap junction, as a communicating junction, mediates the passage of small molecules from one interacting cell to the other. **B,** Electron micrograph of desmosomes. **C,** Connexons. The connexin gap junction proteins have four transmembrane domains and they play a vital role in maintaining cell and tissue function and homeostasis. Cells connected by gap junctions are considered ionically (electrically) and metabolically coupled. Gap junctions coordinate the activities of adjacent cells; for example, they are important for synchronizing contractions of heart muscle cells through ionic coupling and for permitting action potentials to spread rapidly from cell to cell in neural tissues. The reason gap junctions occur in tissues that are not electrically active is unknown. Although most gap junctions are associated with junctional complexes, they sometimes exist as independent structures. (**A and B,** from Raven PH, Johnson GB: *Biology,* St Louis, 1992, Mosby; **C** adapted from Gartner LP, Hiatt JL: *Color textbook of histology,* ed 3, St Louis, 2006, Saunders Elsevier; Sherwood L: *Learning,* ed 8, Belmont, California, 2013, Brooks/Cole CENGAGE.)

hormonal, neurohormonal, and neurotransmitter. Autocrine stimulation occurs when the secreting cell targets itself (Fig. 1.14).

Contact-dependent signaling requires cells to be in close membrane-to-membrane contact. In **paracrine signaling**, cells secrete local chemical mediators that are quickly taken up, destroyed, or immobilized. Paracrine signaling usually involves different cell types; however cells also can produce signals to which they alone respond, and this is called **autocrine signaling** (see Fig. 1.14). For example, cancer cells use this form of signaling to stimulate their survival and proliferation. The mediators act only on nearby cells. **Hormonal signaling** involves specialized endocrine cells that secrete chemicals called *hormones;* hormones are released by one set of cells and travel through the bloodstream to produce a response in other sets of cells (see Chapter 19). In **neurohormonal signaling** hormones are released into blood by neurosecretory neurons. Like endocrine cells, neurosecretory neurons release blood-borne chemical messengers, whereas ordinary neurons secrete short-range neurotransmitters into a small discrete space (i.e., synapse). Neurons communicate directly with the cells they innervate by releasing chemicals or **neurotransmitters** at specialized junctions called **chemical synapses**; the neurotransmitter diffuses across the synaptic cleft and acts on the postsynaptic target cell (see Fig. 1.14). Many of these same signaling molecules are receptors used in hormonal, neurohormonal, and paracrine

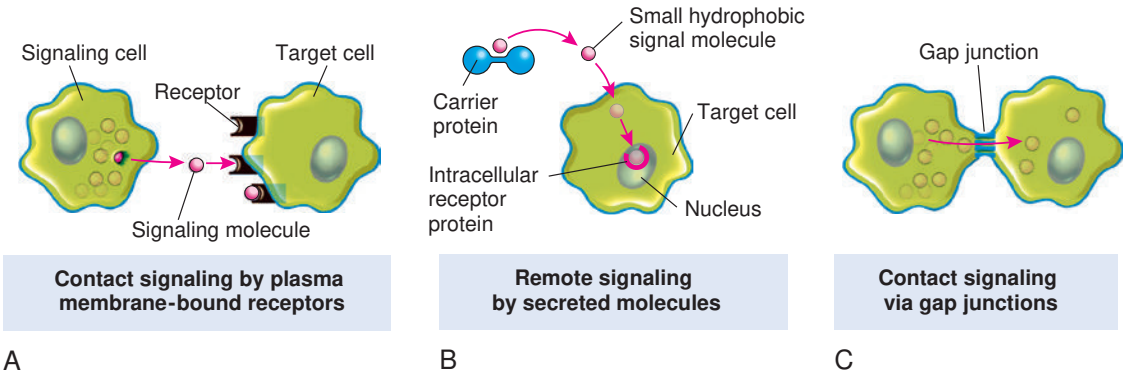


FIGURE 1.13 Cellular Communication. Three primary ways (A–C) cells communicate with one another. (B, adapted from Alberts B et al: *Molecular biology of the cell,* ed 5, New York, 2008, Garland.)

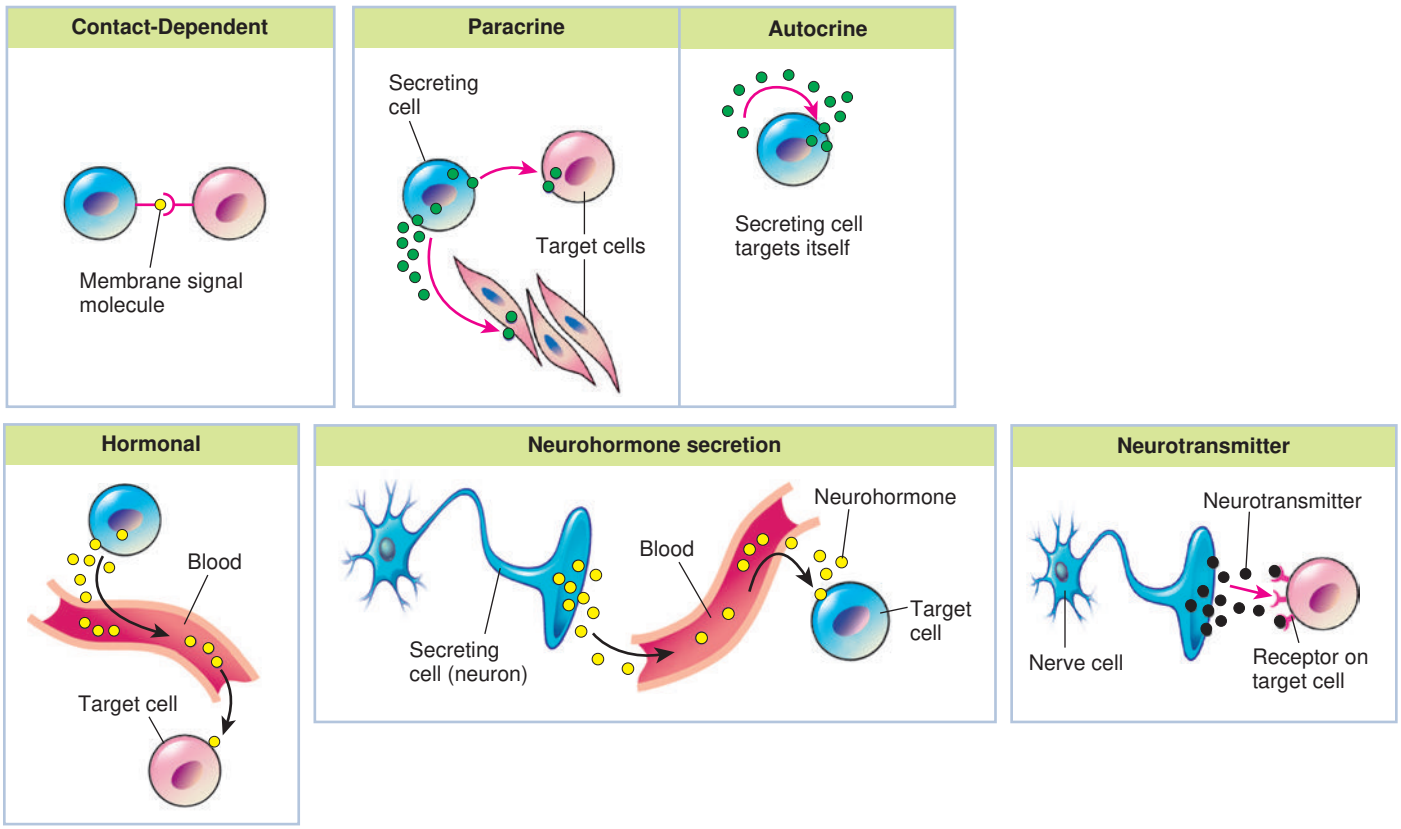


FIGURE 1.14 Primary Modes of Chemical Signaling. Five forms of signaling mediated by secreted molecules. Hormones, paracrines, neurotransmitters, and neurohormones are all intercellular messengers that accomplish communication between cells. Autocrines bind to receptors on the same cell. Not all neurotransmitters act in the strictly synaptic mode shown; some act in a contact-dependent mode as local chemical mediators that influence multiple target cells in the area.

signaling. Important differences lie in the speed and selectivity with which the signals are delivered to their targets.[1]

Plasma membrane receptors belong to one of three classes that are defined by the signaling (transduction) mechanism used. Table 1.3 summarizes these classes of receptors. Cells respond to external stimuli by activating a variety of **signal transduction pathways**, which are communication pathways, or signaling cascades (Fig. 1.15). Signals are passed between cells when a particular type of molecule is produced by one cell—the **signaling cell**—and received by another—the **target cell**—by means of a **receptor protein** that recognizes and responds specifically to the signal molecule (see Fig. 1.15, *A* and *B*). In turn, the signaling molecules activate a pathway of intracellular protein kinases that results in various responses, such as growing and reproducing, dying, surviving, or differentiating (see Fig. 1.15). If deprived of appropriate signals, most cells undergo a form of cell suicide known as *programmed cell death,* or *apoptosis* (see Chapter 4).

Binding of the extracellular signaling messenger (i.e., ligand), or **first messenger**, to the membrane receptors causes (1) opening or closing of specific channels in the membrane to regulate the movement of ions into or out of the cell; and (2) transfer of the signal to an intracellular messenger or **second messenger**, which triggers a cascade of biochemical events within the cell (Fig. 1.16).

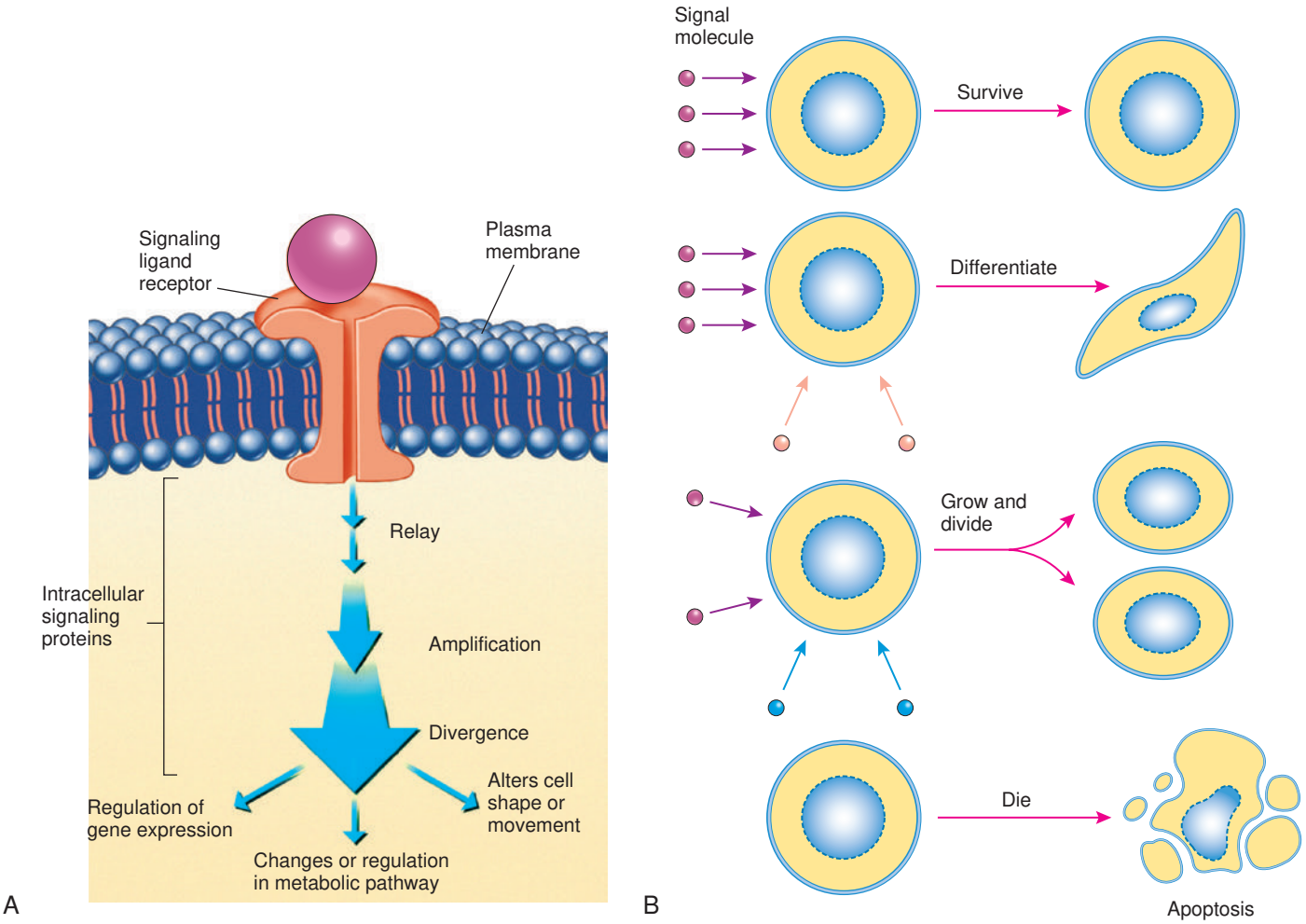


FIGURE 1.15 Schematic of a Signal Transduction Pathway. Like a telephone receiver that converts an electrical signal into a sound signal, a cell converts an extracellular signal. **A,** An extracellular signal molecule (ligand) binds to a receptor protein located on the plasma membrane, where it is transduced into an intracellular signal. This process initiates a signaling cascade that relays the signal into the cell interior, amplifying and distributing it during transit. Amplification is often achieved by stimulating enzymes. Steps in the cascade can be modulated by other events in the cell. **B,** Different cell behaviors rely on multiple extracellular signals.

TABLE 1.3 Classes of Plasma Membrane Receptors

Type of Receptor	Description
Channel linked	Also called *ligand-gated channels;* involve rapid synaptic signaling between electrically excitable cells. Channels open and close briefly in response to neurotransmitters, changing ion permeability of plasma membrane of postsynaptic cell.
Catalytic	Once activated by ligands, function directly as enzymes. Composed of transmembrane proteins that function intracellularly as tyrosine-specific protein kinases.
G-protein linked	Indirectly activate or inactivate plasma membrane enzyme or ion channel; interaction mediated by guanosine triphosphate (GTP)–binding regulatory protein (G protein). When activated, a chain of reactions occurs that alters concentration of intracellular messengers, such as cyclic adenosine monophosphate (cAMP) and calcium, or signaling molecules. Behaviors of other target proteins are also altered. May also interact with inositol phospholipids, which are significant in cell signaling, and molecules involved in the inositol-phospholipid transduction pathway. A G-protein–linked receptor activates the enzyme phosphoinositide-specific phospholipase, which, in turn, generates two intracellular messengers: (1) inositol triphosphate (IP_3) releases calcium (Ca^{++}), and (2) diacylglycerol remains in the plasma membrane and activates protein kinase C. Protein kinase C further activates various cell proteins. Several different plasma membrane receptors are known to use the inositol–phospholipid transduction pathway.

Data from Alberts B et al: *Molecular biology of the cell,* ed 5, New York, 2008, Garland.

