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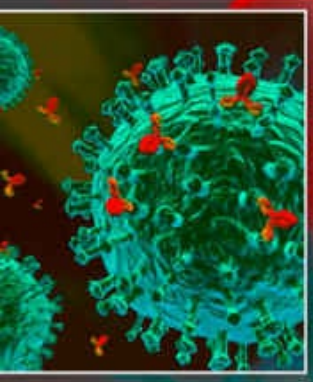
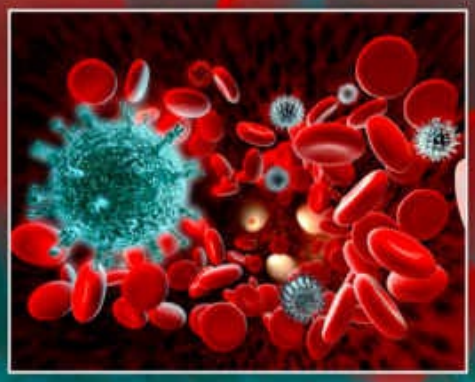

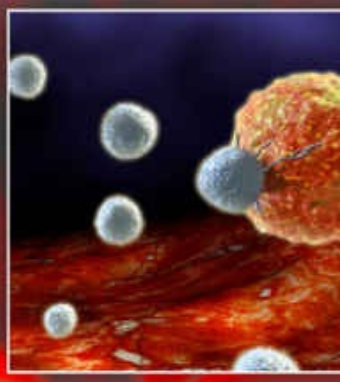

Understanding Pathophysiology

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FIRST CANADIAN EDITION

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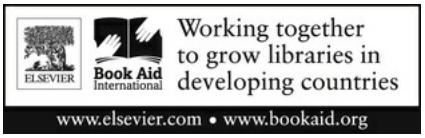

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Preface

Based on the sixth US edition of *Understanding Pathophysiology*, the first Canadian edition has been updated and revised with consideration of the rapid advances in molecular and cellular biology. Many sections have been rewritten or reorganized to provide a foundation for better understanding of the mechanisms of disease. Integrated throughout the text are concepts from the basic sciences, including genetics, epigenetics, gene–environment interaction, immunity, and inflammation. The text has been written to assist students with the translation of the concepts and processes of pathophysiology into clinical practice and to promote lifelong learning. All laboratory values were changed to measure results in SI units and to fit the Canadian context. Canadian statistics were also embedded, based on updated data from Health Canada, the Canadian Institute for Health Information, and other relevant governmental organizations. Furthermore, Indigenous perspectives were integrated and explored in relation to the epidemiology of pathophysiological conditions in Canada. Lastly, feedback from Canadian reviewers was addressed with a critical appreciation of relevant issues and application in current nursing practice.

Although the primary focus of the text is pathophysiology, we include discussions of the following interconnected topics to highlight their importance for clinical practice:

- A lifespan 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
- Molecular biology—mechanisms of normal cell function and how their alteration leads to disease
- Clinical manifestations, summaries of treatment, and health promotion/risk reduction

Organization and Content

The book is organized into two parts: Part One, Basic Concepts of Pathophysiology, and Part Two, Body Systems and Diseases.

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 cellular communication; forms of cell injury; genes and genetic disease; epigenetics; fluid and electrolytes and acid and base balance; immunity and inflammation; mechanisms of infection; stress, coping, and illness; and tumour biology. Chapter 3, *Epigenetics and Disease* explains the way heritable changes in gene expression—*phenotype* without a change in *genotype*—are influenced by several factors, including age, environment and lifestyle, and disease state.

The first Canadian edition includes significant revisions to Part One, incorporating new or updated information on the following topics:

- Updated content on cell membranes, cell junctions, intercellular communication, transport by vesicles, and stem cells (Chapter 1)
- Updated content on epigenetics and disease (Chapter 3)
- Updated content on cellular adaptations, oxidative stress, chemical injury, types of cell death, and aging, with a focus on Canadian epidemiology (Chapter 4)
- Updates regarding mechanisms of human defence—characteristics of innate and adaptive immunity (Chapters 6 and 7)
- Updated content on mechanisms of infection, antibiotic-resistant disease, and alterations in immune defence (Chapter 8)
- Updated content on stress, inflammation, hormones, and disease (Chapter 9)
- Updated chapter on tumour biology (after an extensive reorganization in the sixth US edition) (Chapter 10)
- Updated chapters on the epidemiology of cancer (after an extensive reorganization in the sixth US edition) (Chapters 11 and 12)

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 or 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.

The information on reproductive pathophysiology is presented in two chapters, with a new chapter, *Alterations of the Male Reproductive System*. Other significant revisions to Part Two, which have been retained in the first Canadian edition, include new and/or updated information on the following topics:

- Mechanisms of pain transmission, pain syndromes, and categories of sleep disorders (Chapter 14)
- Alterations in levels of consciousness, seizure disorders, and delirium. Pathogenesis of degenerative brain diseases, the dementias, movement disorders, traumatic brain and spinal cord injury, stroke syndromes, headache, and infections and structural malformations of the central nervous system (Chapters 15, 16, 17)
- The pathogenesis of type 2 diabetes mellitus (Chapter 19)
- Platelet function and coagulation; anemias, alterations of leukocyte function and myeloid and lymphoid tumours (Chapters 20 and 21)
- Extensive chapter revisions of alterations of hematological function in children (Chapter 22)
- Extensive chapter revisions on structure and function of the cardiovascular and lymphatic systems (Chapter 23)
- Mechanisms of atherosclerosis, hypertension, coronary artery disease, heart failure, and shock (Chapter 24)
- Pediatric valvular disorders, heart failure, hypertension, obesity, and heart disease (Chapter 25)
- Pathophysiology of acute lung injury, asthma, pneumonia, lung cancer, respiratory distress in the newborn, and cystic fibrosis (Chapters 27 and 28)
- Mechanisms of kidney stone formation, immune processes of glomerulonephritis, and acute and chronic kidney injury (Chapters 30 and 31)
- Female and male reproductive disorders, female and male reproductive cancers, breast diseases and mechanisms of breast cancer, prostate cancer, male breast cancer, and sexually transmitted infections (Chapters 33 and 34)
- Gastroesophageal reflux, nonalcoholic liver disease, inflammatory bowel disease, viral hepatitis, obesity, gluten-sensitive enteropathy, and necrotizing enterocolitis (Chapters 36 and 37)
- Bone cells, bone remodelling, joint and tendon diseases, osteoporosis, rheumatoid arthritis, and osteoarthritis (Chapters 38 and 39)
- Congenital and acquired musculo-skeletal disorders, and muscular dystrophies in children (Chapter 40)
- Psoriasis, discoid lupus erythematosus, and atopic dermatitis

(Chapters 41 and 42)
- Cancer of the various organ systems was updated for all chapters.

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
- *Health Promotion* boxes with a strategic focus on evidence-informed health promotion and current health practices
- *Risk Factors* boxes for selected diseases
- End-of-chapter *Did You Understand?* summaries 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 lifespan alterations

Art Program

All of the figures and photographs have been carefully reviewed, and some have been revised or updated. This edition features approximately 1 000 images. The figures are designed to help students visually understand sometimes difficult and complex material. Hundreds of high-quality photographs show clinical manifestations, pathological specimens, and clinical imaging techniques. Micrographs show normal and abnormal cellular structure. The combination of illustrations, algorithms, photographs, and use of colour for tables and boxes allows a more precise 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, printable key points, and bonus case studies with questions and answers. A comprehensive *Glossary* of pathophysiological conditions for the textbook of more than 600 terms helps students with the often difficult terminology related to pathophysiology; this is available both on Evolve and in the electronic version of the textbook. These electronic resources enhance learning options for students. Go to http://evolve.elsevier.com/Canada/Huether/pathophysiology.

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 1 200 items; PowerPoint Presentations for each chapter, with integrated images, audience response questions, and case studies; and an Image Collection of approximately 1 000 key figures from the text. All of these teaching resources are also available to instructors on the book's Evolve website. 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/Canada/Huether/pathophysiology.

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 expertise of the contributors to the previous US editions. Their reviews and synthesis of the evidence and clear and concise presentation of information are strengths of this text, and facilitated the adaptation of this information for the Canadian context.

The reviewers for this edition provided excellent recommendations for focus of content and revisions, based on the Canadian context, with thoughtful consideration of Indigenous perspectives on health, wellness, and disease. We appreciate their insightful work.

We are thankful to Martina van de Velde, our Content Development Specialist, for overseeing this wonderful project, providing insights regarding formatting, and suggesting content to maintain a streamlined manuscript that flows seamlessly from one section to another. We are also thankful to Roberta A. Spinosa-Millman, Content Strategist, for recruiting such a great team! Collaborating with one another on this project has been a great learning experience, and one that would not have been possible without Roberta having brought us all together.

We have respected the contributions from US authors, Sue E. Huether and Kathryn L. McCance, in this first Canadian edition and recognize the innovation and clarity that these authors bring to pathophysiology.

Lastly, we would like to thank our families for their undying support. They are what makes this work possible!

Mohamed El-Hussein

Kelly Power-Kean

Stephanie Zettel

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 health care providers 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 pathophysiological 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** (e.g., some antibiotics can injure the kidney and cause kidney failure). Diseases that are acquired as a consequence of being in a hospital environment are called **health care–associated diseases**. 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 health care–associated 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 (e.g., 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 tumour. 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 geographical 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 pathological 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 health care providers with the knowledge of how and why disease develops and informs their decision making to ensure optimal health care outcomes. Embedded in the study of pathophysiology is understanding that suffering is a personal, individual experience and a major component of disease.

