FIFTH EDITION

MEDICAL PHYSIOLOGY

PRINCIPLES FOR CLINICAL MEDICINE

Rodney A. Rhoades
David R. Bell

Wolters Kluwer

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EDITED BY

Rodney A. Rhoades, PhD
Professor Emeritus
Department of Cellular and Integrative Physiology
Indiana University School of Medicine
Indianapolis, Indiana

David R. Bell, PhD
Associate Professor
Department of Cellular and Integrative Physiology
Indiana University School of Medicine–Fort Wayne
Fort Wayne, Indiana

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Crystal Taylor
Development Editor: Andrea Vosburgh
Editorial Coordinator: Annette Ferran
Marketing Manager: Michael McMahon
Production Project Manager: Bridgett Dougherty
Design Coordinator: Stephan Druding
Art Manager: Jennifer Clements
Manufacturing Coordinator: Margie Orzech
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PREFACE

Human physiology is the science that explains how cells, tissues, and organs interact and function as an integrated system. The fifth edition of *Medical Physiology: Principles for Clinical Medicine* provides the latest information of how the body's different systems work to allow it to cope with changes in its internal and external environment. In so doing, it addresses how the body maintains optimal health and ensures survival. Although the emphasis of the fifth edition is on normal physiology, discussion of pathophysiology is also undertaken to show how altered functions are involved in disease processes. We have also created a new type of chapter essay for this edition that highlights how physiology integrates with others medical sciences, such as those involving pharmacology, biochemistry, genetics, and clinical diagnostics. This enrichment of basic physiology reinforces fundamental physiologic principles while also demonstrating how basic concepts in physiology connect to clinical medicine.

Our mission for this edition has developed out of our decades of teaching and mentoring medical students and the feedback we have received from them. We have created a multicomponent learning resource to address three questions that medical students have told us most concern them in their academic training; these are, *"What should I know?", "How do I know that I know it well?",* and *"How does what I learn fit into medicine?"* Each component of this textbook presents a learning opportunity with these questions in mind. We have attempted to maximize those opportunities to the fullest, while providing a clear, accurate, and up-to-date introduction to medical physiology.

AUDIENCE AND FUNCTION

This book, like the previous edition, is written for medical students but will be useful to dental, graduate nursing, and veterinary students as well. This is neither an encyclopedic textbook nor is it intended to be a condensed, descriptive review. Rather, the fifth edition focuses on the basic key physiologic principles necessary to understand human function and its fundamental context in clinical medicine. An additional important objective for the fifth edition is to demonstrate to the student that physiology is key to understanding other medical sciences such as pharmacology and pathophysiology. Although the book is written primarily with the student in mind, the fifth edition will also be a clear, concise, and helpful reference for physicians and other health care professionals.

All chapters were substantially revised, updated, and edited to achieve unity of voice and to be as concise and lucid as possible. In the fifth edition, each chapter is written to eliminate minutia and minimize the compilation of isolated facts. The chapters are written by medical school faculty members who are experts in their field and who have had decades of experience teaching physiology. They have focused their material on what is important for medical students to know. We have purposefully avoided discussion of research laboratory methods and/or historical material. Although such issues are important in other contexts, most medical students are too busy to be burdened by such information and prefer to focus on the essentials. We have also avoided topics that are as yet unsettled, while recognizing that new research constantly provides fresh insights and sometimes challenges old ideas.

CONTENT AND ORGANIZATION

This book begins with a discussion of basic physiological concepts, such as homeostasis and cell signaling, in Chapter 1. Chapter 2 covers the cell membrane, membrane transport, and the cell membrane potential. Most of the remaining chapters discuss the different organ systems: nervous (Chapters 3–7), muscle (Chapter 8), cardiovascular (Chapters 11–17), respiratory (Chapters 18–21), renal (Chapters 22–23), gastrointestinal (Chapters 25–26), endocrine (Chapters 30–35), and reproductive physiology (Chapters 36–38). Special chapters on the blood (Chapter 9) and immunology (Chapter 10) are included. The immunology chapter emphasizes physiological applications of immunology. Chapters on acid–base regulation (Chapter 24), temperature regulation (Chapter 28), and exercise (Chapter 29) discuss these complex, integrated functions. The order of presentation of topics follows that of most United States medical school courses in physiology. After the first two chapters, the other chapters may be read pretty much as stand-alone units, and some chapters may be skipped if the subjects are taught in other courses (e.g., neurobiology or immunology).

CHANGES FOR THE FIFTH EDITION

For the fifth edition, new expert contributing authors have been brought on board to update and rewrite major sections of the text and their associated ancillary learning tools. The entire Neurophysiology, Gastrointestinal, and Renal physiology sections of the text, as well as the chapters on Blood and Immunology, have been revised by these new authors.

In addition, in response to requests from students and instructors from around the globe, we have moved a portion of our formative assessment tools, formally only available online, into the print copy of the fifth edition of *Medical Physiology: Principles for Clinical Medicine*. Annotated, multiple choice review questions, in which explanations for the right and wrong answers are provided, as well as similar, annotated *Clinical Application Exercises* have been moved into the print copy of the new edition. The print copy, however, also retains links to additional online review questions, clinical application exercises, and advanced clinical problem-solving exercises.

Finally, we have replaced the Bench to Bedside essays found in the previous edition with new *Integrated Medical Sciences* essays. This new feature for the fifth edition is designed to highlight for the novice student the connections between physiology and the other basic medical sciences they are studying, such as pharmacology, pathology, and introductory clinical medicine.

KEY FEATURES AND LEARNING TOOLS

As with previous editions, the fifth edition includes numerous ancillary student-learning tools as complements to the basic text.

Active Learning Objectives

Medical students deal with huge amounts of information from their courses and an ever-expanding electronic medium. This often makes the task of determining what they really need to know difficult for them. Students benefit greatly if they have a set of clear objectives placed in front of them *before* trying to sift through their learning materials. Our active learning objectives direct the student to apply the concepts and processes contained in the chapter, rather than memorize facts. Basic descriptors or table of content-type lists at the start of a chapter do not tell students what they should really know. Simply naming items in a chapter that the student has not yet learned does not help students cope with what they should do with material once it is mastered. *Active Learning Objectives* at the start of each chapter in this text are purposely designed to indicate what a student should be able to do with chapter material once it has been mastered. Medical students need to have understanding of the workings of physiology to become competent problem solvers. Toward that end, our *active learning objectives* direct students to explain, predict, and postulate rather than simply describe, define, and recite.

Annotated Chapter Review Questions, Clinical Application Exercises, and Advanced Clinical Problem-Solving Exercises

Providing students with formative assessment tools is essential if they are to determine what they know, whether they know it well, and what they do not know or do not know well. The fifth edition of *Medical Physiology: Principles for Clinical Medicine* provides the student with a multitiered approach to formative self-assessment. This edition provides student with over 350 USMLE-type multiple choice questions that are organized by chapter content and keyed with explanations for both the right and all the wrong answers. In this manner, students are able to gauge their understanding of the physiology they are learning at the moment. It is very frustrating for students to study hard, get a practice question wrong, and then be clueless as to both why another choice was right and theirs and the remaining choices wrong. We have found that the inability to recognize wrong choices as such is a leading cause of poor student performance. By providing students with explanation for the wrong as well as the right answers with their chapter practice questions, we allow them to identify gaps in their understanding while at the same time avoiding the frustration that arises when they are given review questions without explanations for the answers. Just as important, when given a complete explanation for the choices in a question, students can better determine whether they know material well.

In the fifth edition, we take this type of formative assessment to additional, more complex levels in order to hone student problem-solving skills. We provide two *Clinical Application Exercises* with each of the 38 chapters in the book, with at least one of these placed in the print copy. These exercises are small clinical vignettes purposely circumscribed to the chapter content only. Multiple questions are asked of the student based on the vignette and the chapter content. Explanations are provided for the answers to all the questions. This type of “story problem” method of developing problem-solving skills differs from the typical case study format sometimes used in medical education. In the latter, it is not uncommon to include materials in the case for which the student has not yet learned or to which they have not yet been introduced. This can be counterproductive in that it can confound and misdirect students as they try to focus on the solution to the problem at hand. They can encounter difficulties with solving the case study because they have yet to be taught certain clinical

information and complexity, rather than because their understanding of what they are currently learning is lacking. The latter is most important to them when trying to master physiology. Our *Clinical Application Exercises* are focused. They are designed to help students better learn how to apply the physiology they are learning at the moment to real clinically relevant problems. As such, this type of problem-solving exercise further helps the student identify what physiology they understand well and what they do not. In addition, this type of exercise helps students immediately see the clinical relevance of the physiology they are learning; it shows them where the physiology fits into clinical medicine.

Lastly, the online resources that accompany this book contain 38 *Advanced Clinical Problem-Solving Exercises*. These are longer, more involved clinical scenarios, each with multiple questions asked and explanations for the answers provided. These advanced exercises draw on a student's understanding of multiple disciplines within physiology as well as other biomedical fields. These exercises are more like true clinical case studies. They allow a student to evaluate their ability to integrate multiple disciplines within physiology and apply their collective understanding toward the answers to a multifaceted clinical problem. These advanced exercises elevate a student's problem-solving skills and further enhance their ability to determine what they do and do not know well. The exercises further illustrate for the student how the study of physiology fits into clinical medicine.

Clinical Focus Essays and Integrated Medical Sciences Essays

For the fifth edition, the *Clinical Focus* boxes of each chapter have again been updated. These short essays deal with pathophysiology, physiopharmacology, and clinical correlates of physiology, including those involved with basic therapeutics and clinical evaluation tools. A new feature, the *Integrated Medical Sciences* essay, has been added to each chapter in the fifth edition. These essays address a growing trend in medical student education of integrating the whole of medical sciences, basic and clinical, within given units of instruction. It is now common for students to be taught pathology, pathophysiology, pharmacology, and introductory medicine simultaneously, so as to create a fuller understanding of a particular disease or medical condition. The *Integrated Medical Sciences Essay* contained in each chapter is directed at connecting the physiology within a chapter to another type of medical science. Together both types of chapter-based essays gives students additional insight into the connection between physiology and the understanding of human disease and its treatment.

ADDITIONAL EDUCATIONAL FEATURES

The fifth edition incorporates many features designed to facilitate learning and guide the student along his or her study of physiology. In-print features included in the fifth edition are as follows.

- **Illustrations and Tables.** The text again contains abundant full-color figures and flow diagrams. Review tables are also provided as useful summaries of material explained in more detail in the text. The illustrations in the text often show interrelationships between different variables or components of a system. These color illustrations are more than just visually appealing. As first employed in the fourth edition, the fifth edition of the text continues the use of color art as an instructive tool. Rather than applying color arbitrarily, color itself is used with purpose and delivers meaning. Graphs, diagrams, and flow charts, for example, incorporate a coordinated scheme; red is used to indicate stimulatory, augmented, or increased effects, whereas blue connotes inhibitory, impaired, or decreased effects.
  A coordinated color scheme is likewise used throughout to depict transport systems. This key, in which membrane pores are blue, primary active transporters are red, facilitated transporters are purple, cell chemical receptors are green, cotransporters are orange, and voltage-gated transporters are yellow, adds a level of instructiveness to the figures not seen in other physiology textbooks. By differentiating these elements integral to the workings of physiology by their function, the fifth edition artwork reinforces their purpose to teach students, rather than merely representing. These beautiful full-color conceptual diagrams guide students to an understanding of the general underpinnings of physiology. Figures work with text to provide meaningful, comprehensible content.
- **Bulleted Chapter Summaries.** These bulleted statements provide a concise summative description of the chapter and provide a good review checklist of the chapter.
- **Key Concept Subheadings.** Secondary chapter subheadings are depicted in bold in the text and written as active concept statements designed to convey the key point(s) of a given section. Unlike typical textbook subheadings that simply title a section, these are given in active full sentence form. For example, instead of heading a section “Edema,” the heading instead becomes “Edema impairs diffusional transport across capillaries.” In this way, the key idea in a section is immediately obvious. When taken together in a chapter,

these statement subheadings give the student another means of chapter review.

- **Boldfacing.** Key terms are boldfaced upon their first appearance in a chapter. These terms are explained in the text and defined in the glossary for quick reference.
- **Abbreviations and Normal Values.** An appendix of common abbreviations in physiology and a table of normal blood, plasma, or serum values are included inside the book covers for convenient access. All abbreviations are defined when first used in the text, but the table of abbreviations in the appendix serves as a useful quick access of abbreviations commonly used in physiology and medicine. Normal values for blood are also embedded in the text, but the table on the inside front and back covers provides a more complete and easily accessible reference.
- **Index.** A comprehensive index allows the student to easily look up material in the text.
- **Glossary.** A glossary of all boldfaced terms in the text is included for quick access to definition of terms. Students will appreciate the book's inclusion of such a helpful and useful tool.