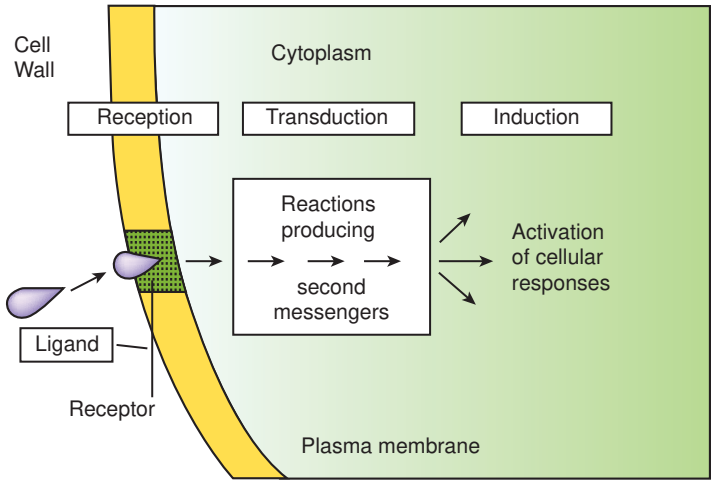


FIGURE 1.16 First and Second Messengers. The first messenger or ligand attaches to the membrane receptor relaying the message across the membrane and intracellular messengers or second messengers trigger the cascade of intracellular events. The two major second-messenger pathways are cyclic adenosine monophosphate (cAMP) and calcium (Ca^{++}). A large number of human disorders involve problematic signaling.

CELLULAR METABOLISM

All of the chemical tasks of maintaining essential cellular functions are referred to as **cellular metabolism**. The energy-using process of metabolism is called **anabolism** (*ana* = upward), and the energy-releasing process is known as **catabolism** (*kata* = downward). Metabolism provides the cell with the energy it needs to produce cellular structures.

Dietary proteins, fats, and starches (i.e., carbohydrates) are hydrolyzed in the intestinal tract into amino acids, fatty acids, and glucose, respectively. These constituents are then absorbed, circulated, and incorporated into the cell, where they may be used for various vital cellular processes, including the production of ATP. The process by which ATP is produced is one example of a series of reactions called a **metabolic pathway**. A metabolic pathway involves several steps whose end products are not always detectable. A key feature of cellular metabolism is the directing of biochemical reactions by protein catalysts or enzymes. Each enzyme has a high affinity for a **substrate**, a specific substance converted to a product of the reaction.

Role of Adenosine Triphosphate

What is best known about ATP is its role as a universal "fuel" *inside* living cells. This fuel or energy drives biologic reactions necessary for cells to function. For a cell to function, it must be able to extract and use the chemical energy in organic molecules. When 1 mole (mol) of glucose metabolically breaks down in the presence of oxygen into CO_2 and water, 686 kilocalories (kcal) of chemical energy are released. The chemical energy lost by one molecule is transferred to the chemical structure of another molecule by an energy-carrying or energy-transferring molecule, such as ATP. The energy stored in ATP can be used in various energy-requiring reactions and in the process is generally converted to adenosine diphosphate (ADP) and inorganic phosphate (Pi). The energy available as a result of this reaction is about 7 kcal/mol of ATP. The cell uses ATP for muscle contraction and active transport of molecules across cellular membranes. ATP not only stores energy but also *transfers* it from one molecule to another. Energy stored by carbohydrate, lipid, and protein is catabolized and transferred to ATP.

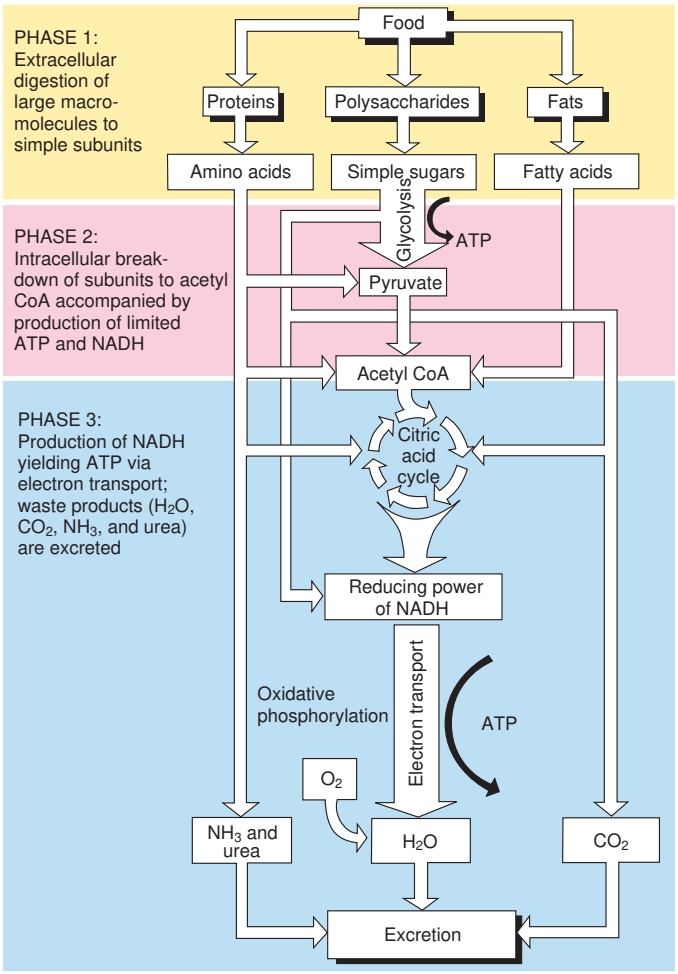


FIGURE 1.17 Three Phases of Catabolism, Which Lead From Food to Waste Products. These reactions produce adenosine triphosphate (ATP), which is used to power other processes in the cell.

Emerging understandings are the role of ATP *outside* cells—as a messenger. In animal studies, using the newly developed ATP probe, ATP has been measured in pericellular spaces. New research is clarifying the role of ATP as an extracellular messenger and its role in many physiologic processes, including inflammation.[2,3]

Food and Production of Cellular Energy

Catabolism of the proteins, lipids, and polysaccharides found in food can be divided into the following three phases (Fig. 1.17):

Phase 1: **Digestion**. Large molecules are broken down into smaller subunits: proteins into amino acids, polysaccharides into simple sugars (i.e., monosaccharides), and fats into fatty acids and glycerol. These processes occur outside the cell and are activated by secreted enzymes.

Phase 2: **Glycolysis** and **oxidation**. The most important part of phase 2 is glycolysis, the splitting of glucose. Glycolysis produces two molecules of ATP per glucose molecule through oxidation, or the removal and transfer of a pair of electrons. The total process is called *oxidative cellular metabolism* and involves 10 biochemical reactions (see Fig. 1.17).

Phase 3: **Citric acid cycle (Krebs cycle, tricarboxylic acid cycle)**. Most of the ATP is generated during this final phase, which begins with

the citric acid cycle and ends with oxidative phosphorylation. About two-thirds of the total oxidation of carbon compounds in most cells is accomplished during this phase. The major end products are CO_2 and two dinucleotides—reduced nicotinamide adenine dinucleotide (NADH) and the reduced form of flavin adenine dinucleotide ($FADH_2$)—both of which transfer their electrons into the electron-transport chain.

Oxidative Phosphorylation

Oxidative phosphorylation occurs in the mitochondria and is the mechanism by which the energy produced from carbohydrates, fats, and proteins is transferred to ATP. During the breakdown (catabolism) of foods, many reactions involve the removal of electrons from various intermediates. These reactions generally require a coenzyme (a nonprotein carrier molecule), such as nicotinamide adenine dinucleotide (NAD), to transfer the electrons and thus are called **transfer reactions**.

Molecules of NAD and flavin adenine dinucleotide (FAD) transfer electrons they have gained from the oxidation of substrates to molecular O_2. The electrons from reduced NAD and FAD, NADH and $FADH_2$, respectively, are transferred to the **electron-transport chain** on the inner surfaces of the mitochondria with the release of hydrogen ions. Some carrier molecules are brightly colored, iron-containing proteins known as **cytochromes**, which accept a pair of electrons. These electrons eventually combine with molecular oxygen.

If oxygen is not available to the electron-transport chain, ATP will not be formed by the mitochondria. Instead, an anaerobic (without oxygen) metabolic pathway synthesizes ATP. This process, called **substrate phosphorylation** or **anaerobic glycolysis**, is linked to the breakdown (glycolysis) of carbohydrate (Fig. 1.18). Because glycolysis occurs in the cytoplasm of the cell, it provides energy for cells that lack mitochondria. The reactions in anaerobic glycolysis involve the conversion of glucose to pyruvic acid (pyruvate) with the simultaneous production of ATP. With the glycolysis of one molecule of glucose, two ATP molecules and two molecules of pyruvate are liberated. If oxygen is present, the two molecules of pyruvate move into the mitochondria, where they enter the citric acid cycle (Fig. 1.19).

If oxygen is absent, pyruvate is converted to lactic acid, which is released into the extracellular fluid (ECF). The conversion of pyruvic acid to lactic acid is reversible; therefore once oxygen is restored, lactic acid is quickly converted back to either pyruvic acid or glucose. The anaerobic generation of ATP from glucose through glycolysis is not as efficient as the aerobic generation process. Adding an oxygen-requiring stage to the catabolic process (phase 3; see Fig. 1.18) provides cells with a much more powerful method for extracting energy from food molecules.

MEMBRANE TRANSPORT: CELLULAR INTAKE AND OUTPUT

Cell survival and growth depend on the constant exchange of molecules with their environment. Cells continually import nutrients, fluids, and chemical messengers from the extracellular environment and expel metabolites, or the products of metabolism, and end products of lysosomal digestion. Cells also must regulate ions in their cytosol and organelles. Simple diffusion across the lipid bilayer of the plasma membrane occurs for such important molecules as O_2 and CO_2. However the majority of molecular transfer depends on specialized **membrane transport proteins** that span the lipid bilayer and provide private conduits for select molecules.[1] Membrane transport proteins occur in many forms

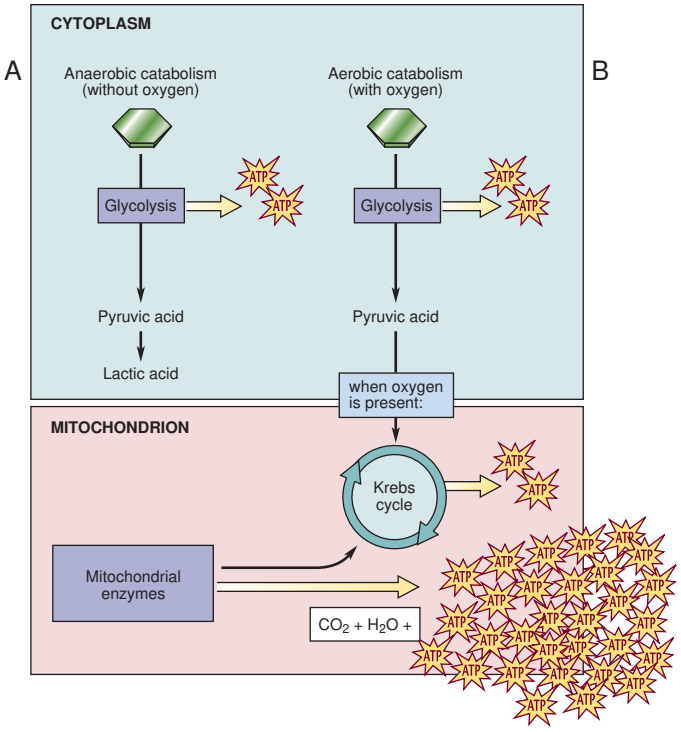


FIGURE 1.18 Glycolysis. Sugars are important for fuel or energy and they are oxidized in small steps to carbon dioxide (CO_2) and water. Glycolysis is the process for oxidizing sugars or glucose. Breakdown of glucose. **A,** Anaerobic catabolism, to lactic acid and little ATP. **B,** Aerobic catabolism, to carbon dioxide, water, and lots of ATP. (From Herlihy B: *The human body in health and illness,* ed 5, St Louis, 2015, Saunders.)

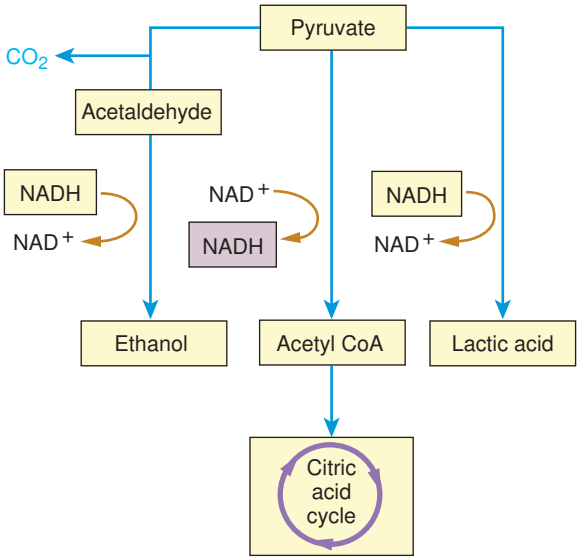


FIGURE 1.19 What Happens to Pyruvate, the Product of Glycolysis? In the presence of oxygen, pyruvate is oxidized to acetyl coenzyme A *(Acetyl CoA)* and enters the citric acid cycle. In the absence of oxygen, pyruvate instead is reduced, accepting the electrons extracted during glycolysis and carried by reduced nicotinamide adenine dinucleotide *(NADH).* When pyruvate is reduced directly, as it is in muscles, the product is lactic acid. When carbon dioxide (CO_2) is first removed from pyruvate and the remainder is reduced, as it is in yeasts, the resulting product is ethanol.

and are present in all cell membranes.[1] Transport by membrane transport proteins is sometimes called **mediated transport**. Most of these transport proteins allow selective passage (e.g., Na^+ but not K^+, or K^+ but not Na^+). Each type of cell membrane has its own transport proteins that determine which solute can pass into and out of the cell or organelle.[1] The two main classes of membrane transport proteins are *transporters* and *channels*. These transport proteins differ in the type of **solute**—small particles of dissolved substances—they transport. A **transporter** is specific, allowing only those ions that fit the unique binding sites on the protein (Fig. 1.20, *A*). A transporter undergoes conformational changes to enable membrane transport. A **channel**, when open, forms a pore across the lipid bilayer that allows ions and selective polar organic molecules to diffuse across the membrane (see Fig. 1.20, *B*). Transport by a channel depends on the size and electrical charge of the molecule. Some channels are controlled by a gate mechanism that determines which solute can move into it. Ion channels are responsible for the electrical excitability of nerve and muscle cells and play a critical role in the membrane potential.

The mechanisms of membrane transport depend on the characteristics of the substance to be transported. In **passive transport**, water and small, electrically uncharged molecules move easily through pores in the plasma membrane's lipid bilayer (see Fig. 1.20). This process occurs naturally through any semipermeable barrier. Molecules will easily flow "downhill" from a region of high concentration to a region of low concentration; this movement is called *passive* because it does not require expenditure of energy or a driving force. It is driven by osmosis, hydrostatic pressure, and diffusion, all of which depend on the laws of physics and do not require life.