PART ONE
Basic Concepts of Pathophysiology

OUTLINE

Unit 1 The Cell
Unit 2 Mechanisms of Self-Defence
Unit 3 Cellular Proliferation: Cancer

UNIT 1

The Cell

OUTLINE

1 Cellular Biology
2 Genes and Genetic Diseases
3 Epigenetics and Disease
4 Altered Cellular and Tissue Biology
5 Fluids and Electrolytes, Acids and Bases

Cellular Biology

Kathryn L. McCance, Stephanie Zettel

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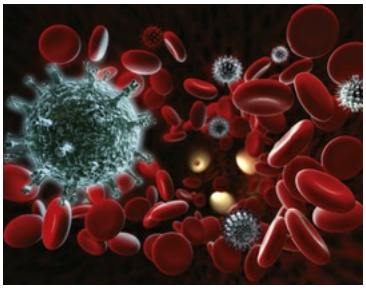


All body functions depend on the integrity of cells. Therefore an understanding of cellular biology is increasingly necessary to comprehend disease processes. An overwhelming amount of information reveals how cells behave as a multicellular "social" organism. At the heart of it all is cellular communication (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 communicate with other cells in a way to promote the integrity of the entire organism (i.e., they are well differentiated), and cells that resemble each other interact with each other more effectively. For example, prokaryotic and eukaryotic cells are organized differently, which accounts for the difference in response to pharmacotherapy. Anti-infectives, such as penicillin, are only effective against bacteria. Pharmacotherapy against eukaryotic cells results in more severe adverse effects, because the cells that are being targeted with the therapy more closely resemble human cells. When cells become less differentiated (as a result of injury or mutation) or less like the surrounding cells, the conversation breaks down, and cells either adapt (sometimes altering function) or become vulnerable to isolation, injury, or diseases such as cancer.

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

Figure 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** (Figure 1-1, *B*); and the "organs" of the cell—the membrane-bound intracellular **organelles**, among them the nucleus.

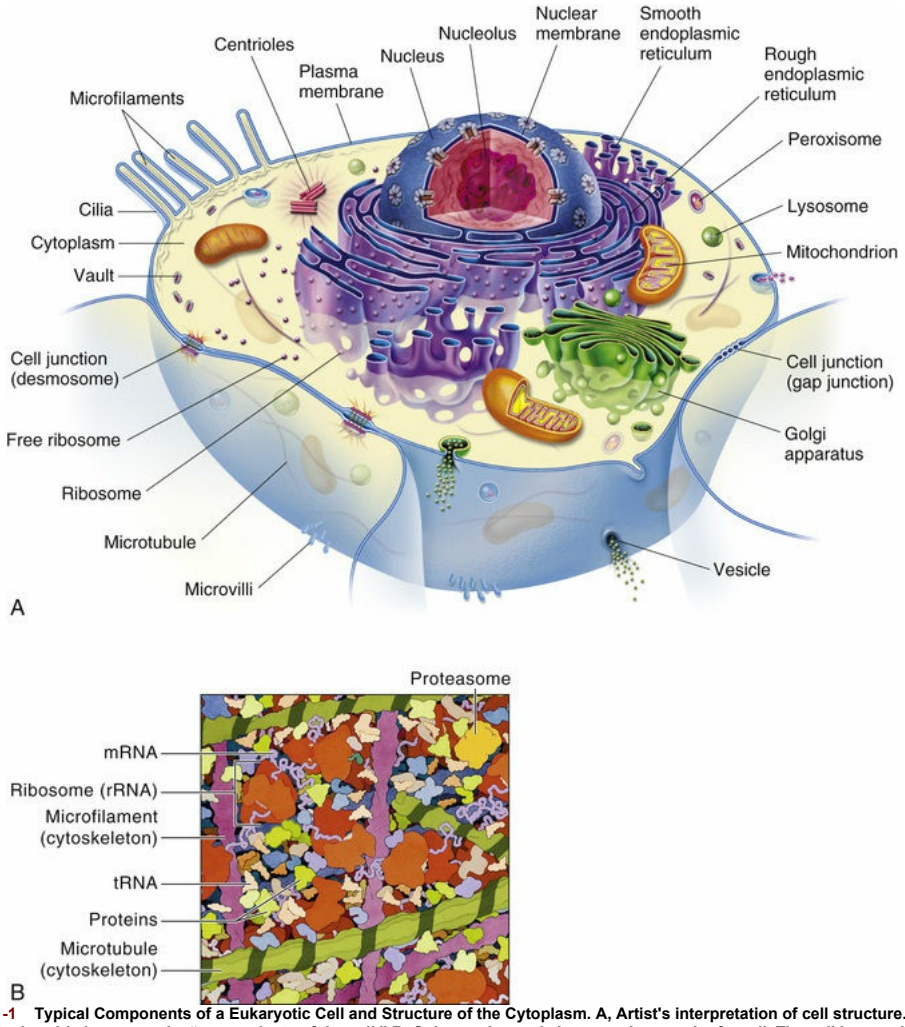


FIGURE 1-1 **Typical Components of a Eukaryotic Cell and Structure of the Cytoplasm. A, Artist's interpretation of cell structure. Note the many mitochondria known as the "power plants of the cell." B, Colour-enhanced electron micrograph of a cell. The cell is crowded. Note, too, the innumerable dots bordering the endoplasmic reticulum. These are ribosomes, the cell's "protein factories." *mRNA*, messenger RNA; *tRNA*, transfer RNA.** (B, from Patton, K.T., & Thibodeau, G.A. [2013]. *Anatomy & physiology* [8th ed.]. St. Louis: Mosby.)

Nucleus

The **nucleus**, which is surrounded by the cytoplasm and generally is located in the centre of the cell, is the largest membrane-bound organelle. Two pliable membranes compose the **nuclear envelope** (Figure 1-2, *A*). The nuclear envelope is pockmarked with pits, called **nuclear pores**, which allow chemical messages to exit and enter the nucleus (Figure 1-2, *B*). The outer membrane is continuous with membranes of the endoplasmic reticulum (see Figure 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 (Figure 1-2, *C*), which decreases the risk of breakage and is essential for cell division in eukaryotes.

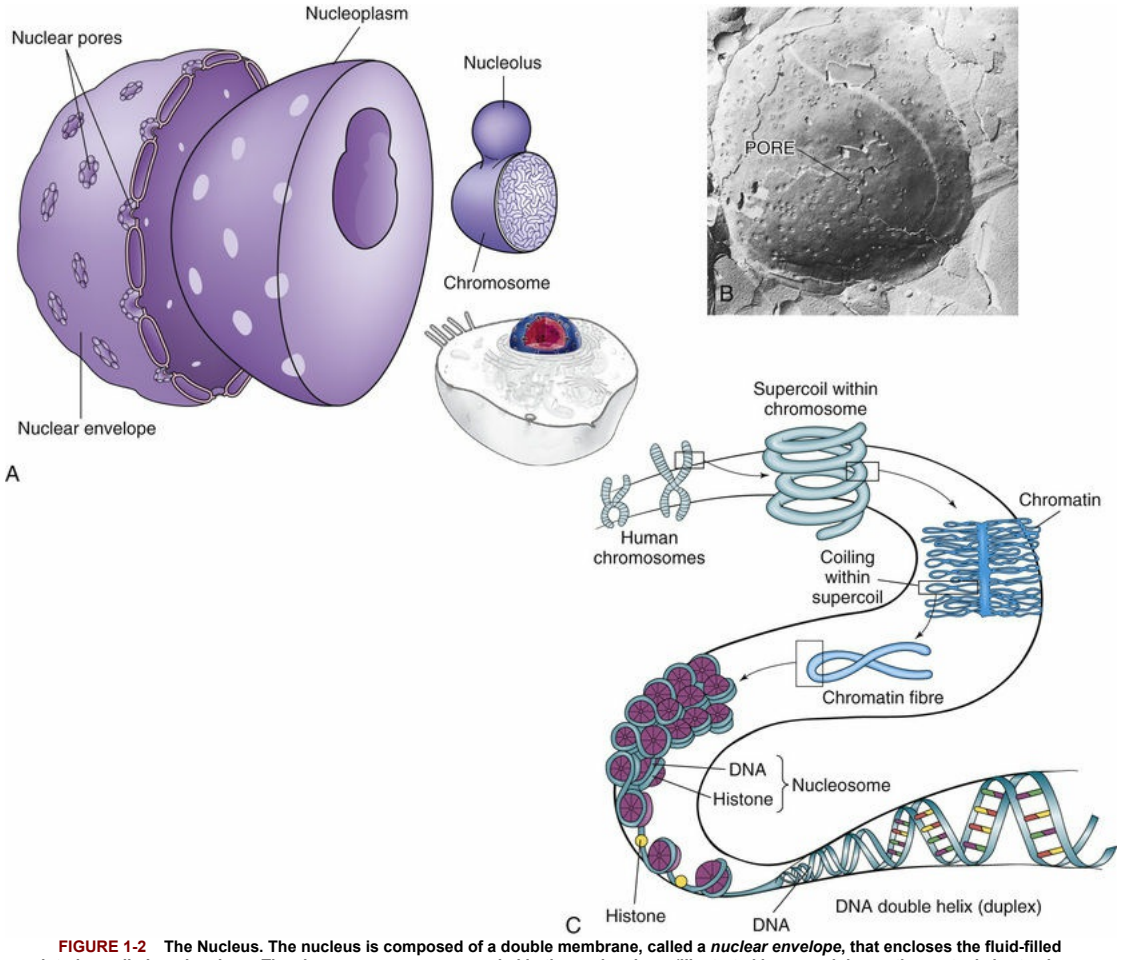


FIGURE 1-2 **The Nucleus. The nucleus is composed of a double membrane, called a *nuclear envelope*, that encloses the fluid-filled interior, called *nucleoplasm*. The chromosomes are suspended in the nucleoplasm (illustrated here much larger than actual size to show the tightly packed DNA strands). Swelling at one or more points of the chromosome, shown in A, occurs at a nucleolus where genes are being copied into 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.** (B, from Raven, P.H., & Johnson, G.B. [1992]. *Biology*. St. Louis: Mosby.)

