9th EDITION

McCance & Huether's PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults and Children

JULIA L. ROGERS

SECTION EDITOR

VALENTINA L. BRASHERS

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9th EDITION

McCance & Huether's PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults And Children

Julia L. Rogers, DNP, APRN, CNS, FNP-BC, FAANP
Assistant Professor, College of Nursing
Purdue University Northwest
Hammond, Indiana;
Certified Nurse Practitioner
Northwest Medical Group Pulmonary and Critical Care Medicine
Valparaiso, Indiana

SECTION EDITOR
Valentina L. Brashers, MD, FACP, FNAP
Professor Emerita, School of Nursing
Attending Physician in Internal Medicine
University of Virginia Health System
Charlottesville, Virginia

ELSEVIER

Elsevier
3251 Riverport Lane
St. Louis, Missouri 63043

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Senior Content Development Specialist: Laura Goodrich
Publishing Services Manager: Julie Eddy
Senior Project Manager: Rachel E. McMullen
Design Direction: Maggie Reid

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This book is dedicated to all those who think they can't: guess what—YOU CAN!

To my family, Dwayne, Zachery, and Shane. Your willingness to support this endeavor means more than I can express. I appreciate all the time and space you provided me to work on and complete this project. Your love surrounds me in every aspect of my life and inspires me to be a better human.

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P.S. Thanks for introducing me to dunking Oreos; life has not been the same since, Oh, and I almost forgot: you have lost the game.

J.L.R.

CONTRIBUTORS

Jodi A. Allen, DNP, RN, FNP-C
Assistant Professor and FNP Program Coordinator
College of Nursing
Purdue University Northwest
Hammond, Indiana

Rose Ann U. Baker, PhD, PMHCNS-BC
Assistant Lecturer, School of Nursing
College of Health Professions
University of Akron
Akron, Ohio

Casey Bor, MS, CPNP-AC, BSN, RN
Pediatric Cardiothoracic Surgery Nurse Practitioner
Pediatric Cardiothoracic Surgery and Pediatric Critical Care
University of Maryland Medical Center
Baltimore, Maryland

Valentina L. Brashers, MD, FACP, FNAP
Professor Emerita, School of Nursing
Attending Physician in Internal Medicine
University of Virginia Health System
Charlottesville, Virginia

Dennis J. Cheek, PhD, RN, FAHA
Professor
Harris College of Nursing and Health Sciences
Texas Christian University
Fort Worth, Texas

Devra Davis, PhD, MPH, FACE
Visiting Professor
Ondokuz Mayis Medical University
Samsun, Turkey;
President, Environmental Health Trust
Teton Village, Wyoming

Corinne M. Djuric, MSN, FNP-C
Assistant Clinical Professor
College of Nursing
Purdue University Northwest
Hammond, Indiana

Linda Felver, PhD, RN
Associate Professor
School of Nursing
Oregon Health & Science University
Portland, Oregon

Diane P. Genereux, PhD
Scientist
Vetebrate Genome Biology
Broad Institute of MIT and Harvard
Cambridge, Massachusetts

Victoria Gray, MS
Biologist
Science Department
Michigan City High School
Michigan City, Indiana

Anne Harvey, DNP
Nurse Practitioner
Hematology
Primary Children's Hospital;
APP Director—Pediatric Hem/Onc/BMT
Intermountain Healthcare
Salt Lake City, Utah

Mary Fran Hazinski, RN, MSN, FAAN, FAHA, FERC
Professor
Vanderbilt University School of Nursing
Assistant
Departments of Surgery and Pediatrics
Vanderbilt University School of Medicine;
Clinical Nurse Specialist
Monroe Carell, Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Kathleen E. Hubner, DNP, APRN, ACNS-BC, ANVP, CNRN
Clinical Assistant Professor
Science of Nursing Care
Indiana University School of Nursing
Indianapolis, Indiana

Sue E. Huether, MS, PhD
Professor Emeritus
College of Nursing
University of Utah
Salt Lake City, Utah

Lynn B. Jorde, PhD
Mark and Kathie Miller Presidential Professor and Chair
Department of Human Genetics
University of Utah School of Medicine
Salt Lake City, Utah

Lauri A. Linder, PhD, APRN, CPON
Associate Professor
College of Nursing
University of Utah;
Clinical Nurse Specialist
Center for Cancer and Blood Disorders
Primary Children's Hospital
Salt Lake City, Utah

Kathryn L. McCance, RN, MS, PhD
Professor Emeritus
Nursing
University of Utah
Salt Lake City
Utah

Sean McConnell, PhD
President
Genomics
McConnell Consulting
Valparaiso, Indiana

Mary A. Mondozzi, MSN, BSN, WCC
Burn Center Education/Outreach Coordinator
The Paul and Carol David Foundation Burn Institute
Akron Children's Hospital
Akron, Ohio

Noreen Heer Nicol, PhD, RN, FNP, NEA-BC
Associate Professor
College of Nursing
University of Colorado
Aurora, Colorado

Judith O'Haver, PhD, RN, CPNP-PC, FAANP, FAAN
Pediatric Nurse Practitioner
Pediatric Dermatology
Phoenix Children's Hospital,
Assistant Professor of Pediatrics
Mayo Clinic College of Medicine,
Clinical Assistant Professor
Department of Child Health
University of Arizona College of Medicine
Phoenix, Arizona;
Nurse Scientist
Rady Children's Hospital
San Diego, California

Jan Powers, PhD, RN, CCNS, CCRN, NE-BC, FCCM
Director Nursing Research and Professional Practice
Nursing, Patient Care System
Parkview Health
Fort Wayne, Indiana

Geri Cage Reeves, PhD, APRN, FNP-BC
Associate Professor
School of Nursing
Vanderbilt University
Nashville, Tennessee

George W. Rodway, PhD
Adjunct Professor of Family Medicine—Sports Medicine
School of Medicine
University of Nevada—Reno
Reno, Nevada

Julia L. Rogers, DNP, APRN, CNS, FNP-BC, FAANP
Assistant Professor, College of Nursing
Purdue University Northwest
Hammond, Indiana;
Certified Nurse Practitioner
Northwest Medical Group Pulmonary and Critical Care Medicine
Valparaiso, Indiana

Kaveri Roy, DNP, RN
Assistant Professor
School of Nursing
MGH Institute of Health Professions
Boston, Massachusetts

John Ruge, MD, FAANS
Chairman
Neurosurgery
Advocate Lutheran General;
Chief
Pediatric Neurosurgery
Advocate Children's Hospital
Park Ridge, Illinois

Suzanne M. Ruiz, MBA, MSN, NP-C
Adjunct Faculty, Nursing
Purdue University Northwest
Hammond, Indiana

Melanie L. Scala, MS, CRNP-AC
Senior Nurse Practitioner II
Pediatric Cardiac Surgery Nurse Practitioner
University of Maryland Medical Center
Baltimore, Maryland

Mary C. Selzer, DNP, APRN, ACNP-BC
Assistant Professor Professional Practice
Nursing
Texas Christian University;
Manager
Trauma & Acute Care Surgery Advanced Practice Surgery
John Peter Smith Hospital
Fort Worth, Texas

Benjamin Allan Smallheer, PhD, RN, ACNP-BC, FNP-BC, CCRN, CNE
Associate Professor
School of Nursing
Duke University,
Acute Care Nurse Practitioner
Critical Care Medicine
Duke Regional Hospital
Durham, North Carolina;
Acute Care Nurse Practitioner
Critical Care Medicine
Duke Raleigh Hospital
Raleigh, North Carolina

William E. Somerall, Jr., MD, MAEd
Associate Professor of Nursing
Acute, Chronic, and Continuing Care
University of Alabama at Birmingham
Birmingham, Alabama

Scarlet R. Spain, DNP, RN, CNS, FNP-BC
Assistant Professor
CONHP
Valparaiso University
Valparaiso, Indiana;
Occupational Health Nurse Practitioner
Community Healthcare Systems
Hobart, Indiana;
Occupational Health Consultant
Medix
Chicago, Illinois

Lorey K. Takahashi, PhD
Professor of Psychology
Department of Psychology
University of Hawaii at Manoa
Honolulu, Hawaii

Karen C. Turner, BS
Freelance Editor
TurnKey Content, LLC
Melbourne, Florida

Mary Beth Winton, PhD, RN, ACANP-BC
Associate Professor
School of Nursing
Tarleton State University
Stephenville, Texas

PREFACE

The intent of the ninth edition of *Pathophysiology* is to continue the extraordinary work of Kathy McCance and Sue Huether, which started 30 years ago, by illustrating the principles of pathophysiology with clarity and accuracy.

Pathophysiology incorporates basic, translational, and clinical research to advance the understanding of disease and dysfunction. The study of pathophysiology involves many biomedical sciences and a wide range of research activities. Multiple aspects of cellular physiology are progressing rapidly, generating vast amounts of data to understand. This was made ever more present during the writing of this edition, when the world began to see the effects of cellular changes and adaptations from the coronavirus (COVID-19; severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) pandemic. The information gained provided a greater understanding of the behavior of individual cells, their neighboring microenvironment, and the molecules that not only make up those cells but also communicate with their surroundings. Importantly, the forward movement of biomedical sciences occurs within the context of social, economic, and political processes that determine how disease is defined, experienced, and treated.

Interdisciplinary research has led to significant advancements in genetics, epigenetics, cell signaling and communication, control of cell behavior, metabolism, and cell fate. Knowledge about normal cell structures, function, and signaling pathways is at the forefront of translational science and foundational to the understanding of pathophysiology. Advancements in technology that allow close observation of cells are providing new understanding of cellular processes, including how cells function and prioritize their activities, monitor their environment, move, differentiate, and regenerate. Advances in the molecular mechanisms of disease, particularly cell signaling, genetic directives, and immune and metabolic modulators, are providing an understanding of individual differences in disease risk, biologic markers, diagnostic strategies, and individualized treatment.

Although these advancements have created an ever-increasing state of excitement, they have also created the problem of how students, professors, and clinicians can cope with the expanding new information. Translating and compressing these data into simplified discussions for students and clinicians is challenging. The approach for this edition of the book was to streamline the content and present the information in an organized, logical sequence of content based on current literature and research reports with understandable explanations and accompanied by illustrations and summary tables. The primary focus is on pathophysiology, and there is less emphasis on the evaluation and treatment that is found in clinical management textbooks.

This edition has been extensively revised with the following specific goals:

- Organize the content in a logical and uniformed format to facilitate learning and teaching.
- Place emphasis on the readability of the material for improved comprehension.
- Focus on updating outdated terminology and use inclusive language.
- Present emerging new data on disease including controversial topics.
- Provide the most current and relevant information on the etiology, epidemiology, pathophysiology, clinical manifestations, and treatment for disease processes.
- Integrate health promotion and disease prevention by updating risk factors, explaining relationships between nutrition and disease, and referencing screening recommendations.

ORGANIZATION AND CONTENT: WHAT'S NEW IN THE NINTH EDITION

The book is organized into two parts. Part One presents the cellular and tissue responses common to disease. Normal organ system structure and function and the pathophysiology of disease, organized by body systems, are presented in Part Two. All content has been reviewed and updated with extensive new references and revised figures. The previous Chapter 18 in the eighth edition titled *Disorders of the Central and Peripheral Nervous Systems and the Neuromuscular Junction* has been renamed in the ninth edition as *Alterations of the Brain, Spinal Cord, and Peripheral Nerves*. Alterations of the hematologic system, which were previously discussed over two chapters, have been combined into one chapter.

PART ONE: CENTRAL CONCEPTS OF PATHOPHYSIOLOGY: CELLS AND TISSUES

Part One begins with an in-depth study of the cell and progresses to cover the underlying processes of disease. Concepts covered include cell signaling and cell communication processes; genes and common genetic diseases; epigenetics and disease; fluid, electrolyte, and acid-base balance; inflammation, cytokines and their biologic functions, and normal and altered immunity; infection, stress, coping, and immunity; and tumor biology, epidemiology of cancer, and cancer in children. Revisions and updated additions to Part One include the following:

- Updated content on cellular organelles, the plasma membrane, cell signaling, and communication (Chapter 1)
- Reorganized with extensive updates throughout the chapter with close attention to air pollution and climate change (Chapter 2)
- Updated content on fluids, electrolytes and acids and bases (Chapter 3)
- Updated content on genes and diseases related to genetics, the environment and lifestyle patterns (Chapter 4 and 5)
- Updated content on epigenetics and disease (Chapter 6)

- Updated to content on normal innate and adaptive immunity (Chapters 7 and 8)
- Extensively updated to content on alterations of immunity and inflammation including up-to-date information on coronavirus (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chapter 9)
- Extensively revised with up-to-date information on COVID-19 and SARS-CoV-2 (Chapter 10)
- Updated content on stress and disease (Chapter 11)
- Updated content on tumor biology and invasion and metastases (Chapter 12)
- Updated content on the epidemiology of cancer (Chapter 13)

PART TWO: PATHOPHYSIOLOGIC ALTERATIONS: ORGANS AND SYSTEMS

Part Two is a systematic survey of diseases within body systems. Each unit focuses on a specific body system and begins with an anatomy and physiology chapter to provide a basis of comparison for understanding the alterations created by disease. A brief summary of geriatric considerations is included at the end of the section on anatomy and physiology. The discussion of each disease in the alterations chapters is developed in a logical manner that begins with an introductory paragraph on etiology and epidemiology, followed by pathophysiology, clinical manifestations, and evaluation and treatment. Separate chapters are dedicated to pediatric pathophysiology, with a particularly sensitive approach to sex at birth and age. Significant revisions and updated additions to Part Two include the following:

- Updated content on pediatric cancers (Chapter 14)
- Updated content on the anatomy and physiology of the neurologic system (Chapter 15)
- Updated content on pain syndromes and sleep disorders (Chapter 16)
- Rewritten and extensively revised content on Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, and myasthenia gravis with updates to content on consciousness, memory, dementia, and delirium syndromes (Chapter 17)
- Chapter renamed as Alterations of the Brain, Spinal Cord, and Peripheral Nerves. Rewritten and extensively revised content on the manifestations for specific central and peripheral nervous system disorders including brain and spinal cord injury, stroke, seizure, and headache syndromes (Chapter 18)
- Updated content and terminology on schizophrenia, mood disorders, and anxiety (Chapter 19)
- Updated content on cerebral palsy, seizure disorders, and pediatric brain tumors (Chapter 20)
- Updated content on the mechanisms of hormonal regulation (Chapter 21)
- Extensive updates on diabetes mellitus, insulin resistance, and thyroid and adrenal gland disorders (Chapter 22)
- Updated content on obesity and disorders of nutrition (Chapter 23)
- Updated content on anatomy and physiology of the reproductive system (Chapter 24)
- Updated content on female reproductive disorders including cancers, benign breast diseases, and breast cancer (Chapter 25)
- Updated content on male reproductive disorders and cancer with extensive updating and reorganization (Chapter 26)
- Extensive updating of sexually transmitted infections (Chapter 27)
- Updated content on the anatomy and physiology of the hematologic system (Chapter 28)
- Extensively rewritten chapter on the alterations of hematologic function, combining two previous chapters into one with updated content on anemia (Chapter 29)
- Updated content on alterations of hematologic function in children (Chapter 30)
- Updated chapter on the anatomy and physiology of the cardiovascular and lymphatic systems (Chapter 31)
- Updated content on atherosclerosis, endothelial injury and dysfunction, coronary artery disease, myocardial infarction, and heart failure (Chapter 32)
- Updated content on the alterations of cardiovascular function in children (Chapter 33)
- Updated content on the anatomy and physiology of the pulmonary system (Chapter 34)
- New content on COVID-19 and SARS-CoV-2, and updated content on pulmonary embolism asthma, chronic lung disease, respiratory tract infection, pulmonary hypertension, and lung cancers (Chapters 35)
- New content on COVID-19 and SARS-CoV-2 with updated content on childhood asthma, respiratory distress syndrome, cystic fibrosis, lung infections, and sudden infant death syndrome (Chapter 36)
- Updated content on the anatomy and physiology of the renal and urologic system (Chapter 37)
- Updated content on kidney stones, urinary tract infection, glomerulopathies, acute and chronic renal failure, and bladder and kidney tumors (Chapter 38)
- Updated content on urinary tract infection and renal failure in children (Chapter 39)
- Updated content on the anatomy and physiology of the digestive system (Chapter 40)
- Updated content on gastroesophageal reflux disease, peptic ulcer disease, irritable bowel syndrome, inflammatory bowel disease, colon cancer, and hepatitis (Chapter 41)
- Updated content on gluten-sensitive enteropathy, necrotizing enterocolitis, infections of the intestine, and liver disease in children (Chapter 42)
- Updated content on the anatomy and physiology of the musculoskeletal system (Chapter 43)
- Updated content on alterations of the musculoskeletal system (Chapter 44)
- Updated content on alterations of the musculoskeletal system in children (Chapter 45)
- Updated content on integumentary system disorders including pressure ulcers, dermatitis, psoriasis, scleroderma, and melanoma (Chapter 46)

- Updated content on childhood atopic dermatitis, skin infections, and immune drug reactions (Chapter 47)
- Extensively updated content on septic shock, multiple organ dysfunction syndrome, included recent guideline updates, and burns for adults (Chapters 48)
- Extensively updated content on septic shock, multiple organ dysfunction syndrome, included recent guideline updates, and burns for children (Chapters 49)

FEATURES TO PROMOTE LEARNING

Ease of learning has been enhanced by designing a number of features that guide and support understanding, including:

- *Chapter Outlines* for each chapter
- *Consistent Headings* to underscore the consistent treatment of each disease—Pathophysiology, Clinical Manifestations, and Evaluation and Treatment
- More than 70 *Emerging Science* boxes that review the most current research and clinical developments of disease.
- End-of-chapter *Summary Review* sections that summarize the content in each chapter and serve as built-in content review guides
- Boldface *Key Terms* found within all the chapters
- A comprehensive *Glossary* with approximately 1000 terms to help students with the often-difficult terminology related to pathophysiology

ART PROGRAM

The art program is extensive and has received as much attention and revision as the narrative. Nearly 100 new or revised full-color illustrations were created and strategically placed throughout the textbook. Also included are many new high-quality, full-color photographs of clinical manifestations, pathologic specimens, and clinical imaging techniques. The combination of illustrations, algorithms, and photographs and the use of color for tables and boxes allow clarification for complex concepts and the emergence of easily recognized essential information.

ANCILLARIES

For Students

On **Evolve**, at http://evolve.elsevier.com/Rogers/pathophysiology/, students can access Evolve-only figures, tables, and boxes, 570 review questions, 100 animations to help them master the text content, 26 case studies with questions and answers, and downloadable chapter summaries documents for each chapter.

The **Study Guide** includes a variety of question styles, aiming to help the diverse way students learn. Question types include the following:

- Respond to Clinical Scenarios
- Categorize Clinical Examples
- Match the Definitions
- Order the Steps
- Choose the Correct Words
- Complete These Sentences
- Explain the Pictures
- Teach People About Pathophysiology
- Plus many more…

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

For Instructors

The **Evolve Instructor Resources** for this textbook provide the following teaching aids:

- Image Collection with all of the approximately 1200 figures from the text
- PowerPoint lecture slides for each chapter (approximately 3300 slides total), including integrated Audience Response Questions in each chapter (218 total), and integrated case studies at the end of each unit (15 total)
- Teach for Nurses Instructor's Manual, broken down by chapter, detailing the resources available to instructors for their lesson planning, and including unique case studies and class activities they can share with students
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Evolve is an Internet-based learning environment that works in coordination with the text. This resource enables you to publish your class syllabus, outline, and lecture notes; set up "virtual office hours" and e-mail communication; share important dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards. Free with qualified adoption. Contact your sales representative or visit http://evolve.elsevier.com for more information about integrating **Evolve** into your curriculum.

ACKNOWLEDGMENTS

It is with gratitude that I dedicate this book to the creative pioneers who started it all, Kathy McCance and Sue Huether. Over the last 30 years, you have worked tirelessly to update the textbook to remain relevant using the most current research advancements, and I applaud your dedication. Thanks for having the confidence to pass the torch to me.

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Seek joy. Live your life as your message. Be the change in the world that you wish to see. Most of all……be kind.

Julia L. Rogers

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Cellular Biology

Victoria Gray and Kathryn L. McCance

http://evolve.elsevier.com/Rogers/pathophysiology/

CHAPTER OUTLINE

All body functions are dependent on the integrity of cells. These trillions of complex cells are the basic building blocks of the human body. Therefore an understanding of cellular biology is fundamental to understanding health, wellness, and disease processes. Cells behave as a multicellular "social" organism in that they message between, among, and within one another through cellular communication (cellular "crosstalk"). Cells have the ability to originate, transmit, receive, interpret, and use information to maintain 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 (e.g., 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 animals and plants are eukaryotes, as are the single-celled organisms, fungi, protozoa, and most algae. Prokaryotes include bacteria and archaea. Prokaryotes traditionally were studied as core subjects of molecular biology, which generated an abundance of data related to prokaryotic genomes (a set of genes carried on molecules of deoxyribonucleic acid [DNA]). Currently, emphasis is on the eukaryotic cell, which contains genomes that are more complex.[1]

Eukaryotes (*eu* = true; *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.

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 DNA and are involved in the supercoiling of DNA. Eukaryotic cells have several chromosomes, the number of which is dependent on species. 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 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:

- *Movement*. Muscle cells can generate forces that produce motion. Muscles that attach to bones produce limb movements, whereas muscles that enclose hollow tubes or cavities move or empty contents when they contract (e.g., the colon).
- *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. (e.g., the brain or heart).
- *Metabolic absorption*. All cells can take in and use nutrients and other substances from their surroundings. (e.g., cells of the intestines or kidneys).
- *Secretion*. Certain cells, such as mucous gland cells, can synthesize new substances from substances they absorb and then secrete the new substances to serve elsewhere as needed.
- *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 (e.g., urine).
- *Respiration*. Cells absorb oxygen, which is used to transform nutrients into energy in the form of adenosine triphosphate (ATP). Carbohydrates, fats, and proteins can be used as fuels. Cellular respiration, or oxidation, occurs in organelles called *mitochondria* (e.g., glucose).
- *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 2) (e.g., mitosis and meiosis).
- *Communication*. Communication is vital for cells to survive as a society of cells. Appropriate communication allows the maintenance of a dynamic steady state. Table 1.1

STRUCTURE AND FUNCTION OF CELLULAR COMPONENTS

Fig. 1.1A shows a "typical" eukaryotic cell, which consists of three components: an outer membrane called the plasma membrane; a fluid "filling" called cytoplasm (see Fig. 1.1B); and 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. 1.2A). The nuclear envelope is pockmarked with pits, called nuclear pores, which allow chemical messages to exit and enter the nucleus (see Fig. 1.2A, B, and D). 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 of DNA, RNA, and ribosomal proteins), 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. 1.2C). The wrapping of DNA into tight packages of chromosomes is essential for cell division in eukaryotes. The primary functions of the nucleus are cell division and control of genetic information. These functions include the replication and repair of DNA and the transcription of the information stored in DNA into RNA.

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 approximately 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. 1.1B). Newly synthesized proteins remain in the cytosol if they lack a signal for transport to a cell organelle.[2]

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. Functions of organelles can be divided into four major categories: (1) genetic control; (2) manufacturing, distributing, and breaking down molecules; (3) energy processing; and (4) structural support, movement, and communication between cells. The cytosol is a storage unit for fat, carbohydrates, and secretory vesicles. Table 1.1 lists the principal cytoplasmic organelles.

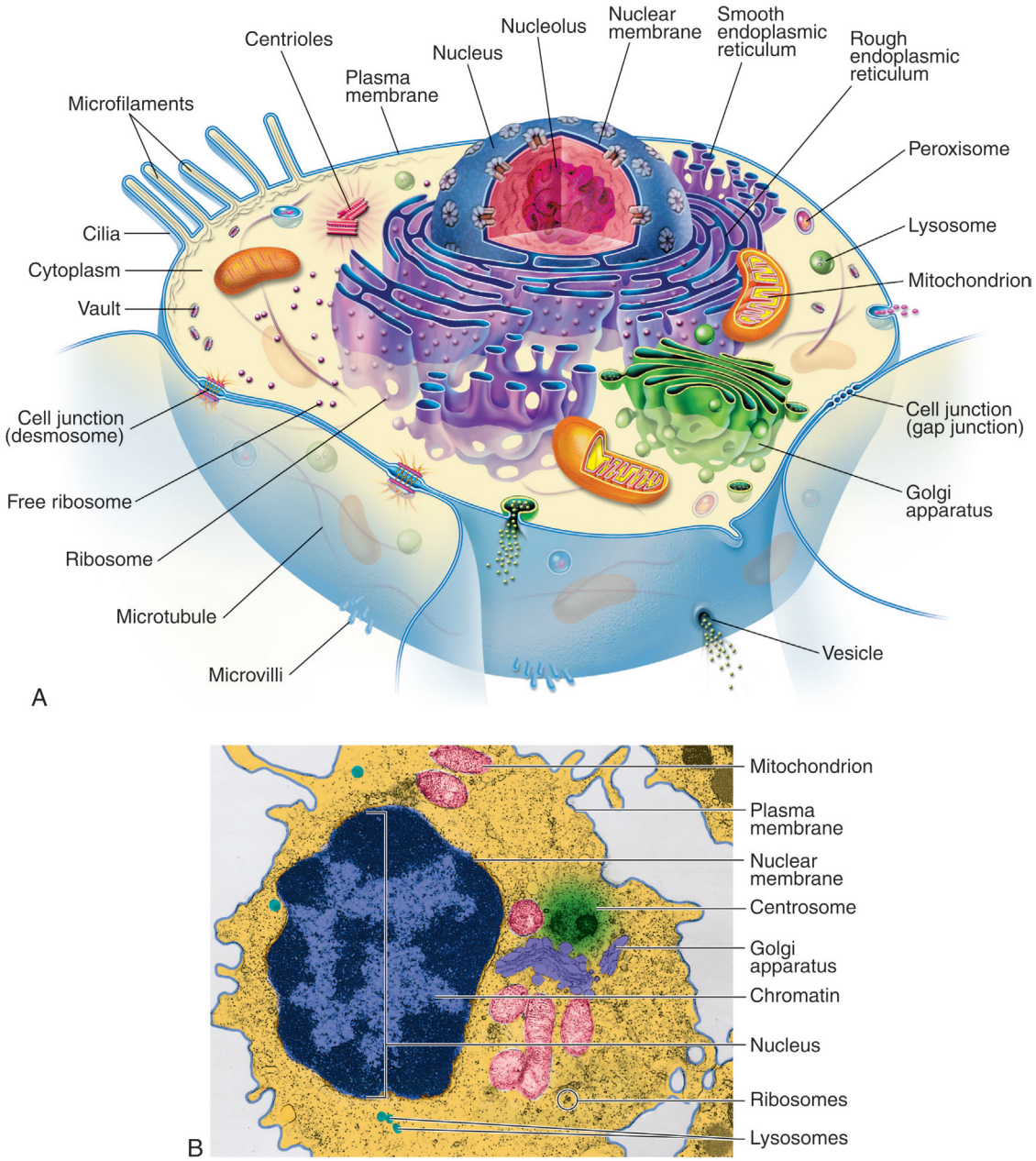


Fig. 1.1 Typical Components of a Eukaryotic Cell and Structure of the Cytoplasm. (**A**) Artist's interpretation of cell structure. (B). Color-enhanced electron micrograph of a cell. Both show the many mitochondria known as the "power plants" of the cell. Note, too, the innumerable dots bordering the endoplasmic reticulum. These are ribosomes, the cell's "protein factories." (**B**, From Patton KT, Thibodeau GA. *Anatomy & physiology,* 9th edition. St. Louis: Mosby; 2016.