Other molecules are too large to pass through pores or are ligands bound to receptors on the cell's plasma membrane. Some of these molecules are moved into and out of the cell by **active transport**, which requires life, biologic activity, and the cell's expenditure of metabolic energy (Fig. 1.21). Unlike passive transport, active transport occurs across only living membranes that have to drive the flow "uphill" by coupling it to an energy source). Movement of a solute against its concentration gradient occurs by special types of transporters called *pumps* (see Fig. 1.21). These transporter pumps must harness an energy source to power the transport process. Energy can come from ATP hydrolysis, a transmembrane ion gradient, or sunlight (see Fig. 1.21). The best-known energy source is the Na^+-K^+–dependent adenosine

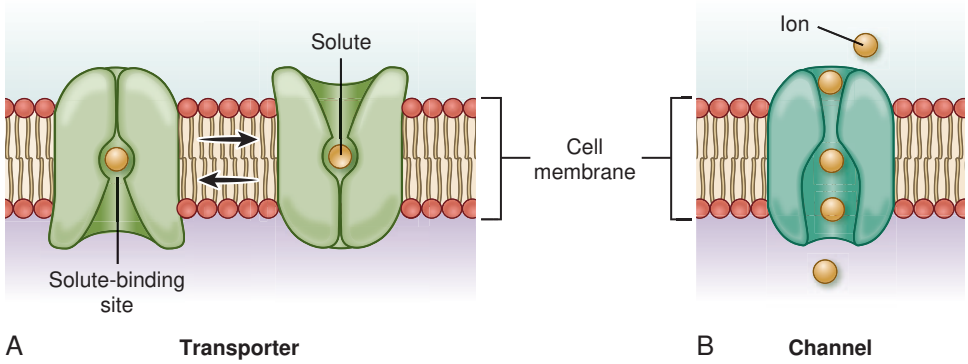


FIGURE 1.20 Inorganic Ions and Small, Polar Organic Molecules Can Cross a Cell Membrane Through Either a Transporter or a Channel. (Adapted from Alberts B et al: *Essential cell biology,* ed 4, New York, 2014, Garland.)

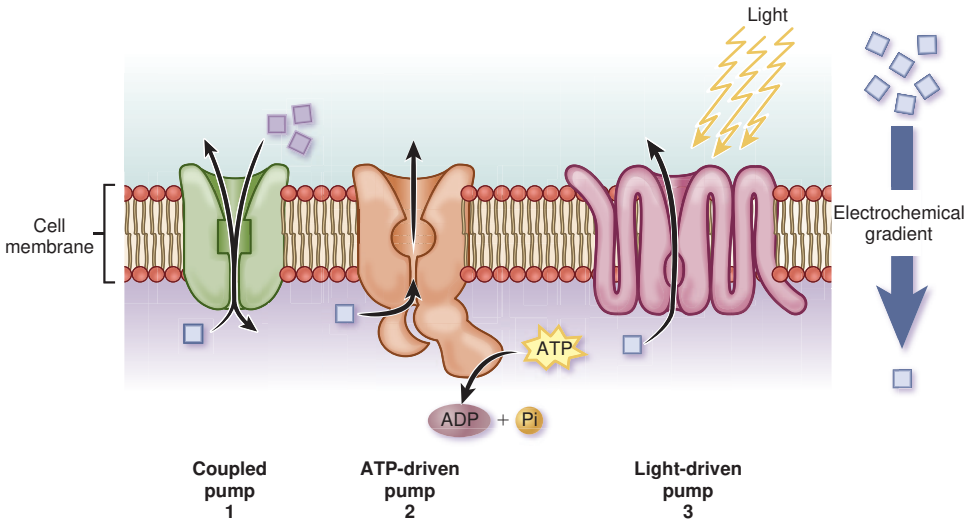


FIGURE 1.21 Pumps Carry Out Active Transport in Three Ways. **1.** *Coupled pumps* link the uphill transport of one solute to the downhill transport of another solute. **2.** *ATP-driven pumps* drive uphill transport from hydrolysis of ATP. **3.** *Light-driven pumps* are mostly found in bacteria and use energy from sunlight to drive uphill transport. (Adapted from Alberts B et al: *Essential cell biology,* ed 4, New York, 2014, Garland.)

triphosphatase (ATPase) pump (see Fig. 1.26 later in the chapter). It continuously regulates the cell's volume by controlling leaks through pores or protein channels and maintaining the ionic concentration gradients needed for cellular excitation and membrane conductivity (see the Active Transport of Na^+ and K^+ section). The maintenance of intracellular K^+ concentrations is required also for enzyme activity, including enzymes involved in protein synthesis. Large molecules (macromolecules), along with fluids, are transported by endocytosis (taking in) and exocytosis (expelling) (see the Transport by Vesicle Formation section). Receptor-macromolecule complexes enter the cell by means of receptor-mediated endocytosis.

Mediated transport systems can move solute molecules singly or two at a time. Two molecules can be moved simultaneously in one direction (a process called **symport**; e.g., sodium–glucose in the digestive tract) or in opposite directions (called **antiport**; e.g., the sodium–potassium pump in all cells), or a single molecule can be moved in one direction (called **uniport**; e.g., glucose) (Fig. 1.22).

Electrolytes as Solutes

Body fluids are composed of **electrolytes**, which are electrically charged and dissociate into constituent **ions** when placed in solution, and nonelectrolytes, such as glucose, urea, and creatinine, which do not dissociate. Electrolytes account for approximately 95% of the solute molecules in body water. Electrolytes exhibit **polarity** by orienting themselves toward the positive or negative pole. Ions with a positive charge are known as **cations** and migrate toward the negative pole, or cathode, if an electrical current is passed through the electrolyte solution. **Anions** carry a negative charge and migrate toward the positive pole, or anode, in the presence of electrical current. Anions and cations are located in both the intracellular fluid (ICF) and the ECF compartments, although their concentration depends on their location. (Fluid and electrolyte balance between body compartments is discussed in Chapter 5.) For example, Na^+ is the predominant extracellular cation, and K^+ is the principal intracellular cation. The difference in ICF and ECF concentrations of these ions is important to the transmission of electrical impulses across the plasma membranes of nerve and muscle cells.

Electrolytes are measured in milliequivalents per liter (mEq/L) or milligrams per deciliter (mg/dL). The term *milliequivalent* indicates the chemical-combining activity of an ion, which depends on the electrical charge, or **valence**, of its ions. In abbreviations, valence is indicated by the number of plus or minus signs. One milliequivalent of any cation can combine chemically with 1 mEq of any anion: one monovalent anion will combine with one monovalent cation. Divalent ions combine more strongly than monovalent ions. To maintain electrochemical balance, one divalent ion will combine with two monovalent ions (e.g., $Ca^{++} + 2Cl^-$ {ReversReact} Calcium dichloride [$CaCl_2$]).

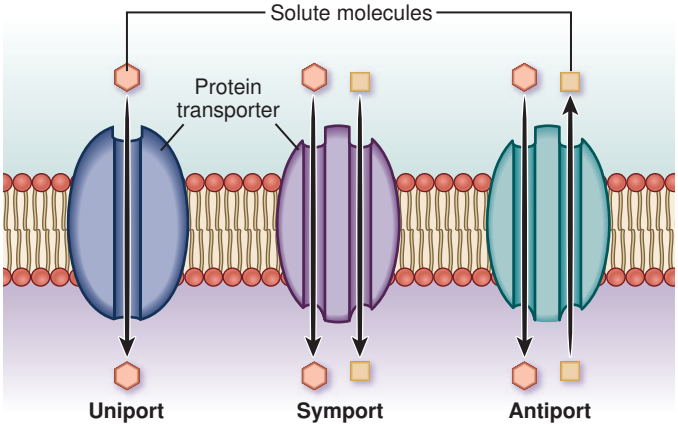


FIGURE 1.22 Mediated Transport. Illustration shows simultaneous movement of a single solute molecule in one direction *(Uniport)*, of two different solute molecules in one direction *(Symport)*, and of two different solute molecules in opposite directions *(Antiport)*.

Passive Transport: Diffusion, Filtration, and Osmosis

Diffusion. **Diffusion** is the movement of a solute molecule from an area of greater solute concentration to an area of lesser solute concentration. This difference in concentration is known as a **concentration gradient**. Although particles in a solution move randomly in any direction, if the concentration of particles in one part of the solution is greater than that in another part, the particles distribute themselves evenly throughout the solution. According to the same principle, if the concentration of particles is greater on one side of a *permeable membrane* than on the other side, the particles diffuse spontaneously from the area of greater concentration to the area of lesser concentration until equilibrium is reached. The higher the concentration on one side, the greater is the diffusion rate.

The diffusion rate is influenced by differences of electrical potential across the membrane (see the Movement of Electrical Impulses: Membrane Potentials section). Because the pores in the lipid bilayer are often lined with Ca^{++}, other cations (e.g., Na^+ and K^+) diffuse slowly because they are repelled by positive charges in the pores.

The rate of diffusion of a substance depends also on its size (diffusion coefficient) and its lipid solubility (Fig. 1.23). Usually, the smaller the molecule and the more soluble it is in oil, the more hydrophobic or nonpolar it is and the more rapidly it will diffuse across the bilayer. O_2, CO_2, and steroid hormones (e.g., androgens and estrogens) are all nonpolar molecules. Water-soluble substances, such as glucose and inorganic ions, diffuse very slowly, whereas uncharged lipophilic ("lipid-loving") molecules, such as fatty acids and steroids, diffuse rapidly. Ions and other polar molecules generally diffuse across cellular membranes more slowly compared with lipid-soluble substances.

Water readily diffuses through biologic membranes because water molecules are small and uncharged. The dipolar structure of water allows it to rapidly cross the regions of the bilayer containing the lipid head groups. The lipid head groups constitute the two outer regions of the lipid bilayer.

Filtration: hydrostatic pressure. **Filtration** is the movement of water and solutes through a membrane because of a greater pushing pressure (force) on one side of the membrane than on the other side. **Hydrostatic pressure** is the mechanical force of water pushing against cellular membranes (Fig. 1.24, *A*). In the vascular system, hydrostatic pressure is the *blood pressure* generated in vessels when the heart contracts. Blood reaching the capillary bed has a hydrostatic pressure of 25 to 30 millimeters of mercury (mm Hg), which is sufficient force to push water across the thin capillary membranes into the interstitial space. Hydrostatic pressure is partially balanced by osmotic pressure, whereby water moving *out* of the capillaries is partially balanced by osmotic forces that tend to *pull* water *into* the capillaries (see Fig. 1.24, *B*). Water that is not osmotically attracted back into the capillaries moves into the lymph system (see the discussion of Starling forces in Chapter 5).

Osmosis. **Osmosis** is the movement of water "down" a concentration gradient—that is, across a semipermeable membrane from a region of higher water concentration to one of lower concentration. For osmosis to occur, (1) the membrane must be more permeable to water than to solutes, and (2) the concentration of solutes on one side of the membrane must be greater than that on the other side so that water moves more

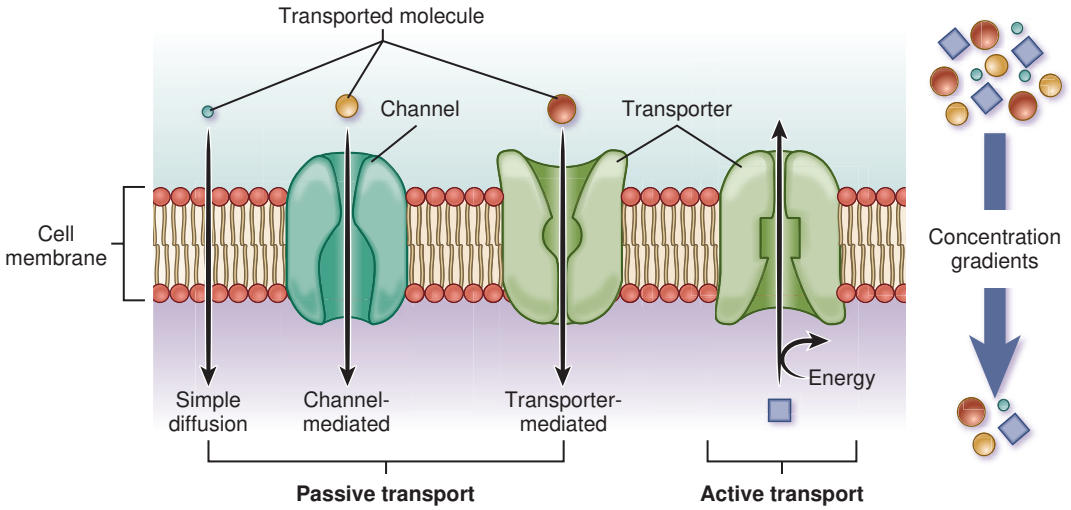


FIGURE 1.23 Passive Diffusion of Solute Molecules Across the Plasma Membrane. Oxygen, nitrogen, water, urea, glycerol, and carbon dioxide can diffuse readily down the concentration gradient. Macromolecules are too large to diffuse through pores in the plasma membrane. Ions may be repelled if the pores contain substances with identical charges. If the pores are lined with cations, for example, other cations will have difficulty diffusing because the positive charges will repel one another. Diffusion can still occur, but it occurs more slowly.

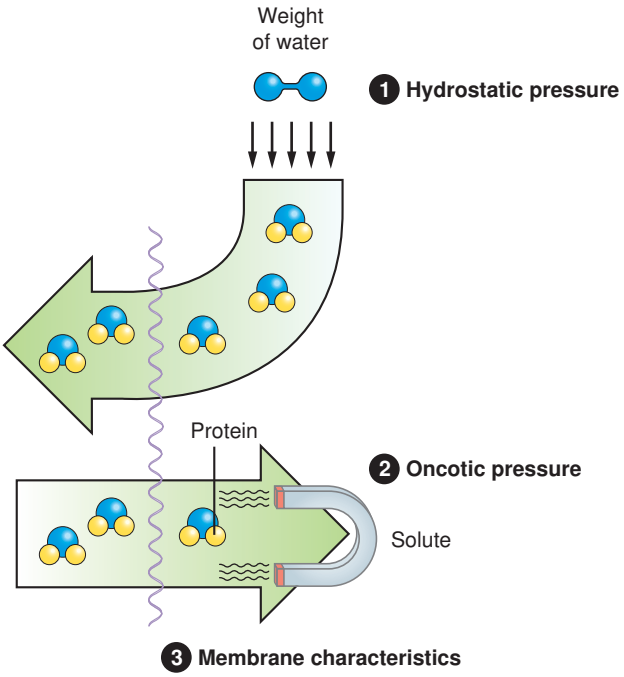


FIGURE 1.24 Hydrostatic Pressure and Oncotic Pressure in Plasma. 1. Hydrostatic pressure in plasma. 2. Oncotic pressure exerted by proteins in the plasma usually tends to *pull* water into the circulatory system. 3. Individuals with low protein levels (e.g., starvation) are unable to maintain a normal oncotic pressure; therefore water is not reabsorbed into the circulation and, instead, causes body edema.

easily. Osmosis is directly related to both hydrostatic pressure and solute concentration but *not* to particle size or weight. For example, particles of the plasma protein albumin are small but are more concentrated in body fluids compared with the larger and heavier particles of globulin. Therefore albumin exerts a greater osmotic force compared with globulin.