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 Figure 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 biological 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, 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.

TABLE 1-1

Principal Cytoplasmic Organelles

Organelle	Characteristics and Description
Ribosomes	RNA-protein complexes (nucleoproteins) synthesized in nucleolus and secreted into cytoplasm. They provide sites for cellular protein synthesis.
Endoplasmic reticulum	Network of tubular channels (cisternae) that extend throughout outer nuclear membrane. It specializes in synthesis and transport of protein and lipid components of most organelles.
Golgi complex	Network of smooth membranes and vesicles located near nucleus. It is responsible for processing and packaging proteins onto secretory vesicles that break away from the complex and migrate to various intracellular and extracellular destinations, including the 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.
Lysosomes	Saclike structures that originate from the Golgi complex and 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.
Peroxisomes	Structures similar to lysosomes, but contain several oxidative enzymes (e.g., catalase, urate oxidase) that produce or use hydrogen peroxide; reactions detoxify various wastes.
Mitochondria	Structures that contain metabolic machinery needed for cellular energy metabolism. Enzymes of respiratory chain (electron-transport chain), found in the inner membrane of mitochondria, generate most of a cell's ATP (oxidative phosphorylation). They have a role in osmotic regulation, pH control, calcium homeostasis, and cell signalling.
Cytoskeleton	"Bone and muscle" of a cell. It is composed of a network of protein filaments, including microtubules and actin filaments (microfilaments); it forms cell extensions (microvilli, cilia, flagella).
Caveolae	Tiny indentations (caves) that can capture extracellular material and shuttle it inside the cell or across the cell.
Vaults	Cytoplasmic ribonucleoproteins shaped like octagonal barrels. They are thought to act as "trucks," shuttling molecules from the nucleus to elsewhere in the cell.

✓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 physiological 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 (Figure 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 (Figure 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).

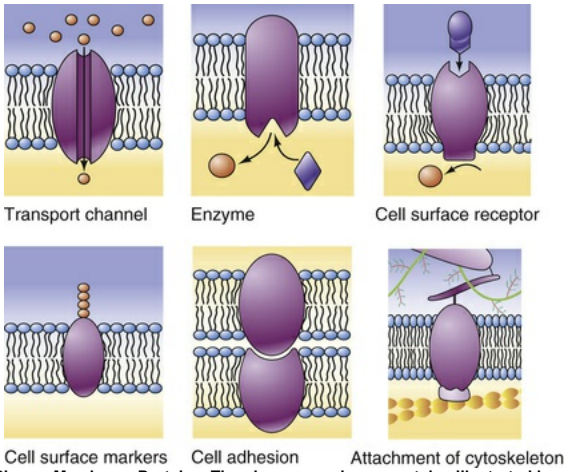


FIGURE 1-3 **Functions of Plasma Membrane Proteins. The plasma membrane proteins illustrated here show a variety of functions performed by the different types of plasma membranes.** (From Raven, P.H., & Johnson, G.B. [1995]. *Understanding biology* [3rd ed.]. Dubuque, IA: Brown.)

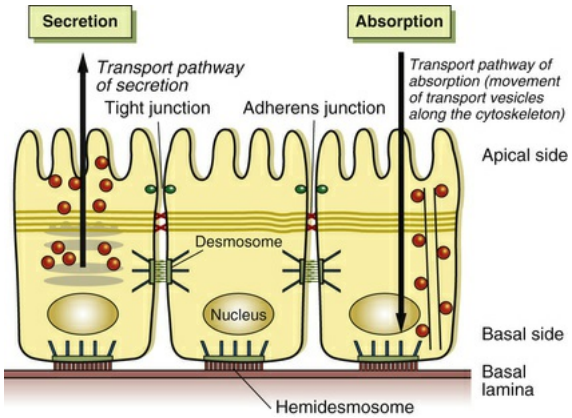


FIGURE 1-4 **Cell Polarity of Epithelial Cells. Schematic of cell polarity (cell direction) of epithelial cells. Shown are the directions of the basal side and the apical side. Organelles and cytoskeleton are also arranged directionally to enable, for example, intestinal cell secretion and absorption.** (Adapted from *Life science web textbook*, The University of Tokyo.)

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 Outer surfaces of plasma membranes in many cells are not smooth but are dimpled with cavelike 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 6) Growth factors (proliferation and differentiation; see Chapter 10)
Storage	Storage site for many receptors Transport Diffusion and exchange diffusion Endocytosis (pinocytosis, phagocytosis) Exocytosis (secretion) Active transport
Cell-to-cell interaction	Communication and attachment at junctional complexes Symbiotic nutritive relationships Release of enzymes and antibodies to extracellular environment Relationships with extracellular matrix

Modified from King, D.W., Fenoglio, C.M., & Lefkowitch, J.H. (1983). *General pathology: Principles and dynamics*. Philadelphia: Lea & Febiger.

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 (Figure 1-5). Lipid research is growing, and principles of membrane organization are being overhauled.[2] 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. It now appears that the lipid bilayer is a much more complex structure where lipids and proteins are not uniformly distributed but can separate into discrete units called *microdomains*, differing in their protein and lipid compositions.[3] 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*. The lipid bilayer can be structured in three main phases: solid gel phase, fluid liquid-crystalline phase, and liquid-ordered phase (Figure 1-5, *B*). These phases can change under physiological 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 Figure 1-5).