Plasma Membranes

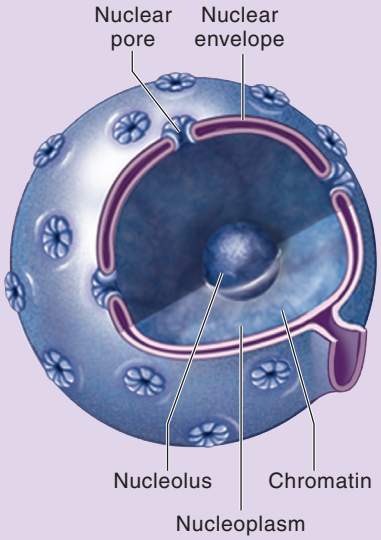
Membranes define the cell's boundaries. Membranes surround the cell or enclose an intracellular organelle and are exceedingly important to normal physiologic function because they control the composition of the space, or compartment, they enclose. Membranes can allow or exclude various molecules, and 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. The plasma membrane also has an important role in cell-to-cell recognition, cellular mobility, and the maintenance of cellular shape (Table 1.2).

Membrane Composition

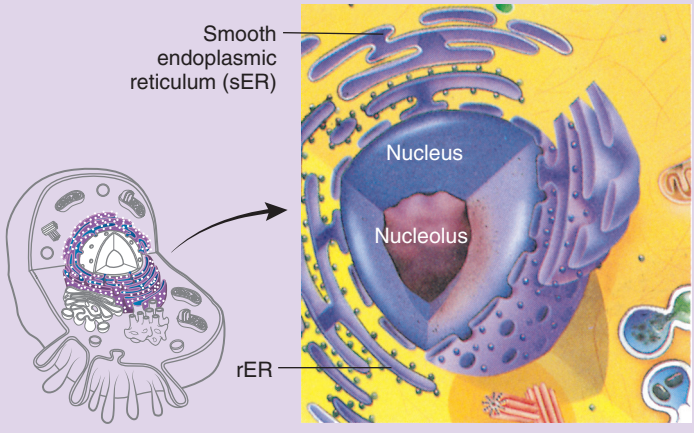
The main components of cell membranes are lipids and proteins. The cell membrane is a lipid bilayer, composed of two opposing leaflets and proteins that span the bilayer or interact with the lipids on either side of the two leaflets (Fig. 1.4). Historically, the plasma membrane was described as a fluid lipid bilayer *(fluid mosaic model)* composed of a uniform lipid distribution with

TABLE 1.1 Principal Cytoplasmic Organelles

Genetic Control

Organelle	Characteristics and Description
Nucleus  (From Patton KT: *Anatomy & Physiology, 10 ed.,* Mosby, 2019, Elsevier.)	*(See text for further description of function and structure)*
Nucleolus	*(See text for further description of function and structure)*

Manufacturing, Distributing and Breaking Down Molecules

Organelle	Characteristics and Description
Ribosomes	Ribonucleic acid (RNA)-protein complexes (nucleoproteins) synthesized in nucleolus and secreted into cytoplasm. Provide sites for cellular protein synthesis. Uses the information from deoxyribonucleic acid (DNA), written in messenger RNA (mRNA), to build proteins.
Endoplasmic reticulum (rough and smooth)  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)	Network of tubular channels (cisternae) that extend throughout the outer nuclear membrane. **Rough Endoplasmic Reticulum (RER)**—bumpy exterior due to ribosomes and ribonucleoprotein particles attached to it; is responsible for much of a cell's protein synthesis and folding. **Smooth Endoplasmic Reticulum (SER)**—does not contain ribosomes or ribonucleoprotein particles. Rather, membranous surfaces of the SER contain enzymes involved in the synthesis of steroid hormones and are responsible for a variety of reactions required to remove toxic substances from the cell. The SER communicates with the Golgi complex and interacts with other organelles, particularly lysosomes and peroxisomes.

Continued

TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Manufacturing, Distributing and Breaking Down Molecules

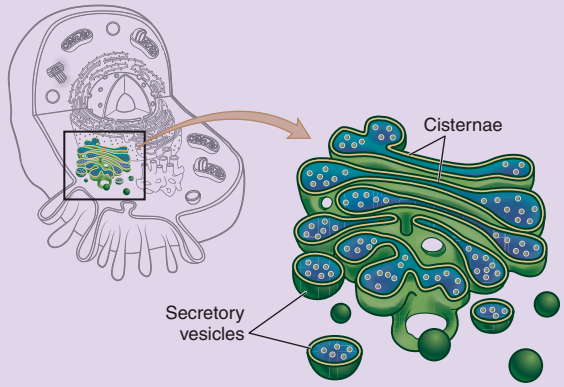
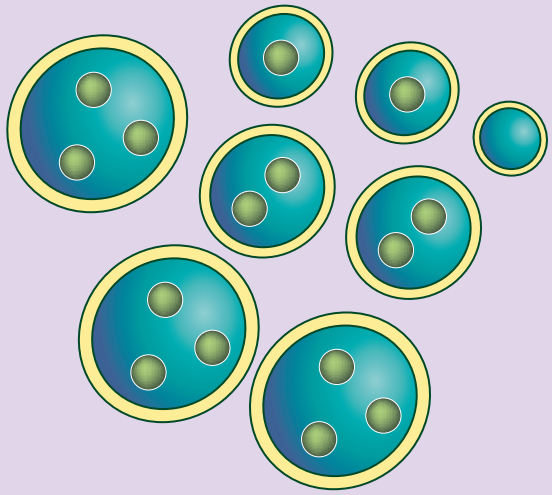
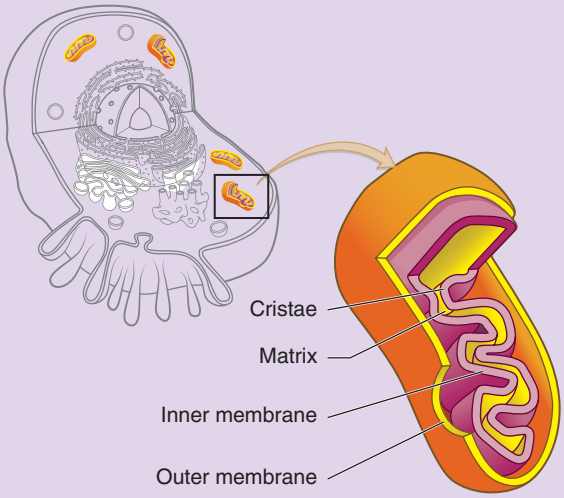
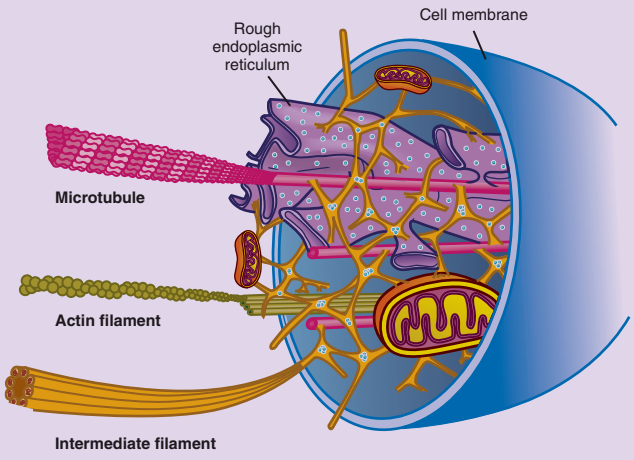
Organelle	Characteristics and Description
Golgi complex  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)	Network of flattened, smooth membranes and vesicles located neared the nucleus and the RER. Proteins from the endoplasmic reticulum are processed and packaged into small membrane-bound sacs or vesicles called **secretory vesicles**, which collect at the end of the membranous folds of the Golgi bodies—called **cisternae** (like a stack of pita breads). The secretory vesicles then break off from the Golgi complex and migrate to a variety of intracellular and extracellular destinations, including the plasma membrane. The vesicles fuse with the plasma membrane, and their contents are released from the cell. The best-known vesicles are those that have coats made largely of the protein **clathrin** and are called *clathrin-coated vesicles*. The Golgi complex is a refining plant and directs cellular traffic (e.g., protein, polynucleotide, polysaccharide molecules) in the cell.
Lysosomes  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children,* St. Louis, 2019, Elsevier.)	Sac-like, membrane-bound structures containing enzymes for digesting most cellular substances to their basic forms, such as amino acids, fatty acids, and carbohydrates (sugars). The lysosomal membrane acts as a protective shield between the powerful digestive enzymes within the lysosome and the cytoplasm, preventing their leakage into the cytoplasmic matrix. Lysosomes maintain cellular health because of efficient removal of toxic cellular components, removal of useless organelles, termination of signal transduction, and maintenance of metabolic homeostasis. Aging can lead to progressive loss of lysosomal efficiency and decline of the regenerative capacity of organs and tissues. Cellular injury leads to release of lysosomal enzymes that cause cellular self-digestion.
Peroxisomes	Similar to lysosomes in appearance but contain several oxidative enzymes (e.g., catalase, urate oxidase) that can detoxify compounds and fatty acids. Peroxisomes are so named because they usually contain enzymes that use oxygen to remove hydrogen atoms from specific substrates in an oxidative reaction that produces hydrogen peroxide (H_2O_2). Hydrogen peroxide is a powerful oxidant, potentially destructive if it accumulates or escapes from peroxisomes. Peroxisomes also have an important role in the synthesis of specialized phospholipids necessary for nerve cell myelination. Such reactions are important in detoxifying various wastes within the cell or foreign components that enter the cell, such as ethanol. Impairment of peroxisomes can lead to disease (see Fig. 1.1A).

TABLE 1.1 Principal Cytoplasmic Organelles—cont'd

Energy Processing

Organelle	Characteristics and Description
Mitochondria  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)	Organelles, found in large numbers in most cells, are responsible for cellular respiration and energy production. These cytoplasmic organelles appear as spheres, rods, or filamentous bodies that are bound by a double membrane. The **outer membrane** is smooth and surrounds the mitochondrion itself; the inner membrane is convoluted in the mitochondrial matrix to form partitions called **cristae**. The **inner membrane** contains the enzymes of the **respiratory chain**—the name given to the electron transport chain. These enzymes are essential to the process of oxidative phosphorylation that generates most of the cell's adenosine triphosphate. Metabolic pathways involved in the metabolism of carbohydrates, lipids, and amino acids and special pathways involving urea and heme synthesis are located in the mitochondrial matrix. Mitochondria contain their own DNA that codes for enzymes needed for oxidative phosphorylation.

Structural Support, Movement, and Communication Between Cells

Structures	Characteristics and Description
Cytoskeleton  (From McCance KL, Huether S: *Pathophysiology: the biologic basis for disease in adults and children*, St. Louis, 2019, Elsevier.)	All eukaryotic cells contain elaborate and specialized internal structures in the cytosol that provide the "bones and muscles" of the cell—the **cytoskeleton**. The cytoskeleton maintains the cell's shape and internal organization, and it permits movement of substances within the cell and movement of external projections (cilia or microvilli; flagella in sperm) outside the plasma membrane. The internal skeleton is composed of a network of protein filaments; the three main types of filaments include actin filaments, microtubules, and intermediate filaments. These filaments collectively promote cell strength, shape, and movement. Intermediate filaments bridge the cytoplasm from one cell junction to another, strengthening and supporting the sheet of epithelium.

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 (Fig. 1.5).

The outer surface of the plasma membrane in many types of cells, especially endothelial cells and adipocytes, is not smooth

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: Lea & Febiger; 1983.

but dimpled with flask-shaped invaginations known as *caveolae* ("tiny caves"). Caveolae, considered 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 polar, or amphipathic, which means that one part is hydrophobic (uncharged, or "repelled by water") and another part is hydrophilic (charged, or "attracted to water") (see Fig. 1.4B). 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.

Cell membranes may contain many different lipid classes, but in animals, the main ones are phospholipids, cholesterol, and glycolipids. Phospholipids, the most abundant lipids, 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. Phospholipids are key for repairing the membrane—they tend to spontaneously rearrange themselves to avoid a tear by folding on themselves and forming a sealed compartment.[2]

Proteins. Proteins perform most of the plasma membrane's tasks and are the major workhorses of the cell. 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 4) 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. PTMs have become very important in understanding disease processes. An emerging field of study in science is proteomics, the study of the proteome. This molecular approach is used to study an entire set of proteins expressed by a genome from synthesis, translocation, and modification (e.g., folding). Biologists are analyzing and uncovering information related to the roles of proteomes in a staggering number of diseases.

