PRINCIPLES OF PHYSIOLOGY

BERNE • LEVY

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With **620** *illustrations*

The C. V. Mosby Company

ST. LOUIS • BALTIMORE • PHILADELPHIA • TORONTO 1990

Editor Stephanie Bircher Manning
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Project Manager Patricia Gayle May
Book Design John Rokusek and Candace Conner
Cover Design Candace Conner

Cover Photo © Manfred Kage-Peter Arnold Inc.

Printed in the United States of America

The C. V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63146

Library of Congress Cataloging-in-Publication Data

Principles of physiology / edited by Robert M. Berne, Matthew N. Levy. p. cm.
Includes bibliographical references.
ISBN 0-8016-0548-2
1. Human physiology. I. Berne, Robert M., - . II. Levy, Matthew N.,
[DNLM: 1. Physiology. QT 104 P957]
QP34.5.P744 1990
612—dc20
DNLM/DLC
for Library of Congress 89-14598
CIP

TSI/VH/VH 9 8 7 6 5 4 3 2 1

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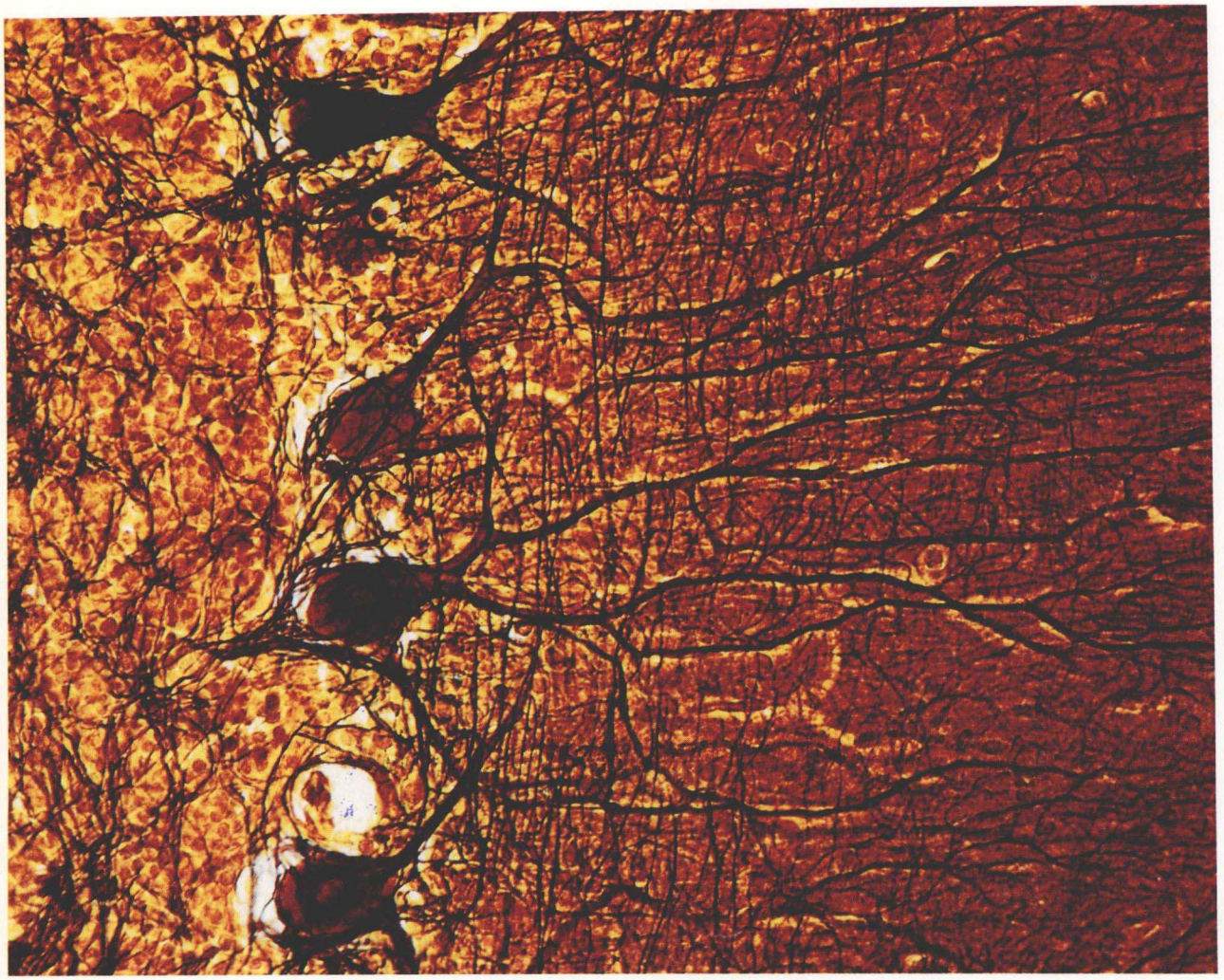