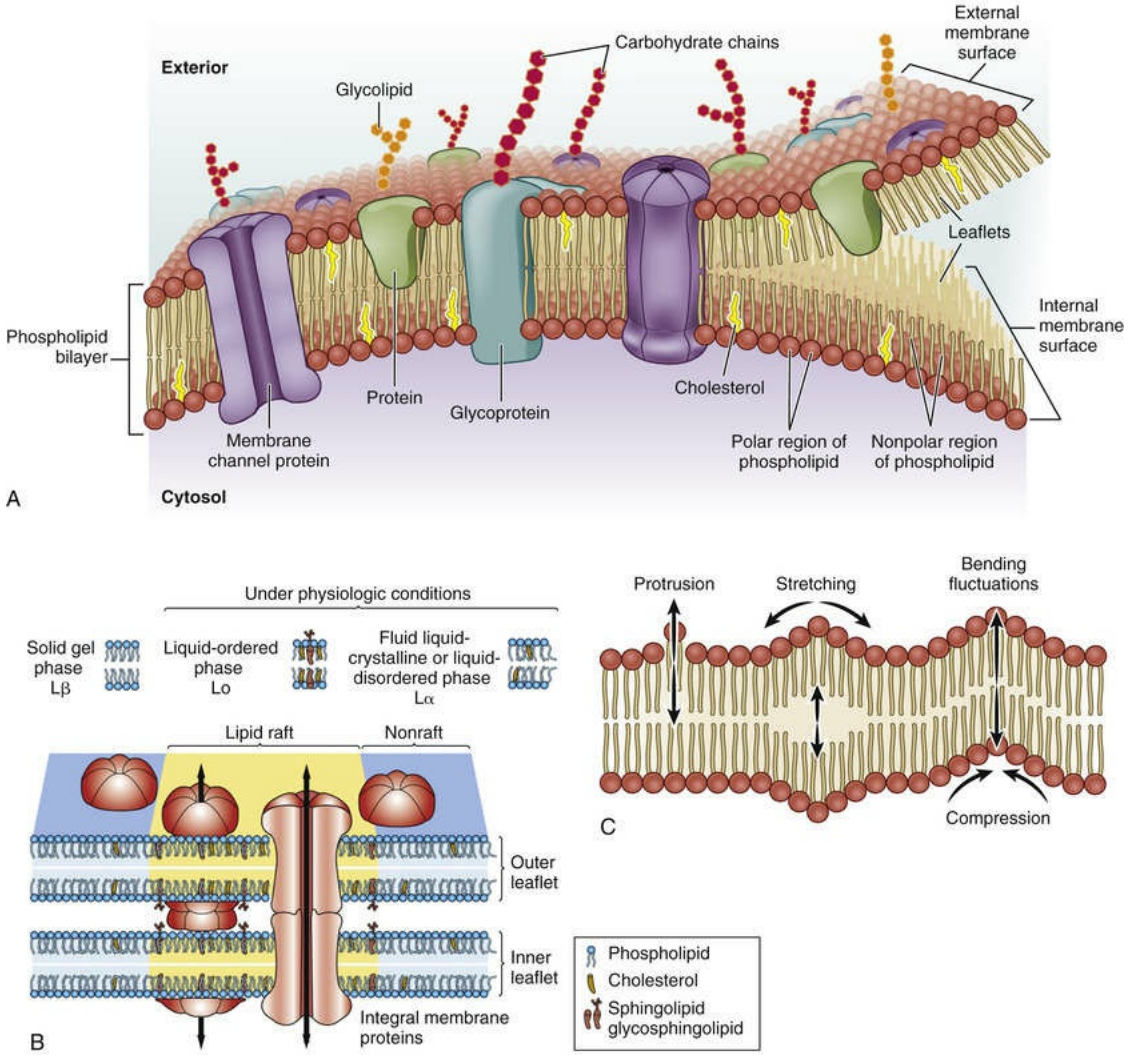


FIGURE 1-5 **Lipid Bilayer Membranes. A, Concepts of biological membranes have markedly changed in the last two decades, from the classic fluid mosaic model to the current model that lipids and proteins are not evenly distributed but can isolate into microdomains, differing in their protein and lipid composition. B, An example of a microdomain is lipid rafts (*yellow*). Rafts are dynamic domain structures composed of cholesterol, sphingolipids, and membrane proteins important in different cellular processes. Various models exist to clarify the functions of domains. The three major phases of lipid bilayer organization include a solid gel phase (e.g., with low temperatures), a liquid-ordered phase (high temperatures), and a fluid liquid-crystalline (or liquid-disordered) phase. Some membrane-associated proteins are integrated into the lipid bilayer; other proteins are loosely attached to the outer and inner surfaces of the membrane. Transmembrane proteins protrude through the entire outer and inner surfaces of the membrane, and they can be attracted to microdomains through specific interactions with lipids. Interaction of the membrane proteins with distinct lipids depends on the hydrophobic thickness of the membrane, the lateral pressures of the membrane (mechanical force may shift protein channels from an open to closed state), the polarity or electrical charges at the lipid-protein interface, and the presence on the protein side of amino acid side chains. 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. C, 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 Institut Laue-Langevin (ILL).** (Adapted from Bagatolli, L.A., Ipsen, J.H., Simonsen, A.C., et al. [2010]. *Prog Lipid Res, 49*[4], 378–389; Contreras, F.X., Ernst, A.M., Wieland, F., et al. [2011]. *Cold Spring Harb Perspect Biol, 3*[6], pii: a004705; Cooper, G.M. [2000]. *The cell—a molecular approach* [2nd ed.]. Sunderland (MA): Sinauer Associates; Defamie, N., & Mesnil, M. [2012]. *Biochim Biophys Acta, 1818*[8], 1866–1869; Woodka, A.C., Butler, P.D., Porcar, L. et al. [2012]. *Phys Rev Lett, 109*[5], 058102.)

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 serve as a storage site for many receptors, provide a route for transport into the cell, and act as the initiator for relaying signals from several extracellular chemical messengers into the cell's interior (see p. 23).

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") (Figure 1-6). 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 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. The structure of the cell membrane also makes it more difficult for water-soluble medications and ionized medications to enter the cell.

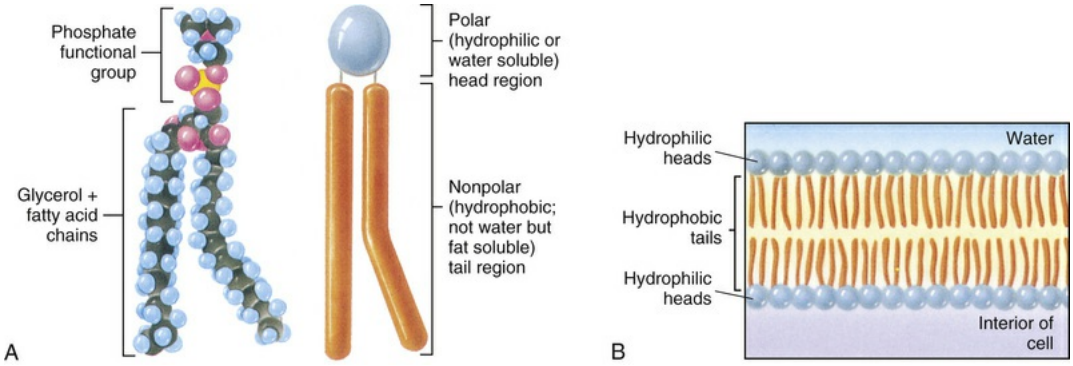


FIGURE 1-6 Structure of a Phospholipid Molecule. A, Each phospholipid molecule consists of a phosphate functional group and two fatty acid chains attached to a glycerol molecule. B, The fatty acid chains and glycerol form nonpolar, hydrophobic "tails," and the phosphate functional group forms the polar, 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. (From Raven, P.H., & Johnson, G.B. [1995]. *Understanding biology* [3rd ed.]. Dubuque, IA: Brown.)

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. **Membrane lipid rafts (MLRs)** appear to be structurally and functionally distinct regions of the plasma membrane[4,5] and consist of cholesterol and sphingolipid-dependent microdomains that form a network of lipid–lipid, protein–protein, and protein–lipid interactions (Figures 1-5, *B*, and 1-7) Although discrepancies between experimental results exist, two main types of MLRs are hypothesized: those that contain the cholesterol-binding protein caveolin (see p. 24) and those that do not.[4] Researchers hypothesize that there are lipid rafts that have several functions, including (1) providing cellular polarity and organization of signalling trafficking; (2) acting as platforms for extracellular matrix (ECM) adhesion and intracellular cytoskeletal tethering to the plasma membrane through cell adhesion molecules (CAMs); (3) enabling signalling across the membrane, which can rearrange cytoskeletal architecture and regulate cell growth, migration, and other functions; and (4) allowing entry of viruses, bacteria, toxins, and nanoparticles.[4]

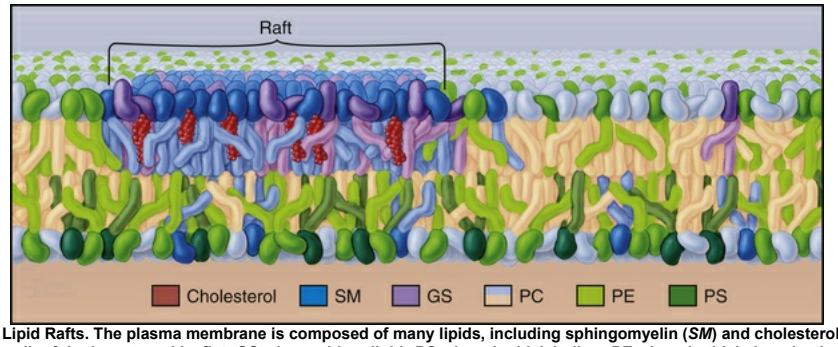


FIGURE 1-7 **Lipid Rafts. The plasma membrane is composed of many lipids, including sphingomyelin (*SM*) and cholesterol, shown here as a small raft in the external leaflet. *GS*, glycosphingolipid; *PC*, phosphatidylcholine; *PE*, phosphatidylethanolamine; *PS*, phosphatidylserine.** (From Pollard, T.D., & Ernshaw, W.C. [2004]. *Cell biology*. St. Louis: Saunders Elsevier.)

Proteins.

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. Proteins are the major workhorses of the cell. After translation (the synthesis of protein from RNA, see Chapter 2) of a protein, **post-translational 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.[6] 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.

Membrane proteins associate with the lipid bilayer in different ways (Figure 1-8), including (1) **transmembrane proteins** that extend across the bilayer and are exposed to an aqueous environment on both sides of the membrane (Figure 1-8, *A*); (2) proteins located almost entirely in the cytosol and are associated with the cytosolic half of the lipid bilayer by an α helix exposed on the surface of the protein (Figure 1-8, *B*); (3) proteins that exist outside the bilayer, on one side or the other, and are attached to the membrane by one or more covalently attached lipid groups (Figure 1-8, *C*); and (4) proteins bound indirectly to one or the other bilayer membrane face and are held in place by their interactions with other proteins (Figure 1-8, *D*).[1]

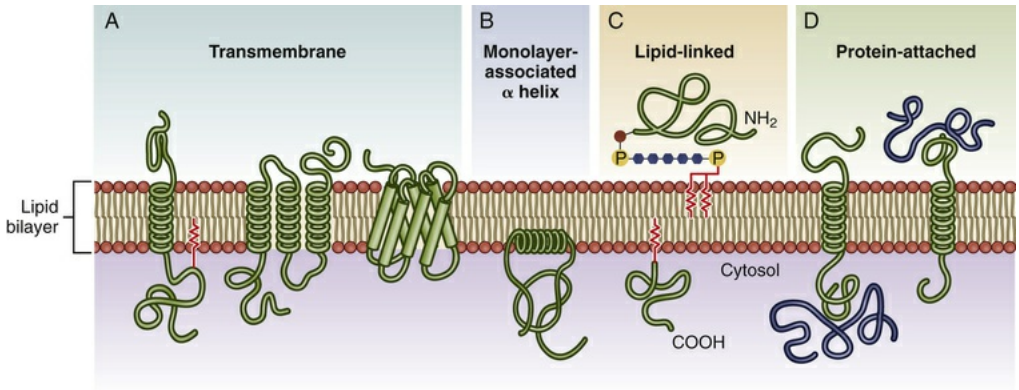


FIGURE 1-8 **Proteins Attach to the Plasma Membrane in Different Ways. A, Transmembrane proteins extend through the membrane as a single α helix, as multiple α helices, or as a rolled-up barrel-like sheet called a β barrel. B, Some membrane proteins are anchored to the cytosolic side of the lipid bilayer 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. *COOH*, carboxyl group; *NH_2*, amino group; *P*, protein.** (D, adapted from Alberts, B. [2014]. *Essential cell biology* [4th ed.]. New York: Garland.)