Osmolality controls the distribution and movement of water between body compartments. The terms *osmolality* and *osmolarity* often are used interchangeably in reference to osmotic activity, but they define different measurements. **Osmolality** measures the number of milliosmoles per kilogram (mOsm/kg) of water, or the concentration of molecules per *weight* of water. **Osmolarity** measures the number of milliosmoles per liter of solution, or the concentration of molecules per *volume* of solution.

In solutions that contain only dissociable substances, such as Na and chloride (Cl^-), the difference between the two measurements is negligible. When considering all the different solutes in plasma (e.g., proteins, glucose, lipids), however, the difference between osmolality and osmolarity becomes more significant. Less of plasma's weight is water, and the overall concentration of particles is therefore greater. The osmolality will be greater than the osmolarity because of the smaller proportion of water. Osmolality is thus preferred in human clinical assessment.

The normal osmolality of body fluids ranges from 280 to 294 mOsm/kg. The osmolalities of ICF and ECF tend to equalize, providing a measure of body fluid concentration and thus the body's hydration status. Hydration is affected also by hydrostatic pressure because the movement of water by osmosis can be opposed by an equal amount of hydrostatic pressure. The amount of hydrostatic pressure required to oppose the osmotic movement of water is called the **osmotic pressure** of the solution. Factors that determine osmotic pressure are the type and thickness of the plasma membrane, the size of the molecules, the concentration of molecules or the concentration gradient, and the solubility of molecules within the membrane.

Effective osmolality is sustained osmotic activity and depends on the concentration of solutes remaining on one side of a permeable membrane. If the solutes penetrate the membrane and equilibrate with the solution on the other side of the membrane, the osmotic effect will be diminished or lost.

Plasma proteins influence osmolality because they have a negative charge (see Fig. 1.24, *B*). The principle involved is known as *Gibbs-Donnan equilibrium;* it occurs when the fluid in one compartment contains small, diffusible ions, such as Na^+ and Cl^-, together with large,

nondiffusible, charged particles, such as plasma proteins. Because the body tends to maintain an electrical equilibrium, the nondiffusible protein molecules cause asymmetry in the distribution of small ions. Anions such as Cl^- are thus driven out of the cell or plasma, and cations, such as Na^+, are attracted to the cell. The protein-containing compartment maintains a state of electroneutrality, but the osmolality is higher. The overall osmotic effect of colloids, such as plasma proteins, is called the **oncotic pressure**, or **colloid osmotic pressure**.

Tonicity describes the effective osmolality of a solution. (The terms *osmolality* and *tonicity* may be used interchangeably.) Solutions have relative degrees of tonicity. An isotonic solution (or isosmotic solution) has the same osmolality or concentration of particles (285 mOsm) as ICF or ECF. A hypotonic solution has a lower concentration and is thus more dilute than body fluids (Fig. 1.25). A hypertonic solution has a concentration of more than 285 to 294 mOsm/kg. The concentration of tonicity is important when correcting water and solute imbalances by administering different types of replacement solutions (see Fig. 1.25 and Chapter 5).

QUICK CHECK 1.2

1. What does glycolysis produce?
2. Define membrane transport proteins.
3. What are the differences between passive and active transport?
4. Why do water and small, electrically charged molecules move easily through pores in the plasma membrane?

Active Transport of Na^+ and K^+

The active transport system for Na^+ and K^+ is found in virtually all mammalian cells. The Na^+-K^+–antiport system (i.e., Na^+ moving out of the cell and K^+ moving into the cell) uses the direct energy of ATP to transport these cations. The transporter protein is ATPase, which requires Na^+, K^+, and magnesium (Mg^{++}) ions. The concentration of ATPase in plasma membranes is directly related to Na^+-K^+–transport activity. Approximately 60% to 70% of the ATP synthesized by cells, especially muscle and nerve cells, is used to maintain the Na^+-K^+–transport system. Excitable tissues have a high concentration of Na^+-K^+ ATPase, as do other tissues that transport significant amounts of Na^+. For every ATP molecule hydrolyzed, three molecules of Na^+ are transported out of the cell, whereas only two molecules of K^+ move into the cell. The process leads to an electrical potential and is called *electrogenic*, with the inside of the cell more negative than the outside. Although the exact mechanism for this transport is uncertain, it is possible that ATPase induces the transporter protein to undergo several conformational changes, causing Na^+ and K^+ to move short distances (Fig. 1.26). The conformational change lowers the affinity for Na^+ and K^+ to the ATPase transporter, resulting in the release of the cations after transport.

Table 1.4 summarizes the major mechanisms of transport through pores and protein transporters in the plasma membranes. Many disease states are caused or manifested by loss of these membrane transport systems.

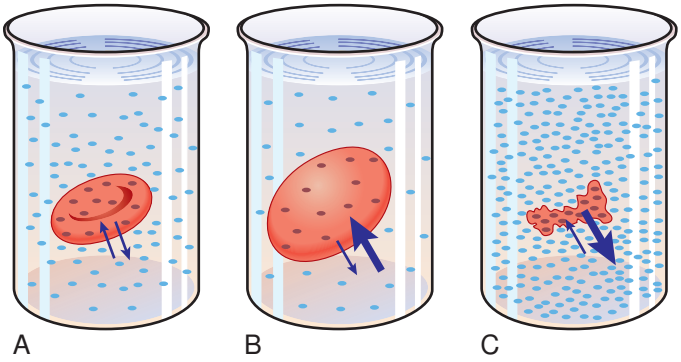


FIGURE 1.25 Tonicity. Tonicity is important, especially for red blood cell function. **A,** Isotonic solution. **B,** Hypotonic solution. **C,** Hypertonic solution. (From Waugh A, Grant A: *Ross and Wilson anatomy and physiology in health and illness,* ed 12, London, 2012, Churchill Livingstone.)

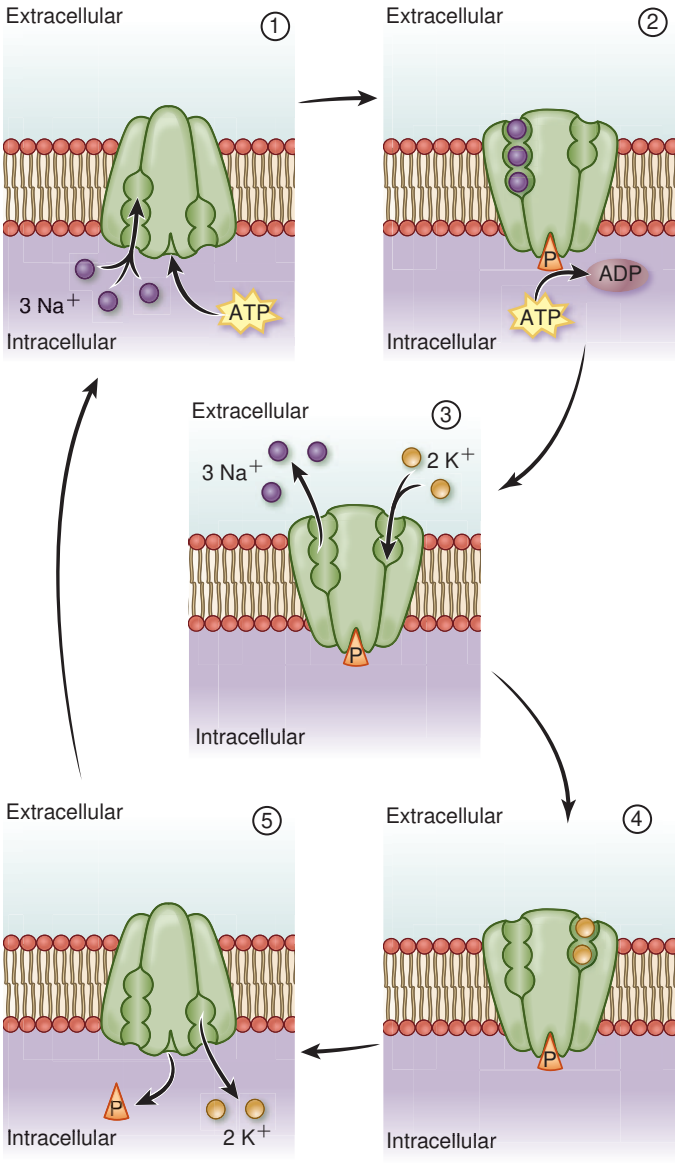


FIGURE 1.26 Active Transport and the Sodium–Potassium (Na^+–K^+) Pump. 1. Three sodium (Na^+) ions bind to Na-binding sites on the carrier's inner face. **2.** At the same time, an energy-containing adenosine triphosphate *(ATP)* molecule produced by the cell's mitochondria binds to the carrier. Adenosine triphosphate (ATP) dissociates, transferring its stored energy to the carrier, and changes shape. **3 and 4.** The ATP releases the three Na^+ ions to the outside of the cell, and attracts two potassium *(K^+)* ions to its potassium-binding sites. **5.** The carrier then returns to its original shape, releasing the two K^+ ions and the remnant of the ATP molecule to the inside of the cell. The carrier is now ready for another pumping cycle.

TABLE 1.4 Major Transport Systems in Mammalian Cells

Substance Transported	Mechanism of Transport*	Tissues
Carbohydrates		
Glucose	Passive: protein channel Active: symport with Na^+	Most tissues
Fructose	Active: symport with Na^+ Passive	Small intestines and renal tubular cells Intestines and liver
Amino Acids		
Amino acid specific transporters	Coupled channels	Intestines, kidney, and liver
All amino acids except proline	Active: symport with Na^+	Liver
Specific amino acids	Active: group translocation Passive	Small intestine
Other Organic Molecules		
Cholic acid, deoxycholic acid, and taurocholic acid	Active: symport with Na^+	Intestines
Organic anions (e.g., malate, α-ketoglutarate, glutamate)	Antiport with counter-organic anion	Mitochondria of liver cells
ATP-ADP	Antiport transport of nucleotides; can be active	Mitochondria of liver cells
Inorganic Ions		
Na^+	Passive	Distal renal tubular cells
Na^+/H^+	Active antiport, proton pump	Proximal renal tubular cells and small intestines
Na^+/K^+	Active: ATP driven, protein channel	Plasma membrane of most cells
Ca^{++}	Active: ATP driven, antiport with Na^+	All cells, antiporter in red cells
H^+/K^+	Active	Parietal cells of gastric cells secreting H^+
Cl^-/HCO_3 (perhaps other anions)	Mediated: antiport (anion transporter–band 3 protein)	Erythrocytes and many other cells
Water	Osmosis passive	All tissues

*NOTE: The known transport systems are listed here; others have been proposed. Most transport systems have been studied in only a few tissues and their sites of activity may be more limited than indicated.

ADP, Adenosine diphosphate; *ATP,* adenosine triphosphate; *Ca^{++},* calcium; *Cl^-/HCO_3,* chloride/bicarbonate; *H^+,* hydrogen; *K^+,* potassium; *Na^+,* sodium.

Data from Alberts B et al: *Molecular biology of the cell,* ed 4, New York, 2001, Wiley; Alberts B et al: *Essential cell biology,* ed 4, New York, 2014, Garland; Devlin TM, editor: *Textbook of biochemistry: with clinical correlations,* ed 3, New York, 1992, Wiley; Raven PH, Johnson GB: *Understanding biology,* ed 3, Dubuque, IA, 1995, Brown.

Transport by Vesicle Formation

Endocytosis and Exocytosis

The active transport mechanisms by which the cells move large proteins, polynucleotides, or polysaccharides (macromolecules) across the plasma membrane are very different from those that mediate small solute and ion transport. Transport of macromolecules involves the sequential formation and fusion of membrane-bound vesicles.

In **endocytosis**, a section of the plasma membrane enfolds substances from outside the cell, invaginates (folds inward), and separates from the plasma membrane, forming a vesicle that moves into the cell (Fig. 1.27, *A*). Two types of endocytosis are designated based on the size of the vesicle formed. **Pinocytosis** (cell drinking) involves the ingestion of fluids, bits of the plasma membrane, and solute molecules through formation of small vesicles; and **phagocytosis** (cell eating) involves the ingestion of large particles, such as bacteria, through formation of large vesicles (vacuoles).

Because most cells continually ingest fluid and solutes by pinocytosis, the terms *pinocytosis* and *endocytosis* often are used interchangeably. In pinocytosis, the vesicle containing fluids, solutes, or both fuses with a lysosome, and lysosomal enzymes digest the vesicle's contents for use by the cell. Vesicles that bud from membranes have a particular protein coat on their cytosolic surface and are called **coated vesicles**. The best studied are those that have an outer coat of bristle-like structures—the protein **clathrin**. Pinocytosis occurs mainly by the clathrin-coated pits and vesicles (Fig. 1.28). After the coated pits pinch off from the plasma membrane, they quickly shed their coats and fuse with an endosome. An **endosome** is a vesicle pinched off from the plasma membrane from which its contents can be recycled to the plasma membrane or sent to lysosomes for digestion. In phagocytosis, the large molecular substances are engulfed by the plasma membrane and enter the cell so that they can be isolated and destroyed by lysosomal enzymes (see Chapter 6). Substances that are not degraded by lysosomes are isolated in residual bodies and released by exocytosis. Both pinocytosis and phagocytosis require metabolic energy and often involve binding of the substance with plasma membrane receptors before membrane invagination and fusion with lysosomes in the cell. New data are revealing that endocytosis has an even larger and more important role than previously known (Box 1.3). **Exosomes** are small membrane vesicles of endocytic origin containing protein, lipid, and RNA species in a single unit. Exosomes are secreted by many cell types and confer messages between cells as mediators of cell-to-cell communication. Researchers are revealing this communication through exosomes, including those released from cancer cells, taken up by neighboring cells, and capable of inducing pathways involved in cancer initiation and progression (Fig. 1.29).[4]

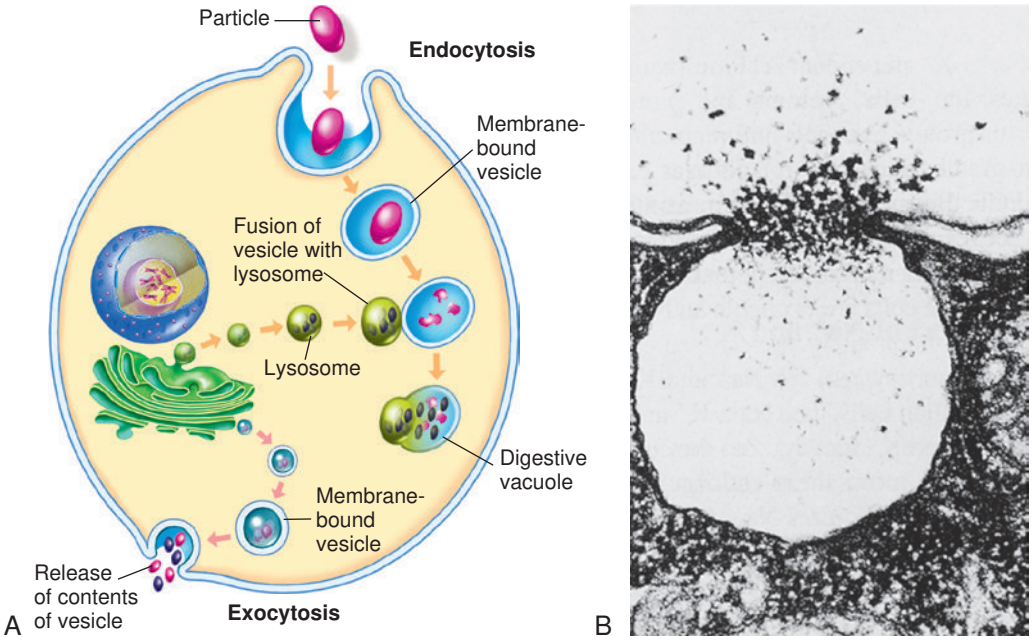


FIGURE 1.27 Endocytosis and Exocytosis. **A,** Endocytosis and fusion with lysosome and exocytosis. **B,** Electron micrograph of exocytosis. (**B,** from Raven PH, Johnson GB: *Biology,* ed 5, New York, 1999, McGraw-Hill.)

