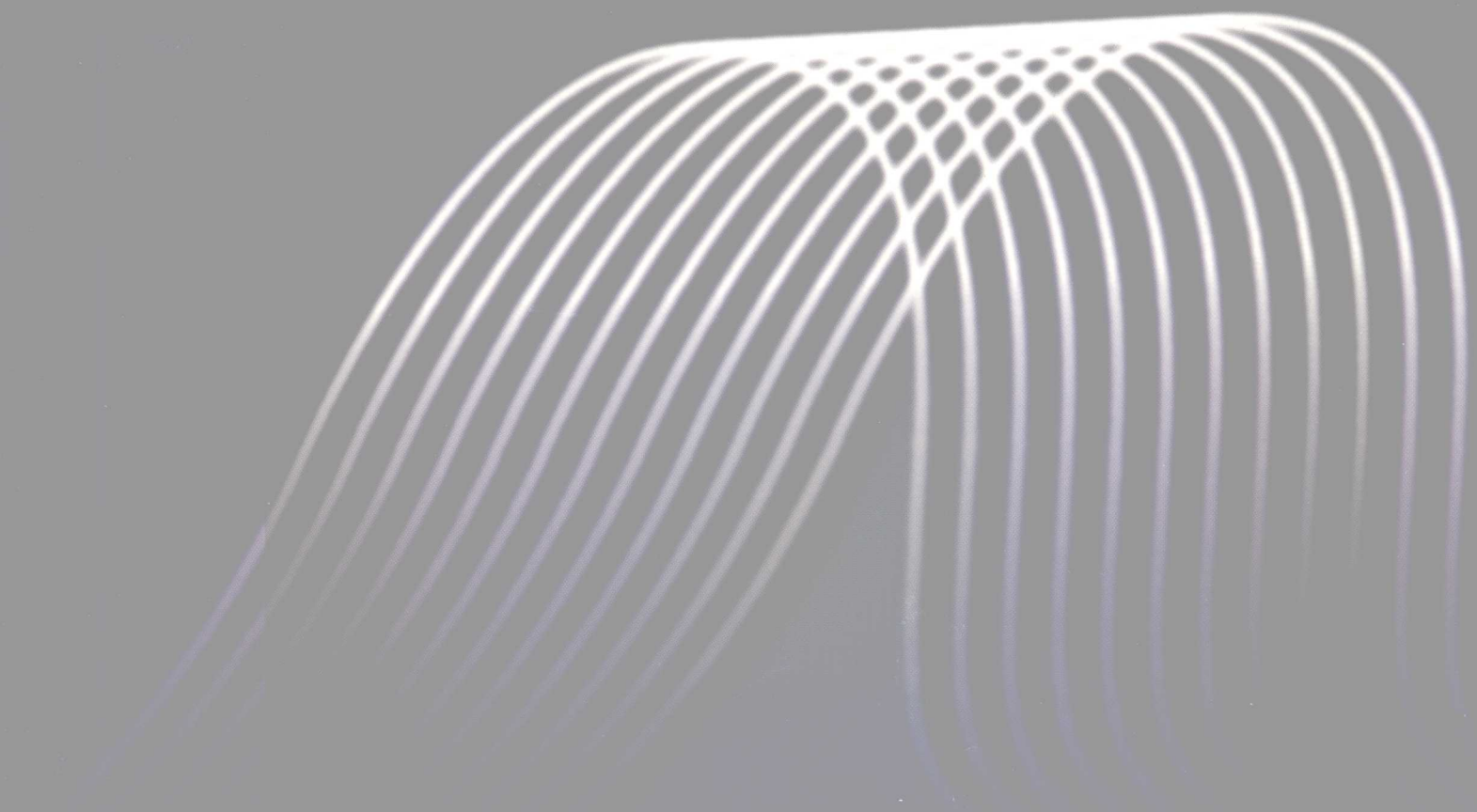
PHYSIOLOGY

Fourth Edition



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PHYSIOLOGY

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Dedicated to

Alex, Ari, Chris, Daniel, Kyle, Madelyn, Maggie,
Molly, Nicolas, Sarah, Todd, and Tracy

