SECOND EDITION

PRINCIPLES OF PHYSIOLOGY

ROBERT M. BERNE

MATTHEW N. LEVY

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With 620 illustrations

Mosby

St. Louis Baltimore Boston Carlsbad Chicago Naples New York Philadelphia Portland
London Madrid Mexico City Singapore Sydney Tokyo Toronto Wiesbaden

Mosby
Dedicated to Publishing Excellence

A Times Mirror
Company

Publisher: Anne S. Patterson
Editor: Emma D. Underdown
Developmental Editor: Christy Wells
Editorial Assistant: Alicia E. Moten
Project Manager: Mark Spann
Production Editor: Stephen C. Hetager
Designer: David Zielinski
Manufacturing Supervisor: Betty Richmond
Cover Design: Bill Schraeder

SECOND EDITION

Greek edition: Crete University Press
Indonesian edition: Binarupa Aksara
Italian edition: Casa Editrice Ambrosiana
Portugese edition: Editôra Guanabara Koogan

Printed in the United States of America
Composition by The Clarinda Company
Printing/binding by Von Hoffmann Press

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, Missouri 63146

ISBN 0-8151-0523-1

96 97 98 99 00 / 9 8 7 6 5 4 3 2 1

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PREFACE

Principles of Physiology has been carefully designed to present the important features of mammalian physiology clearly and concisely. General principles and underlying mechanisms are emphasized, and nonvital details are minimized. Considerable attention is directed to cell physiology, which serves as the basis for body functions. The first section of the text is devoted to this topic, and a new chapter on the mechanisms of cell signaling has been added to this section. Furthermore, the relevant cell physiology has been included in each of the succeeding sections. We have tried to show that the processes that take place in living cells in general are usually also applicable to the specific cell types in the various organ systems.

The major emphasis in *Principles of Physiology* is on regulation. The mechanisms that regulate the functions of the individual organ systems are thoroughly described. These mechanisms are then applied to the complex interactions among the systems as they maintain the internal environment constant, a process that is so important for the optimal function of the constituent cells.

In this edition, Dr. Norman Staub has rewritten the section on respiratory physiology. At the end of the section on cardiovascular physiology, a chapter has been added on the responses to physical exercise and to hemorrhage. The purpose of this chapter is mainly to illustrate the ways in which the various components of the circulatory system are coordinated to allow the body to adapt to certain substantial stresses.

To contribute to our goal of clarity, multicolored illustrations are used to portray concepts as simply as possible. When sequential mechanisms are involved, multipaneled diagrams have been designed to illustrate each step clearly. Block diagrams are used to depict the interrelationships among the various factors that may affect a specific function. Finally, figures are included to illustrate some of the concepts that appear in the text and to inform the reader about important investigative techniques.

Because the intent of this text is to offer, clearly and concisely, all information needed to master a complete course in physiology, the use of mathematics has been minimized, and succinct, lucid descriptions have been substituted wherever feasible. Controversial issues have been omitted to allow ample room for the explanation of important, generally accepted physiological mechanisms. We have refrained from citing the sources of the statements or assertions that appear in the text. Throughout the book, we have used italics to emphasize important concepts, and we have used boldface to denote new terms and definitions. We have also emphasized many of the important concepts by citing clinical conditions in which such concepts are involved. These clinical illustrations are highlighted in screened areas throughout the text.

Summaries are provided at the end of each chapter to emphasize the key points in the chapter, and brief bibliographies are included to direct the student to more detailed information. The references listed in these bibliographies are mainly review articles or recent, relevant scientific papers. At the end of the book, we have included a number of multiple-choice review questions and answers. These questions can serve as a guide for the readers to evaluate their comprehension of the material covered in the text.

Robert M. Berne

Matthew N. Levy

CONTENTS

PART VII
Renal System

Bruce M. Koeppen
Bruce A. Stanton

PART VIII
Endocrine System

Saul M. Genuth

CHAPTER 1

Cellular Membranes and Transmembrane Transport of Solutes and Water

CELLULAR MEMBRANES

Each cell is surrounded by a plasma membrane that separates it from the extracellular milieu. The **plasma membrane** serves as a permeability barrier that allows the cell to maintain a cytoplasmic composition far different from the composition of the extracellular fluid. The plasma membrane contains enzymes, receptors, and antigens that play central roles in the interaction of the cell with other cells and with hormones and other regulatory agents in the extracellular fluid.