Readability and Design

The text is a pleasure to read, and topics are developed logically. Difficult concepts are explained clearly, in a unified voice, and supported with plentiful illustrations. Minutiae and esoteric topics are avoided. The fifth edition interior design not only makes navigating the text easier but also draws the reader in with immense visual appeal and strategic use of color. Likewise, the design highlights the pedagogical features, making them easier to find and use.

Ancillary Package

Still more features round out the colossal ancillary package online at www.thePoint.com/Rhoades. These bonus offerings provide ample opportunities for self-assessment, additional reading on tangential topics, and animated versions of the artwork to further elucidate the more complex concepts. Look for this icon thePoint® appearing throughout the text indicating associated online features.

- **Additional Formative Assessments.** In addition to the formative assessment tools now placed in the print copy of the textbook, additional chapter review questions and clinical application exercises are available online along with advanced clinical problem solving exercises. As with the print copy of the textbook, all questions are analytical in nature and test the student's ability to apply physiological principles to solving problems rather than test basic fact-based recall. They contain explanations for right and wrong answers. These chapter-based questions were written by the author of the corresponding chapter and not contracted out to a question-writing service.
- **Suggested Reading.** A short list of recent review articles, monographs, book chapters, classic papers, or Web sites where students can obtain additional information associated with each chapter is provided online.
- **Animations.** The fifth edition contains online animations illustrating difficult physiology concepts.
- **Image Bank for Instructors.** An image bank containing all of the figures in the book, in both pdf and jpeg formats, is available for download from our Web site at thePoint®.
- **Instructor Test Bank.** Also, for the fifth edition, the extensive test bank written by subject matter experts has been updated and expanded for instructors using this textbook in their course.

In closing, we would like to add that the discipline of physiology is changing. In the past 20 years, there has been an overemphasis of genetics placed into our understanding of "what makes us tick." This has resulted in the belief that genes control human biology, which has had a major impact on medical physiology and the way diseases are treated. This has recently changed with the emergence of the new science of epigenetics, which means regulation above the gene. Epigenetics

can be defined as a mechanism by which genes can be switched off and on, but the genes themselves and their genetic code are not altered. This means protein synthesis and other cellular functions can be controlled above the level of the gene. New research shows that lifestyle and environmental signals can modify and regulate gene activity and shows such things as exercise, nutrition, stress, trauma, emotions, attitude, social engagement, and toxins can modify gene function without altering the genetic code. More striking is that these epigenetic modifications can be passed onto the next generation. Epigenetics is upending our understanding of physiologic regulation and has opened up a new frontier in human physiology and the future of medicine. Physiology is moving from structure–function relationships to epigenetics-induced functional relationships. This has resulted in new research that shows only approximately 15% of chronic diseases (e.g., hypertension, heart disease, asthma, obesity, diabetes, osteoporosis, arthritis, cancer, etc.) are specifically linked to genetics. The remaining 85% are factors due to lifestyle choices (e.g., diet, exercise, physical stress, emotional stress) and to environmental factors (toxins, smoking, pesticides, substance abuse, etc.). The fifth edition of *Medical Physiology: Principles of Clinical Medicine* provides all students with a strong foundation to be built upon by this new and exciting field of epigenetics.

We would like to express our deepest thanks and appreciation to all of the contributing authors. Without their expertise and cooperation, this fifth edition would have not been possible. We also wish to express our appreciation to all of our students and colleagues who have provided helpful comments and criticisms during the revision of this book. We would also like to give thanks for a job well done to our editorial staff for their guidance and assistance in significantly improving each edition of this book. A very special thanks goes to our Developmental Editor, Kelly Horvath, who was a delight to work with and whose patience and editorial talents were essential to the completion of the fifth edition of this book. We are indebted as well to our artist, Jennifer Clements. Finally, we would like to thank Crystal Taylor, our Acquisitions Editor at Wolters Kluwer, for her support, vision, and commitment to this book. We are indebted to her administrative talents and her managing of the staff and material resources for this project.

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Rodney A. Rhoades, PhD

David R. Bell, PhD

CONTRIBUTORS

David R. Bell, PhD
Associate Professor
Department of Cellular and Integrative Physiology
Indiana University School of Medicine–Fort Wayne
Fort Wayne, Indiana

Bonnie L. Blazer-Yost, PhD
Professor
Departments of Biology, Integrative and Cellular Physiology, and Anatomy and Cell Biology
Indiana University–Purdue University
Indianapolis, Indiana

Robert V. Considine, PhD
Associate Professor
Departments of Medicine and Physiology
Indiana University School of Medicine
Indianapolis, Indiana

Jeffrey S. Elmendorf, PhD
Associate Professor of Cellular and Integrative Physiology
Department of Physiology
Indiana University School of Medicine
Indianapolis, Indiana

Jennelle Durnett Richardson, PhD

Assistant Professor
Department of Clinical Pharmacology and Toxicology
Indiana University School of Medicine
Indianapolis, Indiana

Rodney A. Rhoades, PhD
Professor Emeritus
Department of Cellular and Integrative Physiology
Indiana University School of Medicine
Indianapolis, Indiana

Denise Slayback-Barry, PhD
Lecturer
Department of Biology
Indiana University–Purdue University Indianapolis
Indianapolis, Indiana

Robert Sweazey, PhD
Associate Professor of Anatomy and Cell Biology
Indiana University School of Medicine–Fort Wayne
Fort Wayne, Indiana

Frank A. Witzmann, PhD
Professor
Department of Cellular and Integrative Physiology
Indiana University School of Medicine
Indianapolis, Indiana

Robert W. Yost, PhD
Senior Lecturer

Department of Biology
Indiana University–Purdue University
Indianapolis, Indiana

REVIEWERS

Faculty

Rebecca Brown, MPAS, PA-C
Le Moyne College
Syracuse, New York

Douglas J. Gould, PhD
Oakland University William Beaumont School of Medicine
Rochester, Michigan

Atanas Ignatov, PhD, MS
Logan University
Chesterfield, Missouri

Molly Ann Johannessen, PhD, MSc, MEd
Lake Erie College of Osteopathic Medicine
Erie, Pennsylvania

Anthony Olinger, PhD
Kansas City University of Medicine and Biosciences
Kansas City, Missouri

Omid B. Rahimi, PhD
University of Texas Health Science Center
San Antonio, Texas

Peter Zajac, DO, FACOFP
University of Pikeville
Pikeville, Kentucky

Students

Tania Benjamin
California State University
Northridge, California

Talayesa Buntinx-Krieg
University of Central Florida College of Medicine
Orlando, Florida

Dana Ferrari
A.T. Still University School of Osteopathic Medicine
Mesa, Arizona

Michael Gallagher
New Jersey Medical School
Newark, New Jersey

Arden Gewirtz
International University of the Health Sciences School of Medicine
Basseterre, Saint Kitts and Nevis

Jacqueline Hairston
Icahn School of Medicine at Mount Sinai
New York, New York

Michael Nickas
New York Institute of Technology
New York, New York

Jennifer Schwenk
University of Miami, Miller School of Medicine
Miami, Florida

Christine Tran

University of Vermont
Burlington, Vermont

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PART I CELLULAR PHYSIOLOGY

1 Medical Physiology: An Overview

Human physiology is the science that explains how cells, tissues, and organs interact to allow the body to function while coping with changes in the internal and external environment. Accordingly, an important facet of physiology is to examine how the body's different systems are integrated to maintain optimal health and our survival.

SCOPE OF MEDICAL PHYSIOLOGY

This book is designed to examine the connection between the basic sciences, human function, and health. As such, the basic concepts discussed in this book highlight the relationship between physiology and foundational principles for clinical medicine. Often, interns, residents, and practicing physicians become so focused on medical diagnoses, bodily traumas, and the treatment of diseases that they lose sight of the most important part of medicine—that is, *living* and *thriving*. Long before any disease leads to dysfunction and threatens a person's life, the human body is faced with difficulties and constraints to its survival that are dictated by natural chemical, physical, and biological laws. The body expends enormous energy to maintain normal function and to survive. In short, the body encounters many challenges to simply *stay alive*.

Organ systems are designed to regulate the body's internal environment.

The human body is made up of more than 65 trillion cells. That is correct—over 65 *trillion*, not 65 billion—that are organized into specialized tissues and organs that regulate our internal environment in a manner compatible to sustain cell function and survival. Organ systems are responsible for regulating many essential cellular processes to maintain the physical and chemical conditions of the extracellular fluid within a narrow range. These include water volume and osmolality, essential electrolyte concentrations, metabolic substrates, oxygen and carbon dioxide gas concentrations, pH, and temperature, to name a few. The ability to maintain a relative consistency in the chemical and physical environment surrounding the cells of our body, in the face of a variable external environment, is called **homeostasis**.

The ability to control our internal environment against the very intense challenges to our survival is part of the scientific essence of physiology. For example, the human body can be viewed as a warm, wet organism that has to survive in a cool, dry, and harsh world. The energy our body needs to keep all cellular processes running is derived from the oxidation of basic organic molecules. However, this essential metabolic process consumes enormous amounts of oxygen and, in the process, dumps enough carbon dioxide into the extracellular fluid to potentially quickly lower the blood pH from 7.4 to 1. Therefore, the body must contend constantly with the threat of dehydration, hypothermia, and acidosis. The metabolic fuel required for energy-producing oxidation reactions in our body is needed continually by the cells. Some organs, particularly the brain, can only use glucose as a source of energy for this purpose. Moreover, the nutrient sources that originate from the foods in our diet comprise complex polymer molecules of highly different chemical natures. These complex sources require energy and coordinated processing in the body in order to be rendered into monomeric substrates that can be taken up and utilized by the cells. The oxygen needed to combine with these substrates to produce energy for cellular functions moves into cells by simple diffusion, which itself does not require expenditure of energy by the cells. However, considerable effort is required for the lungs to take up enough oxygen to meet the consumption required by the body. Furthermore, the energy-saving process of diffusion will not work unless oxygen is brought to within 100 μM of all cells in the body. Without some sort of mechanism to bring oxygen from the external environment into our body

and then transport it to within 100 μM of our cells, we could not survive. Similarly, carbon dioxide cannot simply percolate out of the body from wherever it is produced. It must be neutralized, transported away from cells, and expelled from the body via the lungs. The transport of nutrients, oxygen, carbon dioxide, and waste products to and from cells is carried out by the circulatory system. In tandem with the circulatory system is the respiratory system, also with a mechanical component, that takes oxygen from the atmosphere and transfers it to the circulatory system and expels acid-producing CO_2 as well. It is little wonder that should either our cardiovascular or pulmonary systems become dysfunctional, major complications can occur in a manner of minutes, even death.

Finally, normal function of the body and its survival as a whole require communication between our internal and external environment. Our survival is, therefore, very much dependent on such communication in support of the regulation of basic physiologic conditions within our body.

The neuroendocrine system provides a communication network to tissues and organs.

In the form of a central and peripheral nervous system, we exploit the existence of electrolytes in our body fluids to create voltages and currents that can be used to very rapidly trigger and transmit information about our external and internal environment in the form of electrical signals. These nerve signals, in turn, synthesize and deliver chemical messengers to specialized tissue and different organs. Not only does our body use such a neurological sensing and signaling system to regulate functions throughout our body, but also it exploits the existence of the blood transport system afforded by the cardiovascular system to transmit chemical signal and regulatory molecules from one organ system to another. This type of internal long-distance electrochemical information system dovetails with neurogenic mechanisms in what is collectively called the **neuroendocrine system**.

This system is essential in regulating growth, development, tissue repair, and defense. The neuroendocrine system is also involved in the maintenance of all cellular metabolic pathways, storage of metabolic substrates, electrolyte composition of the extracellular fluid, maintenance of bone structure, sexual maturation, reproduction, and birth.

In addition to long-distance electrochemical transmission, nerve signals are conducted through simple reflex circuits of the nervous system. These simple reflexes send neural signals to various systems that coordinate the activity of the different systems so that the whole body can work efficiently. For example, these simple reflexes are involved in activating muscles in our body to generate the force and motion needed for the survival advantage of physical mobility, the pumping of blood by the heart through our circulatory system, the mechanical movement of air in and out of our lungs, and the processing of complex foods by our digestive tract.

Nerve transmission and simple reflexes that are distributed across the entire system are also important in protective functions. For example, the withdrawal reflex (e.g., withdrawing the hand from a hot stove), cough reflex, stretch reflex, and scratch reflex are all part of the body's protective defense system. These simple reflexes set in motion a process to ensure that the body's tissues and organs are protected from exposure to heat, light, pressure, and toxic chemicals.