Preface

The fourth edition of this text, like the previous editions, emphasizes broad concepts and minimizes the compilation of isolated facts. Each of the chapters in this edition has been altered significantly to make the text as lucid, accurate, and current as possible. We have revised many of the illustrations and we have substituted many new ones in an effort to assist the readers in comprehending some of the more difficult physiological concepts and to introduce them to some of the modern techniques that are being used to acquire physiological knowledge. Finally, in keeping with our emphasis on broad principles, we have highlighted the important mechanistic homologies and critical interactions among the various organ systems wherever possible. We have tried to maintain similar goals and formats among the various sections of the book, without altering materially the writing styles of the section authors. We hope that this will actually enhance the overall readability of the book.

Physiology is distinguished from the other basic biomedical sciences by its concern with the function of the intact organism and its emphasis on the processes that regulate the important properties of living systems. In the healthy human, many variables are maintained within narrow limits. The list of controlled variables includes body temperature, blood pressure, ionic composition of the body's various fluid compartments, blood glucose levels, and oxygen and carbon dioxide contents of the blood. This ability to maintain the relative constancy of such critical variables, even in the face of substantial environmental changes, is known as homeostasis. A central goal of physiological research is the elucidation of the mechanisms responsible for homeostasis.

In Section I, Cellular Physiology, and at the beginnings of several other sections, certain important physiochemical principles of physiology are analyzed in detail. Among these principles we have included considerable information about major advances in cellular and molecular biology. To emphasize the clinical relevance of selected advances, we have directed the readers' attention to specific diseases in which the applicable physiological mechanism plays an important role. Interspersed throughout each chapter, these clinical examples have been highlighted by enclosing them in colored boxes.

When important principles could be represented profitably by equations, the bases of the equations and the major underlying assumptions have been stated. This approach provides students with a more quantitative understanding of these principles. However, because some of the readers might not favor a rigorous analytical approach to certain topics or might not have the requisite mathematical background, these more extensive mathematical analyses have been presented in gray boxes.

Section II, The Nervous System, provides a functional neuroanatomic framework for its presentation of contemporary cellular neurophysiology. Substantial attention has been directed toward the sensory and motor systems because of their relevance to clinical problems. The theoretical foundation common to all sensory systems has been constructed so as to facilitate the learning of the various components.

Throughout Section III, Muscle, we have refrained from describing the three types of muscle in sequence, but instead we have emphasized and integrated their common characteristics. We have stressed that the basic mechanisms of contraction are similar in skeletal, cardiac, and smooth muscles, and that the differences lie mainly in the relative importance of certain critical components of those basic processes.

To clarify cardiovascular physiology, in Section IV, The Cardiovascular System, we have dissected the entire system initially into its major components. One such component, namely blood composition and function, has been condensed and simplified, and it has been included in this section, whereas previously it had been treated as a separate section. In the subsections related to the heart and vasculature, we have first examined the functions of these individual components in isolation. Toward the end of the cardiovascular section, we have analyzed the sys-

tem as a whole and have described how the various parts of this closed loop system interact under certain important physiological and pathophysiological conditions.

Section V, The Respiratory System, emphasizes the physical principles that underly the mechanics of breathing and the processes of gas exchange between the blood and the alveoli and between the blood and the peripheral tissues. Also the various neural and chemical processes that regulate respiration have been described in detail.

Section VI, The Gastrointestinal System, considers first the details about the motility and secretions of the gastrointestinal tract, and then analyzes how these functions are integrated by neural, endocrine, and paracrine mechanisms. Dysfunction of certain critical mechanisms has been shown to be involved in the pathogenesis of various important gastrointestinal disturbances.

In Section VII, The Kidney, homologies influence the presentation of factual material. The mechanisms whereby the kidneys handle a few important solutes have been described in detail. The specific information about the transport of the myriad substances that pass through the kidneys has been condensed.