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

1. Transmembrane proteins that extend across the bilayer and are exposed to an aqueous environment on both sides of the membrane (see Fig. 1.6A)
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. 1.6B)
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. 1.6C)
4. Proteins bound indirectly to one or the other bilayer membrane face and held in place by their interactions with other proteins (see Fig. 1.6D).[3]

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

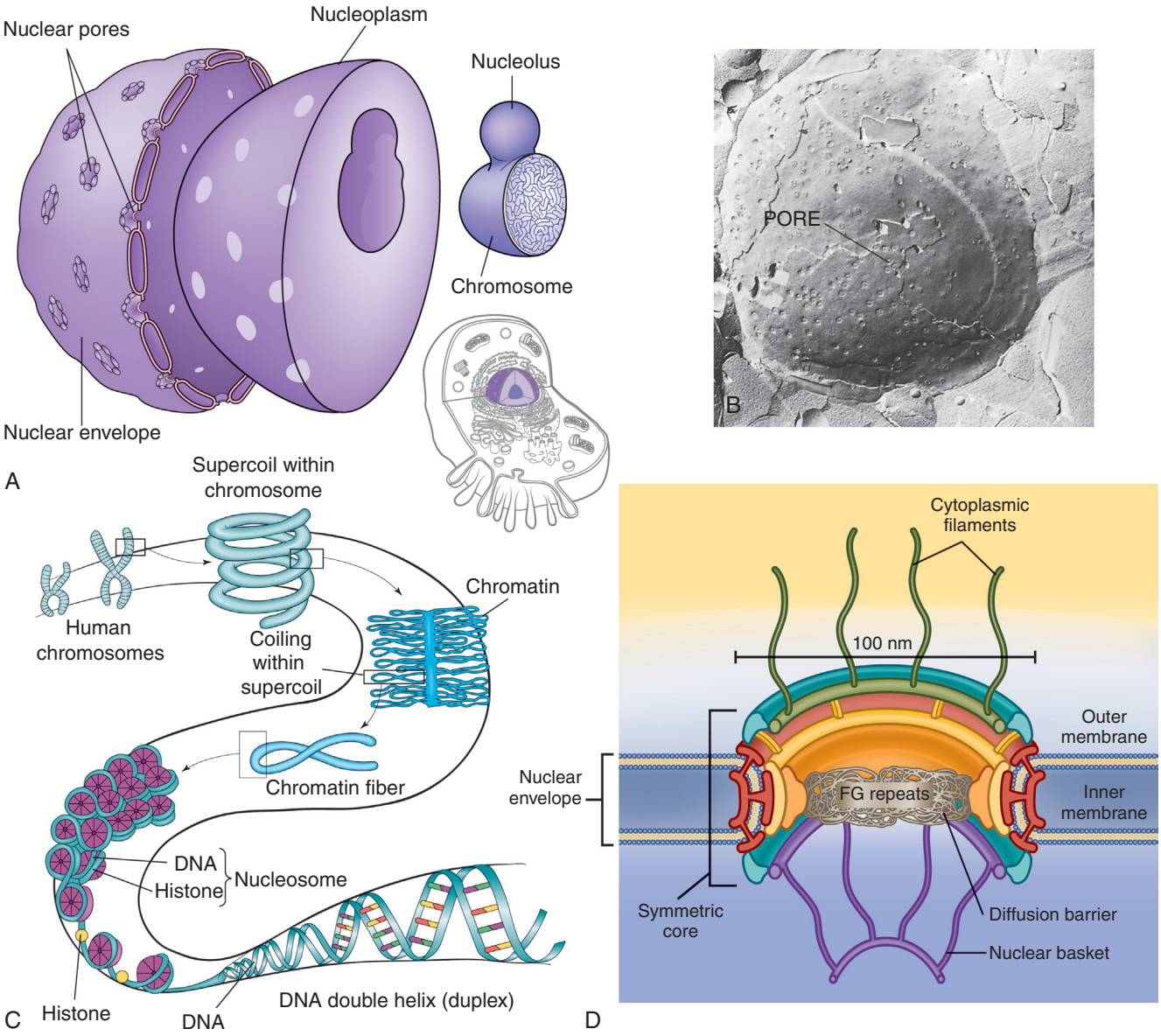


Fig. 1.2 The Nucleus. The nucleus is composed of a double membrane, called a nuclear envelope, which encloses the fluid-filled interior, called *nucleoplasm*. The chromosomes are suspended in the nucleoplasm (illustrated here much larger than actual size to show the tightly packed deoxyribonucleic acid [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. 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. **(D)** Nuclear pore complex. (A, C, From McCance KL, Huether S *Pathophysiology: The biologic basis for disease in adults and children*. St. Louis: Elsevier; 2019 B, From Raven PH, Johnson GB. *Biology*. St. Louis: Mosby; 1992. D, Adapted from The-scientist infographic: the nuclear pore complex. Available at https://www.The-scientist.com/infographics/infographic-the-nuclear-pore-complex-32456)

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.

Although membrane structure is determined by the lipid bilayer, membrane functions are determined largely by proteins (see Fig. 1.3). Proteins act as:

1. Recognition and binding units (receptors) for substances moving into and out of the cell

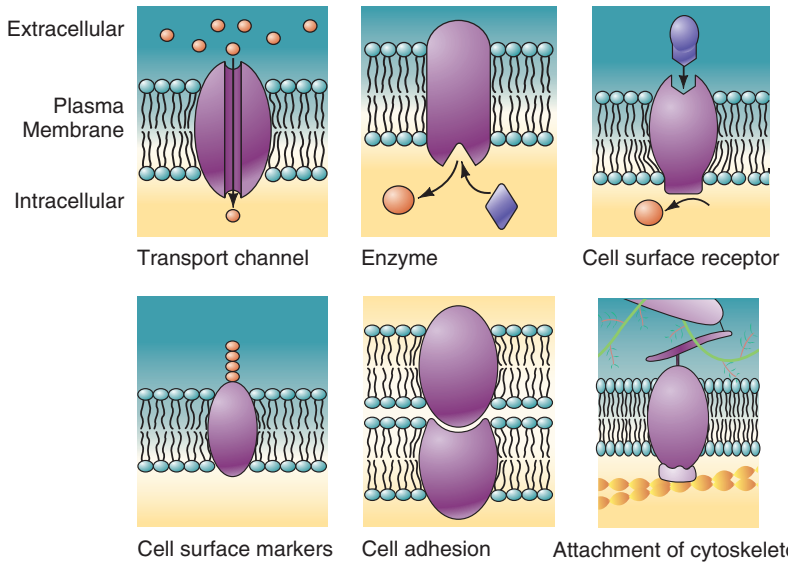


Fig. 1.3 Functions of Plasma Membrane Proteins. The plasma membrane proteins illustrated here show a variety of functions performed by the different types of plasma membranes. (From Raven PH, Johnson GB. *Understanding biology,* 3rd edition. Dubuque, IA: Brown; 1995.

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)

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.[4]

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.[3]

The cellular protein pool is in constant change or flux. Proteostasis is the process that regulates protein synthesis, folding, and degradation within and around a cell. 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. Proteostasis is vital to health, and failure to maintain protein homeostasis is associated with aging and numerous degenerative diseases (Fig. 1.7).

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 to protect the cell from mechanical damage.[5] In addition, 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.[3] 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.[3]

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. For example, hormones are ligands. Numerous receptors are found in

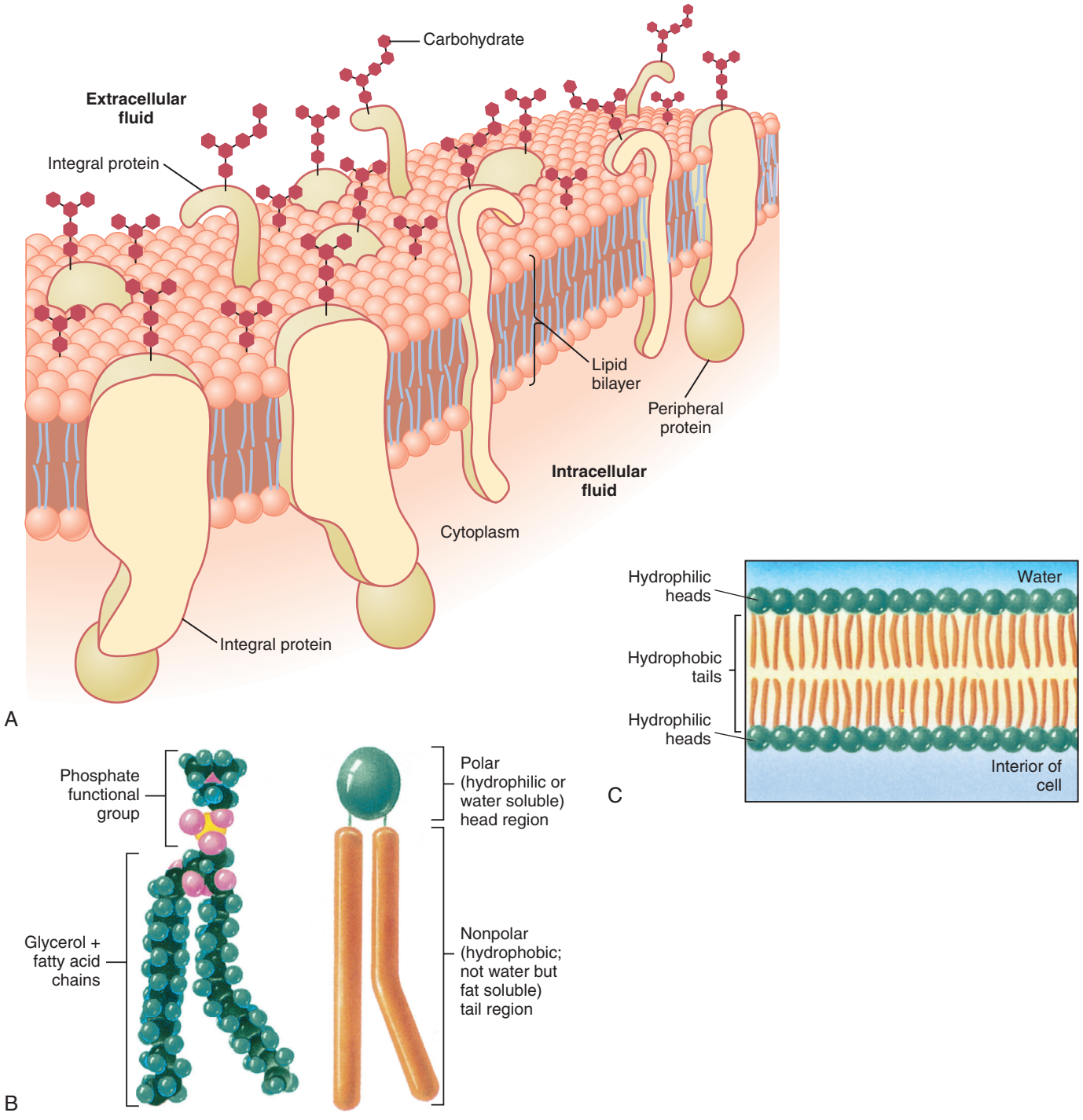


Fig. 1.4 Lipid Bilayer Membranes. **(A)** The structure of a cell membrane showing the lipid bilayer, embedded proteins, and attached extracellular carbohydrates. **(B)** Each phospholipid molecule consists of a phosphate functional group and two fatty acid chains attached to a glycerol molecule. **(C)** 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. (A, From Guyton AC, Hall JE. *Textbook of medical physiology,* 11th edition. Amsterdam: Elsevier Saunders; 2006. B and C, From Raven PH, Johnson GB. *Understanding biology,* 3rd edition. Dubuque, IA: Brown; 1995.

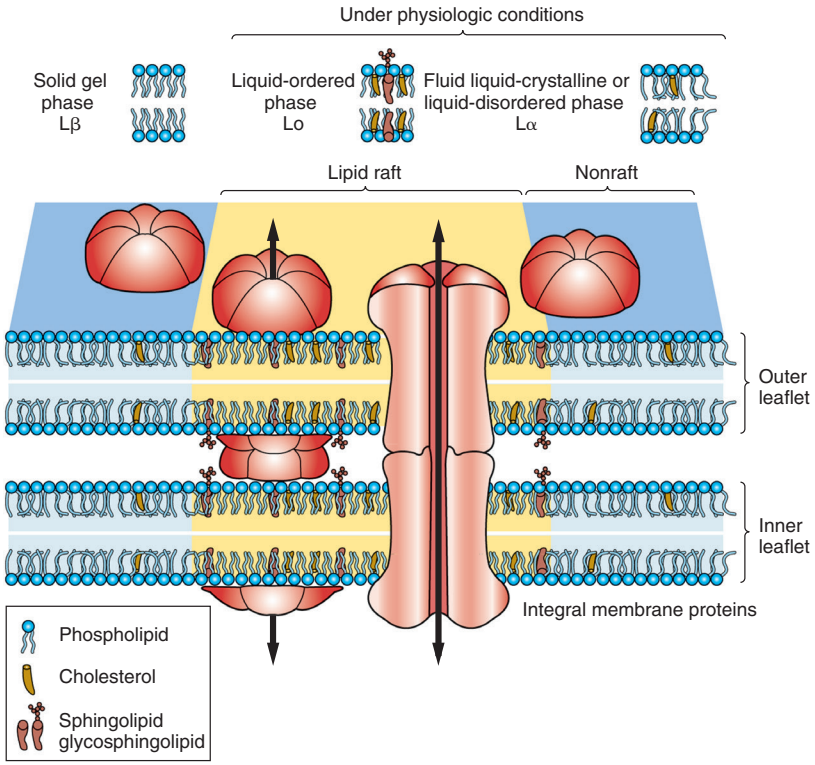


Fig. 1.5 Lipid Bilayer Membranes. Concepts of biologic membranes have markedly changed in the last two decades, from the classic fluid mosaic model to the current model that lipids and proteins are not evenly distributed but can isolate into microdomains, differing in their protein and lipid composition. 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.