Another example of how these simple reflexes act as part of the body's

defenses is by turning a contractile skeletal muscle into an endocrine organ. When skeletal muscle contracts, cytokines and peptides, called **myokines**, are released and work in an endocrine-like fashion. The myokines exert a local effect on muscle metabolism and are involved in muscle repair and hypertrophy (increased muscle mass). These myokines are also involved in other tissue regeneration, repair, and immunomodulation. In fact, immunoregulation was the focus of early myokine research. One of the first myokines to be identified and found to be secreted into the bloodstream in response to muscle contractions was **interleukin-6** (**IL-6**). IL-6 is a cytokine that is involved in the body's inflammatory response to fighting infection and repairing wounds. The secretion of IL-6 increases in exponential fashion proportional to the length of exercise and muscle mass. In practical terms, the exercise-induced IL-6 secretion assumes physiological importance in the protection against certain types of chronic diseases.

Another myokine, brain-derived neurotrophic factor (BDNF), is also activated with exercise. Although BDNF is produced by contracting muscle, it is not released into the circulation but rather stays within skeletal tissue to enhance mitochondrial oxidation of fat. Paradoxically, BDNF activation through exercise also increases in the brain. BDNF is structurally related to growth factors and exerts its effects on neuronal development, growth, maintenance, and repair. BDNF secretion is also involved as a key component in the hypothalamic pathway that controls body mass and energy homeostasis.

To date, exercise-induced BDNF is the only mechanism known to stimulate growth of new nerve tissue. Moreover, long-term aerobic exercise has been shown to improve brain function and causes a significant enlargement in the hippocampus and cortex in the human brain. These exercise-induced changes in neural function have major practical implications in maintaining brain health and the treatment of neurological disorders. For example, dementia is a neurological disorder in which the brain loses its plasticity (i.e., loss of cellular function, circuit repair, and nerve restoration), particularly in the hippocampus.

Another structural component of the body's communication network that is involved in the body's defense system is the **autonomic nervous system**. For example, the vagus nerve, which receives and sends neural reflex signals to many organs, plays an important role in cardiac and gastrointestinal functions as well as inflammation. Stimulation of the vagus nerve inhibits the synthesis of key inflammatory mediators, which are known to exacerbate the conditions of rheumatoid arthritis and other autoimmune diseases. The use of bioelectrical stimulation at specific sites in the autonomic nervous system holds the promise of treating autoimmune diseases physiologically without the use of drugs.

Lastly, the neuroendocrine system as well as other organ systems will not work well, if at all, unless the chemical composition and volume of the aqueous environment surrounding all our cells is well regulated. The renal system has this primary responsibility in the body. Together the renal, neural, endocrine, cardiovascular, and pulmonary systems work in an integrated fashion to make valuable survival functions in our body possible.

▶ FUTURE DIRECTION OF MEDICAL PHYSIOLOGY

Physiology is playing an ever-important role in creating the framework for the maintenance of optimal health and the body's defenses. Moreover, new discoveries in physiology are continuing to provide insight into our understanding of "what makes us tick," as well as charting new directions for future medical therapies and interventions. Many of these discoveries are due to the fact that physiology applies new knowledge from other disciplines (e.g., molecular biology, genetics, immunology, biophysics, and bioengineering) to address important questions about the function and maintenance of human systems and their regulation.

Physiology is the bridge to the new science of epigenetics.

Many of the new discoveries regarding human function and survival are a result of the convergence of several of these disciplines with physiology providing a bridge between molecular/cellular events and organ function. In the past, there has been an overemphasis of genetic determination that has resulted in a scientific belief that the genes control human biology. For a long time, medical scientists thought human function and survival were controlled primarily by the body's DNA blueprint. This belief has had a major impact on the way medical scientists thought about human function. However, DNA is not the real business end of physiology, because it does not carry out many of the activities at the cellular and organ level that are required to keep the body functional and healthy. Those activities are performed mainly by proteins that get expressed by the cell's DNA, and it is these proteins that cause muscles to contract, that power the brain, that turn consumed food into nutrients that can be absorbed, and that transport oxygen throughout the circulatory system. The role of the DNA is to carry the code for all these different proteins. There is no doubt that the genetic code is a starting point and is certainly necessary. But it does not explain many of the functional variations at the tissue and organ levels or the body's ability to survive.

If only the DNA mattered, then identical twins would always be functionally identical, but this is not the case. A number of studies demonstrate that identical twins who are genetically identical show phenotypical and other differences. For instance, in one case of identical twins living together in the same family and being exposed to essentially the same environment, one twin is thin and the other overweight, one tall and the other not, one diabetic and the other not, and one an alcoholic and the other not.

Phenotypical differences between twins become even more striking when they live apart. One could argue that these phenotypic differences seen in identical twins are due to DNA mutation. However, new research shows that this is very seldom the case with twins, yet their lives are different. If nothing happened to the DNA blueprint in these individuals, then the question is, why are the differences occurring? The answer comes from an emerging field in biology called **epigenetics** that is having a major impact on human physiology. Epigenetics involves regulation at a level above the gene and shows that many of the body's functions, capabilities, and personality are not fixed at birth. Epigenetics is

upending our understanding of how life is controlled. Epigenetics studies how lifestyle and environmental signals modify and regulate gene activity. The discipline is providing a link between the external environment, genetics, and human function and shows that such things as exercise, nutrition, stress, emotions, trauma, substance abuse, and social engagement can modify gene function without altering the genes themselves or their genetic code. Even more striking is the fact that epigenetic modifications can be passed on to the next generation.

Epigenetics can be defined as a mechanism by which genes can be switched off and on, but the genes themselves and their genetic code are not altered. Epigenetics controls how the genes in the cell's DNA are used. There are regions on the outer structure of the genes, called the *epigenome*, that act like switches that can turn the cell's DNA on and off. Epigenetics is now recognized as the mechanism during development that determines whether cells, which have the same genetic code, become liver, brain, or muscle cells during cell differentiation.

Finally, epigenetics has opened a new frontier in human physiology and medicine. For example, new research shows that ~15% of the chronic diseases (e.g., obesity, diabetes, hypertension, heart attacks, strokes, and certain types of cancer) are specifically linked to genetics. The remaining factors (85%) are due to lifestyle choices (e.g., diet, exercise, emotional stress) and environmental factors (e.g., toxic agents, smoking, and substance abuse).

A paradigm shift is occurring in human physiology.

Physiologists are no longer seeing the body as just a machine in which descriptive biology is attached to structure–function events. In the last 10 years, physiologists have begun identifying specific cellular mechanisms and finding the missing links between nature and nurture. They can connect specific changes in lifestyles that alter whole body function, sometimes forever. Huge areas of physiology are being influenced by epigenetics and are filled with remarkable intrigue and complexity. This has caused a paradigm shift in physiology. Physiology has moved from structure–function relationships to epigenetics-induced functional relationships.

As a result of the shift, important discoveries are being made in neurophysiology and neuroscience, especially in neurological disorders such as dementia and Alzheimer's disease. Epigenetic-induced functional changes are also leading to new discoveries in obesity, an epidemic that has spread worldwide in the last 15 years. In the United States, approximately two out of every three adults are overweight. Obesity is linked to a wide range of health problems, including cardiovascular diseases and type 2 diabetes. In addition to overeating, the two studies cited in *Cell* and *Nature* provides evidence that a parent's diet can directly influence the epigenetic modification that predisposes the offspring to obesity and diabetes.

Another field in which epigenetic-induced functional changes are playing a significant role is in the field of aging. Aging can be defined as "the progressive decline of organ function that eventually results in disease and mortality." Because identical twins with the same genetic makeup can age differently, the questions for future research will be to determine how epigenetics changes with age. Equally important will be to determine how epigenetics can have both a positive and a negative effect on aging. For example, a sedentary lifestyle with poor eating habits, high stress, smoking, and excessive drinking can cause epigenetic-induced effects that accelerate the aging process, whereas a healthy lifestyle that includes daily exercise, good nutrition, smoking avoidance, and less stress can cause epigenetic-induced changes that keep the body younger.

The paradigm shift also has altered our thinking in unexpected frontiers of human function. In the past, medical scientists have been seeing human health and survival from the level of the gene alone. Epigenetic-induced physiologic changes are making it clear that individuals are no longer doomed by their genes. In practical terms, research indicates that about 20% of an individual's health,

diseases, and how he or she ages is due to genetics, and the remaining 80% is dependent on epigenetic-induced alterations in human function via changes in lifestyle and environment. For example, many of the diseases that cause early death (high blood pressure, obesity, diabetes, heart attacks, strokes, cancer) are classified as 80/20: 20% due to genetics and 80% related to lifestyle.

In summary, physiology has provided remarkable insight into how cells, tissues, and organs interact and how they are regulated. The interaction between physiology and the new science of epigenetics is showing that human health and survival are no longer determined by the limits set by our genes. Moreover, recent medical advances show the extraordinary influence individuals have over the control of their health, quality of life, and how they age. Lastly, the paradigm shift in epigenetic-induced functional changes is providing new directions for the future treatment of human diseases.

2 Cell Signaling, Membrane Transport, and Membrane Potential

Active Learning Objectives

Upon mastering the material in this chapter, you should be able to:

- Compare and contrast negative and positive feedback and explain the importance of these processes to homeostasis.
- Explain the difference between steady state and equilibrium, including the role of energy expenditure in these concepts.
- List the types of molecules that constitute the plasma membrane and explain how they are assembled to form a selectively permeable barrier.
- Describe how the plasma membrane maintains an internal environment that differs significantly from the extracellular fluid.
- Contrast how voltage-gated channels and ligand-gated channels are opened.
- Compare and contrast carrier-mediated transport systems with channels.
- Describe primary active transport and explain how secondary active transport is different.
- Describe the properties of epithelial cells that are necessary to produce directional movement of solutes and water.
- Outline the mechanisms that many cells use to regulate their volume when exposed to osmotic stress.
- List the key components of the Goldman equation and explain why this equation gives the value of the membrane potential.
- Explain why the resting membrane potential of most cells is close to the Nernst potential for K^+.
- Compare and contrast autocrine, paracrine, and endocrine signaling in the control of cell function.
- Describe how second messengers both regulate and amplify signal transduction.
- Explain the major differences between intracellular signal transduction by G-protein–coupled receptors and tyrosine kinase receptors.
- Describe how intracellular calcium concentration is regulated and used in intracellular signal transduction.

The scope of physiology ranges from the functions of individual molecules and cells to the interaction of our bodies with the external world. Understanding how the different cell types that constitute tissues are controlled, how they interact both within and with other tissues, and how they adapt to changing conditions is central to the study of physiology. To maintain health, conditions in the body must be optimized through closely regulated processes that require efficient communication between cells and tissues.

Cells are delineated by their plasma membrane, a barrier that separates the cytosol from the extracellular fluid (ECF). The plasma membrane keeps ions, metabolites, and cell proteins needed for normal cell function from leaking out, allows specific ions and molecules to enter, and blocks entry of factors not needed by the cell. To function in coordination with the rest of the organism, cells send and receive information that is first processed by specific plasma membrane proteins.

This chapter discusses topics related to regulation of cellular homeostasis and communication between cells and tissues. Specific topics include the internal environment, types of membrane transport mechanisms for ions and other solutes, steady state and equilibrium, intercellular and intracellular communication, negative and positive feedback, feedforward control, and intracellular signal transduction cascades.

BASIS OF PHYSIOLOGIC REGULATION

Our bodies are made up of incredibly complex and delicate materials, and we are constantly subjected to all kinds of disturbances, yet we keep going for a lifetime. It is clear that conditions and processes in the body must be closely controlled and regulated—that is, kept within appropriate values. Below, we consider, in broad terms, physiologic regulation in the body.

Stable internal environment is essential for normal cell function.

The 19th-century French physiologist Claude Bernard was the first to formulate the concept of the internal environment (*milieu intérieur*). He pointed out that an external environment surrounds multicellular organisms (air or water) and a liquid internal environment (ECF) surrounds the cells that make up the organism. Cells are not directly exposed to the external world but, rather, interact with it through their surrounding environment, which is continuously renewed by the circulating blood.

For optimal cell, tissue, and organ function in animals, several facets of the internal environment must be maintained within narrow limits. These include but are not limited to (1) oxygen and carbon dioxide tensions; (2) concentrations of glucose and other metabolites; (3) osmotic pressure; (4) concentrations of hydrogen, potassium, calcium, and magnesium ions; and (5) temperature. Departures from optimal conditions may result in dysfunction, disease, or death. Bernard stated, “Stability of the internal environment is the primary condition for a free and independent existence.” He recognized that an animal’s independence from changing external conditions is related to its capacity to maintain a relatively constant internal environment. A good example is the ability of warm-blooded animals to live in different climates. Over a wide range of external temperatures, core temperature in mammals is maintained constant by both physiologic and behavioral mechanisms. This stability offers great flexibility and has an obvious survival value.