The membranes that enclose the various organelles divide the cell into discrete compartments and allow the localization of particular biochemical processes in specific organelles. Many vital cellular processes take place in or on the membranes of the organelles. Striking examples are the processes of electron transport and oxidative phosphorylation, which occur on, within, and across the mitochondrial inner membrane.

Most biological membranes have certain features in common. However, in keeping with the diversity of membrane functions, the composition and structure of the membranes differ from one cell to another and among the membranes of a single cell.

Membrane Structure

Proteins and phospholipids are the most abundant constituents of cellular membranes. A **phospholipid** molecule has a polar head group and two very nonpolar, hydrophobic fatty acyl chains (Figure 1-1, *A*). In an aqueous environment phospholipids tend to form structures that allow the fatty acyl chains to be kept away from contact with water. One such structure is the **lipid bilayer** (Figure 1-1, *B*). Many phospholipids, when dispersed in water, spontaneously form lipid bilayers. Most of the phospholipid molecules in biological membranes have a lipid bilayer structure.

> The phospholipid bilayer is responsible for certain passive permeability properties of biological membranes. Substances that are highly soluble in water typically permeate cellular membranes very slowly, while nonpolar compounds that are more soluble in nonpolar organic solvents cross cell membranes more rapidly. High concentrations of barium salts are administered by mouth or by enema in order to make the interior of the gastrointestinal tract opaque to x-rays and improve the contrast of diagnostic x-ray films of the gastrointestinal tract. Barium ions in this concentration would be highly toxic, but because barium is highly water-soluble, it is barely absorbed at all from the gastrointestinal tract. Hence, the concentrations of barium in the blood rise very little after administration of barium salts.

Figure 1-2 depicts the **fluid mosaic model** of membrane structure. This model is consistent with many of the properties of biological membranes. Note the bilayer structure of most of the membrane phospholipids. The membrane proteins are of two major classes: (1) **integral** or **intrinsic membrane proteins** that are embedded in the phospholipid bilayer and (2) **peripheral** or **extrinsic membrane proteins** that are associated with the surface of the membrane. The peripheral membrane proteins interact with the membrane predominantly by charge interactions with integral membrane proteins. Thus peripheral proteins may often be removed from the membrane by altering the ionic composition of the medium. Integral membrane proteins have important hydrophobic interactions with the interior of the membrane.