Photomicrograph of human brain-nerve cells, by Manfred Kage.

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Preface

Principles of Physiology has been carefully designed to present the important features of mammalian physiology in a clear and concise manner. General principles and underlying mechanisms are emphasized, and relatively nonvital details are minimized. Considerable attention is directed to cell physiology, which serves as the basis for body functions. Not only is the first section of the text devoted to this topic, but it is also provided as foundational information in each succeeding section. We have tried to show that the processes that take place in individual cells are usually applicable to each organ system as a whole.

The major emphasis in *Principles of Physiology* is on *regulation*. The mechanisms that regulate the functions of the individual organ systems are thoroughly described. They are then applied in the complex interactions between the systems as they maintain the constant internal environment so important for optimal function of the constituent cells. All systems are then tied together in the final chapter describing exercise physiology. We hope that this will explain how the body successfully integrates its varied functions to perform a specific task.

Because the intent of this text is to offer, in a clear and concise presentation, *all* information needed to master a complete course in physiology, the use of mathematics has been minimized, and succinct, lucid descriptions substituted wherever feasible. Furthermore, controversial issues in physiology have been purposely omitted to allow ample room for the explanation of important physiological mechanisms.

To contribute to our goal of clarity, many color 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 that reiterate some of the concepts that appear in the text and serve to inform the reader about important investigative techniques.

For clarity and simplicity, the sources of statements or assertions in the text are not cited. Brief bibliographies are included at the end of each chapter to direct the student to more detailed information. The references listed in these bibliographies are mainly review articles or recent scientific papers that can be of interest to the reader.

Robert M. Berne
Matthew N. Levy

Contents

CELL PHYSIOLOGY

HOWARD C. KUTCHAI

PART

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 biologic 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 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 biologic membranes have a lipid bilayer structure.

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.** 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 lipid and proteins

