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PHYSIOLOGY
生 理 学

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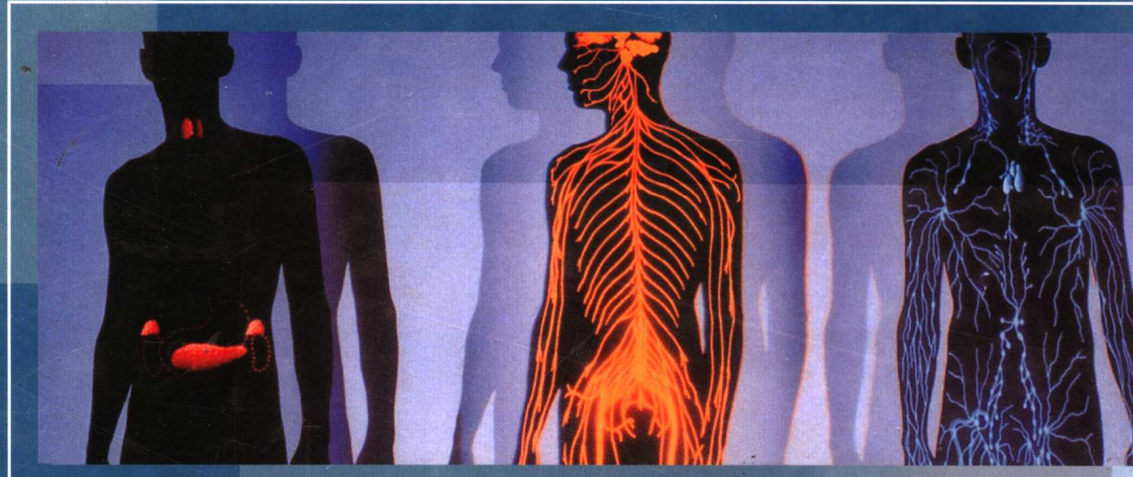

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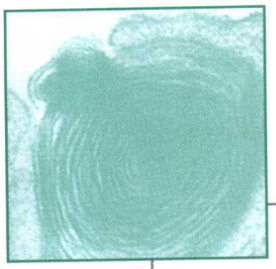

英文影印版

生 理 学

PHYSIOLOGY

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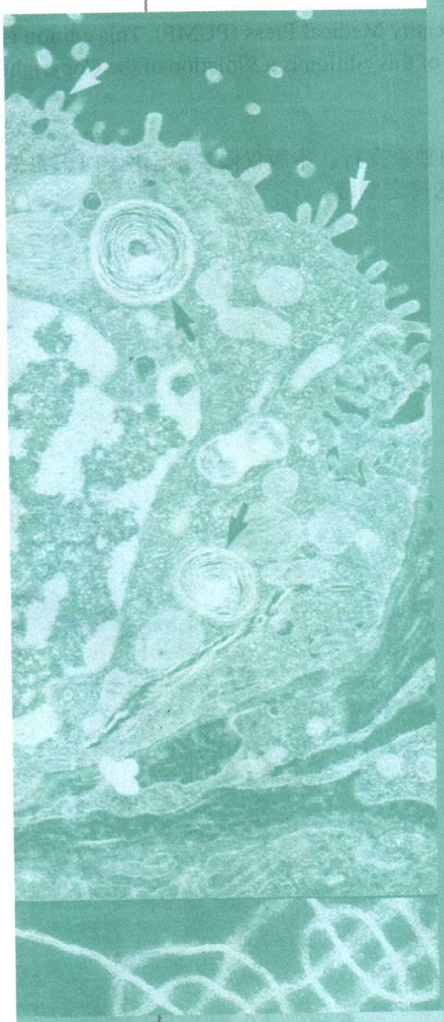
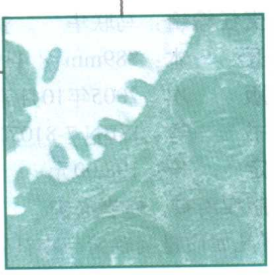


第5版

北京大学医学出版社
Peking University Medical Press



Physiology, fifth edition
Robert M. Berne, et al
ISBN: 0-323-02225-1

Authorized English language reprint edition published by the Proprietor.
Reprint ISBN: 981-2593-80-2

Elsevier (Singapore) Pte Ltd.
3 Kiliney Road, #08-01 Winsland Hose I, Sinagpore 239519,
Tel: (65)6349-0200, Fax: (65)6733-1817

北京市版权局著作权合同登记号：01-2005-5091

SHENG LI XUE

图书在版编目(CIP)数据

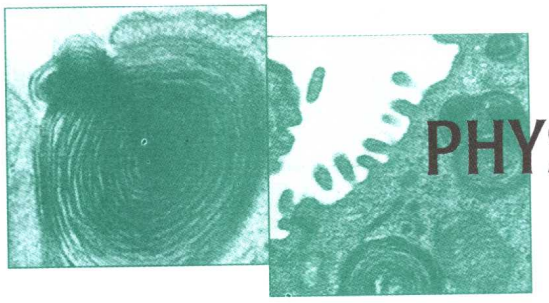
生理学＝Physiology：第5版／(美)伯恩(Berne，R. M.)等著．—影印本．—北京：北京大学医学出版社，2005. 8
ISBN 7-81071-848-7

Ⅰ.生…　Ⅱ.伯…　Ⅲ.人体生理学—英文　Ⅳ. R33

中国版本图书馆CIP数据核字(2005)第071851号

生 理 学

主　　编：Robert M. Berne等
出版发行：北京大学医学出版社（电话：010-82802230）
地　　址：(100083) 北京市海淀区学院路38号　北京大学医学部院内
网　　址：http://www.pumpress.com.cn
E - mail：booksale@bjmu.edu.cn
印　　刷：北京圣彩虹制版印刷技术有限公司
经　　销：新华书店
责任编辑：马联华　　**责任校对**：齐欣　　**责任印制**：郭桂兰
开　　本：889mm × 1194mm　1/ 16　**印张**：64.25　**字数**：1645千字
版　　次：2005年10月第1版　　2005年10月第1次印刷
书　　号：ISBN 7-81071-848-7/R · 848
定　　价：198.00元