Proteins directly attached to the membrane bilayer can be removed by dissolving the bilayer with

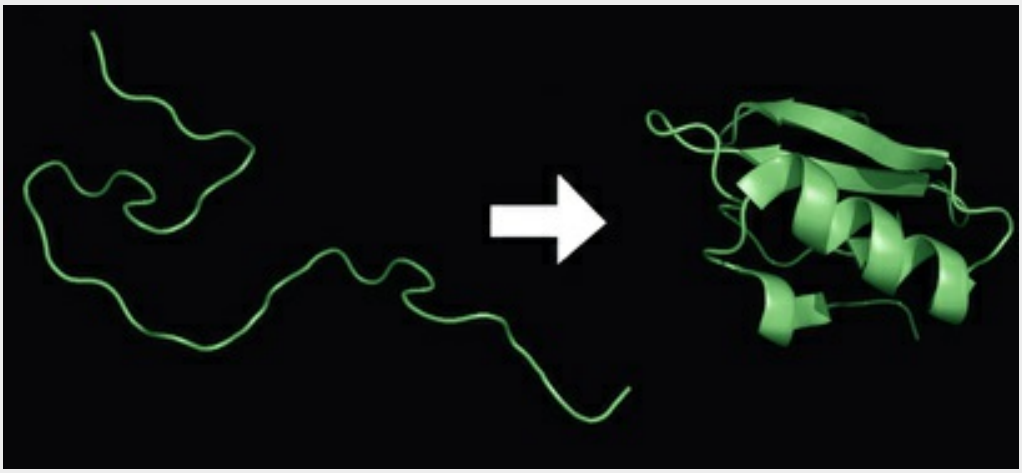
detergents called **integral membrane proteins**. The remaining proteins that can be removed by gentler procedures that interfere with protein–protein interactions but do not dissolve the bilayer are known as **peripheral membrane proteins**.

Proteins exist in densely folded molecular configurations rather than straight chains; so 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 then make their way, called *trafficking*, to different membrane locations of a cell.[7] Trafficking places unique demands on membrane proteins for folding, translocation, and stability.[7] Thus, much research is now being done to understand misfolded proteins (e.g., as a cause of disease; Box 1-1).

Box 1-1

Endoplasmic Reticulum, Protein Folding, and ER Stress

Protein folding in the endoplasmic reticulum (ER) is critical for us. As the biological 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. Pathophysiological 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 *chaperones* 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 endoplasmic reticulum mediates intracellular signalling pathways in response to the accumulation of unfolded or misfolded proteins; collectively, the 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's disease, Parkinson's disease, prion disease, amyotrophic lateral sclerosis, and diabetes mellitus. Additionally being studied is ER stress and how it may accelerate age-related dysfunction.



Protein Folding. Each protein exists as an unfolded polypeptide (*left*) or a random coil after the process of translation from a sequence of 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 Brodsky, J., & Skach, W.R. (2011). *Curr Opin Cell Biol, 23*, 464–475; Jäger, R., Bertrand, M.J.M., Gorman, A.M., et al. (2012). *Biol Cell, 104*(5), 259–270; Ron, D., & Walter, P. (2007). *Nat Rev Mol Cell Biol, 8*, 519–529.

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), that identify a cell to its neighbour; (5) **cell adhesion molecules (CAMs)**, or proteins that allow cells to hook together and form attachments of the cytoskeleton for maintaining cellular shape; and (6) catalysts of chemical reactions (e.g., conversion of lactose to glucose; see Figure 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.[7] Investigators are studying ATP enzymes and the changes in shape of biological membranes, particularly mitochondrial membranes, and their relationship to aging and disease.[8-10]

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: protein homeostasis.

The cellular protein pool is in constant change or flux. The number of copies of a protein in a cell depends on how quickly it is made and how long it survives or is broken down. This adaptable system of protein homeostasis is defined by the "proteostasis" network that 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.[11] Malfunction or failure of the proteostasis network is associated with human disease[12] (Figure 1-9).

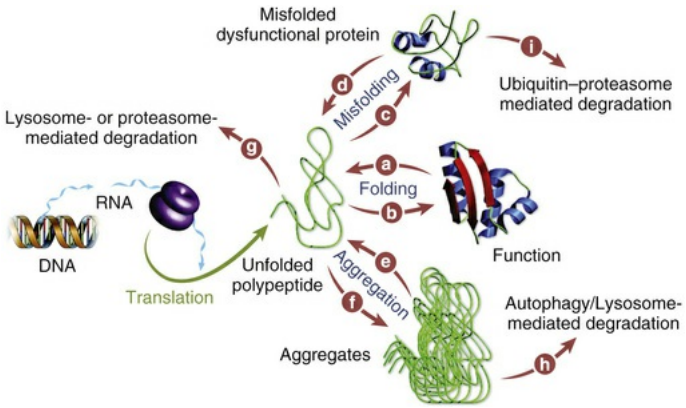


FIGURE 1-9 **Protein Homeostasis System and Outcomes. A main role of the protein homeostasis network (*proteostasis*) is to minimize protein misfolding and protein aggregation. The network includes ribosome-mediated protein synthesis, chaperone- (folding helpers in the endoplasmic reticulum) and enzyme-mediated folding, breakdown systems of lysosome- and proteasome-mediated protein degradation, and vesicular trafficking. The network integrates biological pathways that balance folding, trafficking, and protein degradation depicted by arrows *b*, *d*, *e*, *f*, *g*, *h*, and *i*.** (Adapted from Lindquist, S.L., & Kelly, J.W. [2011]. *Cold Spring Harb Perspect Biol, 3*[12], pii: a004507.)

Carbohydrates.

The short chains of sugars or carbohydrates (oligosaccharides) contained within the plasma membrane are generally 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, like leukocytes, to squeeze through the narrow spaces.[1] The functions of carbohydrates are more than protection and lubrication and include specific cell–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 the 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") (Figure 1-10). The region of a protein that associates with a ligand is called its **binding site**. Hormones, for example, are ligands. Recognition and binding depend on the chemical configuration of the receptor and its smaller ligand, which must fit together somewhat like pieces of a jigsaw puzzle (see Chapter 18). 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 favourable hydrophobic forces.[1] Numerous receptors are found in most cells, and ligand binding to receptors activates or inhibits the receptor's associated signalling or biochemical pathway.

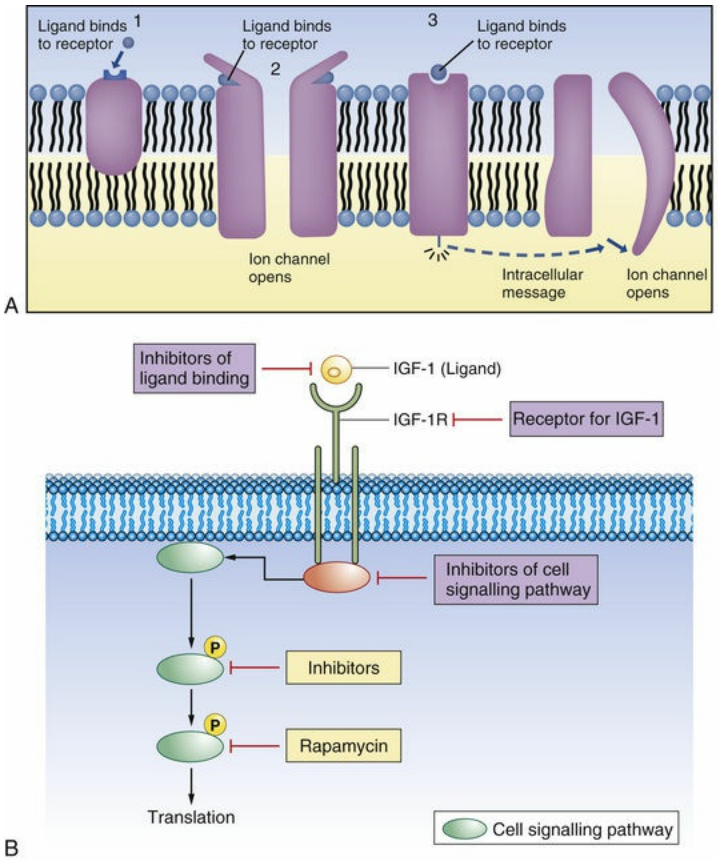


FIGURE 1-10 **Cellular Receptors. (A) 1, Plasma membrane receptor for a ligand (here, a hormone molecule) on the surface of an integral protein. A neurotransmitter can exert its effect on a postsynaptic cell by means of two fundamentally different types of receptor proteins: 2, channel-linked receptors, and 3, non–channel-linked receptors. Channel-linked receptors are also known as *ligand-gated channels.* (B) Example of ligand-receptor interaction. Insulinlike growth factor 1 (*IGF-1*) is a ligand and binds to the insulinlike growth factor 1 receptor**

(*IGF-1R*). With binding at the cell membrane the intracellular signalling pathway is activated, causing translation of new proteins (*P*) to act as intracellular communicators. This pathway is important for cancer growth. Researchers are developing pharmacological strategies to reduce signalling at and downstream of the IGF-1R, hoping this will lead to compounds useful in cancer treatment.

Plasma membrane receptors protrude from or are exposed at the external surface of the membrane and are important for cellular uptake of ligands (see Figure 1-10). The ligands that bind with membrane receptors include hormones, neurotransmitters, antigens, complement components, lipoproteins, infectious agents, medications, 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 based on 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 medications are found on the plasma membrane, in the cytoplasm, and in the nucleus. Membrane receptors have been found for certain anaesthetics, opiates, endorphins, enkephalins, antibiotics, cancer chemotherapeutic agents, digitalis, and other medications. Membrane receptors for endorphins, which are opiatelike peptides isolated from the pituitary gland, are found in large quantities in pain pathways of the nervous system (see Chapters 13 and 14). With binding to the receptor, the endorphins (or medications such as 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).