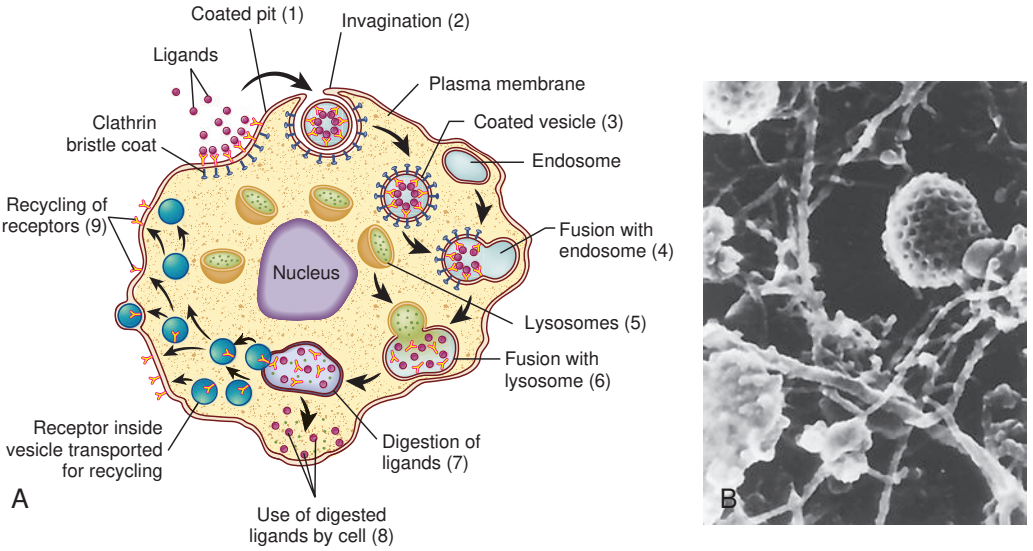


FIGURE 1.28 Ligand Internalization by Means of Receptor-Mediated Endocytosis. **A,** The ligand attaches to its surface receptor (through the bristle coat or clathrin coat **(1)** and receptor-mediated endocytosis), invagination **(2)** and coated pit **(3)**, and enters the cell. The ingested material fuses **(4)** with an endosome and lysosomes **(6)** and is processed by hydrolytic lysosomal enzymes **(7)**. Processed molecules can then be transferred to other cellular components **(8 and 9)**. **B,** Electron micrograph of a coated pit showing different sizes of filaments of the cytoskeleton (×82,000). (**B,** from Erlandsen SL, Magney JE: *Color atlas of histology,* St Louis, 1992, Mosby.)

BOX 1.3 The New Endocytic Matrix

An explosion of new data is disclosing a much more involved role for endocytosis than just a simple way to internalize nutrients and membrane-associated molecules. These new data show that endocytosis not only is a master organizer of signaling pathways but also has a major role in managing signals in time and space. Endocytosis appears to control signaling; therefore it determines the net output of biochemical pathways. This occurs because endocytosis modulates the presence of receptors and their ligands as well as effectors at the plasma membrane or at intermediate stations of the endocytic route. The overall processes and anatomy of these new functions are sometimes called the "endocytic matrix." All of these functions ultimately have a large impact on almost every cellular process, including the nucleus.

In eukaryotic cells, secretion of macromolecules almost always occurs by exocytosis (see Fig. 1.27). **Exocytosis** has two main functions: (1) replacement of portions of the plasma membrane that have been removed by endocytosis and (2) release of molecules synthesized by the cells into the ECM.

Receptor-Mediated Endocytosis

The internalization process, called **receptor-mediated endocytosis (ligand internalization)**, is rapid and enables the cell to ingest large amounts of receptor-macromolecule complexes in clathrin-coated vesicles without ingesting large volumes of extracellular fluid (see Fig. 1.28). The cellular uptake of cholesterol, for example, depends on receptor-mediated endocytosis. Additionally, many essential metabolites (e.g.,

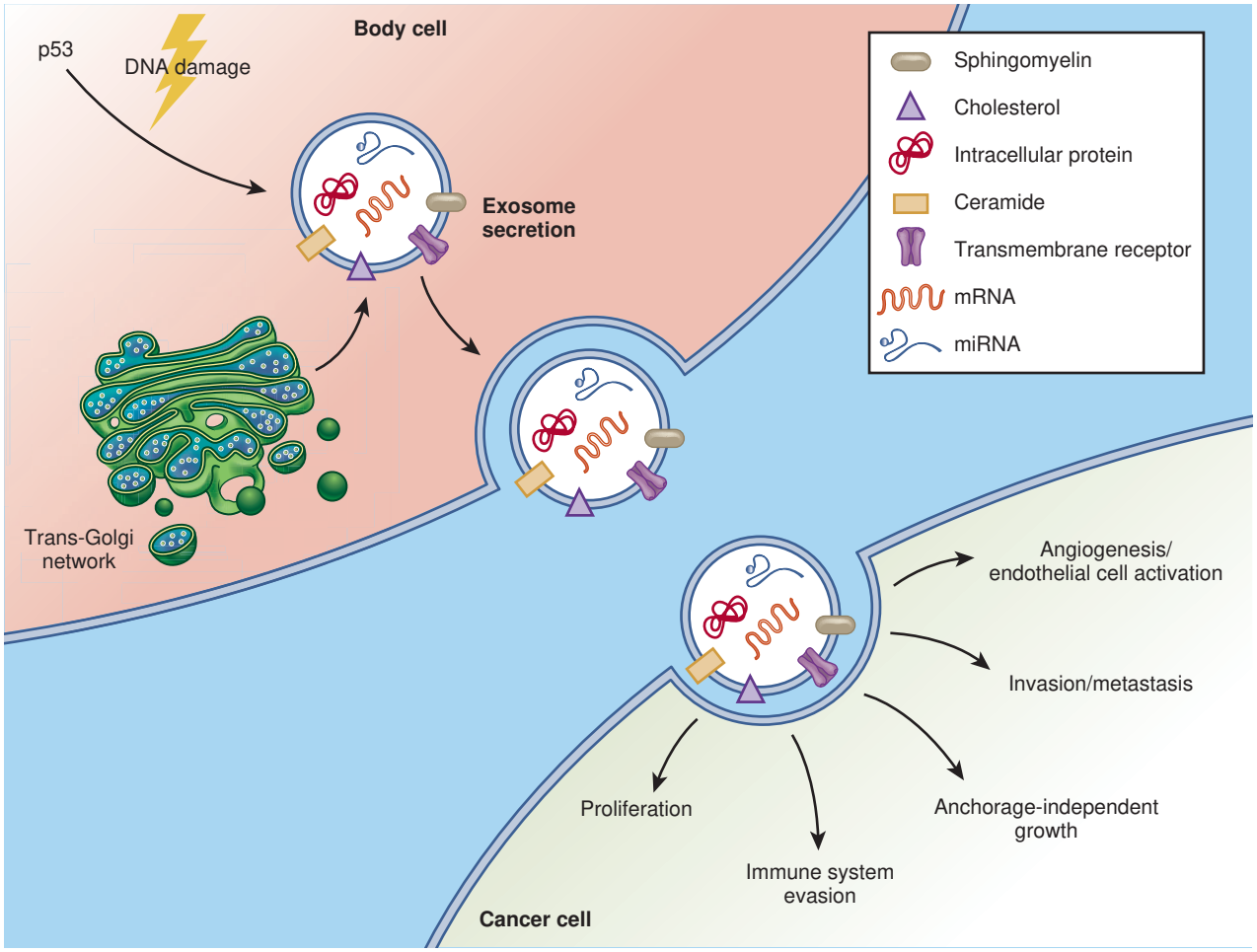


FIGURE 1.29 Exosomes and Cell Signaling: Cancer. From a model of cancer cell signaling, exosomes are secreted with characteristic protein and ribonucleic acid (RNA) components. Exosomes are released from cancer cells and taken up by neighboring cells and are capable of inducing pathways in cancer initiation and progression. A growing interest in defining the clinical relevance of exosomes in cancers is based partially on their ability to alter tumor microenvironment by regulating immunity, angiogenesis, and metastasis. (From Henderson M, Azorsa D: The genomic and proteomic content of cancer cell-derived exosomes, *Front Oncol* 2:38, 2012.)

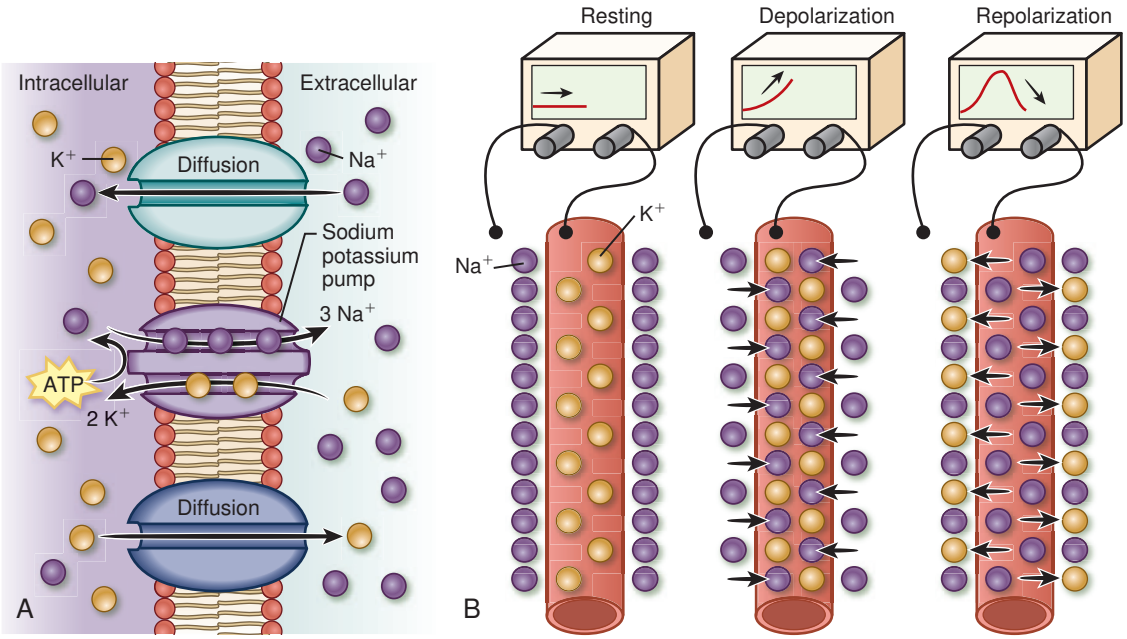


FIGURE 1.30 Sodium–Potassium (Na^+–K^+) Pump and Propagation of an Action Potential. **A,** Concentration difference of sodium *(Na^+)* and potassium *(K^+)* intracellularly and extracellularly. The direction of active transport by the Na^+–K^+ pump is also shown. **B,** The left diagram represents the polarized state of a neuronal membrane when at rest. The middle and right diagrams represent changes in sodium and potassium membrane permeabilities with depolarization and repolarization.

vitamin B_{12} and iron) depend on receptor-mediated endocytosis and, unfortunately, the influenza virus.

Movement of Electrical Impulses: Membrane Potentials

All body cells are electrically polarized, with the inside of the cell more negatively charged compared with the outside. The difference in electrical charge, or voltage, is known as the **resting membrane potential** and is about −70 to −85 millivolts (mV). The difference in voltage across the plasma membrane results from the differences in ionic composition of ICF and ECF. Sodium ions are more concentrated in ECF, and potassium ions are in greater concentration in ICF. The concentration difference is maintained by the active transport of Na^+ and K^+ (the sodium–potassium [Na^+-K^+] pump), which transports Na^+ outward and K^+ inward (Fig. 1.30). Because the resting plasma membrane is more permeable to K^+ than to Na^+, K^+ diffuses easily from ICF to ECF. Because both Na^+ and K^+ are cations, the net result is an excess of anions inside the cell, resulting in the resting membrane potential.

Nerve and muscle cells are excitable and can change their resting membrane potential in response to electrochemical stimuli. Changes in resting membrane potential convey messages from cell to cell. When a nerve or muscle cell receives a stimulus that exceeds the membrane threshold value, a rapid change occurs in the resting membrane potential, known as the **action potential**. The action potential carries signals along the nerve or muscle cell and conveys information from one cell to another in a domino-like fashion. Nerve impulses are described in Chapter 14. When a resting cell is stimulated through voltage-regulated channels, the cell membranes become more permeable to Na^+, so a net movement of Na^+ into the cell occurs and the membrane potential decreases, or moves forward, from a negative value (in mV) to zero. This decrease is known as **depolarization**. The depolarized cell is more positively charged, and its polarity is neutralized.

To generate an action potential and the resulting depolarization, the **threshold potential** must be reached. Generally this occurs when the cell has depolarized by 15 to 20 mV. When the threshold is reached, the cell will continue to depolarize with no further stimulation. The Na^+ gates open, and sodium rushes into the cell, causing the membrane potential to drop to zero and then become positive (depolarization). The rapid reversal in polarity results in the action potential.

During **repolarization**, the negative polarity of the resting membrane potential is reestablished. As the voltage-gated Na^+ channels begin to close, voltage-gated potassium channels open. Membrane permeability to Na^+ decreases and K^+ permeability increases, so K^+ ions leave the cell. The Na^+ gates close and, with the loss of K^+ the membrane potential, becomes more negative. The Na^+-K^+ pump then returns the membrane to the resting potential by pumping K^+ back into the cell and Na^+ out of the cell.

During most of the action potential, the plasma membrane cannot respond to an additional stimulus. This time is known as the **absolute refractory period** and is related to changes in permeability to Na^+. During the latter phase of the action potential, when permeability to K^+ increases, a stronger-than-normal stimulus can evoke an action potential; this time is known as the **relative refractory period**.