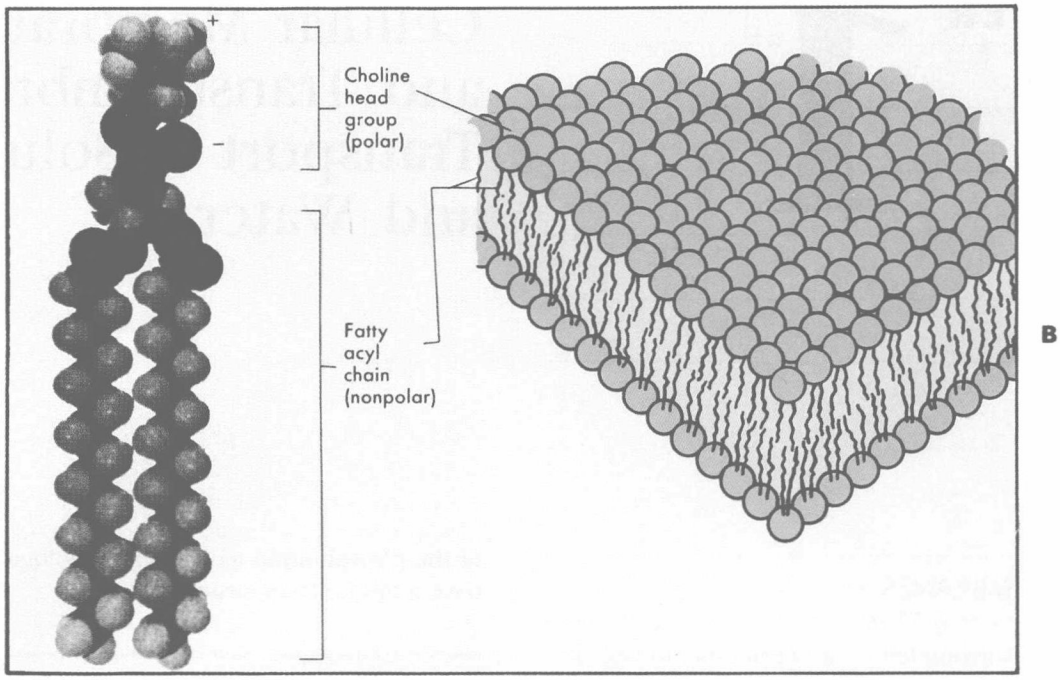

FIGURE 1-1 **A,** Structure of a membrane phospholipid molecule, in this case a phosphatidylcholine. **B,** Structure of a phospholipid bilayer. The open circles represent the polar head groups of the phospholipid molecules. The wavy lines represent the fatty acyl chains of the phospholipids.

These hydrophobic interactions can be disrupted only by detergents that make the integral proteins soluble by interacting hydrophobically with nonpolar amino acid side chains.

Cellular membranes are fluid structures in which many of the constituent molecules are free to diffuse in the plane of the membrane. Most lipids and proteins can move freely in the bilayer plane, but they "flip-flop" from one phospholipid monolayer to the other at much slower rates. A large hydrophilic moiety is unlikely to flip-flop if it must be dragged through the nonpolar interior of the lipid bilayer.

In some cases membrane components are not free to diffuse in the plane of the membrane. Examples of this motional constraint are the sequestration of acetylcholine receptors (integral membrane proteins) at the motor endplate of skeletal muscle and the presence of different membrane proteins in the apical and basolateral plasma membranes of epithelial cells. The cytoskeleton appears to tether certain membrane proteins. The **anion exchanger,** a major protein of the human erythrocyte membrane, is bound to the spectrin network that undergirds the membrane via a protein called **ankyrin.**

If the motor nerve that innervates a skeletal muscle is accidentally severed, the acetylcholine receptors are no longer sequestered at the motor endplate, but instead they spread out over the entire plasma membrane of the muscle cells. Then the entire surface of the cell becomes excitable by acetylcholine, a phenomenon known as **denervation supersensitivity.**

MEMBRANE COMPOSITION

Lipid Composition

Major Phospholipids In animal cell membranes the most abundant phospholipids are often the choline-containing phospholipids: the lecithins (phosphatidylcholines) and the sphingomyelins. Next in abundance are frequently the amino phospholipids: phosphatidylserine and phosphatidylethanolamine. *The phospholipid bilayer is primarily responsible for the passive permeability properties of the membrane.* Other important phos-

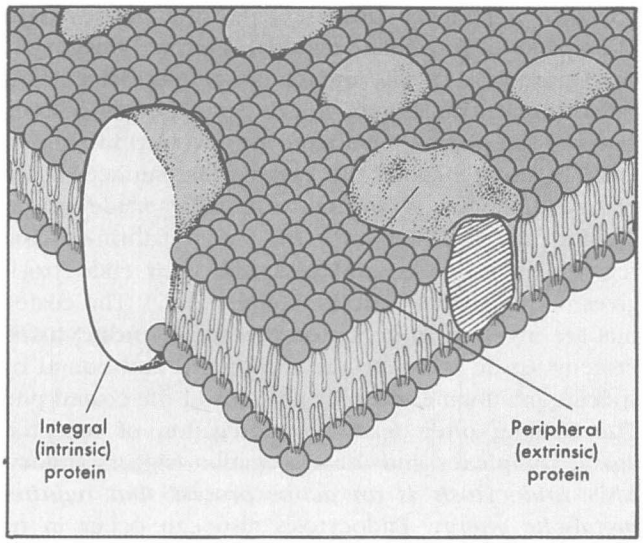

FIGURE 1-2 Schematic representation of the fluid mosaic model of membrane structure. The integral proteins are embedded in the lipid bilayer matrix of the membrane, and the peripheral proteins are associated with the external surfaces of integral membrane proteins.

pholipids present in smaller amounts are phosphatidylglycerol, phosphatidylinositol, and cardiolipin.