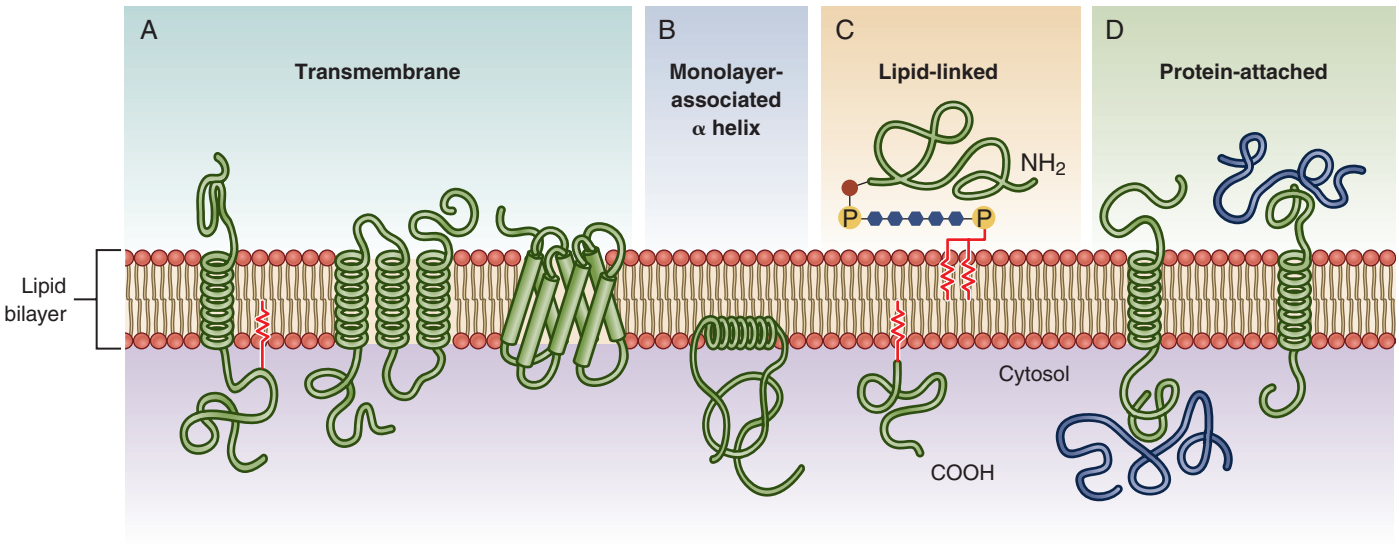


Fig. 1.6 Proteins Attach to the Plasma Membrane in Different Ways. (A) Transmembrane proteins extend through the membrane as a single α helix, as multiple α helices, or as a rolled-up barrel-like sheet called a β barrel. **(B)** Some membrane proteins are anchored to the cytosolic side of the lipid bilayer 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, Bray D, Hopkin K, et al. *Essential cell biology,* 4th edition. New York: Garland; 2014.

most cells. 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. 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.[3]

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. 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 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 15 and 16). 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 7).

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

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).

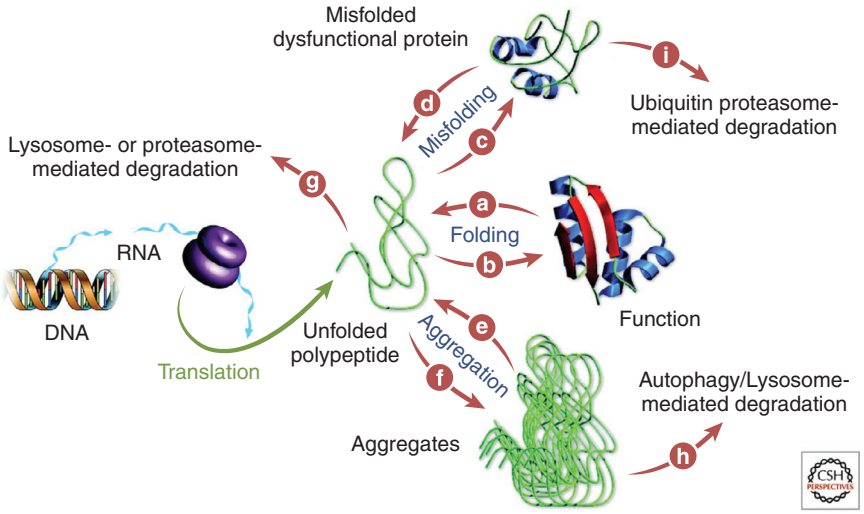


Fig. 1.7 Protein Homeostasis System and Outcomes. A main role of the protein homeostasis network *(proteostasis)* is to minimize protein misfolding and protein aggregation. The network includes ribosome-mediated protein synthesis, chaperone (folding helpers in the ER) and enzyme mediated folding, breakdown 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 Balch WE, Morimoto RI, Dillin A, et al. Adapting proteostasis for disease intervention. *Science* 2008;319:916 -919.)

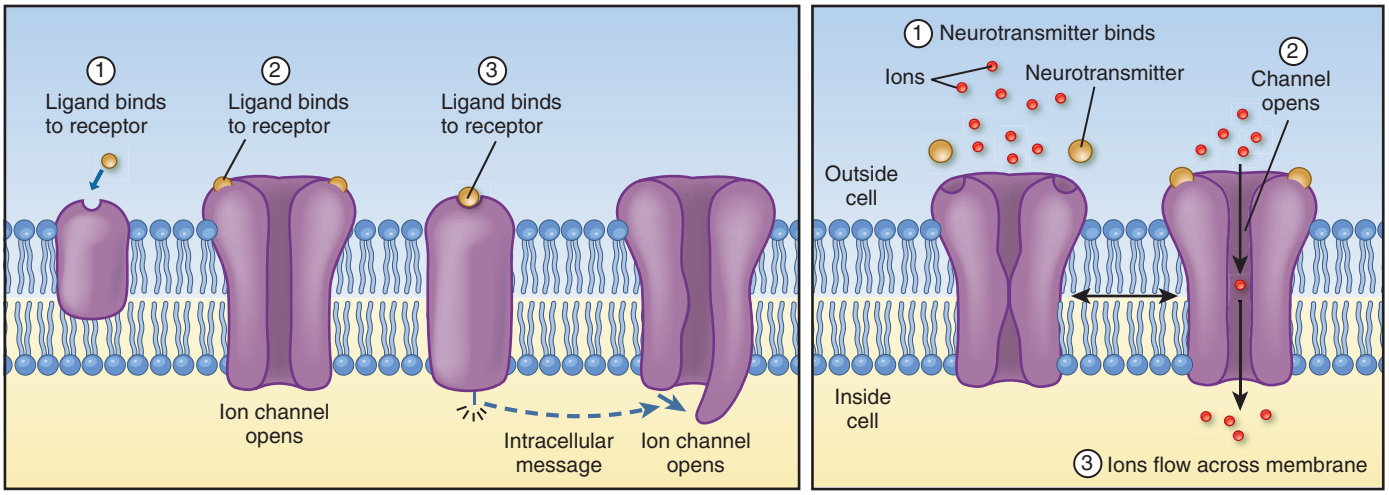
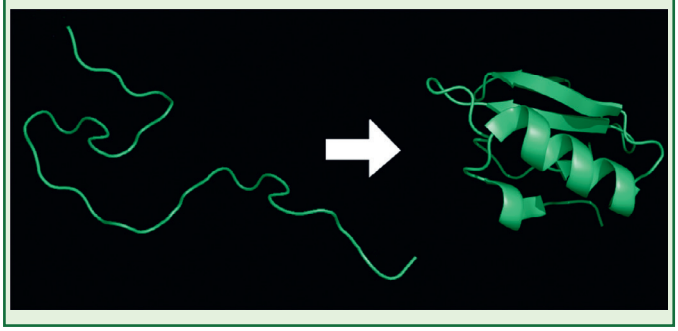


Fig. 1.8 Cellular Receptors. (A) ***1,*** Plasma membrane receptor for a ligand (here, a hormone molecule) on the surface of an integral protein. A neurotransmitter can exert its effect on a postsynaptic cell by means of two fundamentally different types of receptor proteins. ***2,*** Channel-linked 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.

BOX 1.1 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^{2+})-dependent glycoproteins throughout tissue (e.g., epithelial [E-cadherin]). Selectins are proteins that bind some carbohydrates (e.g., mucins). The IgSF CAMs bind integrins and other IgSF CAMs.



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 (e.g., bone), flexible (e.g., tendons or the dermis of the skin), resilient and shock absorbing (e.g., 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 to regulate the function of the cells with which it interacts. The matrix helps to regulate important functions, such as cell growth and differentiation.

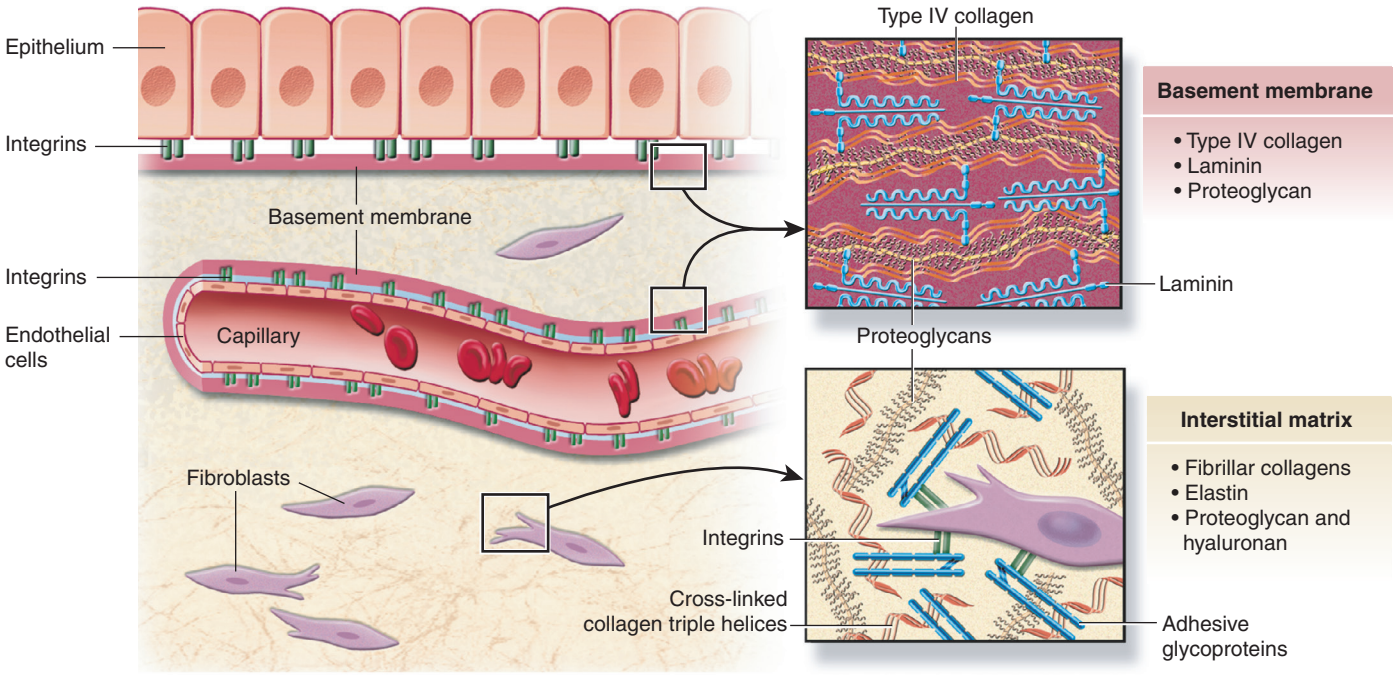


Fig. 1.9 Extracellular Matrix. Tissues are not just cells but also extracellular space. The extracellular space is an intricate network of macromolecules called the *extracellular matrix (ECM)*. The macromolecules that constitute the ECM are secreted locally (by mostly fibroblasts) and assembled into 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 A, Abbas K, Jon C. *Robbins and Cotran pathologic basis of disease*, 9th edition. Philadelphia: Saunders; 2015.

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins that bind the cell to adjacent cells and to components of the ECM. CAMs are divided into four protein families: integrins, cadherins, selectins, and the immunoglobulin superfamily (IgSF).[6] Integrins are a major class of molecules that typically bind to the ECM, whereas selectins, cadherins, and IgSF are associated with cell-to-cell adhesion. Integrins regulate cell interactions with collagen, fibronectin, vitronectin, and fibrinogen in the ECM. Cadherins, an abbreviation of "calcium-dependent adherent proteins," are associated with cell-cell adhesive bonds in solid tissues. They are calcium-dependent glycoproteins that have specific functions and distributions within tissues. For example, epithelial cells express E-cadherin, which cause tight adhesions between cells that interface between the body and the environment to create a protective barrier. Neural and endothelial cells express N-cadherin which helps to maintain the structural integrity of nerve cells and blood vessels.[7] Selectins are a family of proteins that bind certain carbohydrates. Selectins are divided into subgroups based on which cell types they are found in: P—platelets, E—endothelial, and L—leukocytes. Their primary function is to allow blood cells to bind to the endothelial surfaces of blood vessels during the inflammatory response (see Chapter 7). The immunoglobulin superfamily CAMs (IgSF CAMs) is one of the largest and most diverse protein families. These CAMs include vascular (VCAM), intercellular (ICAM), neural (NCAM), and nectins. Their functions include adhesion between immune and endothelial cells, neural development, and cellular migration and growth.