When the membrane potential is more negative than normal, the cell is in a **hyperpolarized state** (less excitable: decreased K^+ levels within the cell). A stronger-than-normal stimulus is then required to reach the threshold potential and generate an action potential. When the membrane potential is more positive than normal, the cell is in a **hypopolarized state** (more excitable than normal: increased K^+ levels within the cell) and a weaker-than-normal stimulus is required to reach the threshold potential. Changes in the intracellular and extracellular concentrations of ions or a change in membrane permeability can cause these alterations in membrane excitability.

QUICK CHECK 1.3

1. Identify examples of molecules transported in one direction (symport) and opposite directions (antiport).
2. If oxygen is no longer available to make ATP, what happens to the transport of Na^+?
3. Define the differences between pinocytosis, phagocytosis, and receptor-mediated endocytosis.
4. Define exosome communication.

CELLULAR REPRODUCTION: THE CELL CYCLE

Humans must make millions of cells every second to just survive.[5] In most tissues, new cells are created as fast as old cells die. Continuity of life depends on constant rounds of cell growth and division; the cycle of repeated rounds of duplication and division is called the **cell cycle**. Reproduction of gametes (sperm and egg cells) occurs through a process called *meiosis*, which is described in Chapter 2. The reproduction, or division, of other body cells (somatic cells) involves two sequential phases—**mitosis**, or nuclear division, and **cytokinesis**, or cytoplasmic division. Before a cell can divide, however, it must double its mass and duplicate all its contents. Most of the work preparing for division occurs during the growth phase, called **interphase**. The cell cycle drives the alternation between mitosis and interphase in all tissues with cellular turnover (Fig. 1.31).

The four designated phases of the cell cycle (Fig. 1.32) are (1) the **G_1 phase** (G = gap), which is the period between the M phase and the start of DNA synthesis; (2) the **S phase** (S = synthesis), in which DNA is synthesized in the cell nucleus; (3) the **G_2 phase**, in which RNA and protein synthesis occurs, the period between the completion of DNA synthesis and the next phase (M); and (4) the **M phase** (M = mitosis), which includes both nuclear and cytoplasmic division.

Phases of Mitosis and Cytokinesis

Interphase (the G_1, S, and G_2 phases) is the longest phase of the cell cycle. During interphase, the chromatin consists of very long, slender rods jumbled together in the nucleus. Late in interphase, strands of

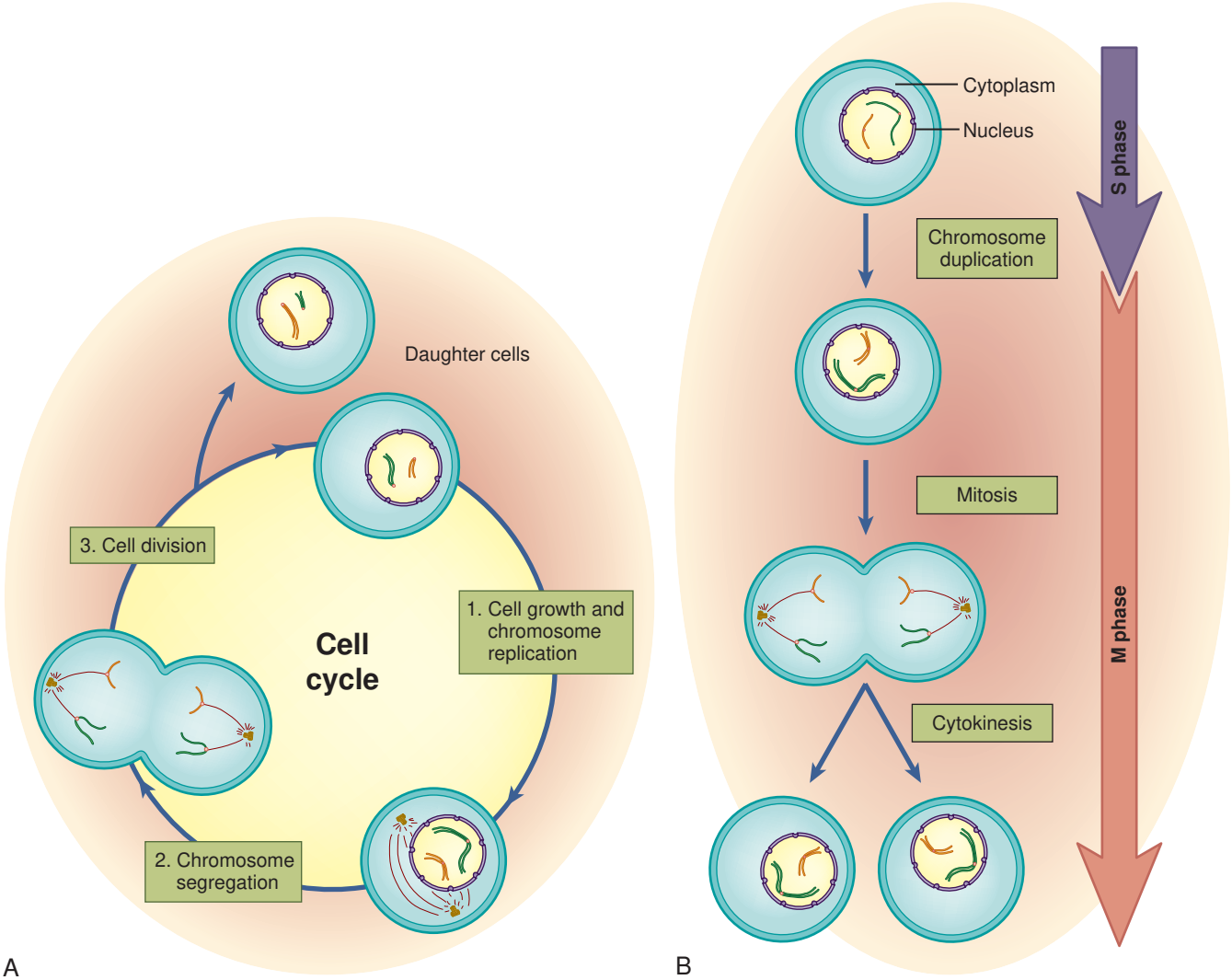


FIGURE 1.31 The Cell Cycle. **A,** Simplified figure of schematic cell with one green chromosome and one yellow chromosome to show how two genetically identical daughter cells are produced in each cycle. **B,** Cell cycle events: mitosis and cytokinesis. (Adapted from Alberts B et al: *Molecular biology of the cell,* ed 6, New York, 2015, Garland Science.)

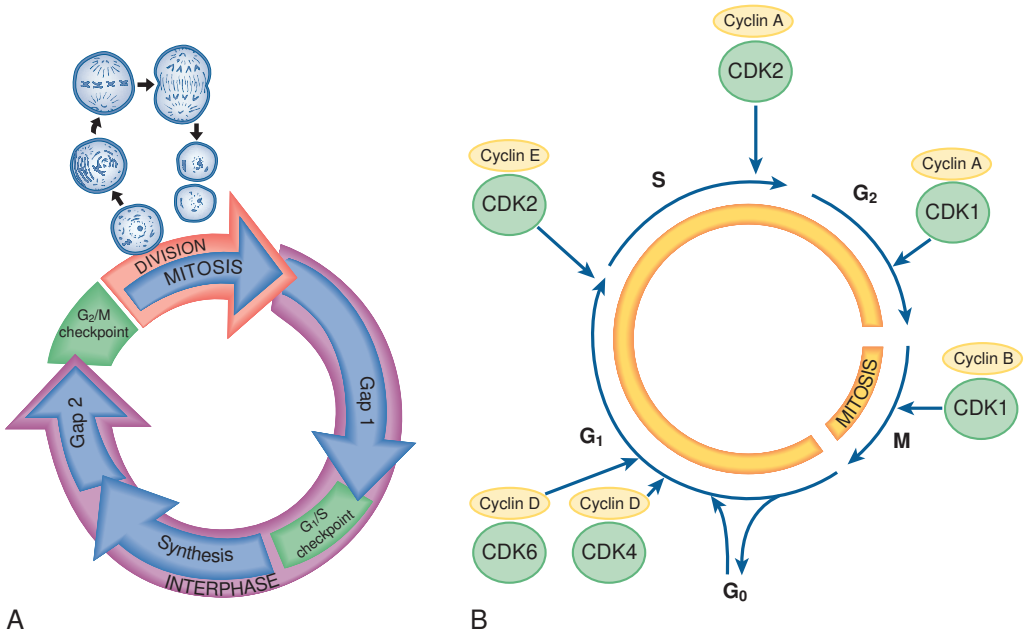


FIGURE 1.32 Interphase and the Phases of Mitosis. **A,** The G_1/S checkpoint is to "check" for cell size, nutrients, growth factors, and deoxyribonucleic acid (DNA) damage. See text for resting phases. The G_2/M checkpoint checks for cell size and DNA replication. **B,** The orderly progression through the phases of the cell cycle is regulated by *cyclins* (so called because levels rise and fall) and *cyclin-dependent protein kinases* (CDKs) and their inhibitors. When cyclins are complexed with CDKs, cell cycle events are triggered.

chromatin (the substance that gives the nucleus its granular appearance) begin to coil, causing shortening and thickening.

The M phase of the cell cycle, mitosis and cytokinesis, begins with **prophase**, the first appearance of chromosomes. As the phase proceeds, each chromosome is seen as identical halves called **chromatids**, which lie together and are attached by a spindle site called a **centromere**. (The two chromatids of each chromosome, which are genetically identical, are sometimes called *sister chromatids.*) The nuclear membrane, which surrounds the nucleus, disappears. **Spindle fibers** are microtubules formed in the cytoplasm. They radiate from two centrioles located at opposite poles of the cell and pull the chromosomes to opposite sides of the cell, beginning the **metaphase**. Next, the centromeres become aligned in the middle of the spindle, which is called the **equatorial plate (or metaphase plate)** of the cell. In this stage, chromosomes are easiest to observe microscopically because they are highly condensed and arranged in a relatively organized fashion.

The **anaphase** begins when the centromeres split and the sister chromatids are pulled apart. The spindle fibers shorten, causing the sister chromatids to be pulled, centromere first, toward opposite sides of the cell. With sister chromatid separation, each is considered to be a chromosome. Thus the cell has 92 chromosomes during this stage. By the end of the anaphase, there are 46 chromosomes lying at each side of the cell. Barring mitotic errors, each of the two groups of 46 chromosomes is identical to the original 46 chromosomes present at the start of the cell cycle.

During the **telophase**, the final stage, a new nuclear membrane is formed around each group of 46 chromosomes, the spindle fibers disappear, and the chromosomes begin to uncoil. Cytokinesis causes the cytoplasm to divide into almost equal parts during this phase. At the end of the telophase, two identical diploid cells, called **daughter cells**, have been formed from the original cell.

Control of Cell Division and Cell Growth: Mitogens, Growth Factors, and Survival Factors

Organ size and body size are determined by three main processes: (1) cell growth, (2) cell division, and (3) cell survival.[5] These processes are tightly regulated by intracellular programs and extracellular signal molecules, usually soluble proteins, proteins bound to cells, or molecules of the ECM. The molecules comprise three main classes: (1) mitogens, (2) growth factors, and (3) survival factors. A **mitogen** is a chemical agent that induces or stimulates mitosis (cell division). Mitogens act as an extracellular signal and they usually come from another neighboring cell. Mitogens can stimulate cell growth, differentiation, migration, and survival.[5]

Growth factors (also called *cytokines*) stimulate an increase in cell mass or cell growth by fostering the synthesis of proteins and other macromolecules and inhibiting their breakdown (Table 1.5), including examples of mitogens and growth factors. Survival factors promote cell survival by inhibiting programmed cell death, or *apoptosis* (see Chapter 4).

DNA Damage Response: Blocks Cell Division

The **DNA damage response** occurs when DNA is damaged with recruitment of protein kinases to the site of damage and signaling that promotes a stop to the progression of the cell cycle, called **cell cycle arrest** (Fig. 1.33).

TISSUES

Cells of common structure and function are organized into **tissues**, of which there are four primary types: *muscle, neural, epithelial,* and *connective.* Epithelial, connective, and muscle tissues are summarized in Tables 1.6, 1.7, and 1.8, respectively. Different types of neurons have special characteristics that depend on their distribution and function within the nervous system (see Chapter 14). Different types of tissues

TABLE 1.5 Examples of Mitogens and Growth Factors and Their Actions

Growth Factor	Physiologic Actions
Platelet-derived growth factor (PDGF)	Stimulates proliferation of connective tissue cells and neuroglial cells
Epidermal growth factor (EGF)	Stimulates proliferation of epidermal cells and other cell types
Insulin-like growth factor 1 (IGF-1)	Collaborates with PDGF and EGF; stimulates proliferation of fat cells and connective tissue cells
Insulin-like growth factor 2 (IGF-2)	Collaborates with PDGF and EGF; stimulates proliferation of fat cells and connective tissue cells
Transforming growth factor-beta (TGF-β)	Stimulates or inhibits response of most cells to other growth factors; regulates differentiation of some cell types (e.g., cartilage)
Fibroblast growth factor (FGF)	Stimulates proliferation of fibroblasts, endothelial cells, myoblasts, and other cell types
Interleukin-2 (IL-2)	Stimulates proliferation of T lymphocytes
Nerve growth factor (NGF)	Promotes axon growth and survival of sympathetic and some sensory and CNS neurons
Hematopoietic cell growth factors (IL-3, GM-CSF, M-CSF, G-CSF, erythropoietin)	Promotes growth of white and red blood cells

CNS, Central nervous system; *CSF,* colony-stimulating factor; *G,* granulocyte; *GM,* granulocyte-macrophage; *M,* macrophage.

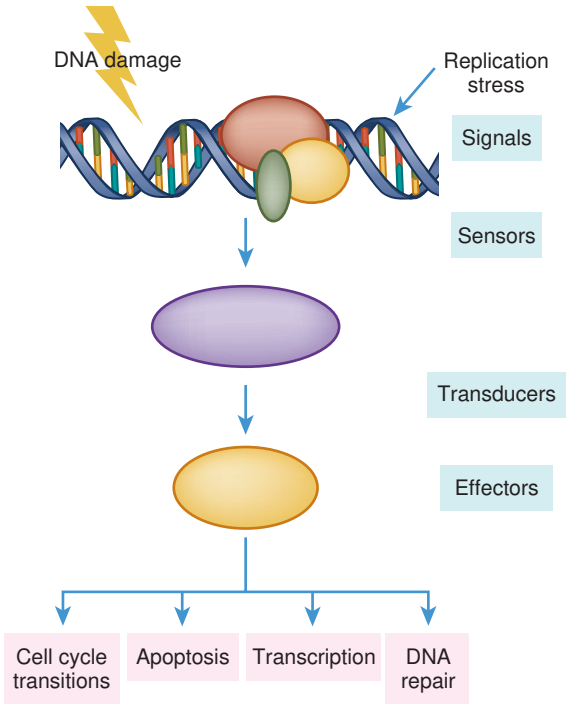


FIGURE 1.33 Deoxyribonucleic Acid (DNA) Damage Response. Several injurious agents can damage DNA. These include exogenous agents such as ultraviolet light; ionizing radiation; chemicals; and endogenous agents; oxidative damage; and replicative stress. Protein kinases are activated and serve as sensors and transducers causing many effector responses. The cell cycle arrest prevents entry into mitosis and several cell fates occur including DNA repair and apoptosis or cell death.

compose organs. Finally, organs are integrated to perform complex functions as tracts or systems.