Certain phospholipids present in tiny proportions in the plasma membrane play a vital role in cellular signal transduction processes. **Phosphatidylinositol bisphosphate,** when cleaved by a receptor-activated phospholipase C, releases **inositol trisphosphate (IP_3)** and **diacyl glycerol.** IP_3 is released into the cytosol, where it acts on receptors in the endoplasmic reticulum to cause release of stored Ca^{++}, which affects a wide variety of cellular processes. Diacylglycerol remains in the plasma membrane, where it participates, along with Ca^{++}, in activating **protein kinase C,** an important signal transduction protein.

Cholesterol Cholesterol is a major constituent of plasma membranes, and its steroid nucleus lies parallel to the fatty acyl chains of membrane phospholipids. Cholesterol functions as a "fluidity buffer" in the plasma membrane in that its presence tends to keep the fluidity of the acyl chain region of the phospholipid bilayer in an intermediate range in the presence of agents, such as alcohols and general anesthetics, that tend to fluidize biological membranes.

Glycolipids Glycolipids are not abundant, but they have important functions. Glycolipids are found mostly in plasma membranes, where their carbohydrate moieties protrude from the external surface of the membrane. The carbohydrate parts of glycolipids frequently function as receptors or antigens.

> The receptor for cholera toxin (Chapter 34) is the carbohydrate moiety of a particular glycolipid, ganglioside (G_{M1}). The A and B blood group antigens (Chapter 15) are the carbohydrate moieties of other gangliosides on the human erythrocyte membrane.

Asymmetry of Lipid Distribution In many membranes the lipid components are not distributed uniformly across the bilayer. The glycolipids of the plasma membrane are located almost exclusively in the outer monolayer. Phospholipids are also distributed asymmetrically between the inner and outer monolayers of membranes. In the red blood cell membrane, for example, the outer monolayer contains most of the choline-containing phospholipids, whereas the inner monolayer contains most of the amino phospholipids.

Membrane Proteins The protein composition of membranes may be simple or complex. The functionally specialized membranes of the sarcoplasmic reticulum of skeletal muscle and the disks of the rod outer segment of the retina contain only a few different proteins. By contrast, plasma membranes, which perform many functions, may have more than 100 different protein constituents. Membrane proteins include enzymes, transport proteins, and receptors for hormones and neurotransmitters.

Glycoproteins Some membrane proteins are glycoproteins with covalently bound carbohydrate side chains. As with glycolipids, the carbohydrate chains of glycoproteins are located almost exclusively on the external surfaces of plasma membranes. The carbohydrate moieties of membrane glycoproteins and glycolipids have important functions. The negative surface charge of cells is caused by the negatively charged sialic acid of glycolipids and glycoproteins.

Fibronectin is a large fibrous glycoprotein that helps cells attach, via cell surface glycoproteins called **integrins,** to proteins of the extracellular matrix. This linkage mediates communication between the extracellular matrix and the cell's cytoskeleton during embryonic development.

> The major membrane proteins of enveloped viruses are glycoproteins. Their carbohydrate moieties stud the outer surface of the virus with "spikes" that are required for the virus to bind to a host cell.

Asymmetry of Membrane Proteins The Na^+-K^+-ATPase of the plasma membrane and the Ca^{++} pump

protein (Ca^{++}-ATPase) of the sarcoplasmic reticulum membrane are examples of the asymmetric disposition of membrane proteins. In both cases ATP is split on the cytoplasmic face of the membrane, and some of the energy liberated is used to pump ions in specific directions across the membrane. In the case of the Na^+-K^+-ATPase, K^+ is pumped into the cell and Na^+ is pumped out, whereas the Ca^{++}-ATPase actively pumps Ca^{++} into the sarcoplasmic reticulum.