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:

1. Tight Junction: To hold cells together and form a tight seal and to maintain apicobasal polarity of individual epithelial cells (Fig. 1.12)
2. Adherens junctions, desmosomes, hemidesmosomes: To provide strong mechanical attachments
3. Gap junctions: 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

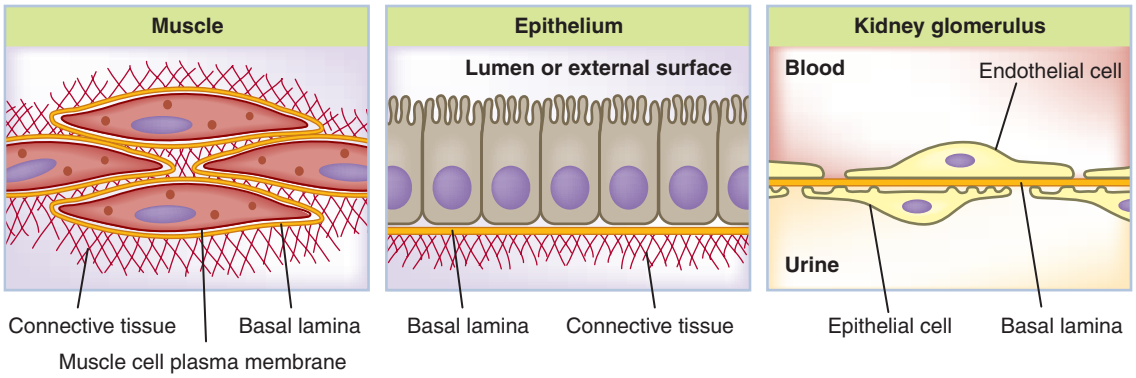


Fig. 1.10 Three Ways Basement Membranes (Basal Laminae) Are Organized. Basal laminae *(yellow)* surround certain cells like skeletal cells, underlie epithelia, and occur between two cell sheets (kidney glomerulus). (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition.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

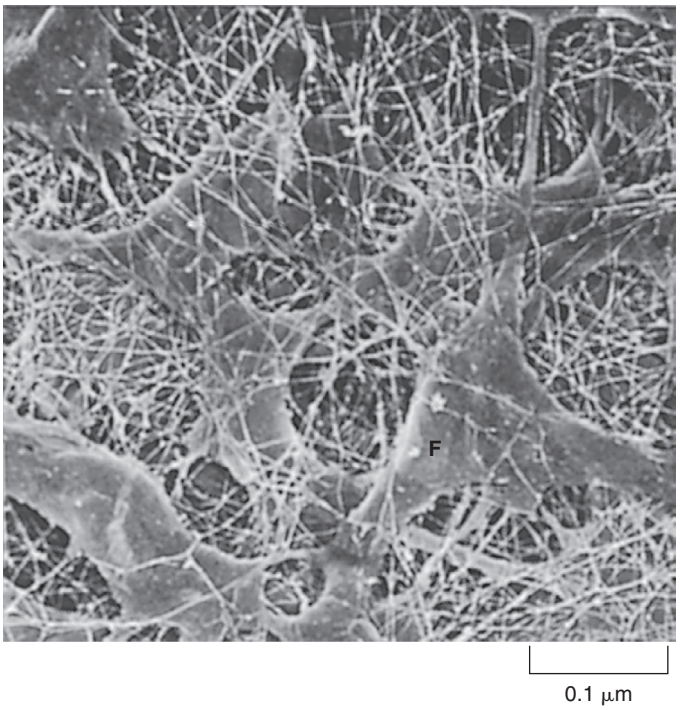


Fig. 1.11 Fibroblasts in Connective Tissue. This micrograph shows tissue from the cornea of a rat. The extracellular matrix surrounds the fibroblasts *(F)*. (Adapted from Nishia T, et al. The extracellular matrix of animal connective tissues. *Invest Ophthalmology Visual Science*, 1998; 29:1887-1880.)

In summary, cell junctions make the epithelium leak-proof and mediate mechanical attachment of one cell to another, allowing communicating tunnels and maintaining cell polarity.[8]

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. 1.12A). Together they form the junctional complex. 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.[9] 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 (see Fig. 1.12B). Gap junctions are composed of integral membrane proteins called connexins. Connexins are hemichannels that extend outward from each of the adjacent plasma membranes (see Fig. 1.12C). Gap junctions facilitate intercellular communication by allowing small ions and signaling molecules to pass directly from the inside of one cell to the inside of another. This process of cell communication is a critical feature for the development, function, and homeostasis of tissues and organs.[10] Multiple factors regulate gap junction intercellular communication, including voltage across the junction, intracellular pH, intracellular calcium (Ca^{2+}) concentration, and protein phosphorylation. 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 (see Fig. 1.12D).

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.

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 signal molecules (e.g., 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. 1.13A).

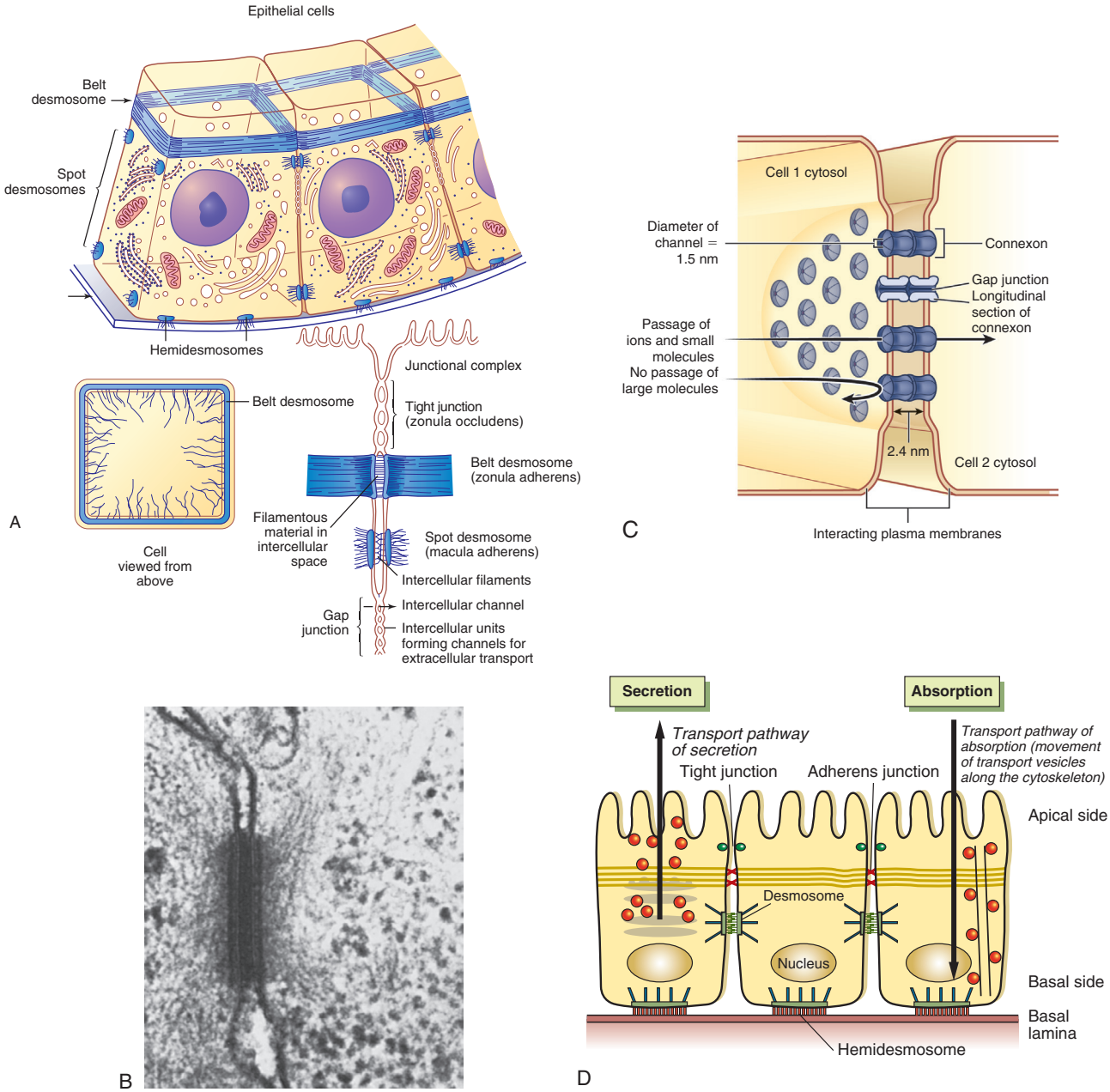


FIG. 1.12 Junctional Complex. (A), Schematic drawing of a belt desmosome between epithelial cells. This junction, also called *zonula adherens*, encircles each interacting cell. The spot desmosomes and hemidesmosomes, like the belt desmosomes, are adhering junctions. The tight junction is an impermeable 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. **(D)** 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. (A and B, From Raven PH, Johnson GB. *Biology*. St. Louis: Mosby; 1992.; C, Adapted from Gartner LP, Hiatt JL. *Color textbook of histology*, 3rd edition. St. Louis: Saunders Elsevier; 2006; Sherwood L. *Learning*, 8th edition. Belmont, CA: Brooks/Cole CENGAGE; 2013; D, Adapted from *Life science web textbook*, The University of Tokyo.)

2. They affect receptor proteins *inside* the target cell and the signal molecule has to enter the cell to bind to them (see Fig. 1.13B).
3. They form protein channels (gap junctions) that directly coordinate the activities of adjacent cells (see Fig. 1.13C). 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 12).

Secreted chemical signals involve communication locally and at a distance. Primary modes of intercellular signaling are contact dependent, paracrine, 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). 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. 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 signaling. Important differences lie in the speed and selectivity with which the signals are delivered to their targets.[2]

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. 1.15A 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 2).

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).

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.

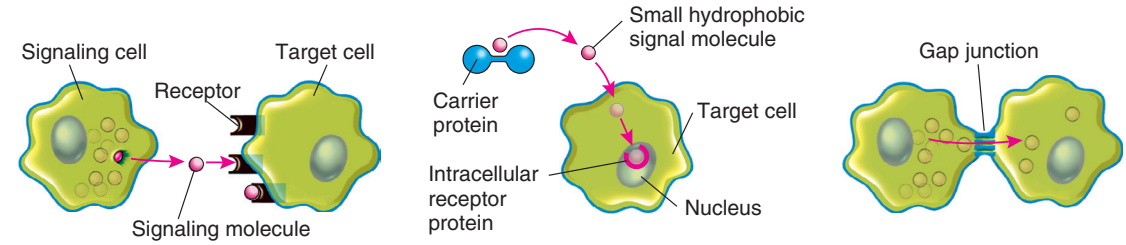


Fig. 1.13 Cellular Communication. Three primary ways **(A–C)** cells communicate with one another. (B, Adapted from Alberts B, Johnson A, Lewis J, et al. *Molecular biology of the cell*, 5th edition. New York: Garland; 2008.

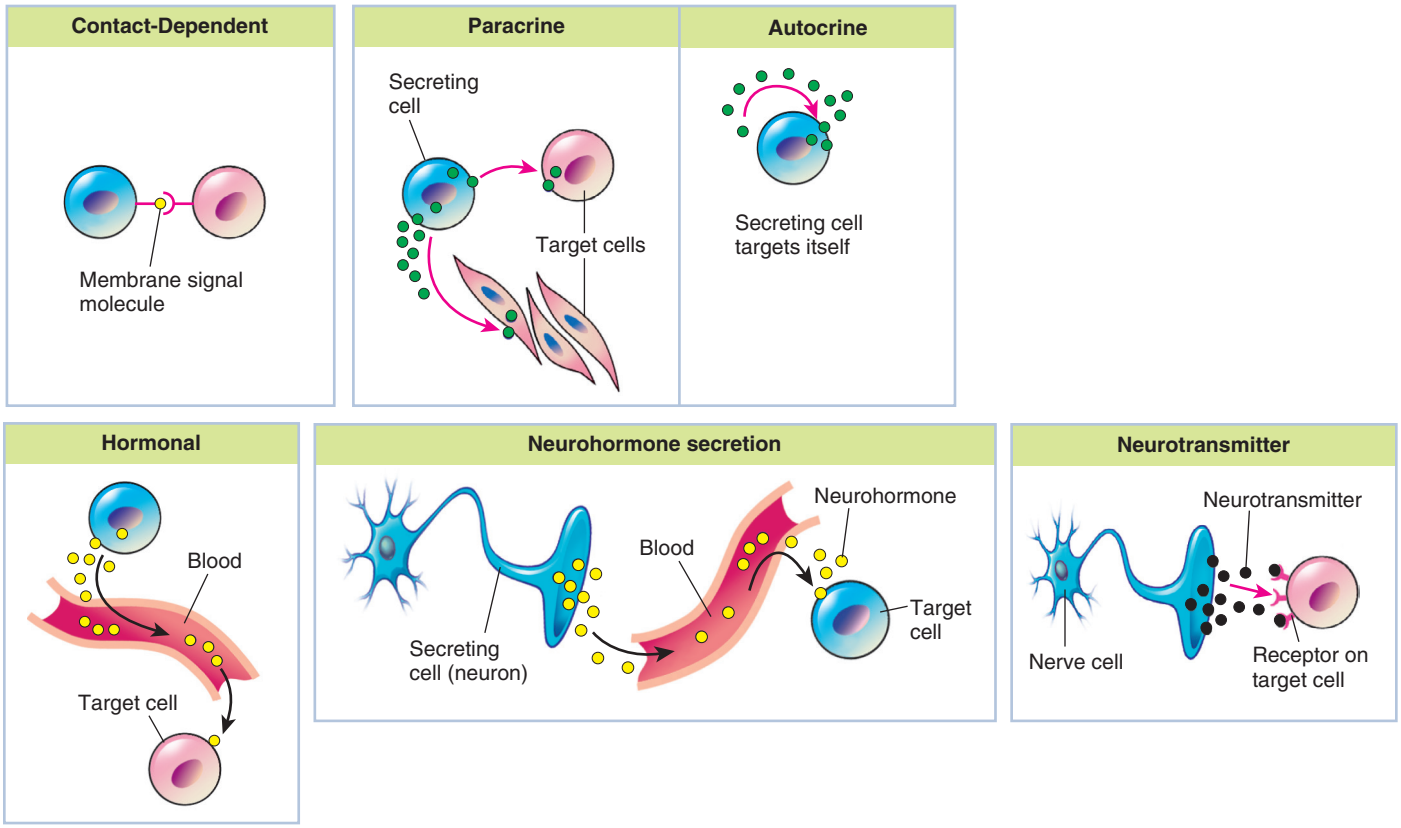


Fig. 1.14 Primary Modes of Chemical Signaling. Five forms of signaling mediated by secreted molecules. Hormones, paracrines, neurotransmitters, and neurohormones are all intercellular messengers that accomplish communication between cells. Autocrines bind to receptors on the same cell. Not all neurotransmitters 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.

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^{2+}), 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, Bray D, Hopkin K, et al. *Molecular biology of the cell*, 5th edition. New York: Garland; 2008.