All cells are in contact with a network of extracellular macromolecules known as the ECM (see the Extracellular Matrix and Basement Membrane section). This matrix not only holds cells and tissues together but also provides an organized latticework within which cells can migrate and interact with one another.

Tissue Formation and Differentiation

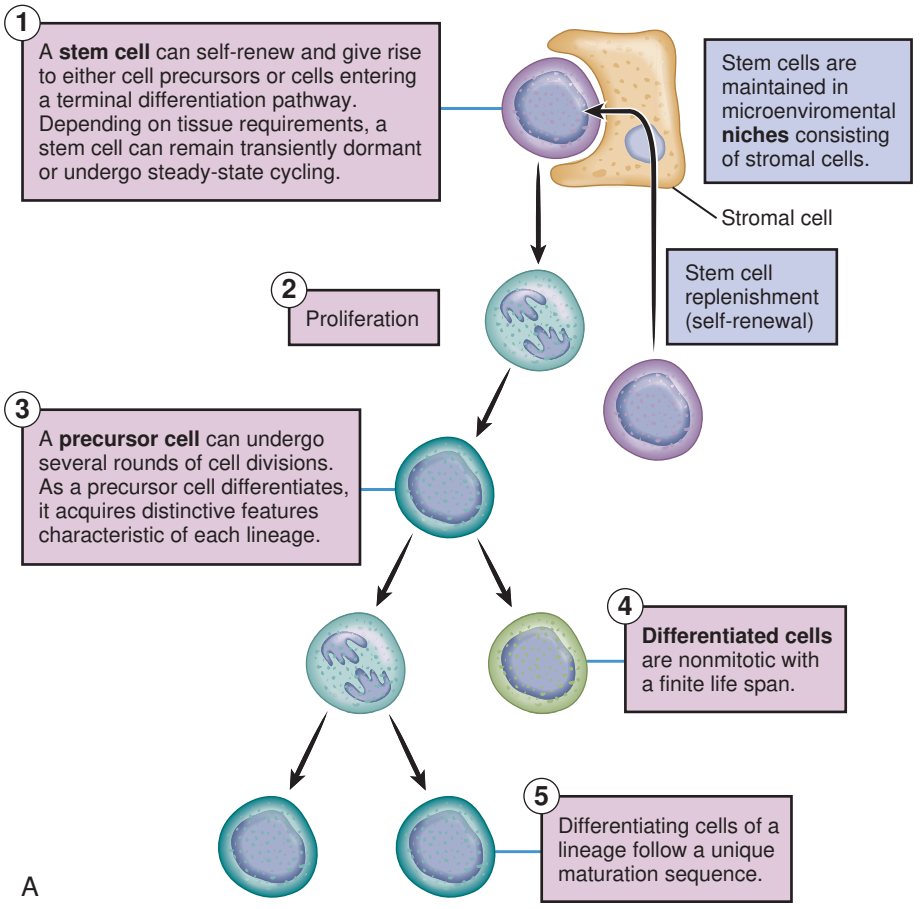
To form tissues, cells must exhibit intercellular recognition and communication, adhesion, and memory. Specialized cells sense their environment through signals, such as growth factors, from other cells. This type of communication ensures that new cells are produced only when and where they are required. Different cell types have different adhesion molecules in their plasma membranes, sticking selectively to other cells of the same type. They can also adhere to the ECM components. Because cells are tiny and squishy and enclosed by a flimsy membrane, it is remarkable that they form a strong human being. Strength can occur because of the ECM and the strength of the cytoskeleton with cell-to-cell adhesions to neighboring cells. Cells have memory because of specialized patterns of gene expression evoked by signals that acted during embryonic development. Memory allows cells to autonomously preserve their distinctive character and pass it on to their progeny.[1]

Fully specialized, or **terminally differentiated**, cells that are lost are regenerated from proliferating *precursor cells.* These precursor cells have been derived from a smaller number of stem cells.[1] **Stem cells** are cells with the potential to develop into many different cell types during early development and growth. In many tissues, stem cells serve as an internal repair and maintenance system, dividing indefinitely. These cells can maintain themselves over very long periods, an ability that is referred to as **self-renewal**, and can generate all the differentiated cell types of the tissue or **multipotency**. This stem cell–driven tissue renewal is very evident in the epithelial lining of the intestine, stomach, blood cells, and skin, which is continuously exposed to environmental factors. When a stem cell divides, each daughter cell has a choice: It can remain as a stem cell, or it can follow a pathway that results in terminal differentiation (Fig. 1.34).

QUICK CHECK 1.4

1. What is the cell cycle?
2. Describe the DNA damage response
3. Discuss the five types of intracellular communication.
4. Why is the ECM important for tissue cells?

Text continued on p. 36



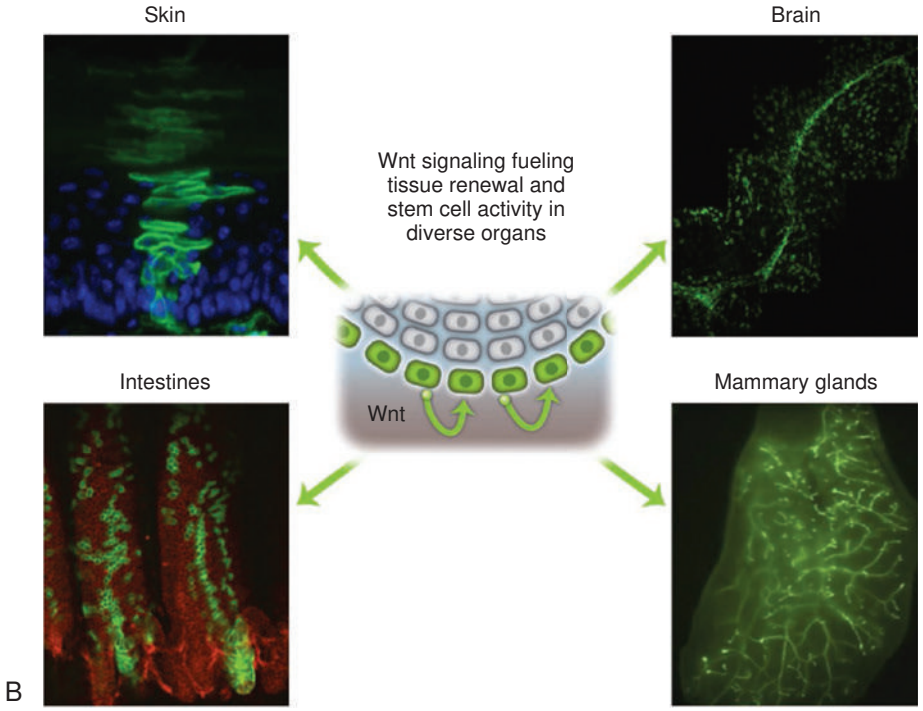


FIGURE 1.34 Properties of Stem Cell Systems. **A,** Stem cells have three characteristics: *self-renewal, proliferation,* and *differentiation* into mature cells. Stem cells are housed in *niches* consisting of *stromal cells* that provide factors for their maintenance. Stem cells of the embryo can give rise to cell precursors that generate all the tissues of the body. This property defines stem cells as *multipotent.* Stem cells are difficult to identify anatomically. Their identification is based on specific *cell surface markers* (cell surface antigens recognized by specific monoclonal antibodies) and on the lineage they generate following *transplantation.* **B,** Wnt signaling fuels tissue renewal. (**A,** from Kierszenbaum A: *Histology and cell biology: an introduction to pathology,* ed 3, St Louis, 2012, Elsevier. B, from Clevers H, et al: *Science* 346(6205):1248012, 2014.)

TABLE 1.6 Characteristics of Epithelial Tissues

Simple Squamous Epithelium

Structure

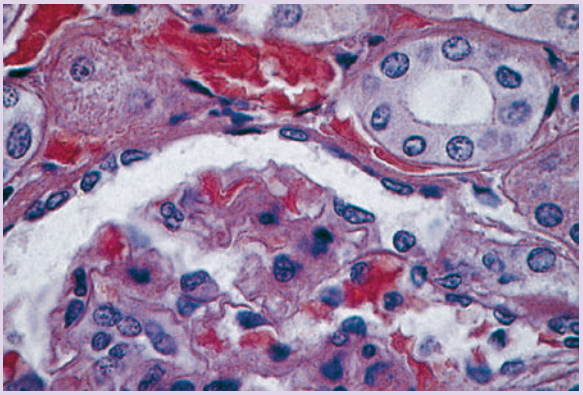
Single layer of cells

Location and Function

Lining of blood vessels leads to diffusion and filtration

Lining of pulmonary alveoli (air sacs) leads to separation of blood from fluids in tissues

Bowman's capsule (kidney), where it filters substances from blood, forming urine



Simple Squamous Epithelial Cell. Photomicrograph of simple squamous epithelial cell in parietal wall of Bowman's capsule in kidney. (From Erlandsen SL, Magney JE: *Color atlas of histology,* St Louis, 1992, Mosby.)

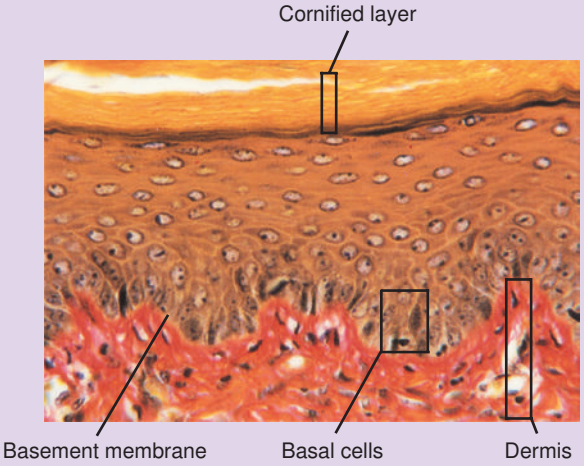
Stratified Squamous Epithelium

Structure

Two or more layers, depending on location, with cells closest to basement membrane tending to be cuboidal

Location and Function

Epidermis of skin and linings of mouth, pharynx, esophagus, and anus provide protection and secretion



Cornified Stratified Squamous Epithelium. Diagram of stratified squamous epithelium of skin. (Copyright Ed Reschke. Used with permission.)

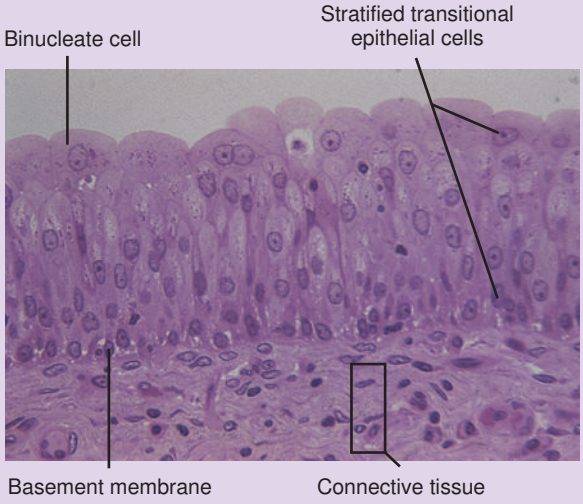
Transitional Epithelium

Structure

Vary in shape from cuboidal to squamous depending on whether basal cells of bladder are columnar or are composed of many layers; when bladder is full and stretched, the cells flatten and stretch like squamous cells

Location and Function

Linings of urinary bladder and other hollow structures stretch, allowing expansion of the hollow organs



Stratified Squamous Transitional Epithelium. Photomicrograph of stratified squamous transitional epithelium of urinary bladder. (Copyright Ed Reschke. Used with permission.)

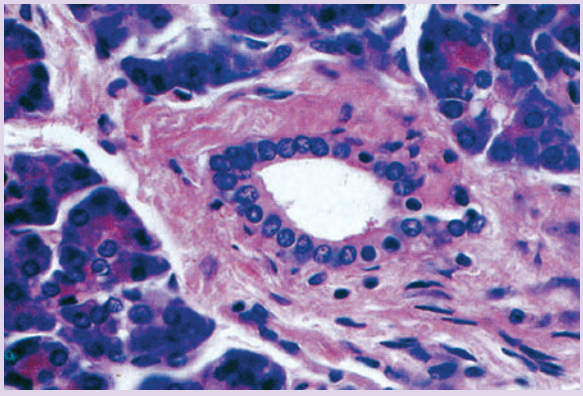
Simple Cuboidal Epithelium

Structure

Simple cuboidal cells; rarely stratified (layered)

Location and Function

Glands (e.g., thyroid, sweat, salivary) and parts of the kidney tubules and outer covering of ovary secrete fluids



Simple Cuboidal Epithelium. Photomicrograph of simple cuboidal epithelium of pancreatic duct. (From Erlandsen SL, Magney JE: *Color atlas of histology,* St Louis, 1992, Mosby.)

Continued

TABLE 1.6 Characteristics of Epithelial Tissues—cont'd

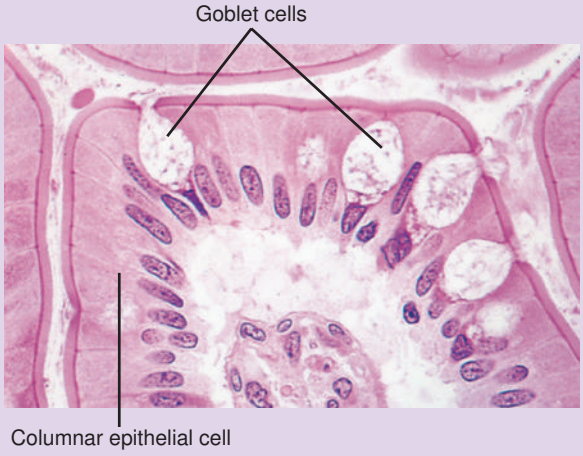
Simple Columnar Epithelium

Structure

Large amounts of cytoplasm and cellular organelles

Location and Function

Ducts of many glands and lining of digestive tract allow secretion and absorption from stomach to anus



Simple Columnar Epithelium. Photomicrograph of simple columnar epithelium. (Copyright Ed Reschke. Used with permission.)

Ciliated Simple Columnar Epithelium

Structure

Same as simple columnar epithelium but ciliated

Location and Function

Linings of bronchi of lungs, nasal cavity, and oviducts allow secretion, absorption, and propulsion of fluids and particles

Stratified Columnar Epithelium

Structure

Small and rounded basement membrane (columnar cells do not touch basement membrane)

Location and Function

Linings of epiglottis, part of pharynx, anus, and male urethra provide protection

Pseudostratified Ciliated Columnar Epithelium

Structure

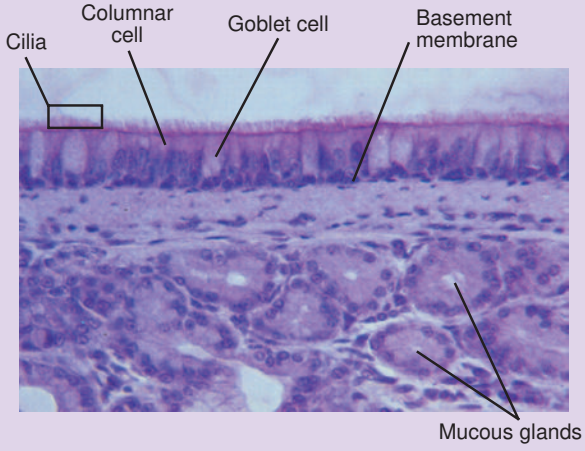
All cells in contact with basement membrane

Nuclei found at different levels within cell, giving stratified appearance

Free surface often ciliated

Location and Function

Linings of large ducts of some glands (parotid, salivary), male urethra, respiratory passages, and eustachian tubes of ears transport substances



Pseudostratified Ciliated Columnar Epithelium. Photomicrograph of pseudostratified ciliated columnar epithelium of trachea. (Copyright Robert L. Calentine. Used with permission.)