MEMBRANES AS PERMEABILITY BARRIERS

Biological membranes serve as **permeability barriers.** Most of the molecules present in living systems are highly soluble in water and poorly soluble in nonpolar solvents. Such molecules are poorly soluble in the nonpolar environment in the interior of the lipid bilayer of biological membranes. As a consequence, biological membranes pose a formidable barrier to most water-soluble molecules. *The plasma membrane is a permeability barrier between the cytoplasm and the extracellular fluid.* This barrier allows the maintenance of large concentration differences for many substances between the cytoplasm and the extracellular fluid.

The localization of various cellular processes in certain organelles depends on the barrier properties of cellular membranes. For example, the inner mitochondrial membrane is impermeable to the enzymes and substrates of the tricarboxylic acid cycle, and thus it allows the localization of the tricarboxylic cycle in the mitochondrial matrix. The spatial organization of chemical and physical processes in the cell depends on the barrier functions of cellular membranes, much as the walls of a house separate rooms with different functions.

The passage of important molecules across membranes at controlled rates is central to the life of the cell. Examples are the uptake of nutrient molecules, the discharge of waste products, and the release of secreted molecules. As discussed in the next section, molecules may move from one side of a membrane to another without actually moving through the membrane itself. In other cases molecules cross a particular membrane by passing through or between the molecules that make up the membrane.

TRANSPORT ACROSS, BUT NOT THROUGH, MEMBRANES

Endocytosis

Endocytosis is the process that allows material to enter the cell without passing through the membrane (Figure 1-3); it includes **phagocytosis** and **pinocytosis.** The uptake of particulate material is termed phagocytosis (Figure 1-3, *A*). The uptake of soluble molecules is called pinocytosis (Figure 1-3, *B*). Sometimes special regions of the plasma membrane are involved in endocytosis. In these regions the cytoplasmic surface of the plasma membrane is covered with bristles made primarily of a protein called **clathrin.** These clathrin-covered regions are called **coated pits,** and their endocytosis gives rise to coated vesicles (Figure 1-3, *C*). The coated pits are involved in **receptor-mediated endocytosis.** Proteins to be taken up are recognized and bound by specific membrane receptor proteins in the coated pits. The binding often leads to aggregation of receptor-ligand complexes, and the aggregation triggers endocytosis. *Endocytosis is an active process that requires metabolic energy.* Endocytosis also can occur in regions of the plasma membrane that do not contain coated pits.

> Most cells cannot synthesize cholesterol, which is needed for synthesis of new membranes (see also Chapter 41). Cholesterol is carried in the blood, predominantly in low-density lipoproteins (LDL). Many cells have LDL receptors in their plasma membranes. When LDL binds to these receptors, the receptor-LDL complexes migrate to coated pits, where they aggregate and are taken into the cell by receptor-mediated endocytosis. Individuals who lack LDL receptors have high levels of cholesterol-laden LDL in their blood. Consequently such individuals tend to develop arterial disease **(atherosclerosis)** at an early age, which makes them more likely to experience heart attacks prematurely.

Exocytosis

Molecules can be ejected from cells by **exocytosis,** a process that resembles endocytosis in reverse. The release of neurotransmitters, which is considered in more detail in Chapter 4, takes place by exocytosis. Exocytosis is responsible for the release of secretory proteins by many cells; the release of pancreatic enzymes from the acinar cells of the pancreas is a well-studied example. The pancreatic enzymes play vital roles in digestion of protein, carbohydrates, and lipids (see Chapter 33). In such cases the proteins to be secreted are stored in secretory vesicles in the cytoplasm. *A stimulus to secrete causes the secretory vesicles to fuse with the plasma membrane and to release the vesicle contents by exocytosis.*