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. Once arranged, cells are linked by three different means: (1) CAMs in the cell's plasma membrane, (2) the ECM, and (3) specialized cell junctions.

Extracellular Matrix

Cells can be united by attachment to one another or through the **extracellular matrix (ECM)** (including the **basement membrane**), which the cells secrete around themselves. The ECM is an intricate meshwork of fibrous proteins embedded in a watery, gel-like substance composed of complex carbohydrates (Figure 1-11). The matrix 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 **macromolecules**: (1) fibrous structural proteins, including collagen and elastin; (2) adhesive glycoproteins, such as fibronectin; and (3) proteoglycans and hyaluronic acid.

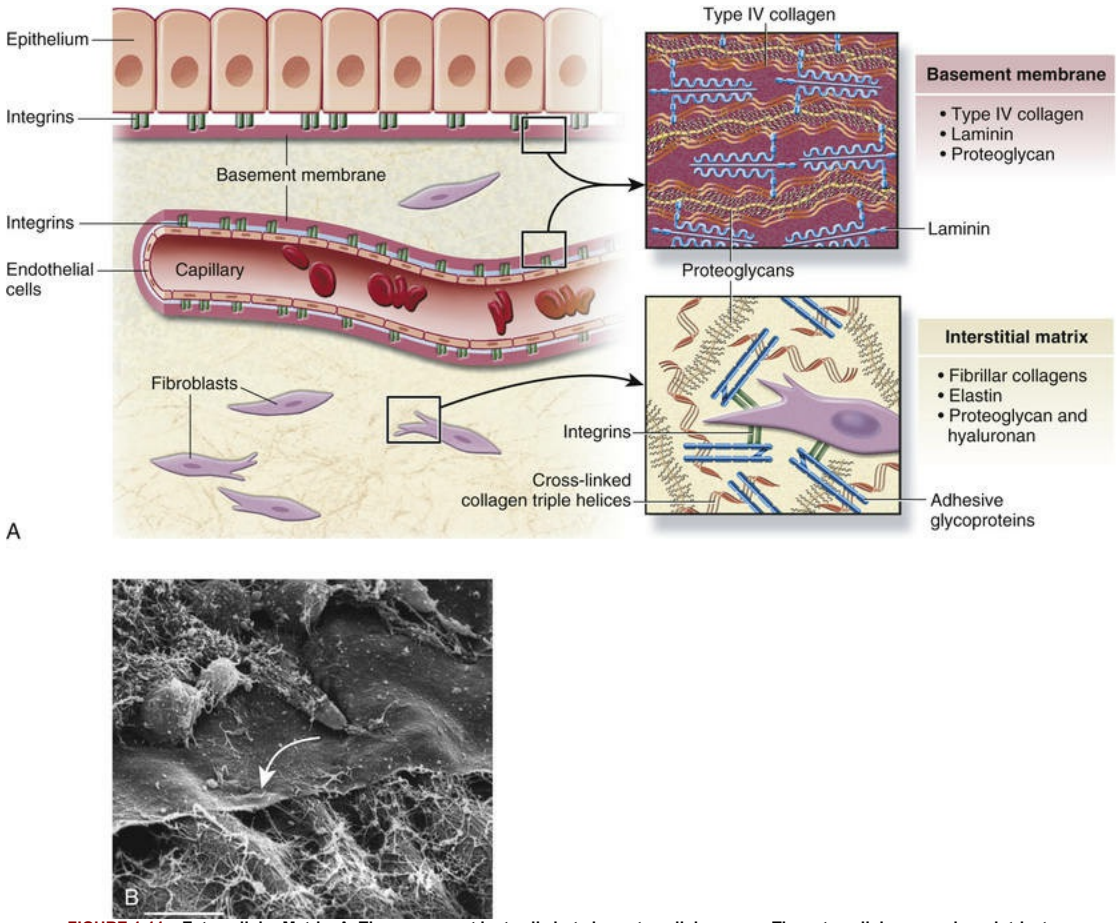


FIGURE 1-11 **Extracellular Matrix. A, Tissues are not just cells but also extracellular space. The extracellular space is an intricate network of macromolecules called the *extracellular matrix* (*ECM*). The macromolecules that constitute the ECM are secreted locally (by mostly fibroblasts) and assembled 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 the blood and the tissue cells. Matrix proteins modulate cell-matrix interactions, including normal tissue remodelling (which can become abnormal, e.g., with chronic inflammation). Disruptions of this balance result in serious diseases such as arthritis, tumour growth, and other pathological conditions. B, Scanning electron micrograph of a chick embryo where a portion of the epithelium has been removed, exposing the curtainlike ECM. (A, adapted from Kumar, V., Abbas, A.K., & Aster, J.C. [Eds.]. [2015]. *Robbins and Cotran pathologic basis of disease* [9th ed.]. Philadelphia: Saunders; B, © Robert L Treistad; from Gartner, L.P., & Hiatt, J.L. [2006]. *Color textbook of histology* [3rd ed.]. St. Louis: Saunders/Elsevier.)

- **Collagen** forms cablelike fibres 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.
- **Elastin** is a rubberlike protein fibre most abundant in tissues that must be capable of stretching and recoiling, such as tissues found in the lungs.
- **Fibronectin**, a large glycoprotein, promotes cell adhesion and cell anchorage. Reduced amounts have been found in certain types of cancerous cells; the reduced amount of this substance 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 basement membrane (see Figure 1-11).

The basement membrane is a thin, tough layer of ECM (connective tissue) underlying the epithelium of many organs and is also called the **basal lamina** (Figure 1-11, *B*).

The ECM is secreted by **fibroblasts** ("fibre formers") (Figure 1-12), 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, like bone; flexible, like tendons or the dermis of the skin; resilient and shock absorbing, like cartilage; or soft and transparent, similar to the jellylike 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 Figure 1-12).

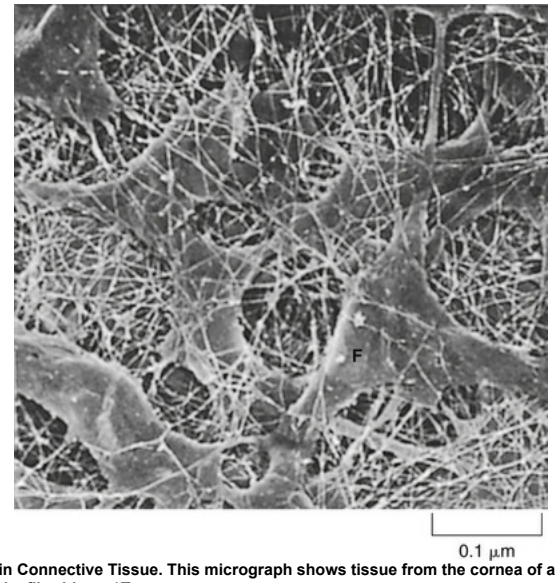


FIGURE 1-12 **Fibroblasts in Connective Tissue. This micrograph shows tissue from the cornea of a rat. The extracellular matrix surrounds the fibroblasts (*F*).** (From Nishida, T., Yasumoto, K., Otori, T., et al. [1988]. *Invest Ophthalmol Vis Sci, 29*, 1887–1890.)

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

Specialized Cell Junctions

Cells in direct physical contact with neighbouring cells are often interconnected at specialized plasma membrane regions called **cell junctions**. Cell junctions are classified by their function: (1) some hold cells together and form a tight seal (tight junctions); (2) some provide strong mechanical attachments (adherens junctions, desmosomes, hemidesmosomes); (3) some 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); and (4) some maintain apicobasal polarity of individual epithelial cells (tight junctions) (Figure 1-13). Overall, cell junctions make the epithelium leak-proof and mediate mechanical attachment of one cell to another, allowing communicating tunnels and maintaining cell polarity.