Homeostasis is the maintenance of steady states in the body by coordinated physiologic mechanisms.

The key to maintaining the stability of the body's internal environment is the masterful coordination of important regulatory mechanisms in the body. The renowned physiologist Walter B. Cannon captured the spirit of the body's capacity for self-regulation by defining the term **homeostasis** as the maintenance of steady states in the body by coordinated physiologic mechanisms.

Understanding the concept of homeostasis is important for understanding and analyzing normal and pathologic conditions in the body. To function optimally under a variety of conditions, the body must sense departures from normal and then be able to activate mechanisms for restoring physiologic conditions to normal. Deviations from normal conditions may vary between too high and too low, so mechanisms exist for opposing changes in either direction.

Homeostatic regulation of a physiologic variable often involves several cooperating mechanisms activated at the same time or in succession. The more important a variable, the more numerous and complicated are the mechanisms that operate to keep it at the desired value. When the body is unable to restore physiologic variables, then disease or death can result. The ability to maintain homeostatic mechanisms varies over a person's lifetime, with some homeostatic mechanisms not being fully developed at birth and others declining with age. For example, a newborn infant cannot concentrate urine as well as an adult and is, therefore, less able to tolerate water deprivation. Older adults are less able to tolerate stresses, such as exercise or changing weather, than are younger adults.

The term *homeostasis* traditionally refers to the ECF that bathes our tissues—but it can also be applied to conditions within cells. In fact, the ultimate goal of maintaining a constant internal environment is to promote intracellular homeostasis, and toward this end, conditions in the cytosol of cells are closely regulated.

Negative feedback promotes stability, and feedforward control anticipates change.

Feedback is a flow of information along a closed loop. The components of a simple negative-feedback control system include a regulated variable, sensor, controller, and effector (Fig. 2.1). Each component controls the next component. Various disturbances may arise within or outside the system and cause undesired changes in the regulated variable. With **negative feedback**, a regulated variable is sensed, information is fed back to the controller, and the effector acts to oppose change (hence the term *negative*).

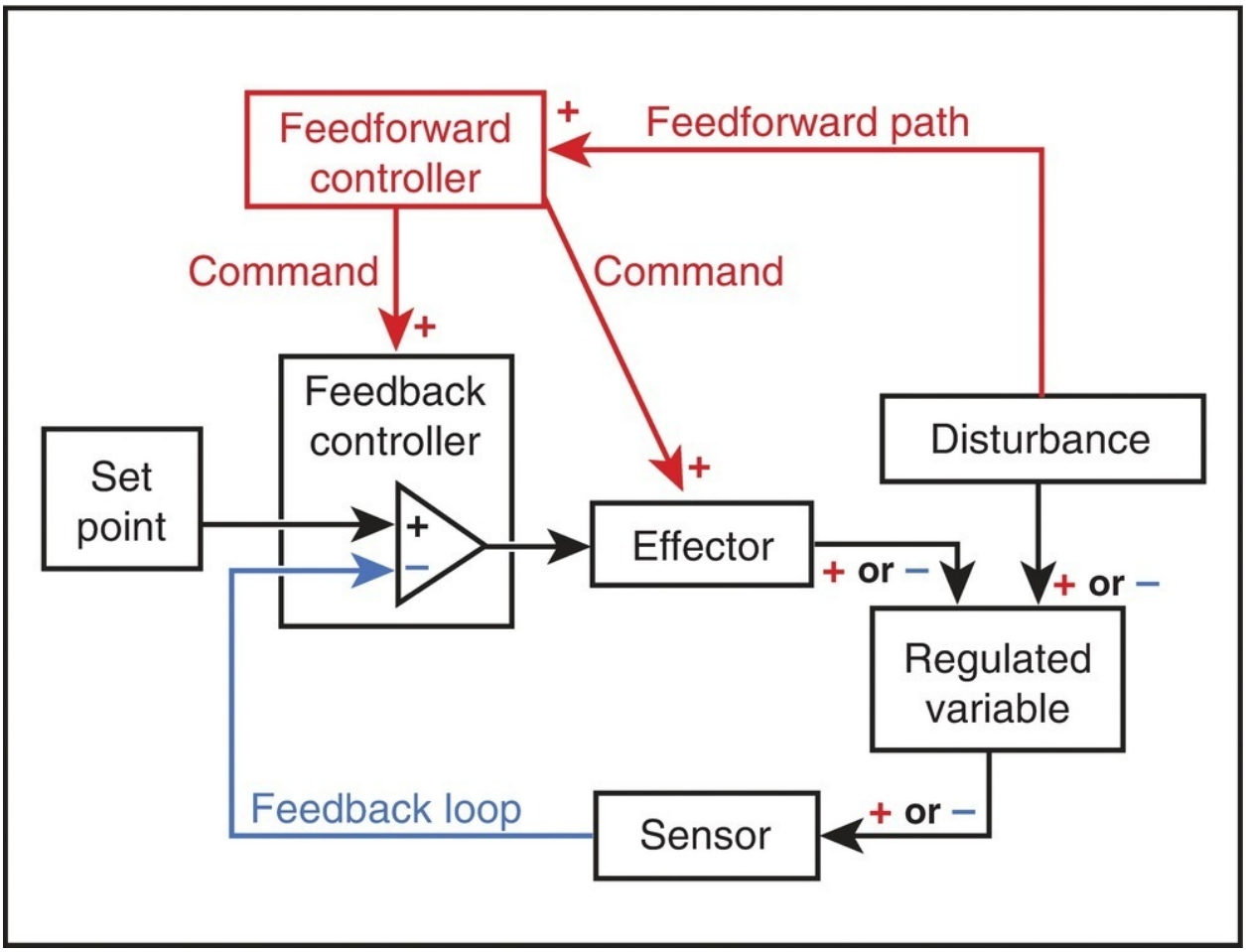

Figure 2.1 Elements of negative-feedback and feedforward control systems. In a negative-feedback control system, information flows along a closed loop. The regulated variable is sensed, and information about its level is provided to a

feedback controller, which compares it with a desired value (set point). If there is a difference, an error signal is generated, which drives the effector to bring the regulated variable closer to the desired value. A feedforward controller generates commands without directly sensing the regulated variable, although it may sense a disturbance. Feedforward controllers often operate through feedback controllers.

A familiar example of a negative-feedback control system is the thermostatic control of room temperature. Room temperature (regulated variable) is subjected to disturbances. For example, room temperature falls on a cold day. A thermometer (sensor) in the thermostat (controller) detects the room temperature. The thermostat is set for a certain temperature (set point). The controller compares the actual temperature (feedback signal) with the set point temperature, and an error signal is generated if the room temperature falls below the set temperature. The error signal activates the furnace (effector). The resulting change in room temperature is monitored, and when the temperature rises sufficiently, the furnace is turned off. Such a negative-feedback system allows some fluctuation in room temperature, but the components act together to maintain the set temperature. Effective communication between the sensor and effector is important in keeping these oscillations to a minimum.

Similar negative-feedback systems exist to maintain homeostasis in the body. For example, the maintenance of water and salts in the body is referred to as **osmoregulation** or fluid balance. During exercise, loss of water from sweating results in an increased concentration of salts in the blood and tissue fluids, which is sensed by the cells in the brain (see Chapter 23). The brain responds by telling the kidneys to reduce secretion of water and also by increasing the sensation of thirst. Together, the reduction in water loss in the kidneys and increased water intake return the blood and tissue fluids to the correct osmotic concentration. This negative-feedback system allows for minor fluctuations in water and salt concentrations in the body but rapidly compensates for disturbances to restore acceptable osmotic conditions.

Feedforward control is another strategy for regulating body systems, particularly when a change with time is desired. In this case, a command signal is generated, which specifies the target or goal. The moment-to-moment operation of the controller is “open loop”; that is, the regulated variable itself is not sensed. Feedforward control mechanisms often sense a disturbance and can, therefore, take corrective action that anticipates change. For example, heart rate and breathing increase even before a person has begun to exercise.

Feedforward control usually acts in combination with negative-feedback systems. One example is picking up a pencil. The movements of the arm, hand, and fingers are directed by the cerebral cortex (feedforward controller); the movements are smooth, and forces are appropriate only in part because of the feedback of visual information and sensory information from receptors in the joints and muscles. Another example of this combination occurs during exercise. Respiratory and cardiovascular adjustments closely match muscular activity, so that arterial blood oxygen and carbon dioxide tensions (the partial pressure of a gas in a liquid) hardly change during all but exhausting exercise (see Chapter 21). Importantly, control system function can adapt over time. Past experience and learning can change the control system's output so that it behaves more efficiently or appropriately.

Although homeostatic control mechanisms usually act for the good of the body, they are sometimes deficient, inappropriate, or excessive. Many diseases, such as cancer, diabetes, and hypertension, develop because of defects in control mechanisms. Formation of a scar is an example of an important homeostatic mechanism for healing wounds, but in many chronic diseases, such as pulmonary fibrosis, hepatic cirrhosis, and renal interstitial disease, scar formation goes awry and becomes excessive.

Positive feedback promotes a change in one direction.

With **positive feedback**, a variable is sensed and action is taken to reinforce a change of the variable. The term positive refers to the response being in the same direction, leading to a cumulative or amplified effect. Positive feedback does not lead to stability or regulation, but to the opposite—a progressive change in one direction. One example of positive feedback is the sensation of needing to urinate. As the bladder fills, mechanosensors in the bladder are stimulated, and the smooth muscle in the bladder wall begins to contract (see Chapter 23). As the bladder continues to fill and become more distended, the contractions increase and the need to urinate becomes more urgent. Responding to the need to urinate results in a sensation of immediate relief upon emptying the bladder, and this is positive feedback. Another example of positive feedback occurs during the follicular phase of the menstrual cycle. The female sex hormone estrogen stimulates the release of luteinizing hormone, which in turn causes further estrogen synthesis by the ovaries. This positive feedback culminates in ovulation (see Chapter 37). Positive feedback, if unchecked, can lead to a vicious cycle and dangerous situations. For example, a heart may be so weakened by disease that it cannot provide adequate blood flow to the muscle tissue of the heart. This leads to a further reduction in cardiac pumping ability, even less coronary blood flow, and further deterioration of cardiac function. The physician's task sometimes is to disrupt detrimental cyclical positive-feedback loops.

Steady state and equilibrium are both stable conditions, but energy is required to maintain a steady state.

Simplistically, the whole body can be divided into two major compartments: intracellular fluid and ECF, which are separated by cell plasma membranes. The fluid component of the body constitutes about 60% of the total body weight. The intracellular fluid compartment constitutes about two thirds of the body's water and contains potassium, other ions, and proteins. The ECF compartment constitutes one third of the body's water (~20% body weight) and consists of all the body fluids outside of cells, including the interstitial fluid that bathes the cells, lymph, blood plasma, and specialized fluids such as cerebrospinal fluid. It is primarily a sodium chloride (NaCl) and sodium carbonate ($NaHCO_3$) solution that can be divided into three subcompartments: the interstitial fluid (lymph and plasma); plasma that circulates as the extracellular component of blood; and transcellular fluid, which is a set of fluids that are outside of normal compartments, such as cerebrospinal fluid, digestive fluids, and mucus.

When two compartments are in **equilibrium**, *opposing forces are balanced*, and there is no net transfer of a particular substance or energy from one compartment to the other. Equilibrium occurs if sufficient time for exchange has been allowed and if no physical or chemical driving force would favor net movement in one direction or the other. For example, osmotic equilibrium between cells and ECF is normally present in the body because of the high water permeability of most cell membranes. An equilibrium condition, if undisturbed, remains stable. No energy expenditure is required to maintain an equilibrium state.

Equilibrium and steady state are sometimes confused with each other. A **steady state** is simply a condition that does not change with time. It indicates that the amount or concentration of a substance in a compartment is constant. In a steady state, there is no net gain or net loss of a substance in a compartment. Steady state and equilibrium both suggest stable conditions, but a steady state does not necessarily indicate an equilibrium condition, and energy expenditure may be required to maintain a steady state. For example, in most body cells, there is a steady state for Na^+ ions; the amounts of Na^+ entering and leaving cells per unit time are equal. But intracellular and extracellular Na^+ ion concentrations are far

from equilibrium. Extracellular [Na^+] is much higher than intracellular [Na^+], and Na^+ tends to move into cells down concentration and electrical gradients. The cell continuously uses metabolic energy to pump Na^+ out of the cell to maintain the cell in a steady state with respect to Na^+ ions. In living systems, conditions are often displaced from equilibrium by the constant expenditure of metabolic energy.