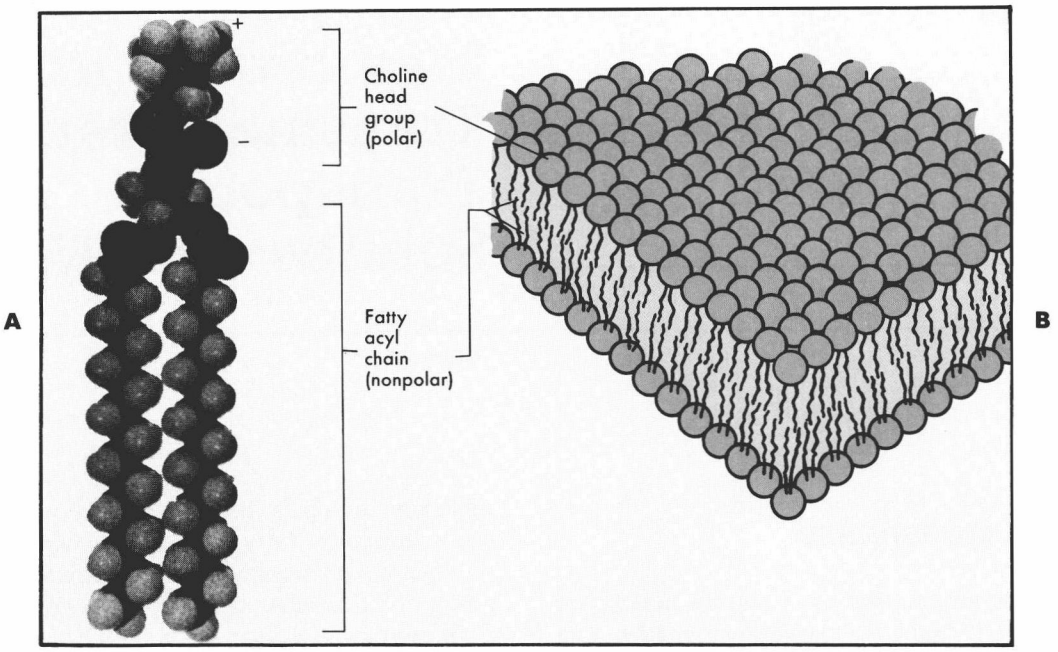

FIGURE 1-1 **A,** Structure of a membrane phospholipid molecule, in this case a phosphatidylcholine. **B,** Structure of a phospholipid bilayer. The open circles represent the polar head groups of the phospholipid molecules. The wavy lines represent the fatty acyl chains of the phospholipids.

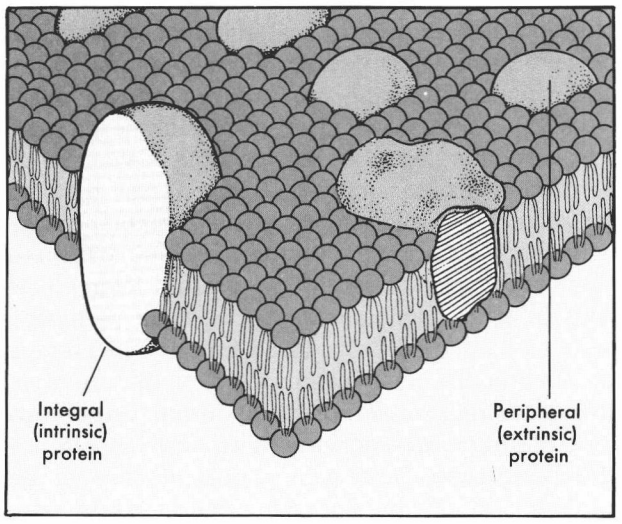

FIGURE 1-2 Schematic representation of the fluid mosaic model of membrane structure. The integral proteins are embedded in the lipid bilayer matrix of the membrane, and the peripheral proteins are associated with the external surfaces of integral membrane proteins.

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. At present little is known about the ways in which membrane constituents are restrained from lateral diffusion. The cytoskeleton appears to tether certain membrane proteins.

MEMBRANE COMPOSITION

Lipid Composition

Major Phospholipids In animal cell membranes the most abundant phospholipids are often the cho-

line-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.

Cholesterol Cholesterol is a major constituent of plasma membranes, and its steroid nucleus lies parallel to the fatty acyl chains of membrane phospholipids.

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.

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. Asymmetry of phospholipids also occurs. 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 highly 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. Plasma membranes, by contrast, perform many functions and 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. Cell surface carbohydrate has important functions. **The negative surface charge of cells is ascribable to the negatively charged sialic acid of glycolipids and glycoproteins.**

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 functions 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. Thus 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 of 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, allowing 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.

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. In some cases molecules 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