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

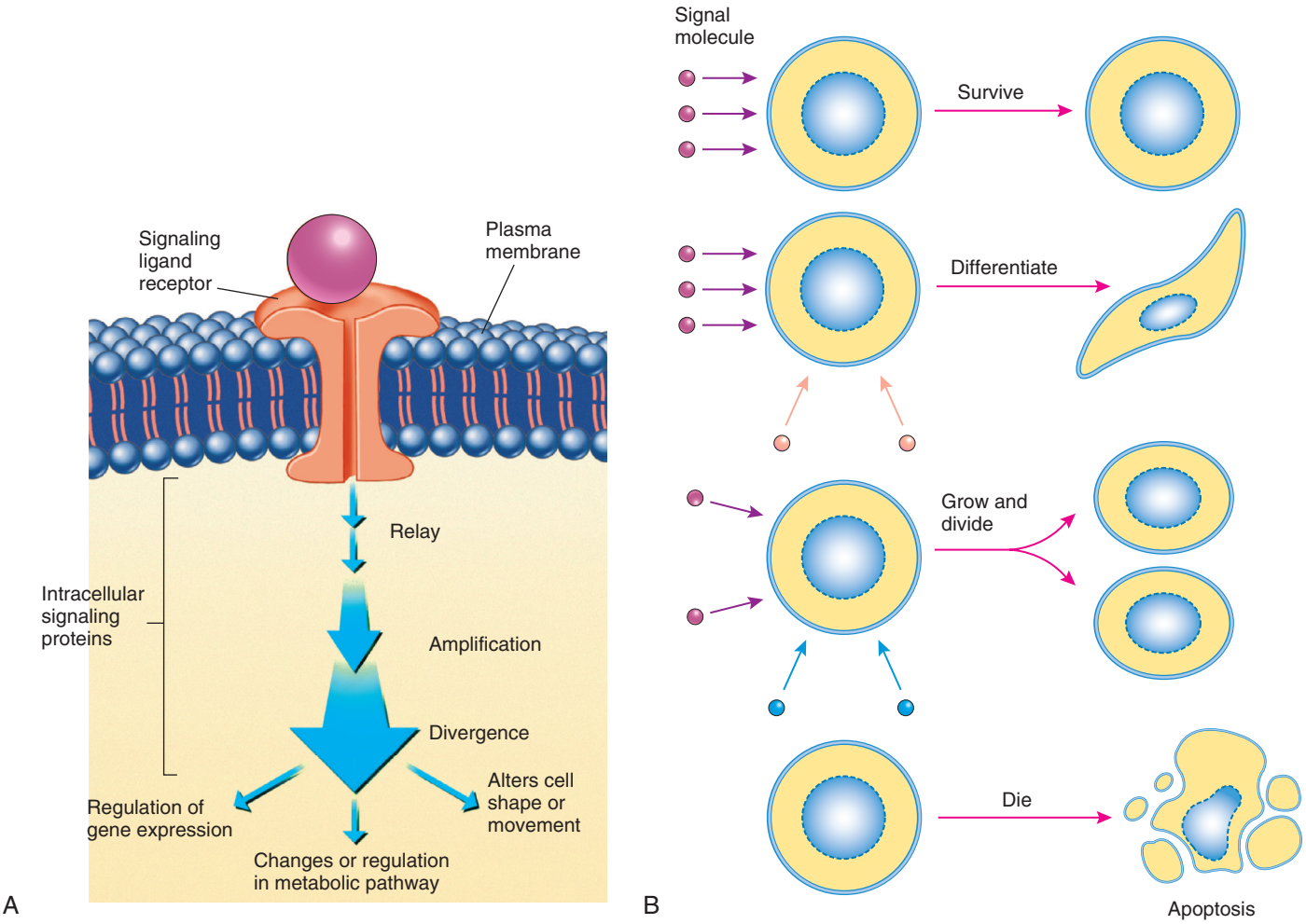


Fig. 1.15 Schematic of a Signal Transduction Pathway. Like a telephone receiver that converts an electrical signal into a sound signal, a cell converts an extracellular signal. **(A)** An extracellular signal molecule (ligand) binds to a receptor protein located on the plasma membrane, where it is transduced 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.

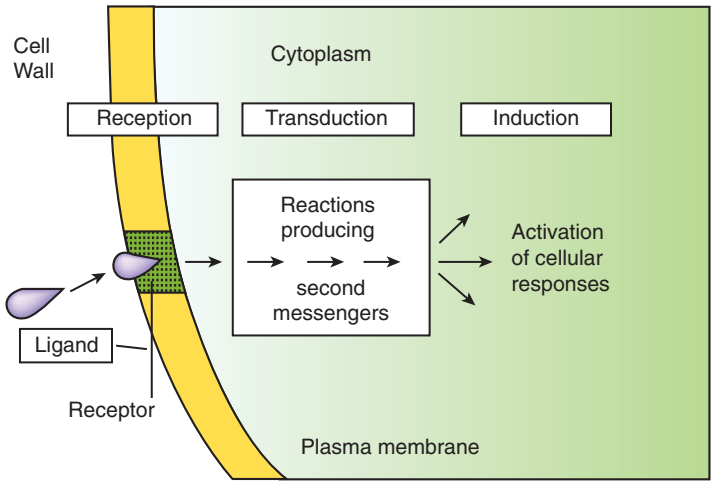


Fig. 1.16 First and Second Messengers. The first messenger or ligand attaches to the membrane receptor relaying the message across the membrane and intracellular messengers or second messengers trigger the cascade of intracellular events. The two major second-messenger pathways are cyclic adenosine monophosphate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

process is generally converted to adenosine diphosphate (ADP) and inorganic phosphate (Pi). The energy available as a result of this reaction is approximately 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.

ATP can also be found outside of cells. *Extracellular ATP* is released from cells in a variety of conditions and is considered important in inflammation and immunity. High levels of extracellular ATP may contribute to chronic inflammatory responses and to metastasis of cancer cells.[11]

Food and Production of Cellular Energy

Catabolism of the proteins, lipids, and polysaccharides found in food must be broken down into smaller molecules before cells can use them as a fuel source for energy or as building blocks for other molecules. The process 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 within the intestines or within the specialized lysosome organelle within 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 one glucose molecule into two molecules of pyruvate. During pyruvate formation, ATP and reduced nicotinamide adenine dinucleotide (NADH) are produced 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. Approximately 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—NADH and the reduced form of flavin adenine dinucleotide ($FADH_2$)—both of which transfer their electrons into the electron transport chain.

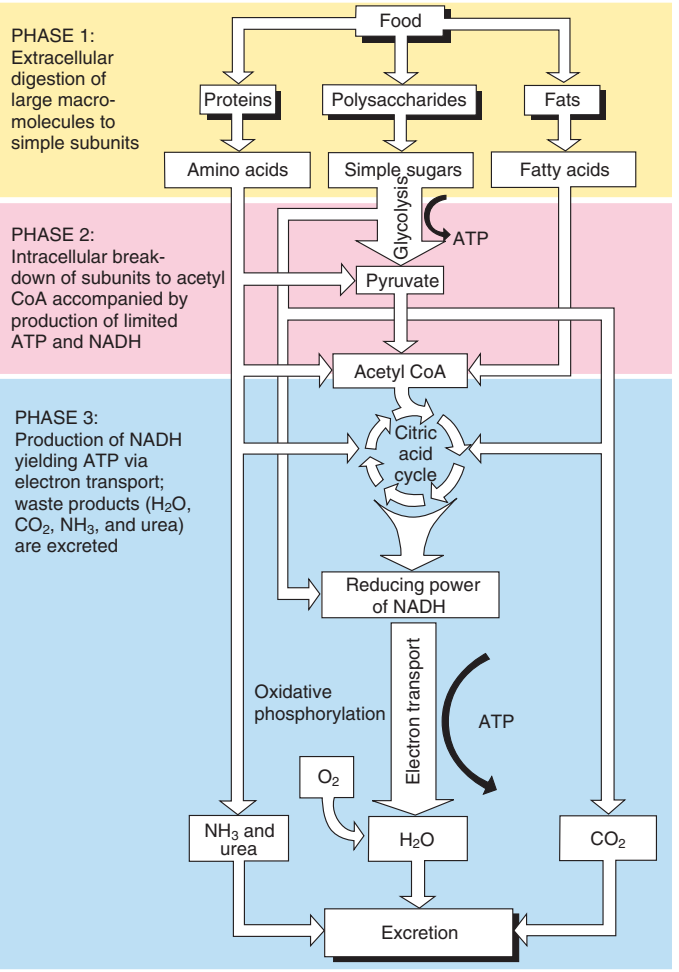


Fig. 1.17 Three Phases of Catabolism, Which Lead From Food to Waste Products. These reactions produce adenosine triphosphate *(ATP)*, which is used to power other processes in the cell. *NADH,* Nicotinamide adenine dinucleotide.

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 O_2 is not available to the electron transport chain, ATP will not be formed by the mitochondria. Instead, an anaerobic (without O_2) metabolic pathway synthesizes ATP. This process, called substrate-level 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 O_2 is present, the two molecules of pyruvate move into the mitochondria, where they enter the citric acid cycle (Fig. 1.19).

If O_2 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 O_2 is restored, lactic ACID is quickly converted back to either pyruvic

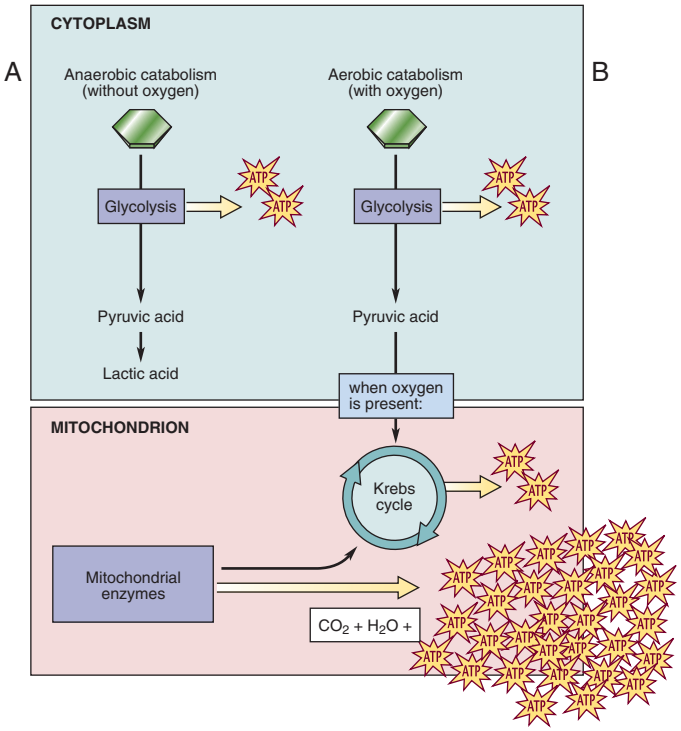


Fig. 1.18 Glycolysis. Sugars are important for fuel or energy, and they are oxidized in small steps to carbon dioxide and water. Glycolysis is the process for oxidizing sugars or glucose. Breakdown of glucose. **(A)** Anaerobic catabolism, to lactic acid and little adenosine triphosphate (ATP). **(B)**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

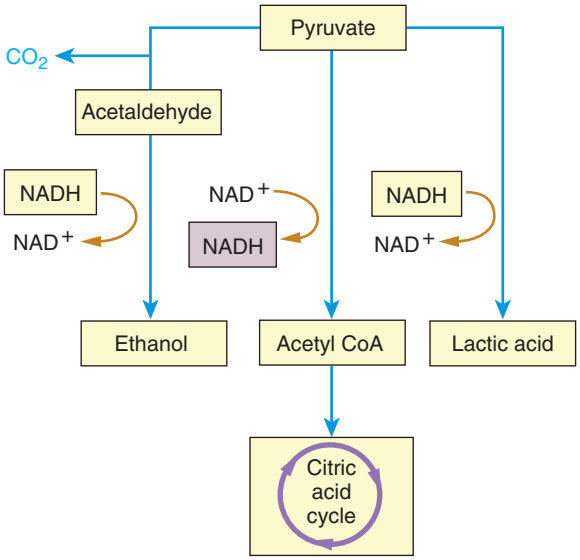


Fig. 1.19 What Happens to Pyruvate, the Product of Glycolysis? In the presence of oxygen, pyruvate is oxidized to acetyl coenzyme A *(Acetyl CoA)* and enters the citric acid cycle. In the absence of oxygen, pyruvate instead is reduced, accepting the electrons extracted during glycolysis and carried by 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.

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; N see Fig. 1.18) provides cells with a much more powerful method for extracting energy from food molecules. A field of cancer research examines how tumor cells are able to alter their metabolic pathways (metabolic reprogramming) to promote cancer progression (see the Emerging Science Box: Metabolic Reprogramming and Cancer Cells box).[12]

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

EMERGING SCIENCE BOX

Metabolic Reprogramming and Cancer Cells

Proliferating cancer cells require a great deal of cellular energy to support their rapid growth and spread through the body. Cancer cells create more energy by altering their metabolic pathways for all types of fuel sources, including carbohydrates, proteins, and lipids. These alterations are known as metabolic reprogramming. An example of metabolic reprogramming is the ability of tumor cells to greatly increase their uptake of glucose and to use it in multiple alternative pathways for generating energy and the molecules required for rapid growth. Not only do cancer cells use glucose to generate ATP in mitochondria, they also can convert glucose-derived pyruvate into lactate even in the presence of oxygen (Warburg effect) and can use nonmitochondrial pathways that do not require high levels of oxygen in order to generate energy and important metabolites. These nonmitochondrial pathways are stimulated by mutated genes (oncogenes such as c-MYC) and by growth factors that promote cancer cell proliferation. Glutamate, serine, and amino acid metabolic pathways may also be altered in cancer cells. An increasing understanding of metabolic reprogramming is leading to innovative experimental approaches toward slowing cancer growth.