Figure 2.2 illustrates the distinctions between steady state and equilibrium. In Figure 2.2A, the fluid level in the sink is constant (a steady state) because the rates of inflow and outflow are equal. If we were to increase the rate of inflow (open the tap), the fluid level would rise, and with time, a new steady state might be established at a higher level. In Figure 2.2B, the fluids in compartments X and Y are not in equilibrium (the fluid levels are different), but the system as a whole and each compartment are in a steady state, because inputs and outputs are equal. In Figure 2.2C, the system is in a steady state and compartments X and Y are in equilibrium. Note that the term *steady state* can apply to a single or several compartments; the term *equilibrium* describes the relation between at least two adjacent compartments that can exchange matter or energy with each other.

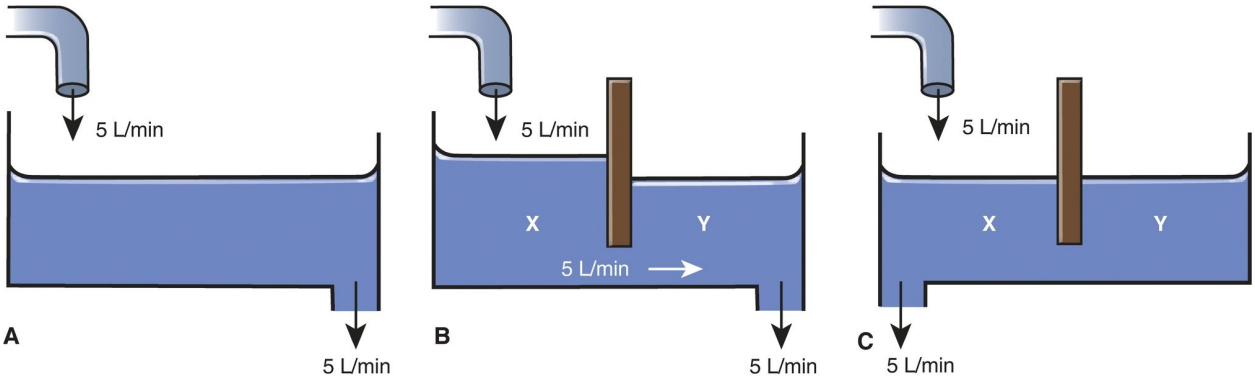

Figure 2.2 Models of the concepts of steady state and equilibrium. Parts **(A–C)** depict a steady state. In **(C)**, compartments X and Y are in equilibrium.

PLASMA MEMBRANE STRUCTURE

The first theory of membrane structure proposed that cells were surrounded by a double layer of lipid molecules, a **lipid bilayer**. However, this theory, based on the knowledge that lipid molecules form bilayers with low permeability to water-soluble molecules, did not explain the selective movement of certain water-soluble compounds, such as glucose and amino acids, across the plasma membrane. In 1972, Singer and Nicolson proposed the **fluid mosaic model** of the plasma membrane, which described the organization and interaction of proteins with the lipid bilayer (Fig. 2.3). With minor modifications, this model is still accepted as the correct picture of the structure of the plasma membrane.

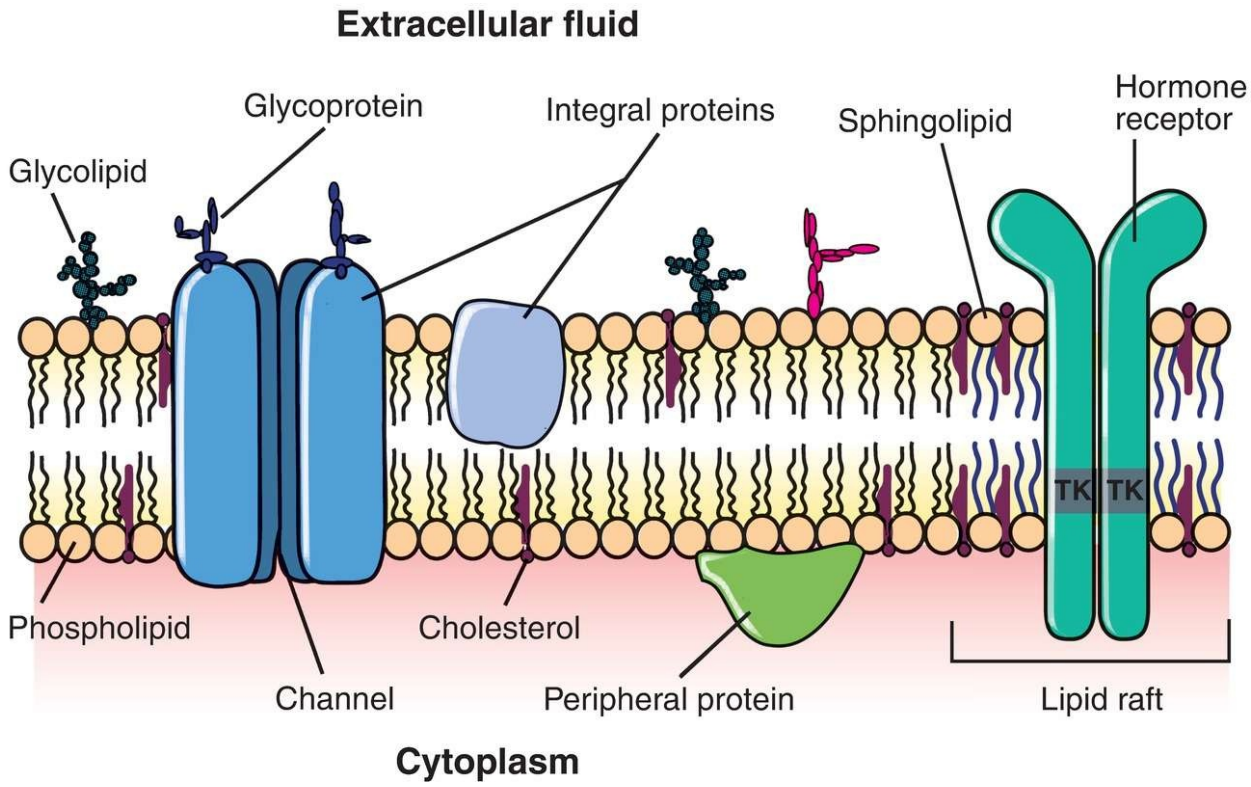

Figure 2.3 The fluid mosaic model of the plasma membrane. Lipids are arranged in a bilayer. Cholesterol provides rigidity to the bilayer. Integral proteins are embedded in the bilayer and often span it. Some membrane-spanning proteins form pores and channels. In some specialized cases, transmembrane pores on adjacent cells fuse together to form gap junctions that facilitate communication between the two cells. Other membrane-spanning proteins are receptors. Peripheral proteins do not penetrate the bilayer. Lipid rafts form stable

microdomains composed of sphingolipids and cholesterol.

Plasma membrane consists of different types of membrane lipids with different functions.

Lipids found in cell membranes can be classified into two broad groups: **phospholipids,** which contain fatty acids as part of the molecule and **cholesterol**, which does not have a fatty acid in its structure.

Phospholipids are the most abundant complex lipids found in cell membranes. They are amphipathic molecules formed by two fatty acids (normally, one saturated and one unsaturated) and one phosphoric acid group substituted on the backbone of a glycerol or sphingosine molecule. This arrangement produces a hydrophobic area formed by the two fatty acids and a polar hydrophilic head. When phospholipids are arranged in a bilayer, the polar heads are on the outside and the hydrophobic fatty acids on the inside (see Fig. 2.3). It is difficult for water-soluble molecules and ions to pass directly through the hydrophobic interior of the lipid bilayer.

The phospholipids, with a backbone of sphingosine (a long amino alcohol), are usually called *sphingolipids* and are present in all plasma membranes in small amounts. They are especially abundant in brain and nerve cells. Ceramide is a lipid second messenger that is generated from the sphingolipid sphingomyelin.

Glycolipids are lipid molecules that contain sugars and sugar derivatives (instead of phosphoric acid) in the polar head. They are located mainly in the outer half of the lipid bilayer, with the sugar molecules facing the ECF. Proteins can associate with the plasma membrane by linkage to the extracellular sugar moiety of glycolipids.

Cholesterol is an important component of mammalian plasma membranes. The proportion of cholesterol in plasma membranes varies from 10% to 50% of total lipids. Cholesterol has a rigid structure that stabilizes the cell membrane and reduces the natural mobility of lipids and proteins to move in the membrane. Some cell functions, such as the response of immune system cells to the presence of an antigen, depend on the ability of membrane proteins to move in the plane of the membrane to bind the antigen. A decrease in membrane fluidity resulting from an increase in cholesterol will impair these functions.

Aggregates of sphingolipids and cholesterol can form stable microdomains termed **lipid rafts** that diffuse laterally in the phospholipid bilayer. The protein **caveolin** is present in a subset of lipid rafts (termed **caveolae**), causing the raft to

form a cavelike structure. It is believed that one function of both noncaveolar and caveolar lipid rafts is to facilitate interactions between specific proteins by selectively including (or excluding) these proteins from the raft microdomain. For example, lipid rafts can mediate the assembly of membrane receptors and intracellular signaling proteins as well as the sorting of plasma membrane proteins for internalization.

Proteins are integrally and peripherally associated with the plasma membrane.

Proteins are the second major component of the plasma membrane, present in about equal proportion by weight with the lipids. Two different types of proteins are associated with the plasma membrane. **Integral proteins** are embedded in the lipid bilayer, and many span it completely. The polypeptide chain of these proteins may cross the lipid bilayer once or may make multiple passes across it. The membrane-spanning segments usually contain amino acids with nonpolar side chains and are arranged in an ordered α-helical conformation. **Peripheral proteins** do not penetrate the lipid bilayer. They are in contact with the outer side of only one of the lipid layers—either the layer facing the cytoplasm or the layer facing the ECF (see Fig. 2.3). Many membrane proteins have carbohydrate molecules (sugar molecules) attached to the part of the protein that is exposed to the ECF and are termed **glycoproteins**. Some of the integral membrane proteins can move in the plane of the membrane, like small boats floating in the "sea" formed by the lipid bilayer. Other membrane proteins are anchored to the cytoskeleton inside the cell or to proteins of the extracellular matrix.

The proteins in the plasma membrane play a variety of roles. Many peripheral membrane proteins are enzymes, and many membrane-spanning integral proteins are carriers or channels for the movement of water-soluble molecules and ions into and out of the cell. **Gap junctions** are specialized protein channels, made of the protein **connexin**, that facilitate direct cell to cell communication. Six connexins assemble in the plasma membrane of a cell to form a half channel called a **connexon**. Two connexons aligned between two neighboring cells then join end to end to form an intercellular channel between the plasma membranes of adjacent cells. Gap junctions allow the flow of ions and small molecules between the cytosol of neighboring cells, thereby providing rapid transmission of electrical signals between cells in the heart, smooth muscle cells, and some nerve cells. Gap junctions are thought to play a role in the control of cell growth and differentiation by allowing adjacent cells to share a common intracellular environment. Often when a cell is injured, gap junctions close, isolating a damaged cell from its neighbors.

Membrane proteins also have a structural role, for example, maintaining the biconcave shape of the erythrocyte. Finally, some membrane proteins serve as highly specific receptors on the outside of the cell membrane to which

extracellular molecules, such as hormones, can bind. If the receptor is a membrane-spanning protein, it provides a mechanism for converting an extracellular signal into an intracellular response.

SOLUTE TRANSPORT MECHANISMS

All cells must import oxygen, sugars, amino acids, and small ions and export carbon dioxide, metabolic wastes, and secretions. At the same time, specialized cells require mechanisms to transport molecules such as enzymes, hormones, and neurotransmitters. The movement of large molecules is carried out by endocytosis and exocytosis: the transfer of substances into or out of the cell by vesicle formation and vesicle fusion with the plasma membrane. Cells also have mechanisms for the rapid movement of ions and solute molecules across the plasma membrane. These mechanisms are of two general types: **passive transport**, which requires no direct expenditure of metabolic energy, and **active transport**, which uses metabolic energy to move solutes across the plasma membrane.

Import of extracellular materials occurs through phagocytosis and endocytosis.

Phagocytosis is the ingestion of large particles or microorganisms, usually occurring only in specialized cells such as macrophages (Fig. 2.4). An important function of macrophages is to remove invading bacteria from the body. The phagocytic vesicle (1 to 2 μm in diameter) is almost as large as the phagocytic cell itself. Phagocytosis requires a specific stimulus. It occurs only after the extracellular particle has bound to the extracellular surface. The particle is then enveloped by expansion of the cell membrane around it.