In Section VIII, The Endocrine System, homologies in the functioning of the various endocrine glands are emphasized. Discussions of the male and female gonads have been included in a common chapter to highlight the similarities between the Sertoli cell functions in spermatogenesis and the granulosa cell functions in oogenesis.

Again, the framework of this textbook comprises firmly established facts and principles. Isolated phenomena generally are ignored unless they are considered to be highly significant, and experimental methods are described sparsely unless they are essential for comprehension. Although controversies exist in virtually all areas of physiology, such controversies are not considered unless they provide a deeper understanding of the subject. The authors of each section have presented what they believe to be the most likely mechanism responsible for the phenomenon under consideration. We have adopted this compromise to achieve brevity, clarity, and simplicity. We have not documented the specific sources for the assertions that appear throughout the book, but we have provided references at the end of each chapter. These references have been selected because they provide a current and comprehensive review of the topic, a clear and detailed description of important mechanisms, or a complete and current bibliography of the subject.

At the end of each chapter, we have included summary statements of the important facts and concepts. We have also included Self-Study Problems, which are essay-type questions. At the end of the book, we have provided the answers to these essay questions (Apppendix A), and have added a substantial set of multiple choice questions and answers that relate to the contents of the entire book (Appendix B, Mini-Exam).

We wish to express our appreciation to all of our colleagues and students who have provided constructive criticism during the revision of this book.

Robert M. Berne
Matthew N. Levy

Contents

SECTION

I

CELLULAR PHYSIOLOGY

Howard C. Kutchai

CHAPTER

1

Cellular Membranes and Transmembrane Transport of Solutes and Water

Cellular Membranes

Membranes are a prominent part of all cells. Every cell is surrounded by a plasma membrane that separates it from the extracellular environment. The plasma membrane serves as a permeability barrier that allows the cell to maintain an interior composition far different from the composition of the extracellular fluid. The plasma membrane also contains enzymes, receptors, and antigens that play important roles in the cell's interaction with other cells and with hormones and other regulatory agents in the extracellular fluid.

Membranes also enclose the various organelles of eukaryotic cells. These membranes divide the cell into discrete compartments within which particular biochemical processes take place. Many vital cellular processes actually take place in or on the membranes of the organelles. Examples of these membrane-localized processes include 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.

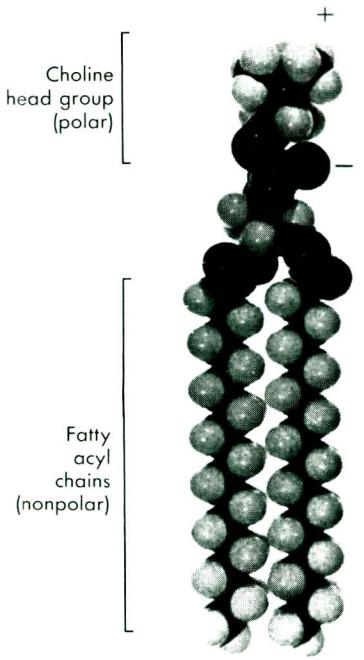
Membrane Structure

The most abundant constituents of cellular membranes are proteins and phospholipids. A **phospholipid** molecule consists of a polar head group and two nonpolar, hydrophobic fatty acyl chains (Fig. 1-1, *A*). In an aqueous environment, phospholipids tend to orient with their hydrophobic fatty acyl chains away from contact with water. This orientation can be seen in the **lipid bilayer** (Fig. 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 **fluid mosaic model** of membrane structure shown in Fig. 1-2 is consistent with many of the properties of biological membranes. Note the bilayer structure of most of the membrane phospholipids. Note also that proteins are abundant in the membrane. These 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. In general, the peripheral membrane proteins associate with the membrane by means of charge interactions with integral membrane proteins. When the ionic composition of the medium is altered, peripheral proteins are often removed from the membrane. Integral membrane proteins are embedded in the membrane by means of hydrophobic interactions with the interior of the membrane. The only substances that can disrupt these hydrophobic interactions are detergents, which make the integral proteins soluble by interacting hydrophobically with nonpolar amino acid side chains.