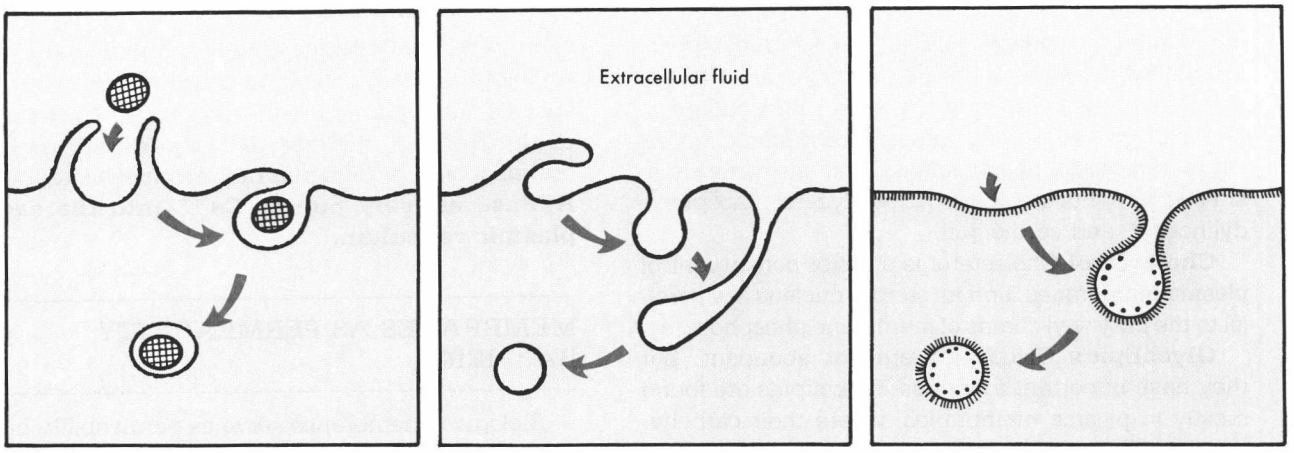

FIGURE 1-3 Schematic depiction of endocytotic processes. **A,** Phagocytosis of a solid particle. **B,** Pinocytosis of extracellular fluid. **C,** Receptor-mediated endocytosis by coated pits.

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 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 in ways that are not yet understood. 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.

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 proenzymes from the acinar cells of the pancreas is a well-studied example. 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.

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.

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 a specific glucose transport protein in the plasma membrane.

Diffusion

Diffusion is the process whereby atoms or molecules intermingle because of their random thermal (Brownian) motion. Imagine a container divided into two compartments by a removable partition. 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 as it is 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 no further net movement will occur; a dynamic equilibrium exists.

Range of Diffusion Diffusion is a rapid process when the distance over which it takes place is small. This can be appreciated from a relation derived by Einstein. He considered the random movements of molecules that are originally located at $x = 0$. Because a given molecule is equally likely to diffuse in one direction as in the other, the average displacement of all the molecules that begin at $x = 0$ will be zero. The average displacement squared, $(\Delta x)^2$, which is a positive quantity, is represented by

$$\overline{(\Delta x)^2} = 2\ Dt \qquad \textbf{(1)}$$

where t is the time elapsed since the molecules started diffusing and D is a constant of proportionality called the *diffusion coefficient*. The Einstein relation (equation 1) tells us how far the average molecule will diffuse in a given time (t). It is a useful but rough estimate of the time scale of a particular diffusion process.

Einstein's relation reveals that 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 the diffusion process will require about 100 times longer to reach a given degree of completion. Table 1-1 shows the results of calculations using Einstein's relation for a typical, small, water-soluble solute. It can be seen that diffusion is extremely rapid on a microscopic scale of distance. For macroscopic distances diffusion is rather slow. A cell that is 100 μm away from the nearest capillary can receive nutrients from the blood by diffusion with a time lag of only 5 seconds or so. This is sufficiently fast to satisfy the metabolic demands of many cells. However, a nerve axon that is 1 cm long cannot rely on diffusion for the intracellular transport of vital metabolites, since the 14 hours required for diffusion over the 1 cm distance is too long on the time scale of cellular metabolism. Some nerve fibers are longer than 1 m. Therefore it is no wonder that intracellular axonal transport systems are involved in transporting important molecules along nerve fibers. Because of the slowness of diffusion over macroscopic distances, it is not surprising that even small multicellular organisms have evolved circulatory systems to bring the individual cells of the organisms within a reasonable diffusion range of nutrients.

Table 1-1 Time Required for Diffusion To Occur over Various Diffusion Distances*

Diffusion Distance (μm)	Time Required for Diffusion
1	0.5 msec
10	50 msec
100	5 seconds
1000 (1 mm)	8.3 minutes
10,000 (1 cm)	14 hours

*The time required for the "average" molecule (with diffusion coefficient taken to be 1×10^{-5} cm·sec^{-1}) to diffuse the required distance was computed from the Einstein relation (equation 1).

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.