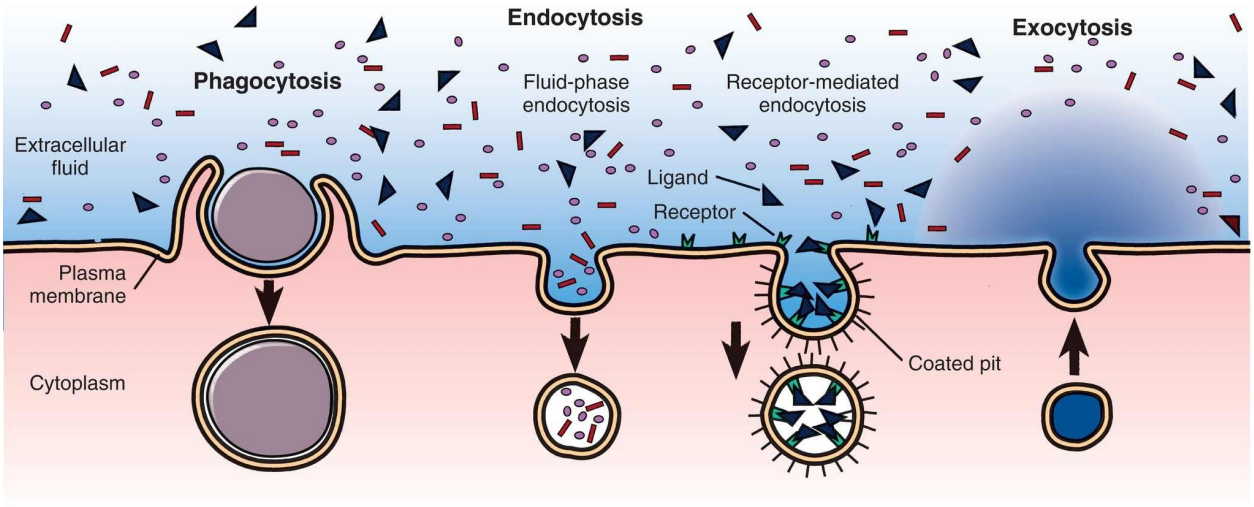

Figure 2.4 The transport of macromolecules across the plasma membrane by the formation of vesicles. Particulate matter in the extracellular fluid (ECF) is engulfed and internalized by phagocytosis. During fluid-phase endocytosis, ECF and dissolved macromolecules enter the cell in endocytic vesicles that pinch off at depressions in the plasma membrane. Receptor-mediated endocytosis uses membrane receptors at coated pits to bind and internalize specific solutes (ligands). Exocytosis is the release of macromolecules destined for export from the cell. These are packed inside secretory vesicles that fuse with the plasma membrane and release their contents outside the cell.

Endocytosis is a general term for the process in which a region of the plasma membrane is pinched off to form an endocytic vesicle inside the cell. During

vesicle formation, some fluid, dissolved solutes, and particulate material from the extracellular medium are trapped inside the vesicle and internalized by the cell. Endocytosis produces much smaller endocytic vesicles (0.1 to 0.2 μm in diameter) than phagocytosis. It occurs in almost all cells and is termed a constitutive process, because it occurs continually and specific stimuli are not required. In further contrast to phagocytosis, endocytosis originates with the formation of depressions in the cell membrane. The depressions pinch off within a few minutes after forming and give rise to endocytic vesicles inside the cell.

Two types of endocytosis can be distinguished (see Fig. 2.4). **Fluid-phase endocytosis** is the nonspecific uptake of the ECF and all its dissolved solutes. The material is trapped inside the endocytic vesicle as it is pinched off inside the cell. The amount of extracellular material internalized by this process is directly proportional to its concentration in the extracellular solution. **Receptor-mediated endocytosis** is a more efficient process, which uses receptors on the cell surface to bind specific molecules. These receptors accumulate at specific depressions known as **coated pits**, so named because the cytosolic surface of the membrane at this site is covered with a coat of several proteins. The coated pits pinch off continually to form endocytic vesicles, providing the cell with a mechanism for rapid internalization of a large amount of a specific molecule without the need to endocytose large volumes of ECF. The receptors also increase the uptake of molecules present at low concentrations outside the cell. Receptor-mediated endocytosis is the mechanism by which cells take up a variety of important molecules, including hormones, growth factors, and serum transport proteins such as the iron carrier **transferrin**. Foreign substances, such as diphtheria toxin and certain viruses, also enter cells by this pathway.

Export of macromolecules occurs through exocytosis.

Many cells synthesize important macromolecules that are destined for **exocytosis** or export from the cell. These molecules are synthesized in the endoplasmic reticulum, modified in the Golgi apparatus, and packed inside transport vesicles. The vesicles move to the cell surface, fuse with the cell membrane, and release their contents outside the cell (see Fig. 2.4).

There are two exocytic pathways—constitutive and regulated. The continuous secretion of mucus by **goblet cells** in the small intestine is an example of the *constitutive pathway* of exocytosis that is present in all cells. In other cells, macromolecules are stored inside the cell in secretory vesicles. These vesicles fuse with the cell membrane and release their contents only when a specific extracellular stimulus arrives at the cell membrane. This process, termed the *regulated pathway*, is responsible for the rapid "on-demand" secretion of many specific hormones, neurotransmitters, and digestive enzymes.

Uncharged solutes cross the plasma membrane by passive diffusion.

Any solute will tend to uniformly occupy the entire space available to it. This movement, known as **diffusion**, is a result of the spontaneous Brownian (random) movement that all molecules experience. A drop of ink placed in a glass of water will diffuse and slowly color all the water. The net result of diffusion is the movement of substances from regions of high concentration to regions of low concentration. Diffusion is an effective way for substances to move short distances.

The speed with which the diffusion of a solute in water occurs depends on the difference of concentration, the size of the molecules, and the possible interactions of the diffusible substance with water. These different factors appear in **Fick's law**, which describes the diffusion of any solute in water. In its simplest formulation, Fick's law can be written as:

$$J = DA(C_1 - C_2)/\Delta X \quad (1)$$

where J is the flow of solute from region 1 to region 2 in the solution; D is the diffusion coefficient of the solute, which is determined by factors such as solute molecular size and interactions of the solute with water; A is the cross-sectional area through which the flow of solute is measured; C is the concentration of the solute at regions 1 and 2; and DX is the distance between regions 1 and 2. Sometimes, J is expressed in units of amount of substance per unit area per unit time, for example, mol/cm^2/h, and is also referred to as the solute **flux**.

The principal force driving the passive diffusion of an uncharged solute across the plasma membrane is the difference of concentration between the inside and the outside of the cell. In the case of an electrically charged solute, such as an ion, diffusion is also driven by the membrane potential, which is the electrical gradient across the membrane. Movement of charged solutes and the membrane potential will be discussed in greater detail later in this chapter.

Diffusion across a membrane has no preferential direction; it can occur from the outside of the cell toward the inside or from the inside of the cell toward the

outside. For any substance, it is possible to measure the **permeability coefficient** (**P**), which gives the speed of the diffusion across a unit area of plasma membrane for a defined driving force. Fick's law for the diffusion of an uncharged solute across a membrane can be written as

$$J = PA(C_1 - C_2) \quad (2)$$

which is similar to equation 1. P includes the membrane thickness, the diffusion coefficient of the solute within the membrane, and the solubility of the solute in the membrane. Dissolved gases such as oxygen and carbon dioxide have high permeability coefficients and diffuse rapidly across the plasma membrane. As a result, gas exchange in the lungs is very effective. Diffusion across the plasma membrane implies that the diffusing solute enter the lipid bilayer to cross it; thus, the solute's solubility in a lipid solvent (e.g., olive oil or chloroform) compared with its solubility in water is important in determining its permeability coefficient.

A substance's solubility in oil compared with its solubility in water is its **partition coefficient**. Lipophilic (lipid-soluble) substances, such as gases, steroid hormones, and anesthetic drugs, which mix well with the lipids in the plasma membrane, have high partition coefficients and, as a result, high permeability coefficients; they tend to cross the plasma membrane easily. Hydrophilic (water-soluble) substances, such as ions and sugars, do not interact well with the lipid component of the membrane, have low partition coefficients and low permeability coefficients, and diffuse across the membrane more slowly.

Solutes such as oxygen readily diffuse across the lipid part of the plasma membrane by simple diffusion. Thus, the relationship between the rate of movement and the difference in concentration between the two sides of the membrane is linear (Fig. 2.5). The larger the difference in concentration ($C_1 - C_2$), the greater the amount of substance crossing the membrane per unit time.

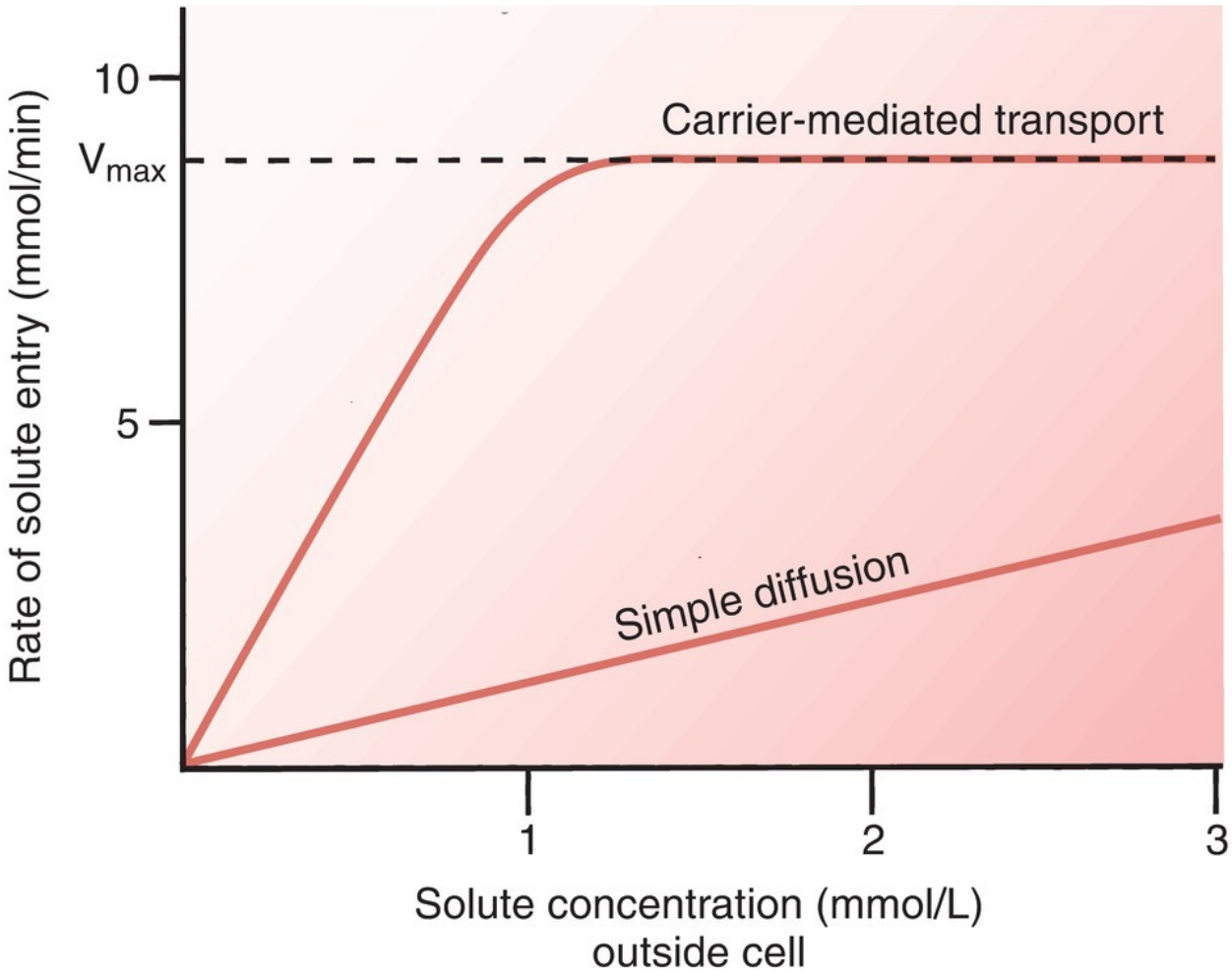

Figure 2.5 Solute transport across a plasma membrane by simple or facilitated diffusion. In simple diffusion, the rate of solute entry increases linearly with extracellular concentration of the solute. Assuming no change in intracellular concentration, increasing the extracellular concentration increases the gradient that drives solute entry. In facilitated diffusion, the rate of transport is much faster, and increases linearly as the extracellular solute concentration increases. The increase in transport is limited by the availability of channels and carriers. Once all are occupied by solute, further increases in extracellular concentration have no effect on the rate of transport. A maximum rate of transport (V_{max}) is achieved that cannot be exceeded.