As the term *fluid mosaic model* suggests, cellular membranes are fluid structures. Many of the constituent molecules of cellular membranes are free to diffuse in the plane of the membrane. Most lipids and proteins move freely in the bilayer plane, but they "flip-flop" from one phospholipid monolayer to the other at much slower rates. A large, hydrophilic membrane component is unlikely to flip-flop if it must be dragged through the nonpolar interior of the lipid bilayer.

Sometimes, membrane components are not free to diffuse in the plane of the membrane. For example, acetyl-



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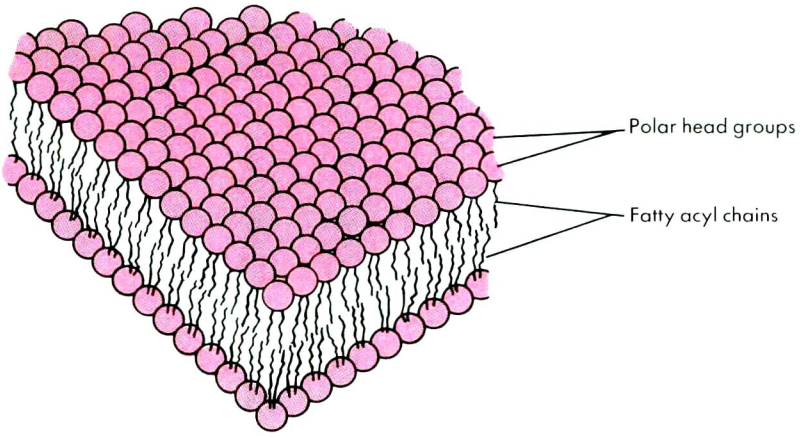
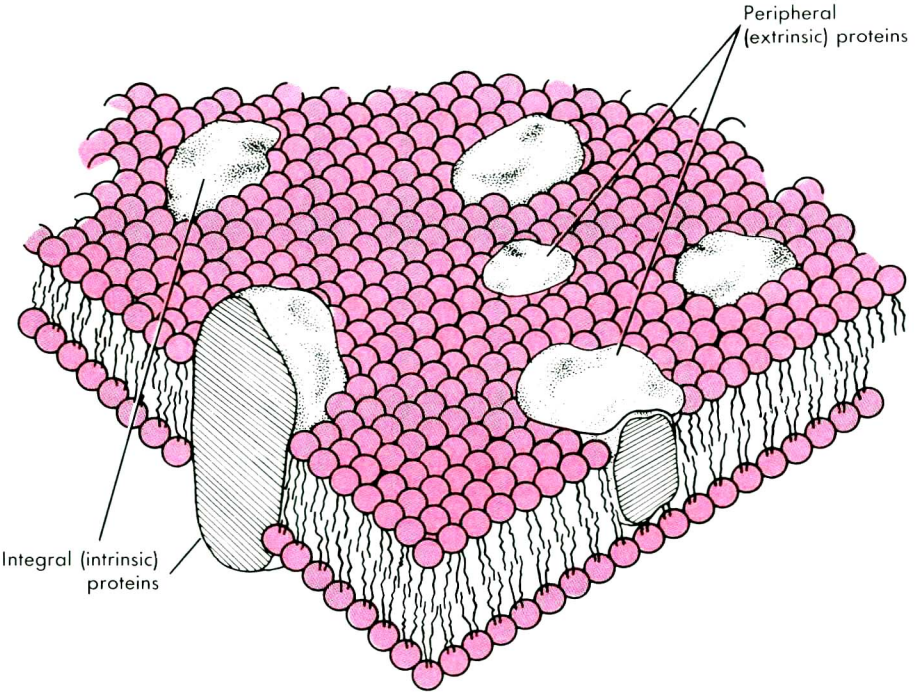


B

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



■ **Fig. 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.