Data from DeBerardinis RJ, et al. We need to talk about the Warburg effect. *Nature Metabolism*, 2020; 2:127–129; Dong Y, et al. Regulation of cancer cell metabolism: oncogenic MYC in the driver's seat. Signal Transduction and Targeted Therapy, 2020;5:124; Lin X, Xiao Z, Chen T, et el. Glucose metabolism on tumor plasticity, diagnosis, and treatment. Frontiers in Oncology, 2020; 10:317; Orang AV, et al. Micromanaging aerobic respiration and glycolysis in cancer cells. Molecular Metabolism, 2019; 23:98–125; Samec M, et al. Flavonoids against the Warburg phenotype—concepts of predictive, preventive and personalised medicine to cut the Gordian knot of cancer cell metabolism. EPMA Journal, 2020; 11:377–398

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.[3]

Membrane transport proteins occur in many forms and are present in all cell membranes. 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.[3] 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. 1.20A). 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. 1.20B). 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 (Fig. 1.21). 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 (see the Passive Transport: Diffusion, Filtration, and Osmosis section).

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. 1.22). 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. 1.22). These transporter pumps must harness an energy source to power the transport process. Energy can come from ATP hydrolysis,

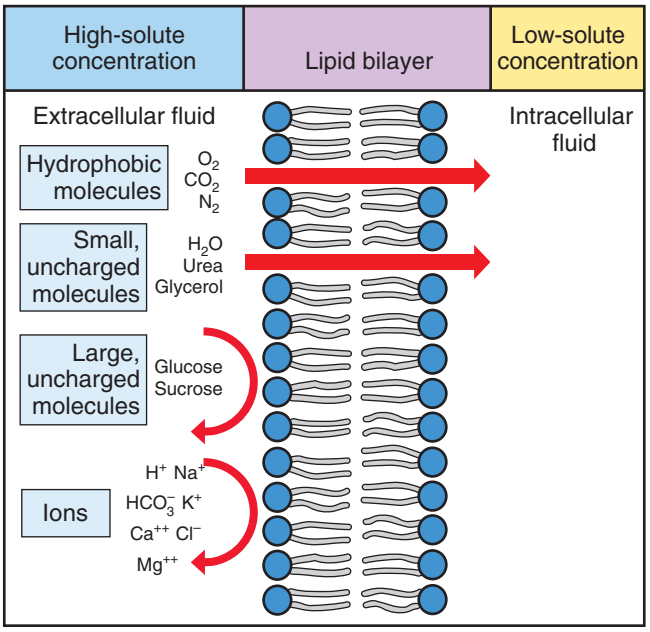


Fig. 1.21 Passive Diffusion of Solute Molecules Across the Plasma Membrane. Oxygen, nitrogen, water, urea, glycerol, and carbon dioxide can diffuse readily down the concentration gradient. Macromolecules are too large to diffuse through the pores in the plasma membrane. Ions may be repelled if the pores 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.

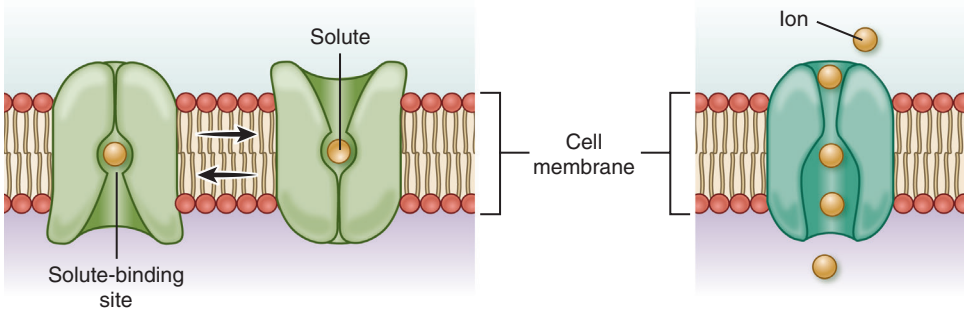


Fig. 1.20 Inorganic Ions and Small, Polar Organic Molecules Can Cross a Cell Membrane Through Either a Transporter or a Channel. (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

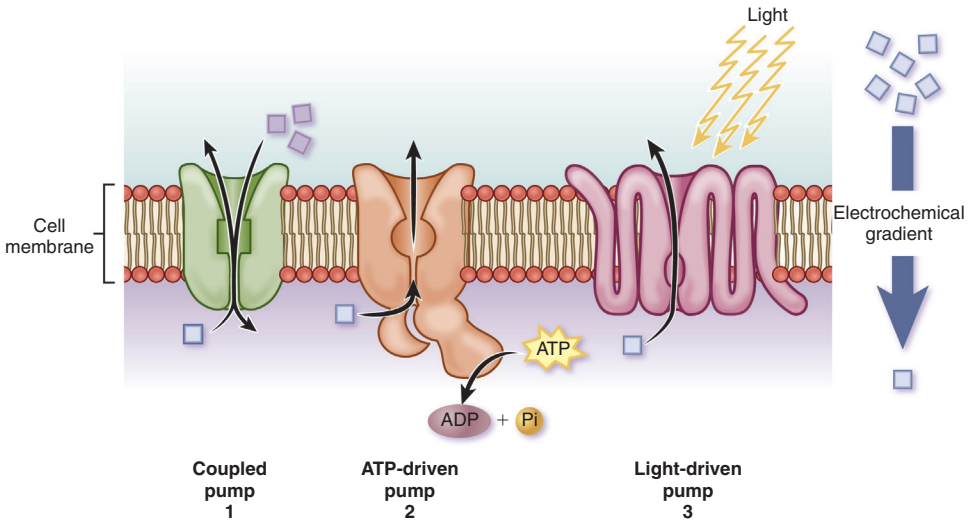


Fig. 1.22 Pumps Carry Out Active Transport in Three Ways. ***1***, *Coupled pumps* link the uphill transport of one solute to the downhill transport of another solute. ***2***, *Adenosine triphosphate (ATP)-driven pumps* drive uphill transport from hydrolysis of ATP. ***3***, *Light-driven pumps* are mostly found in bacteria and use energy from sunlight to drive uphill transport. (Adapted from Alberts B, Bray D, Hopkin K, et al. *Essential cell biology*, 4th edition. New York: Garland; 2014.

a transmembrane ion gradient, or sunlight (see Fig. 1.22). The best-known energy source is the Na^+-K^+–dependent adenosine triphosphatase (ATPase) pump. 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. 1.23).

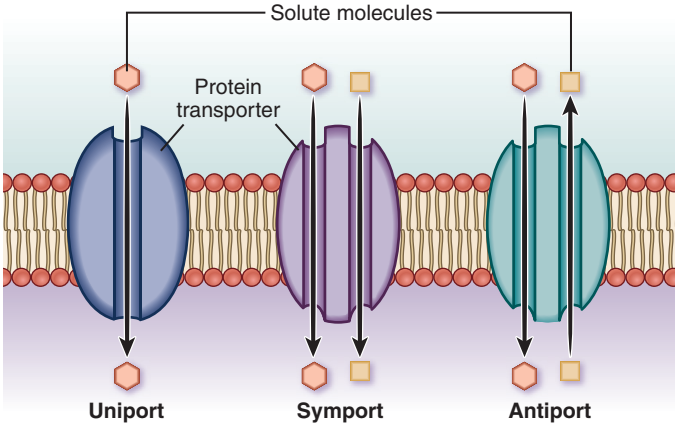


Fig. 1.23 Mediated Transport. Illustration shows simultaneous movement of a single solute molecule in one direction *(uniport)*, of two different solute molecules in one direction *(symport)*, and of two different solute molecules in opposite directions *(antiport)*.

Electrolytes as Solutes

Body fluids are composed of electrolytes, which are electrically charged and dissociate into constituent ions when placed in solution. Nonelectrolytes, such as glucose, urea, and creatinine, 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 3). 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. Monovalent ions, or ions with one charge, include sodium (Na^+), chloride (Cl^-), and potassium (K^+). Divalent ions, which have two charges, include calcium (Ca^{2+}) and

magnesium (Mg^{++}). One milliequivalent (mEq) 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., $Ca^{2+} + 2\ Cl^{-} = CaCl_2$).

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 (see Fig. 1.21). 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 less concentration until equilibrium is reached. Molecules still move back and forth to maintain this equilibrium; however, there is no net change in concentration of the molecules on either side of the permeable membrane. 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^{2+}, 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. 1.24). 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. Oxygen, CO_2, and the 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 polar phosphate head groups. The polar phosphate 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. 1.25A). 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 (Fig. 1.25B). Water that is not osmotically attracted back into the capillaries moves into the lymph system (see the discussion of Starling forces in Chapter 3).

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

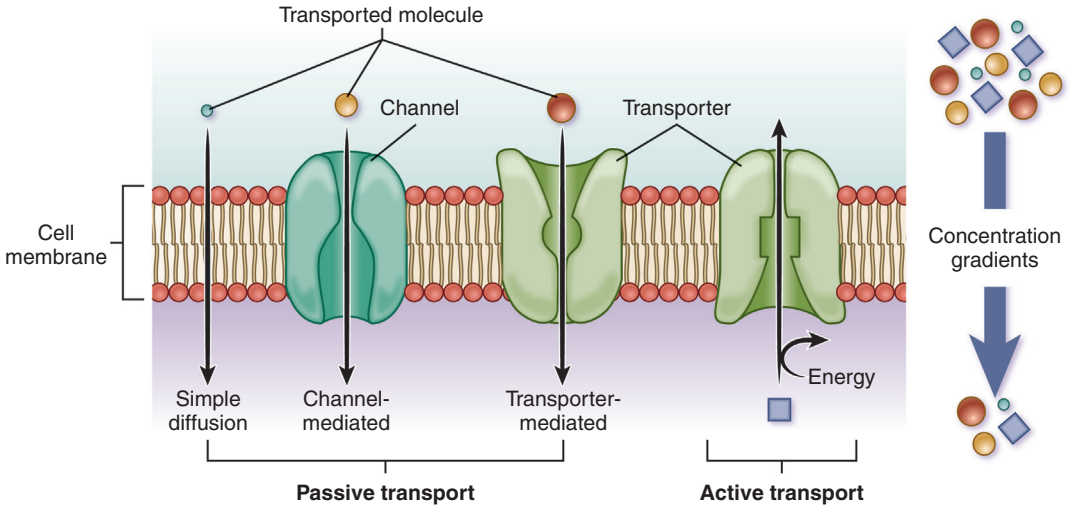


Fig. 1.24 Passive Diffusion of Solute Molecules Across the Plasma Membrane. Oxygen, nitrogen, water, urea, glycerol, and carbon dioxide can diffuse readily down the concentration gradient. Macromolecules are too large to diffuse through pores in the plasma membrane. Ions may be repelled if the pores 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.

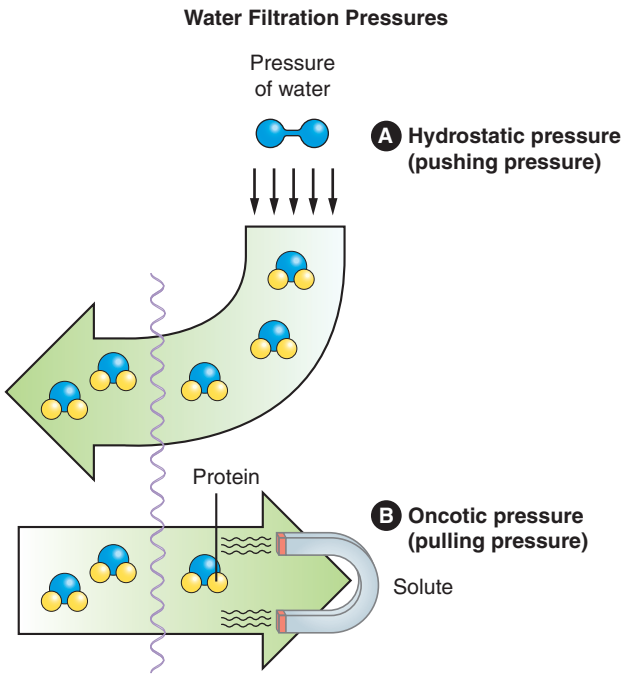


Fig. 1.25 Hydrostatic Pressure and Oncotic Pressure in Plasma. **(A)** Hydrostatic pressure in plasma is a pushing pressure in relation to water. **(B)** Oncotic pressure exerted by proteins in the plasma usually tends to *pull* water into the circulatory system. Individuals with low protein levels (e.g., 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 (mOsm/L) of solution, or the concentration of molecules per *volume* of solution.

In solutions that contain only dissociable substances, such as Na^+ and Cl^-, the difference between the two measurements is negligible. When considering all the different solutes in plasma (e.g., proteins, glucose, lipids), 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. For example, urea is a small solute that readily diffuses across cellular membranes. Solutions containing urea quickly lose their effective osmolality because they rapidly equilibrate. Solutes too large to pass through the membrane sustain an effective osmolality, meaning that they enhance osmotic activity. Plasma proteins are examples of molecules that provide effective osmolality because they normally do not cross cellular membranes.

Plasma proteins influence osmolality because they have a negative charge (Fig. 1.25B). 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 (Fig. 1.26A). Examples of isotonic solutions include 5% dextrose in water and normal (0.9%) saline solution. A hypotonic solution has a lower concentration and is thus more dilute than body fluids (Fig. 1.26B). Water is a hypotonic solution. Consequently, water is osmotically pulled into the cells, causing cells to swell or burst. A hypertonic solution has a concentration of more than 285 to 294 mOsm/kg (Fig. 1.26C). An example of a hypertonic solution is 3% saline solution. Cells shrink in a hypertonic solution because water is being pulled out of the cells. The concept of tonicity is important when correcting water and solute imbalances by administering different types of replacement solutions (see Chapter 3).

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