Integral membrane proteins facilitate diffusion of solutes across the plasma membrane.

For many solutes of physiologic importance, such as ions, sugars, and amino acids, the rate of transport across the plasma membrane is much faster than expected for simple diffusion through a lipid bilayer. Furthermore, the relationship between transport rate and concentration difference of these hydrophilic substances follows a curve that reaches a plateau (see Fig. 2.5). Membrane transport with these characteristics is often called **facilitated diffusion** or **carrier-mediated diffusion**, because an integral membrane protein facilitates the movement of a solute through the membrane. Integral membrane proteins can form pores, channels, or carriers, each of which facilitates the transport of specific molecules across the membrane.

There are a limited number of pores, channels, and carriers in any cell membrane; thus, increasing the concentration of the solute initially uses the existing "spare" pores, channels, or carriers to transport the solute at a higher rate than by simple diffusion. As the concentration of the solute increases further and more solute molecules associate with the pore, channel, or carrier, the transport system eventually reaches saturation, when all the pores, channels, and carriers are involved in translocating molecules of solute. At this point, additional increases in solute concentration do not increase the rate of solute transport (see Fig. 2.5).

The types of integral membrane protein transport mechanisms considered here can transport a solute along its concentration gradient only, as in simple diffusion. Net movement stops when the concentration of the solute has the same value on both sides of the membrane. At this point, with reference to equation 2, $C_1 = C_2$ and the value of J is 0. The transport systems function until the solute concentrations have equilibrated. However, equilibrium is attained much faster than with simple diffusion.

Membrane pores

A pore provides a conduit through the lipid bilayer that is always open to both sides of the membrane. **Aquaporins** in the plasma membranes of specific kidney and gastrointestinal tract cells permit the rapid movement of water. Within the **nuclear pore complex**, which regulates movement of molecules into and out of the nucleus, is an aqueous pore that only allows the passive movement of molecules

smaller than 45 kDa and excludes molecules larger than 62 kDa. The **mitochondrial permeability transition pore** and **mitochondrial voltage-dependent anion channel** (**VDAC**), which cross the inner and outer mitochondrial membranes, promote mitochondrial failure when formed, resulting in the generation of **reactive oxygen species** and cell death.

Gated channels

Small ions, such as Na^+, K^+, Cl^-, and Ca^{2+}, cross the plasma membrane faster than would be expected based on their partition coefficients in the lipid bilayer. The electrical charge of an ion makes it difficult for the ion to move across the lipid bilayer. The excitation of nerves, the contraction of muscle, the beating of the heart, and many other physiologic events are possible because of the ability of small ions to enter or leave the cell rapidly. This movement occurs through selective ion channels.

Ion channels are composed of several polypeptide subunits that span the plasma membrane and contain a gate that determines if the channel is open or closed. Specific stimuli cause a conformational change in the protein subunits to open the gate, creating an aqueous channel through which the ions can move (Fig. 2.6). In this way, ions do not have to enter the lipid bilayer to cross the membrane; they are always in an aqueous medium. When the channels are open, the ions diffuse rapidly from one side of the membrane to the other down the concentration gradient. Specific interactions between the ions and the sides of the channel produce an extremely rapid rate of ion movement; in fact, ion channels permit a much faster rate of solute transport (about 10^8 ions/s) than the carrier-mediated systems discussed below. Ion channels have a selectivity filter, which regulates the transport of certain classes of ions such as anions or cations or specific ions such as Na^+, K^+, Ca^{2+}, and Cl^- (see Fig. 2.6).

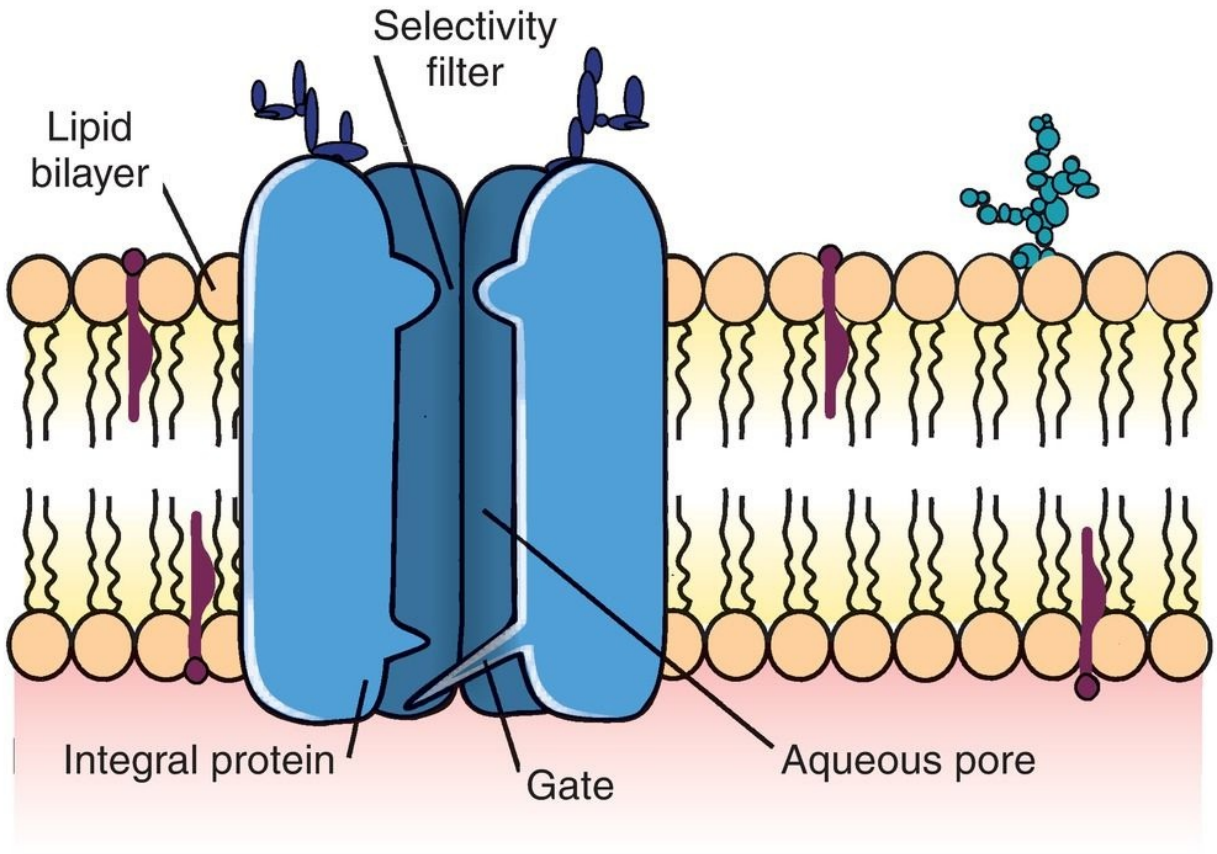

Figure 2.6 An ion channel. The polypeptide subunits of integral proteins that span the plasma membrane provide an aqueous pore through which ions can cross the membrane. Different types of gating mechanisms are used to open and close ion channels that are often selective for a specific ion.

In general, ion channels exist either fully open or completely closed, and they open and close very rapidly. The frequency with which a channel opens is variable, and the time the channel remains open (usually a few milliseconds) is also variable. The overall rate of ion transport across a membrane can be controlled by changing the frequency of a channel opening or by changing the time a channel remains open.

Most ion channels usually open in response to a specific stimulus. Ion channels can be classified according to their gating mechanisms, the signals that make them open or close. There are voltage-gated channels and ligand-gated channels. Some ion channels are more like membrane pores in that they are always open; these ion transport proteins are referred to as *nongated channels*.

Voltage-gated ion channels open when the membrane potential changes

beyond a certain threshold value. Channels of this type are involved in conducting the excitation signal along nerve axons and include sodium and potassium channels (see Chapter 3). Voltage-gated ion channels are found in many cell types. It is thought that some charged amino acids located in a membrane-spanning α-helical segment of the channel protein are sensitive to the transmembrane potential. Changes in the membrane potential cause these amino acids to move and induce a conformational change of the protein that opens the way for the ions.

Ligand-gated ion channels cannot open unless they first bind to a specific agonist. The opening of the gate is produced by a conformational change in the protein induced by the ligand binding. The ligand can be a neurotransmitter arriving from the extracellular medium. It can also be an intracellular second messenger, produced in response to some cell activity or hormone that reaches the ion channel from the inside of the cell. The nicotinic acetylcholine receptor channel found in the postsynaptic neuromuscular junction (see Chapters 3 and 8) is a ligand-gated ion channel that is opened by an extracellular ligand (acetylcholine). Examples of ion channels gated by intracellular messengers also abound in nature. This type of gating mechanism allows the channel to open or close in response to events that occur at other locations in the cell. For example, a sodium channel gated by intracellular cyclic guanosine monophosphate (cGMP) is located in the rod cells of the retina and opens in the presence of cGMP (see Chapter 4). The generalized structure of one subunit of an ion channel gated by cyclic nucleotides is shown in Figure 2.7. There are six membrane-spanning regions, and a cyclic nucleotide-binding site is exposed to the cytosol. The functional protein is a tetramer of four identical subunits. Other cell membranes have potassium channels that open when the intracellular concentration of calcium ions increases. Several known channels respond to inositol 1,4,5-trisphosphate, the activated part of G proteins, or adenosine triphosphate (ATP). The epithelial chloride channel that is mutated in cystic fibrosis is normally gated by ATP.

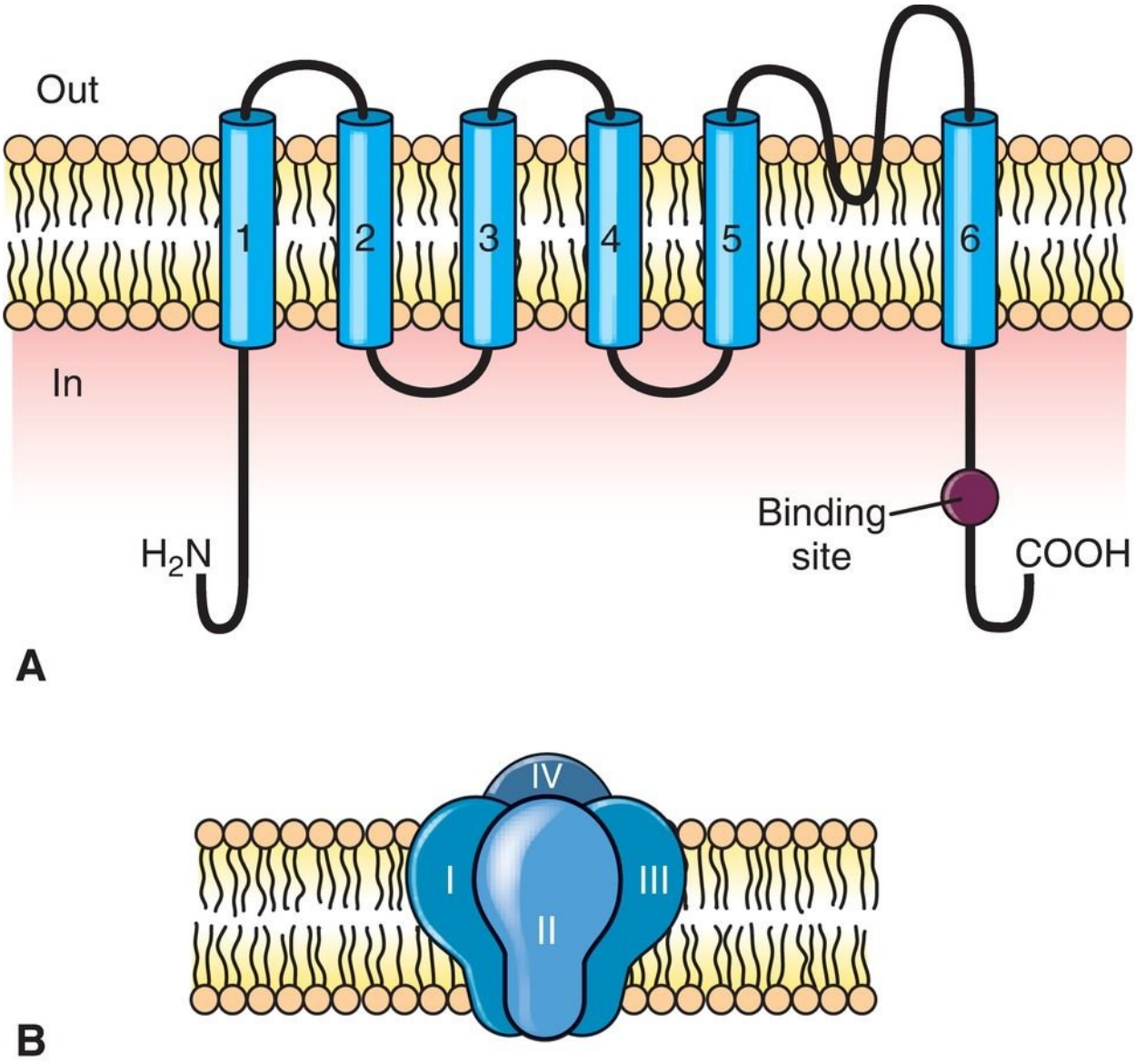

Figure 2.7 Structure of a cyclic nucleotide-gated ion channel. **(A)** The secondary structure of a single subunit has six membrane-spanning regions and a binding site for cyclic nucleotides on the cytosolic side of the membrane. **(B)** Four identical subunits (I–IV) assemble together to form a functional channel that provides a hydrophilic pathway across the plasma membrane.