choline receptors (integral membrane proteins) are sequestered at the motor endplate of skeletal muscle. Different membrane proteins are confined to the apical and basolateral plasma membranes of epithelial cells. In some cells, cytoskeleton appears to tether certain membrane proteins. For example, 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. Instead, they spread out over the entire plasma membrane of the muscle cells. The entire surface of the cell then becomes excitable by acetylcholine, a phenomenon known as **denervation supersensitivity.**

Membrane Composition

Lipid Composition

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

Certain phospholipids that are present in *tiny* amounts in the plasma membrane play vital roles in cellular signal transduction processes. **Phosphatidylinositol bisphosphate,** when cleaved by a receptor-activated phospholipase C, releases **inositol trisphosphate (IP_3)** and **diacylglycerol.** 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 component of plasma membranes. Its steroid nucleus lies parallel to the fatty acyl chains of membrane phospholipids. Cholesterol functions as a "fluidity buffer" in the plasma membrane. It 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 would otherwise make the biological membranes more fluid.

Glycolipids. Although **glycolipids** are not abundant in plasma membranes, 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 39) is the carbohydrate moiety of a particular glycolipid, ganglioside (G_{M1}). The A and B blood group antigens (Chapter 20) 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. For example, 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. In 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 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 allows communication to take place between the extracellular matrix and the cell's cytoskeleton during embryonic development.

The major membrane proteins of enveloped **viruses** are glycoproteins. Their carbohydrate moieties appear as "spikes" that stud the outer surface of the virus. These "spikes" are necessary for the binding of the virus to a host cell.

Asymmetry of membrane proteins. The Na^+, K^+-ATPase (also called the Na^+, K^+-pump) of the plasma membrane and the Ca^{++}-ATPase (also called the Ca^{++} pump) of the sarcoplasmic reticulum membrane are examples of the asymmetric distribution of membrane proteins. In both of these pumps, the cleavage of ATP occurs on the cytoplasmic face of the membrane, and some of the energy liberated is used to pump ions in specific directions across the membrane. The Na^+, K^+-ATPase pumps K^+ into the cell and Na^+ out of the cell, 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. Not surprisingly, molecules are also poorly soluble in the nonpolar environment that exists within the interior of the lipid bilayer of biological membranes. As a consequence, biological membranes pose a formidable barrier to most water-soluble molecules. This barrier allows the maintenance of large concentration differences of many substances between the cytoplasm and the extracellular fluid. However, the plasma membrane is also permeable to some substances. Thus, although it keeps out many substances, it also allows the selective passage of other substances.

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. Much as the walls of a house separate rooms with different functions, barriers imposed by cellular membranes organize the chemical and physical processes within the cell.

The permeability function of membranes, which allows the passage of important molecules across membranes at controlled rates, is central to the life of the cell. Examples include 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 plasma membrane (Fig. 1-3); it includes phagocytosis and pinocytosis. The uptake of particulate material is termed **phagocytosis** ("cell eating") (Fig. 1-3, *A*). The uptake of soluble molecules is called **pinocytosis** ("cell drinking") (Fig. 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** Fig. 1-3, *C*). The coated pits are involved in **receptor-mediated endocytosis.** In this process, specific membrane receptor proteins in the coated pits recognize and bind to the protein to be taken up. This binding often leads to aggregation of receptor-ligand complexes, and the aggregation triggers endocytosis. *Endocytosis is an active process that requires metabolic energy.* Endocytosis can also 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 Chapter 51). Cholesterol is carried in the blood predominantly in low-density lipoproteins (LDLs). 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 or have defective 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 increases the risk of early heart attacks.