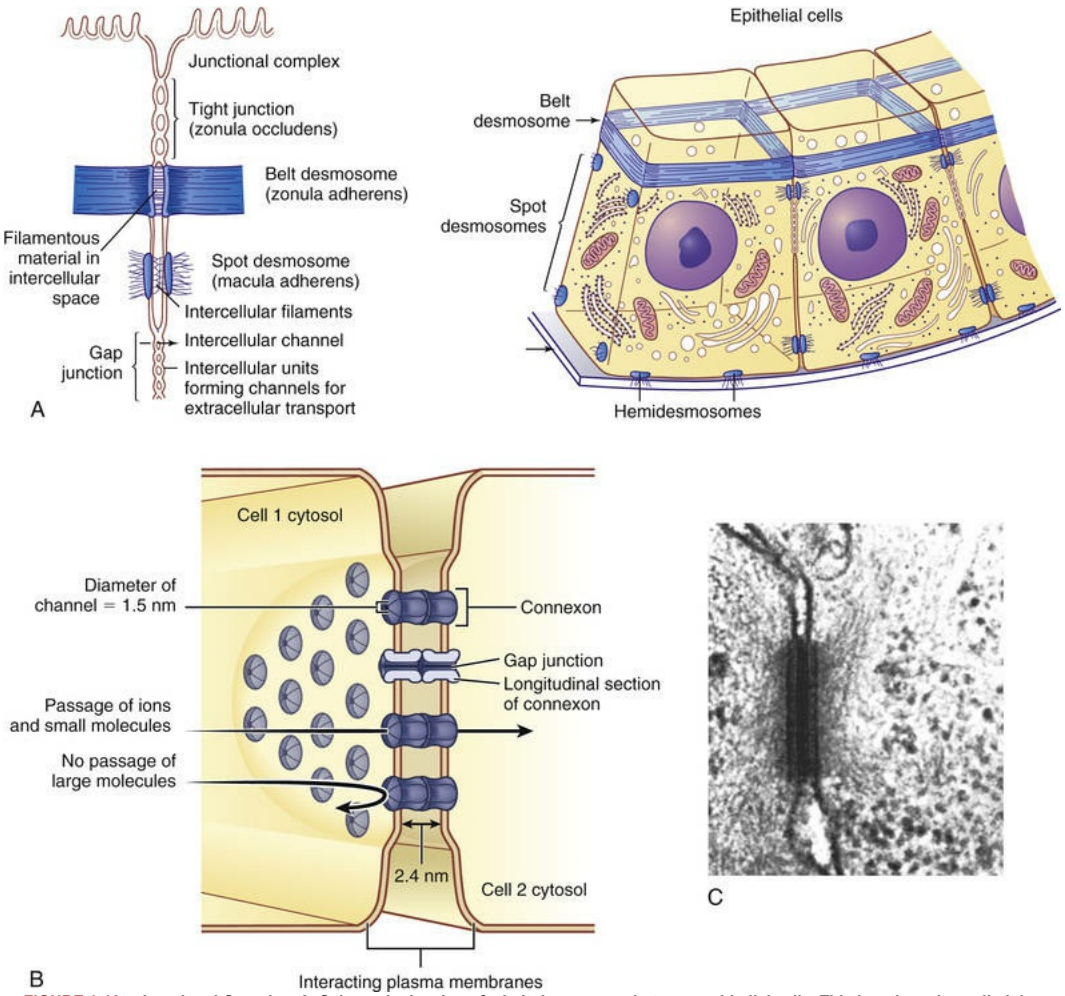


FIGURE 1-13 **Junctional Complex. A, Schematic drawing of a belt desmosome between epithelial cells. This junction, also called the *zonula adherens*, encircles each of the interacting cells. The spot desmosomes and hemidesmosomes, like the belt desmosomes, are adhering junctions. This tight junction 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, 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. C, Electron micrograph of desmosomes.** (A and C, from Raven, P.H., & Johnson, G.B. [1992]. ***Biology***. St. Louis: Mosby; B, adapted from Gartner, L.P., & Hiatt, J.L. [2006]. ***Color textbook of histology*** [3rd ed.]. St. Louis: Saunders Elsevier; Sherwood, L. [2013]. ***Learning*** [8th ed.]. Belmont, CA: Brooks/Cole CENGAGE.)

Cell junctions can be classified as symmetrical and asymmetrical. Symmetrical junctions include tight junctions, the belt desmosome (zonula adherens), desmosomes (macula adherens), and gap junctions (also called *intercellular channels* or *communicating junctions*).[13] An asymmetrical junction is the hemidesmosome (see Figure 1-13). Together they form the **junctional complex**. **Desmosomes** unite cells either by forming continuous bands or belts of epithelial sheets or by developing buttonlike 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 (Figure 1-13, *C*).

Multiple factors regulate gap junction intercellular communication, including voltage across the junction, intracellular pH, intracellular Ca^{++} concentration, and protein phosphorylation. The most abundant human connexin is connexin 43 (Cx43).[14] Investigators recently showed that loss of Cx43

expression in colorectal tumours is correlated with a shorter cancer-free survival rate.[15] This study is the first evidence that Cx43 acts as a tumour suppressor for colorectal cancer (enhances apoptosis) and therefore may be an important prognostic marker and target for therapy.[15] Investigators also recently reported that glycyrrhizic acid (GA), a glycoside of licorice root extracts, may be a strong chemopreventive agent against carcinogens; induced colon cancer in rats and Cx43 is one target.[16] Too much GA often in humans may lead to hypokalemia and hypertension.[17]

The junctional complex is a highly permeable part of the plasma membrane. Its 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 neighbours. 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 (Figure 1-10, *B*). Cells communicate in three main ways: (1) they display plasma membrane–bound signalling molecules (receptors) that affect the cell itself and other cells in direct physical contact (Figure 1-14, *A*); (2) they affect receptor proteins *inside* the target cell and the signal molecule has to enter the cell to bind to them (Figure 1-14, *B*); and (3) they form protein channels (gap junctions) that directly coordinate the activities of adjacent cells (Figure 1-14, *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 favouring cancerous tumour development (see Chapter 10). Secreted chemical signals involve communication locally and at a distance. Primary modes of intercellular signalling are contact-dependent, paracrine, hormonal, neurohormonal, and neurotransmitter. Autocrine stimulation occurs when the secreting cell targets itself (Figure 1-15).

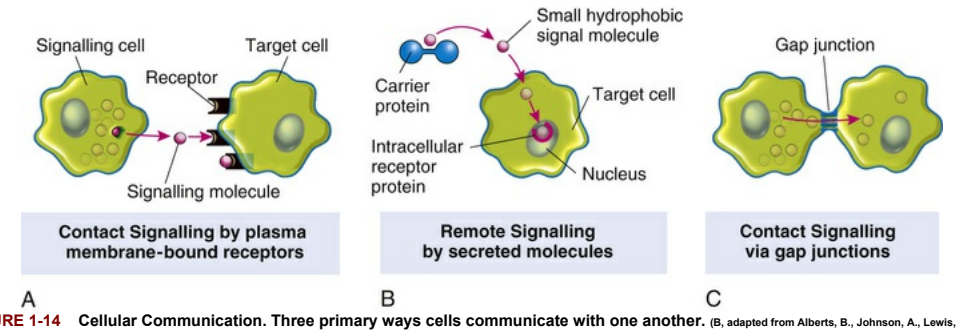


FIGURE 1-14 **Cellular Communication. Three primary ways cells communicate with one another.** (B, adapted from Alberts, B., Johnson, A., Lewis, J., et al. [2008]. *Molecular biology of the cell* [5th ed.]. New York: Garland.)

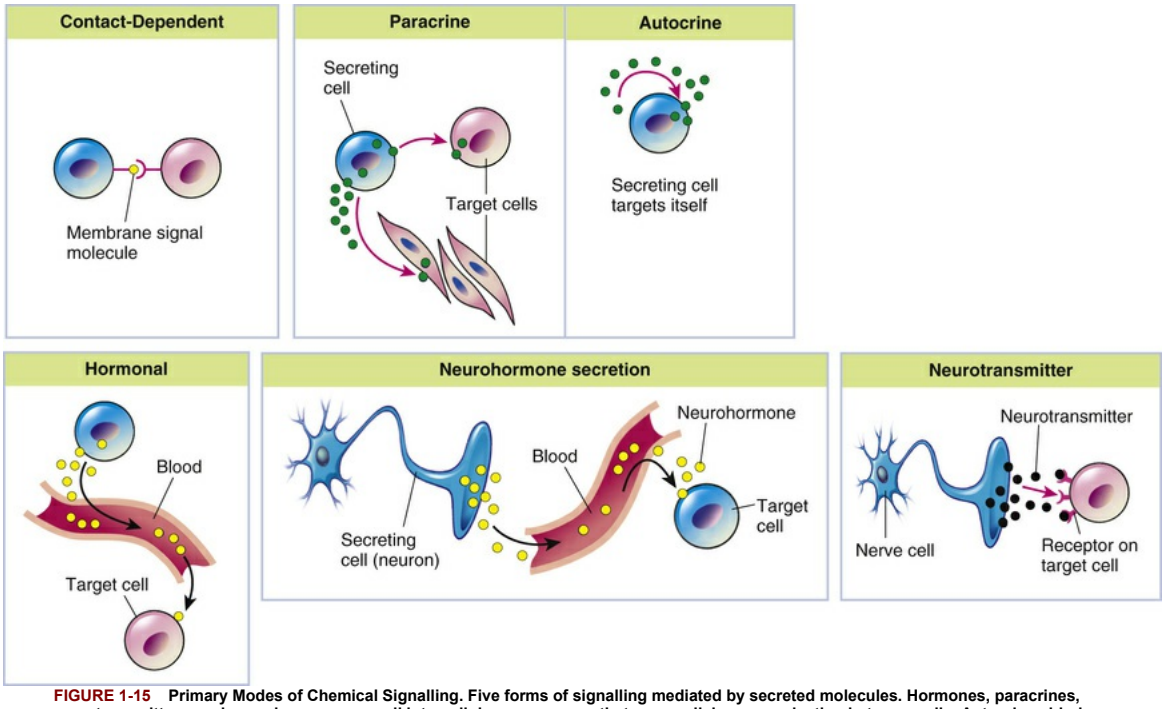


FIGURE 1-15 **Primary Modes of Chemical Signalling. Five forms of signalling mediated by secreted molecules. Hormones, paracrines, neurotransmitters, and neurohormones are all intercellular messengers that accomplish communication between cells. Autocrines bind to receptors on the same cell. Not all 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.**

Contact-dependent signalling requires cells to be in close membrane–membrane contact. In **paracrine signalling**, cells secrete local chemical mediators that are quickly taken up, destroyed, or immobilized. Paracrine signalling usually involves different cell types; however, cells also can produce signals to which they alone respond, called **autocrine signalling** (see Figure 1-15). For example, cancer cells use this form of signalling to stimulate their survival and proliferation. The mediators act only on nearby cells. **Hormonal signalling** 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 18). In **neurohormonal signalling**, hormones are released into the blood by neurosecretory neurons. Like endocrine cells, neurosecretory neurons release bloodborne 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 Figure 1-15). Many of these same signalling molecules are receptors used in hormonal, neurohormonal, and paracrine signalling. 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 signalling (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 signalling cascades (Figure 1-16, *C*). Signals are passed between cells when a particular type of molecule is produced by one cell—the **signalling cell**—and received by another—the **target cell**—by means of a **receptor protein** that recognizes and responds specifically to the signal molecule (Figure 1-16, *A* and *B*). In turn, the signalling molecules activate a pathway of intracellular protein kinases that results in various responses, such as grow and reproduce, die, survive, or differentiate (Figure 1-16, *D*). If deprived of appropriate signals, most cells undergo a form of cell suicide known as *programmed cell death*, or *apoptosis* (see p. 105).