Einstein obtained the following equation for the diffusion coefficient of a spherical solute molecule that is much larger than the surrounding solvent molecules:

$$D = kT/(6\pi r\eta) \qquad \textbf{(2)}$$

where

- k = Boltzmann's constant
- T = Absolute temperature (kT is proportional to the average kinetic energy of a solute molecule)
- r = Molecular radius
- η = Viscosity of the medium

The equation is called the *Stokes-Einstein equation,* and the molecular radius defined by this equation is known as the Stokes-Einstein radius.

For large molecules equation 2 predicts that D will be inversely proportional to the radius of the diffusing molecule. Because the molecular weight (MW) is approximately proportional to r^3, D should be inversely proportional to $\sqrt[3]{MW}$. Thus a molecule that has ⅛ the mass of another molecule will have a diffusion coefficient only twice as large as the other molecule. For smaller solutes, with a molecular weight less than about 300, D is inversely proportional to $\sqrt{MW}$ rather than $\sqrt[3]{MW}$.

Diffusion Across a Membrane Diffusion leads to a state in which the concentration of the diffusing species is constant in space and time. Diffusion across cellular membranes tends to equalize the concentrations on the two sides of the membrane. The diffusion rate across a membrane is proportional to the area of the membrane and to the difference in concentration of the diffusing substance on the two sides of the membrane. *Fick's first law of diffusion* states that

$$J = -DA\frac{\Delta c}{\Delta x} \qquad (3)$$

where

J = Net rate of diffusion in moles or grams per unit time
D = Diffusion coefficient of the diffusing solute in the membrane
A = Area of the membrane
Δc = Concentration difference across the membrane
Δx = Thickness of the membrane

Diffusive Permeability of Cellular Membranes

Permeability to Lipid-Soluble Molecules The plasma membrane serves as a diffusion barrier that enables the cell to maintain cytoplasmic concentrations of many substances that differ greatly from their extracellular concentrations. As early as the turn of the century, the relative impermeability of the plasma membrane to most water-soluble substances was attributed to its "lipoid nature."

The hypothesis that the plasma membrane has a lipoid character is supported by experiments showing that compounds that are soluble in nonpolar solvents (e.g., benzene or olive oil) enter cells more readily than do water-soluble substances of similar molecular weight. Figure 1-4 shows the relationship between membrane permeability and solubility in a nonpolar solvent for a number of different solutes. The ratio of the solubility of the solute in olive oil to its solubility in water is used as a measure of solubility in nonpolar solvents. This ratio is called the *olive oil/water partition coefficient.* The permeability of the plasma membrane to a particular substance increases with the "lipid solubility" of the substance. For compounds with the same olive oil/water partition coefficient, permeability decreases with increasing molecular weight. As described previously, the fluid mosaic model of membrane structure envisions the plasma membrane as a lipid bilayer with proteins embedded in it (Figure 1-2). The data of Figure 1-4 support the idea that the lipid bilayer is the principal barrier to substances that permeate the membrane by simple diffusion.

Permeability to Water-Soluble Molecules Very small, uncharged, water-soluble molecules pass through cell membranes much more rapidly than predicted by their lipid solubility. For example, water permeates cell membranes much more rapidly than is predicted from its molecular radius and its olive oil/water partition coefficient. The reason for the unusually high permeability to water is controversial. Some evidence suggests that very small water-soluble molecules can pass between adjacent phospholipid molecules without actually dissolving in the region occupied by the fatty acid side chains. Other evidence suggests that membrane proteins are responsible for the high membrane permeability to water.

As the size of uncharged, water-soluble molecules increases, their membrane permeativity decreases. Most plasma membranes are essentially impermeable to water-soluble molecules whose molecular weights are greater than about 200.

Because of their charge, ions are relatively insoluble in lipid solvents, and thus membranes are not very permeable to most ions. Ionic diffusion across membranes occurs mainly through protein "channels" that span the membrane. Some channels are highly specific with respect to the ions allowed to pass, whereas others allow all ions below a certain size to pass. Some ion channels are controlled by the voltage difference across the membrane, and others are controlled by neurotransmitters or certain other regulatory molecules.

Although certain water-soluble molecules such as sugars and amino acids are essential for cellular survival, they do not cross plasma membranes appreciably by simple diffusion. **Plasma membranes have specific proteins that allow the transfer of vital**