Exocytosis

Molecules can be ejected from cells by **exocytosis,** a process that resembles endocytosis in reverse. The release of neurotransmitters from the presynaptic nerve endings (discussed in more detail in Chapter 4) takes place by exocytosis. Exocytosis is responsible for the

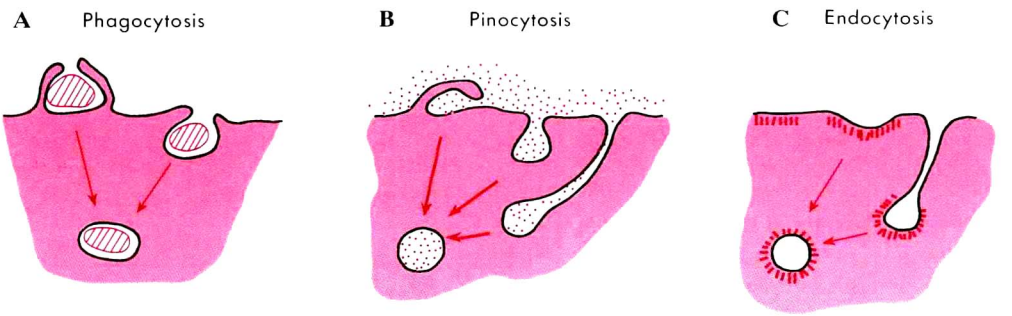


Fig. 1-3 Schematic depiction of endocytotic processes. **A,** Phagocytosis of a solid particle. **B,** Pinocytosis of extracellular fluid. **C,** Receptor-mediated endocytosis by coated pits. (Redrawn from Silverstein SC et al: *Annu Rev Biochem* 46:669, 1977. With permission by Annual Reviews.)

release of secretory proteins by many cells. A well-studied example is the release of pancreatic enzymes from the acinar cells of the pancreas. These proteins are stored in secretory vesicles in the cytoplasm of pancreatic cells. *A stimulus to secrete causes the secretory vesicles to fuse with the plasma membrane and to release the vesicle contents by exocytosis.*

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 vesicles. In this process, endoplasmic reticulum vesicles fuse 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 that allows the insertion of 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. Other molecules move through membranes via 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 occurs because of the random thermal motion of atoms or molecules, also called **Brownian motion.** Diffusion eventually results in the uniform distribution of the atoms or molecules. Imagine a container divided into two compartments by a removable partition (Fig. 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. The probability that a molecule that is located initially on side A will move to side B in a given time is equal to the probability that a molecule initially located 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. Eventually, 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 no further net movement will occur; a dynamic equilibrium exists.

Range of diffusion. Diffusion is rapid when the distance over which it takes place is small. A rule of thumb is that a typical molecule takes 1 msec to diffuse 1 μm. However, the time required for diffusion increases with the square of the distance over which diffusion occurs. *Thus, a tenfold increase in the diffusion distance means that it will take 100 times longer for diffusion to reach a given degree of completion.*

Table 1-1 shows the results of calculations for a typical, small, water-soluble solute. Diffusion is extremely rapid on a microscopic scale of distance. For macroscopic distances, however, diffusion is rather slow. A cell that is 100 μm away from the nearest capillary can receive nutrients from the blood by diffusion about 5 seconds or so, which is sufficiently fast to satisfy the metabolic demands of many cells. However, a skeletal muscle cell that is 1 cm long cannot rely on diffusion for the intracellular transport of vital metabolites. It would take 14 hours for the diffusion of these metabolites to be completed, and this time requirement is not feasible for efficient cellular metabolism. Some nerve fibers are longer than 1 m. To overcome this difficulty, intracellular axonal transport systems are involved in transporting important molecules along nerve fibers. Because of the slowness of diffusion over macroscopic distances, even small multicellular organisms have evolved circulatory systems to bring the individual cells of the organisms within a reasonable diffusion range of nutrients.

Diffusion coefficient. The **diffusion coefficient** (D) is proportional to the speed with which the diffusing molecule can move in the surrounding medium. The larger the molecule and the more viscous the medium, the smaller is D. For small molecules, D is inversely proportional to $MW^{1/2}$. (*MW* refers to molecular weight). For macromolecules, D is inversely proportional to $MW^{1/2}$. *Thus, a protein that has one eighth the mass of another molecule will have a diffusion coefficient only two times larger than the larger molecule.*