TABLE 1.7 Connective Tissues

Loose or Areolar Tissue

Structure

Unorganized; spaces between fibers

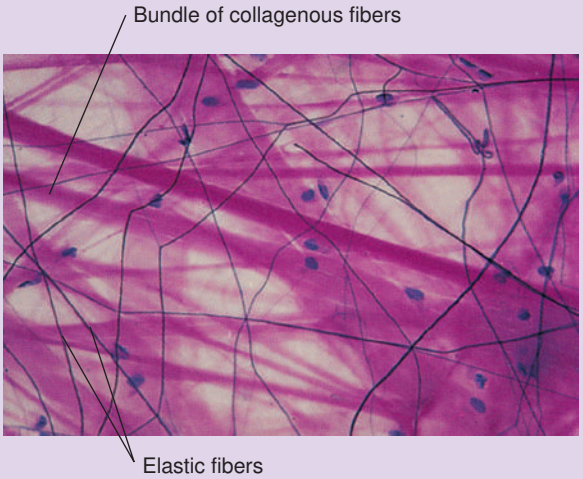
Most fibers collagenous, some elastic and reticular

Includes many types of cells (fibroblasts and macrophages most common) and large amount of intercellular fluid

Location and Function

Attaches skin to underlying tissue; holds organs in place by filling spaces between them; supports blood vessels

Intercellular fluid transports nutrients and waste productsFluid accumulation causes swelling (edema)



Loose Areolar Connective Tissue. (Copyright Ed Reschke. Used with permission.)

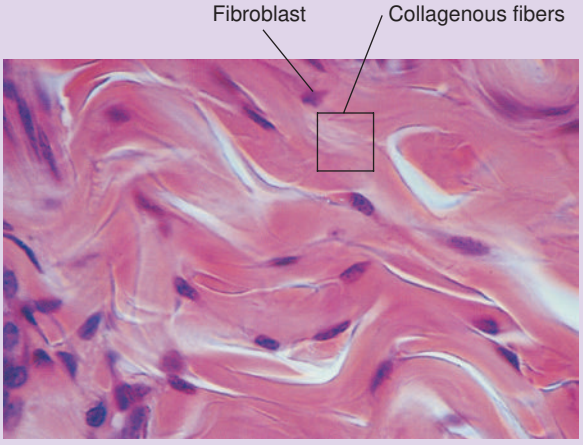
Dense Irregular Tissue

Structure

Dense, compact, and areolar tissue, with fewer cells and greater number of closely woven collagenous fibers than in loose tissue

Location and Function

Dermis layer of skin; acts as protective barrier



Dense, Irregular Connective Tissue. (Copyright Ed Reschke. Used with permission.)

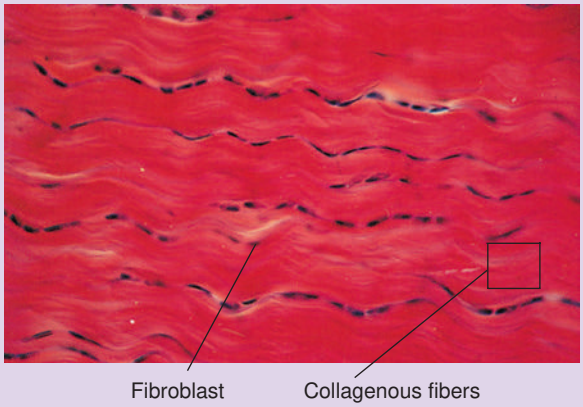
Dense, Regular (White Fibrous) Tissue

Structure

Collagenous fibers and some elastic fibers, tightly packed into parallel bundles, with only fibroblast cells

Location and Function

Forms strong tendons of muscle, ligaments of joints, some fibrous membranes, and fascia that surrounds organs and muscles



Dense, Regular (White Fibrous) Connective Tissue. (Copyright Phototake. Used with permission.)

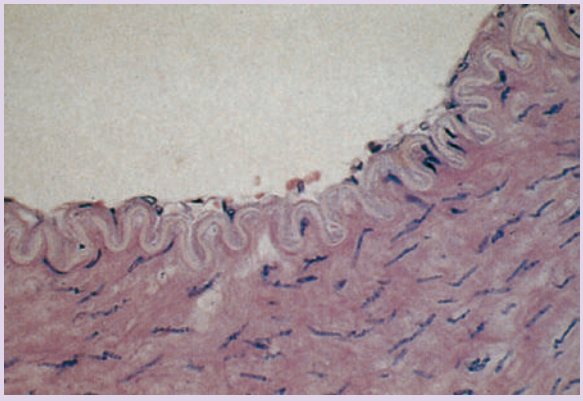
Elastic Tissue

Structure

Elastic fibers, some collagenous fibers, fibroblasts

Location and Function

Lends strength and elasticity to walls of arteries, trachea, vocal cords, and other structures



Elastic Connective Tissue. (From Erlandsen SL, Magney JE: *Color atlas of histology,* St Louis, 1992, Mosby.)

Continued

TABLE 1.7 Connective Tissues—cont'd

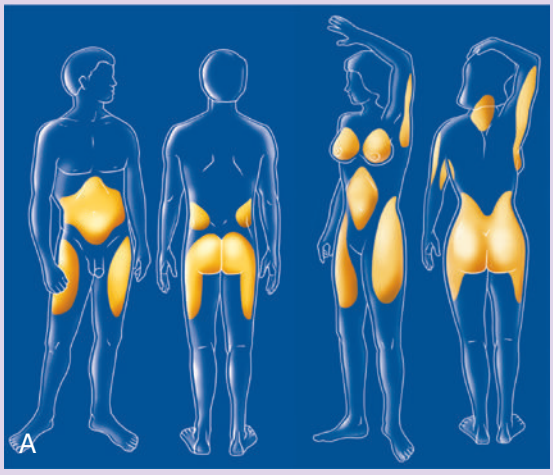
Adipose Tissue

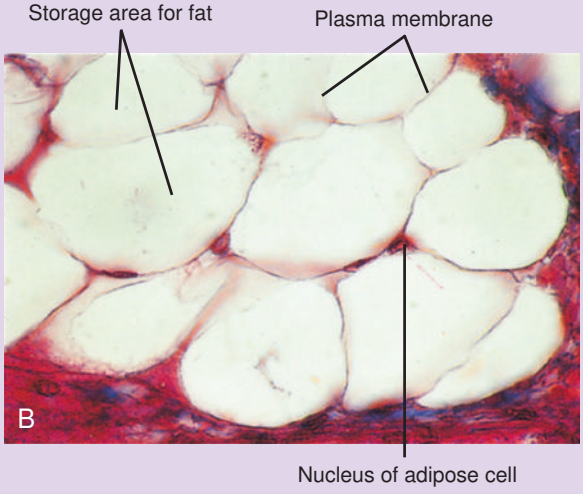
Structure

Fat cells dispersed in loose tissues; each cell containing a large droplet of fat flattens nucleus and forces cytoplasm into a ring around cell's periphery

Location and Function

Stores fat, which provides padding and protection





Adipose Tissue. A, Fat storage areas—distribution of fat in male and female bodies. **B,** Photomicrograph of adipose tissue. (**A** from Thibodeau GA, Patton KT: *Anatomy & physiology,* ed 6, St Louis, 2007, Mosby; **B** copyright Ed Reschke. Used with permission.)

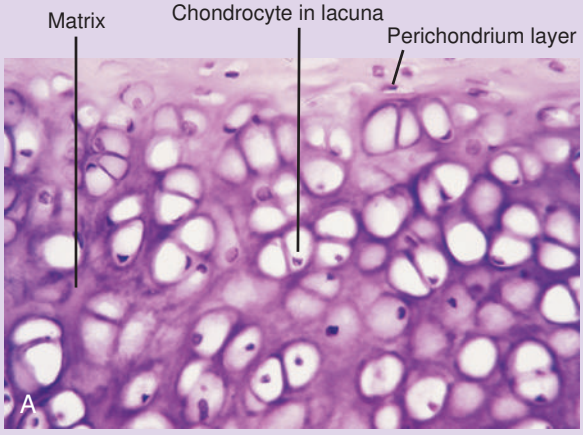
Cartilage (Hyaline, Elastic, Fibrous)

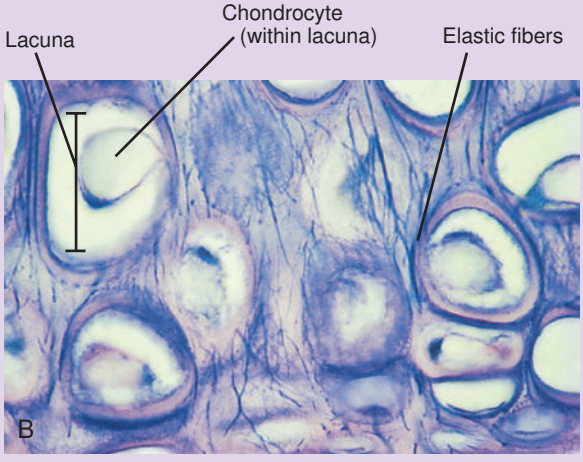
Structure

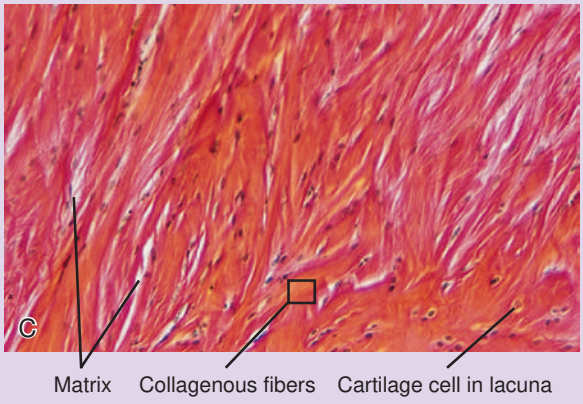
Collagenous fibers embedded in a firm matrix (chondrin); no blood supply

Location and Function

Gives form, support, and flexibility to joints, trachea, nose, ear, vertebral disks, embryonic skeleton, and many internal structures







Cartilage. A, Hyaline cartilage. **B,** Elastic cartilage. **C,** Fibrous cartilage. (**A and C,** copyright Robert L. Calentine. **B,** copyright Ed Reshke. Used with permission.)

TABLE 1.7 Connective Tissues—cont'd

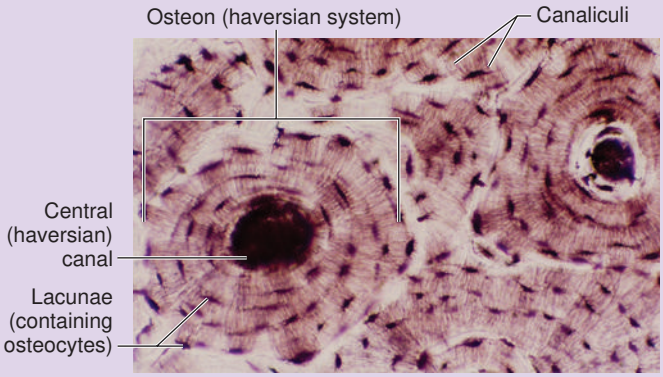
Bone

Structure

Rigid connective tissue consisting of cells, fibers, ground substances, and minerals

Location and Function

Lends skeleton rigidity and strength



Bone. (From Patton KT, Thibodeau GA: *Anatomy & physiology*, ed 10, St. Louis, 2019, Elsevier.)

Special Connective Tissues

Plasma

Structure

Fluid

Location and Function

Serves as matrix for blood cells

Macrophages in Tissue, Reticuloendothelial, or Macrophage System

Structure

Scattered macrophages (phagocytes) called *Kupffer cells* (in liver), alveolar macrophages (in lungs), microglia (in central nervous system)

Location and Function

Facilitate inflammatory response and carry out phagocytosis in loose connective, lymphatic, digestive, medullary (bone marrow), splenic, adrenal, and pituitary tissues

TABLE 1.8 Muscle Tissues

Skeletal (Striated) Muscle

Structure Characteristics of Cells

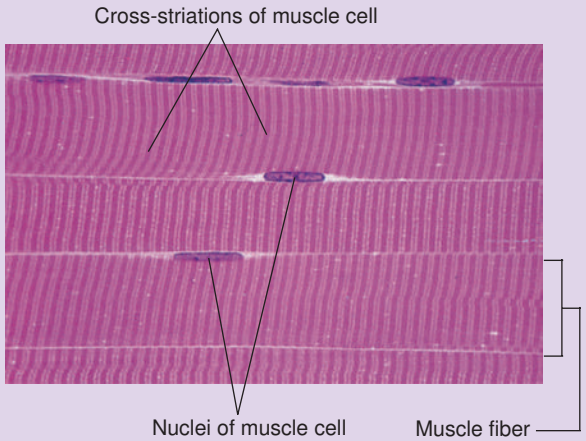
Long, cylindrical cells that extend throughout length of muscles

Striated myofibrils (proteins)

Many nuclei on periphery

Location and Function

Attached to bones directly or by tendons and provide voluntary movement of skeleton and maintenance of posture



Skeletal (Striated) Muscle. (From Thibodeau GA, Patton KT: *Anatomy & physiology,* ed 6, St Louis, 2007, Mosby.)

Cardiac Muscle

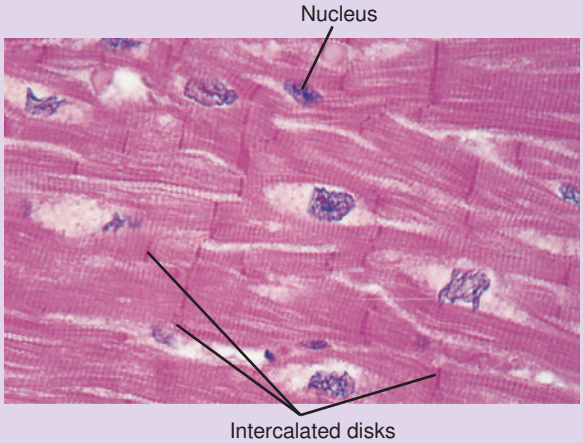
Structure Characteristics of Cells

Branching networks throughout muscle tissue

Striated myofibrils

Location and Function

Cells attached end-to-end at intercalated disks with tissue forming walls of heart (myocardium) to provide involuntary pumping action of heart



Cardiac Muscle. (Copyright Ed Reschke. Used with permission.)

Continued