TABLE 1-3

Classes of Plasma Membrane Receptors

Type of Receptor	Description
Ion channel coupled	Involve rapid synaptic signalling between electrically excitable cells; also called *transmitter-gated* ion channels. Channels open and close briefly in response to neurotransmitters, changing ion permeability of plasma membrane of postsynaptic cell.
Enzyme coupled	Once activated by ligands, function directly as enzymes or associate with enzymes.
G-protein coupled	Indirectly activate or inactivate plasma membrane enzyme or ion channel; interaction mediated by *GTP-binding regulatory protein (G-protein)*. May also interact with inositol phospholipids, which are significant in cell signalling, and with molecules involved in *inositol-phospholipid transduction pathway*.

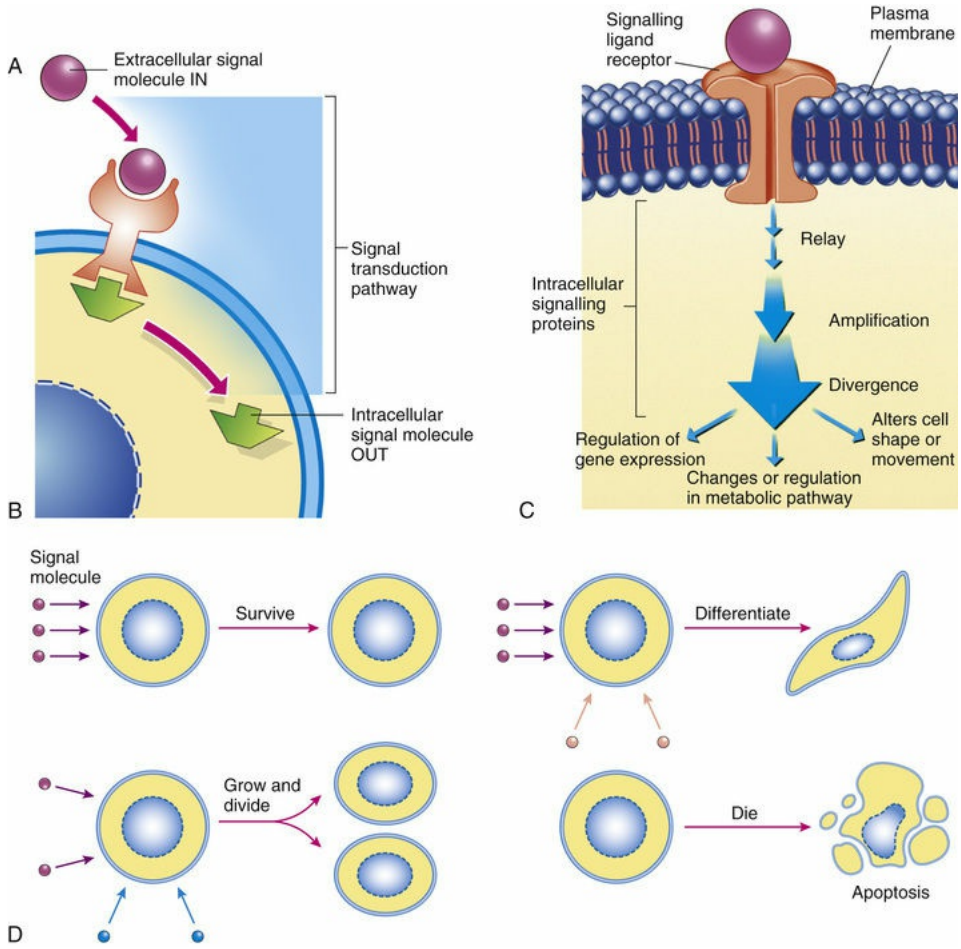


FIGURE 1-16 **Schematic of a Signal Transduction Pathway. Like a telephone receiver that converts an electrical signal into a sound signal, a cell converts an extracellular signal, A, into an intracellular signal, B. C, An extracellular signal molecule (ligand) bonds to a receptor protein located on the plasma membrane, where it is transduced into an intracellular signal. This process initiates a signalling 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. D, Different cell behaviours rely on multiple extracellular signals.**

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

Best known about ATP is its role as a universal "fuel" *inside* living cells. This fuel or energy drives biological 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 mol of glucose metabolically breaks down in the presence of oxygen into carbon dioxide and water, 686 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 (Box 1-2).

Box 1-2

Role of Adenosine Triphosphate Outside Cells

Emerging understandings are the role of adenosine triphosphate (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 physiological processes, including inflammation.

From Burnstock, G. (2007). *Physiol Rev, 87*(2), 659–797. doi:10.1152/physrev.00043.2006; Falzoni, S., Donvito, G., & Di Virgilio, F. (2013). *Interface Focus, 3*(3), 20120101. doi:10.1098/rsfs.2012.0101; Nurse, C.A., & Piskuric, N.A. (2012). *Semin Cell Dev Biol, 24*(1), 22–30. doi:10.1016/j.semcdb.2012.09.006.

Food and Production of Cellular Energy

Catabolism of the proteins, lipids, and polysaccharides found in food can be divided into the following three phases (Figure 1-17):

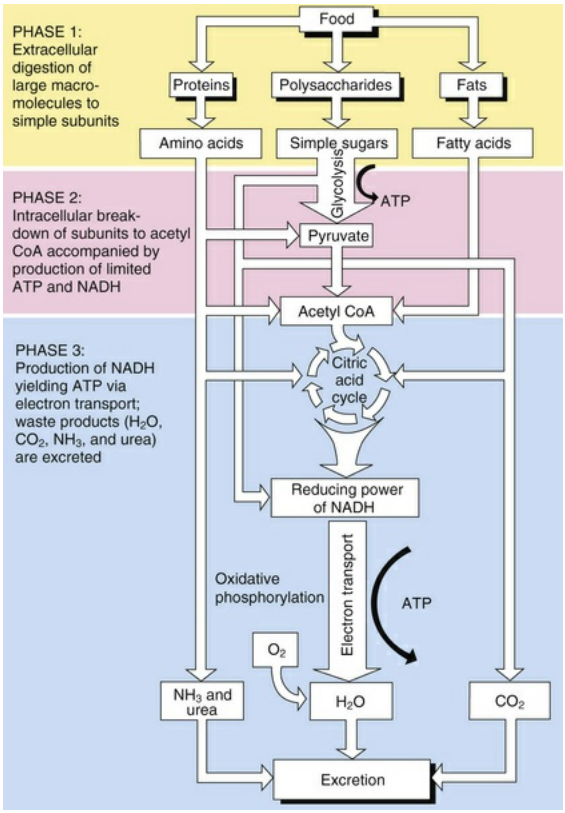


FIGURE 1-17 **Three Phases of Catabolism, Which Lead from Food to Waste Products. These reactions produce adenosine triphosphate (*ATP*), which is used to power other processes in the cell. *CO_2*, carbon dioxide; *CoA*, coenzyme A; *H_2O*, water; *NADH*, reduced nicotinamide adenine dinucleotide; *NH_3*, ammonia; *O_2*, oxygen.**

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 (Figure 1-18).

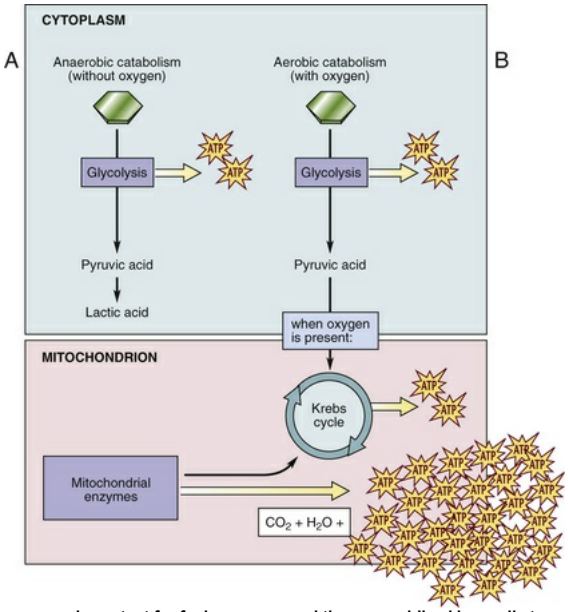


FIGURE 1-18 **Glycolysis. Sugars are important for fuel or energy and they are oxidized in small steps to carbon dioxide (CO_2) and water (H_2O). Glycolysis is the process for oxidizing sugars or glucose. Breakdown of glucose. A, Anaerobic catabolism, to lactic acid and little adenosine triphosphate (*ATP*). B, Aerobic catabolism, to carbon dioxide, water, and lots of ATP.** (From Herlihy, B. [2015]. *The human body in health and illness* [5th ed.]. St. Louis: Saunders.)

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 oxygen. 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 coloured, iron-containing proteins known as *cytochromes* that 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 (see Figure 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 (Figure 1-19).