Carrier-mediated transport moves a range of ions and organic solutes passively across membranes.

In contrast to pores and ion channels, integral membrane proteins that form carriers provide a conduit through the membrane that is never open to both sides of the membrane at the same time. This is due to the presence of two gates (Fig. 2.8). During carrier-mediated transport, binding of the solute to one side of the carrier induces a conformational change in the protein, which closes one gate and opens the second gate, allowing the solute to pass through the membrane. As with pores and channels, carriers function until the solute concentrations have equilibrated.

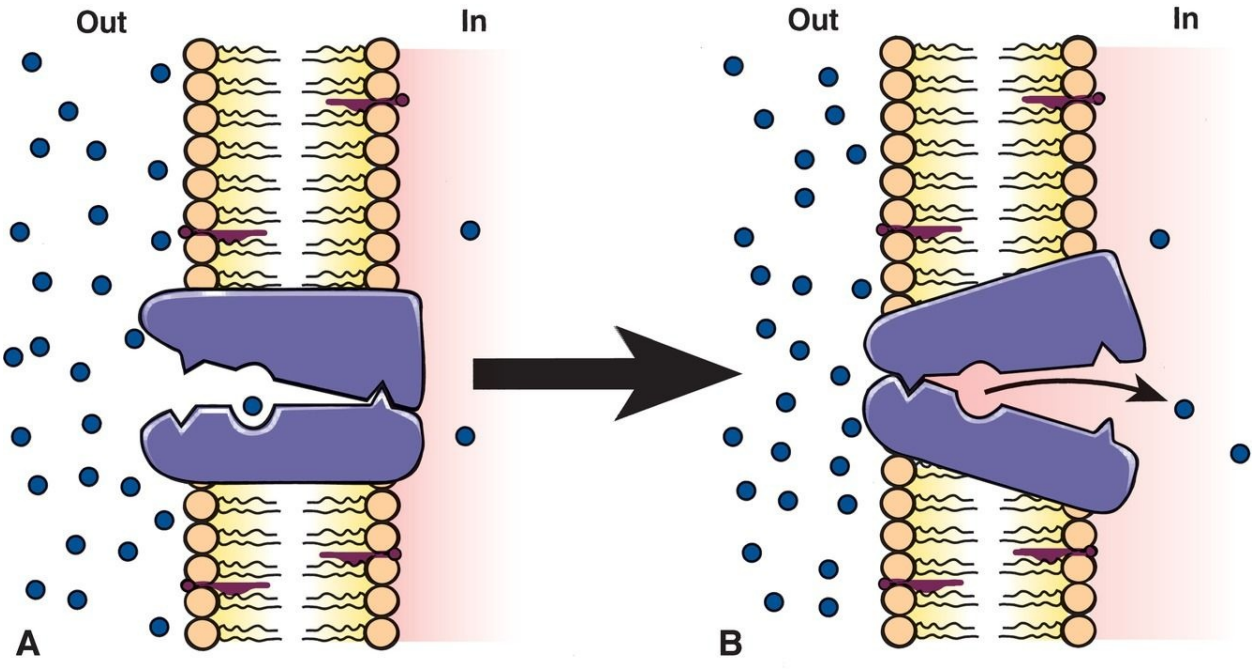

Figure 2.8 The role of a carrier protein in facilitated diffusion of solute molecules across a plasma membrane. In this example, solute transport into the cell is driven by the high solute concentration outside compared with inside. **(A)** Binding of extracellular solute to the membrane-spanning integral protein triggers a change in conformation that exposes the bound solute to the interior of the cell. **(B)** Bound solute readily dissociates from the carrier because of the low intracellular concentration of solute. The release of solute allows the carrier to revert to its original conformation **(A)** to begin the cycle again.

Carrier-mediated transport systems have several characteristics:

- They allow the transport of polar (hydrophilic) molecules at rates much higher than that expected from the partition coefficient of these molecules.
- They eventually reach saturation at high substrate concentration (see Fig. 2.5).
- They have structural specificity, meaning each carrier system recognizes and binds specific chemical structures (a carrier for D-glucose will not bind or transport L-glucose).
- They show competitive inhibition by molecules with similar chemical structure. For example, carrier-mediated transport of D-glucose occurs at a slower rate when molecules of D-galactose are also present. This is because galactose, structurally similar to glucose, competes with glucose for the available glucose carrier proteins.

A specific example of carrier-mediated transport is the movement of glucose from the blood to the interior of cells. Most mammalian cells use blood glucose as a major source of cellular energy, and glucose is transported into cells down its concentration gradient. The transport process in many cells, such as erythrocytes and the cells of fat, liver, and muscle tissues, involves a plasma membrane protein called *GLUT1* (glucose transporter-1). The erythrocyte GLUT1 has an affinity for D-glucose that is about 2,000-fold greater than the affinity for L-glucose. It is an integral membrane protein that contains 12 membrane-spanning α-helical segments.

Carrier-mediated transport, like simple diffusion, does not have a directional preference. It functions equally well bringing its specific solutes into or out of the cell, depending on the concentration gradient. Net movement by carrier-mediated transport ceases once the concentrations inside and outside the cell become equal.

The **anion exchange protein** (**AE1**), the predominant integral protein in the mammalian erythrocyte membrane, provides a good example of the reversibility of transporter action. AE1 is folded into at least 12 transmembrane a helices and normally permits the one-for-one exchange of Cl^- and HCO_3^- ions across the plasma membrane. The direction of ion movement is dependent only on the concentration gradients of the transported ions. AE1 has an important role in transporting CO_2 from the tissues to the lungs. The erythrocytes in systemic capillaries pick up CO_2 from tissues and convert it to HCO_3^-, which exits the cells via AE1. When the erythrocytes enter pulmonary capillaries, the AE1 allows

plasma HCO_3^- to enter erythrocytes, where it is converted back to CO_2 for expiration by the lungs (see Chapter 21).

Active transport systems move solutes against gradients.

All the passive transport mechanisms tend to bring the cell into equilibrium with the ECF. Cells must oppose these equilibrating systems and preserve intracellular concentrations of solutes, in particular ions that are compatible with life.

Primary active transport

Integral membrane proteins that directly use metabolic energy to transport ions against a gradient of concentration or electrical potential are known as **ion pumps**. The direct use of metabolic energy to carry out transport defines a **primary active transport mechanism**. The source of metabolic energy is ATP synthesized by mitochondria, and the different ion pumps hydrolyze ATP to ADP using the energy stored in the third phosphate bond to carry out transport. Ion pumps also are called **ATPases**, because of the ability to hydrolyze ATP.

The most abundant ion pump in higher organisms is the sodium–potassium pump or **Na^+/K^+-ATPase**. It is found in the plasma membrane of practically every eukaryotic cell and is responsible for maintaining the low sodium and high potassium concentrations in the cytoplasm by transporting sodium out of the cell and potassium ions in. The sodium–potassium pump is an integral membrane protein consisting of two subunits. The α subunit has 10 transmembrane segments and is the catalytic subunit that mediates active transport. The smaller β subunit has one transmembrane segment and is essential for the proper assembly and membrane targeting of the pump. The Na^+/K^+-ATPase is known as a **P-type ATPase** because the protein is phosphorylated during the transport cycle (Fig. 2.9). The pump counterbalances the tendency of sodium ions to enter the cell passively and the tendency of potassium ions to leave passively. It maintains a high intracellular potassium concentration, which is necessary for protein synthesis. It also plays a role in the resting membrane potential by maintaining ion gradients. The sodium–potassium pump can be inhibited either by metabolic poisons that stop the synthesis and supply of ATP or by specific pump blockers, such as **digoxin**, a **cardiac glycoside** used to treat a variety of cardiac conditions.

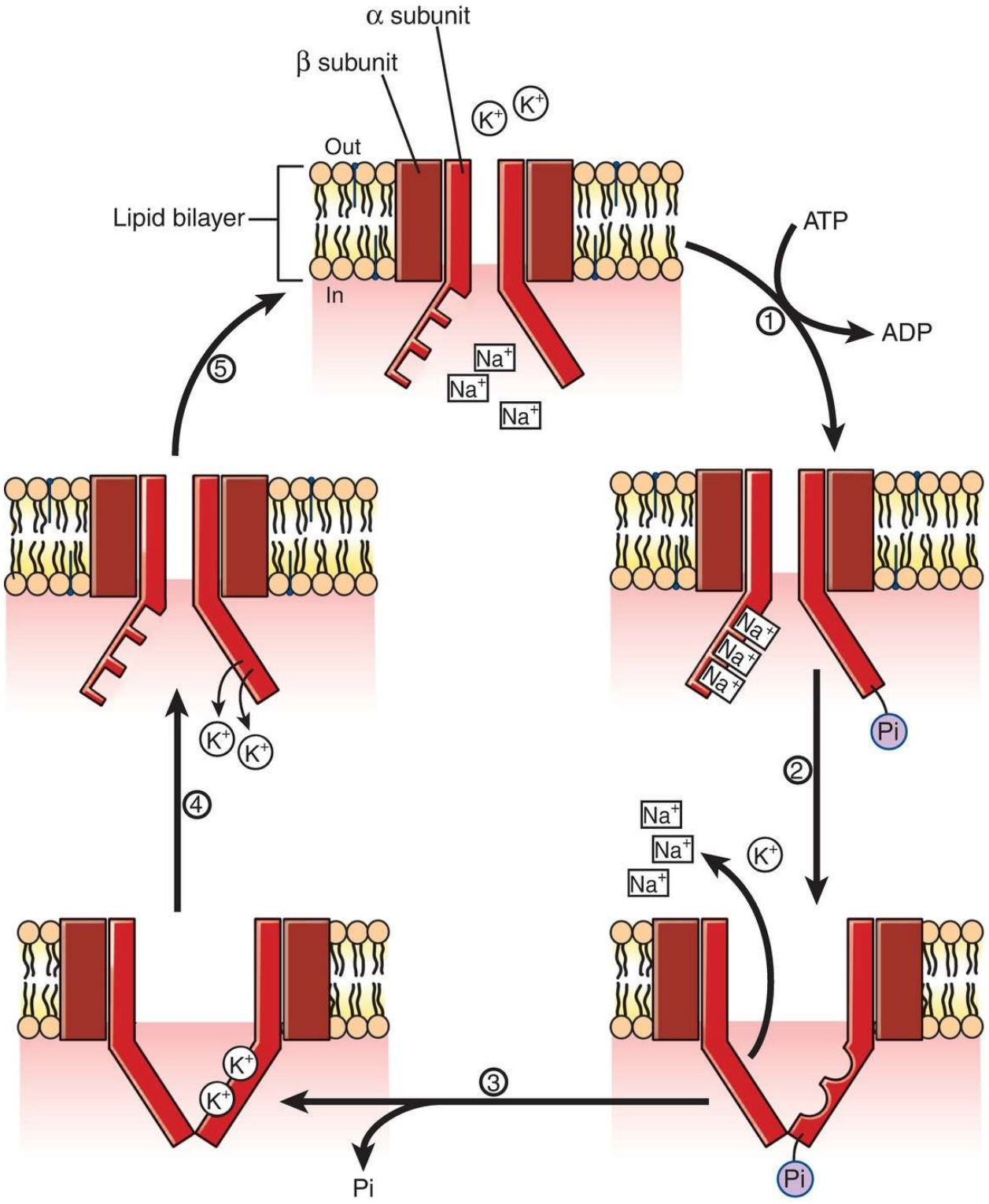

Figure 2.9 Function of the sodium–potassium pump. The pump is composed of two large α subunits that hydrolyze ATP and transport the ions. The two smaller β subunits are molecular chaperones that facilitate the correct integration of the α