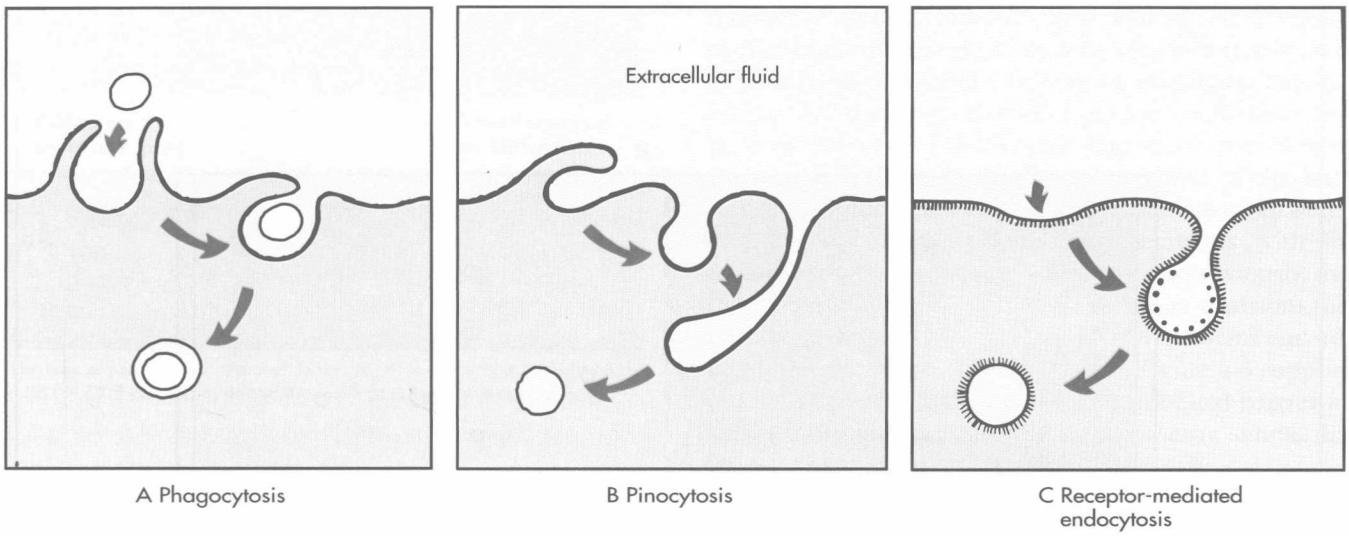

FIGURE 1-3 Schematic depiction of endocytotic processes. **A,** Phagocytosis of a solid particle. **B,** Pinocytosis of extracellular fluid. **C,** Receptor-mediated endocytosis by coated pits.

Fusion of Membrane Vesicles

The contents of one type of organelle can be transferred to another organelle by fusion of the membranes of the organelles. In some cells, secretory products are transferred from the endoplasmic reticulum to the Golgi apparatus by fusion of endoplasmic reticulum vesicles with membranous sacs of the Golgi apparatus. Fusion of phagocytic vesicles with lysosomes allows the phagocytosed material to be digested by proteolytic enzymes in the lysosomes. The turnover of many normal cellular constituents involves their destruction in lysosomes, followed by their resynthesis.

Influenza viruses have membrane proteins that undergo a dramatic conformational change to insert a "fusion peptide" into the host cell. The fusion peptide promotes the fusion of the viral membrane with the plasma membrane of the host cell, allowing entry of the viral genome into the host cell.

TRANSPORT OF MOLECULES THROUGH MEMBRANES

The traffic of molecules through biological membranes is vital for most cellular processes. Some molecules move through biological membranes simply by diffusing among the molecules that make up the membrane, whereas the passage of other molecules involves the mediation of specific transport proteins in the membrane.

Oxygen, for example, is a small molecule that is fairly soluble in nonpolar solvents. It crosses biological membranes by diffusing among membrane lipid molecules. Glucose, on the other hand, is a much larger molecule that is not very soluble in the membrane lipids. Glucose enters cells via specific glucose transport proteins in the plasma membrane.

Diffusion

Diffusion is the process whereby atoms or molecules intermingle because of their random thermal motion, also called **Brownian motion.** Imagine a container divided into two compartments by a removable partition (Figure 1-4). A much larger number of molecules of a compound is placed on side A than on side B, and then the partition is removed. Every molecule is in random thermal motion. It is equally probable that a molecule that begins on side A will move to side B in a given time and that a molecule beginning on side B will end up on side A. Because many more molecules are present on side A, the total number of molecules moving from side A to side B will be greater than the number moving from side B to side A. In this way the number of molecules on side A will decrease, whereas the number of molecules on side B will increase. This process of net diffusion of molecules will continue until the concentration of molecules on side A equals that on side B. Thereafter the rate of diffusion of molecules from A to B will equal that from B to A, and