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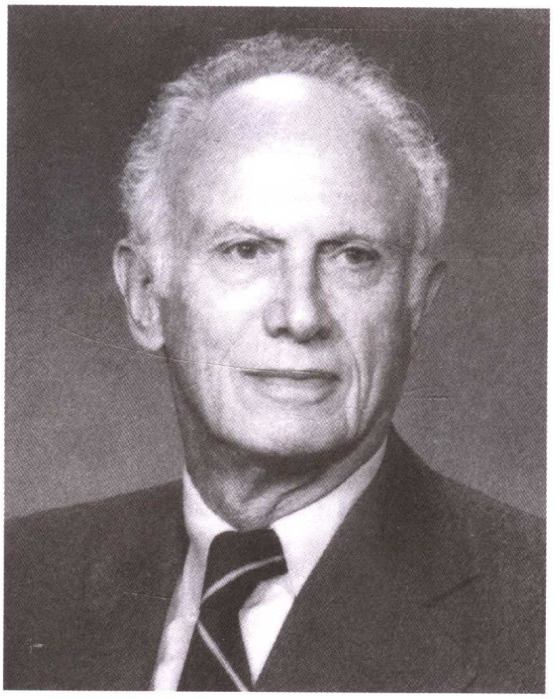

Dedication

This book is dedicated to Professor Robert M. Berne, who died October 4, 2001. Dr. Berne was a superb scientist, an acclaimed author, an excellent teacher, and a very amiable person. His devotion to the field of Physiology has inspired students and colleagues over the past half-century.

注 意

生理学在不断进步。虽然有关安全问题的注意事项必须遵守，但是由于新的研究和临床经验在不断拓宽我们的知识，在治疗和用药方面做出某些改变也许是必需的或适宜的。建议读者核对所开每种药品生产厂商的最新产品信息，确认推荐剂量、服药方法与时间及禁忌证。决定患者服药剂量和最佳治疗方式的责任在实施治疗的医师，即有赖于其个人经验和对每位患者的了解。出版商和著者对可能引起的人身或财产的任何损伤和(或)损失，不承担任何责任。

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影印出版说明

由Bobert M. Berne等人主编的“生理学(第5版)”是一本适时更新的综合性人体生理学教科书，从1983年第1版开始，每5年修订一次，第5版为2004年最新版。

本教科书涵盖了生理学的主要内容，按器官系统编排，清晰准确地描述了所有控制和调节身体功能的重要机制。一如以前各版，最新的第5版力图加强主要概念，着重于不同器官系统的生理机制和相互作用，同时尽可能将孤立的事实化繁为简。为了使内容更加清晰、准确，并反映生理学领域的最新进展，本版各章均进行了修订。新的第5版的特点是增加了大量分子生物学和遗传性疾病的内容，神经系统部分根据医学教育的最新发展趋势进行了全面改编。为了加深理解，本版的许多插图也进行了修订，并增加了许多新的插图，全书插图有550幅之多。

作为生理学领域的一流教科书，本教科书因其对论述生理学问题所采取的客观和科学严谨的方法而闻名。本书引用具体的疾病案例讲述适用的生理机制所起的作用，自始至终强调临床资料的应用。当重要的概念可以通过公式表达获得定量理解时，本书还引入了这种更严格的分析方式及其所依据的基本假设，供感兴趣的读者选读。临床相关资料和数学分析资料采用了加阴影的文本格式。

本书著者均为在全世界享有极高威望的医学教育领域的专家，他们为了打造这部当今医学生理学课程的理想教科书，进行了通力合作。本书内容全面、系统，极具权威性，可读性强，是医学院校生理学教师重要的教学参考书，也是研究生及长学制学生学习专业知识、提高专业英语水平的一本生理学必读教科书。

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Preface

As in the previous editions of this textbook, we have attempted to emphasize broad concepts and to minimize the compilation of isolated facts. Each chapter in this edition has been altered to make the text as lucid, accurate, and current as possible. In an effort to improve comprehension, we have revised many of the illustrations, and have added many new figures. Finally, in order to emphasize broad principles, we have highlighted many of the important physiological mechanisms and critical interactions among the various organ systems.

Physiology is concerned with the function of organisms at many stages of organization, from the subcellular level to the intact organism. In the healthy human, many variables are maintained within narrow limits. The list of controlled variables includes body temperature, blood pressure, the ionic composition of the body's various fluid compartments, the blood glucose levels, and the 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.** One of the central goals of physiological research is the elucidation of homeostatic mechanisms.

In section I, **(Cellular Physiology),** of this book, and at the beginnings of several other sections, various important physiological principles are analyzed in detail. We have included considerable information about major advances in cellular and molecular biology. Such data includes the roles of membrane transport proteins and of the structure and function of ion-transporting ATPases. In order to emphasize the clinical relevance of certain advances, we have cited specific diseases in which the applicable physiological mechanism plays an important role. Scattered throughout each chapter, these clinical examples have been highlighted by enclosing them in shaded boxes.

When important principles can be represented profitably by equations, we have cited the underlying assumptions that serve as the bases of those equations. This approach provides students with a more quantitative understanding of these principles. Furthermore, because some of the readers might not favor a rigorous analytical approach, we have sequestered the more extensive mathematical analyses in shaded boxes.

Section II, **(The Nervous System),** provides a neuroanatomical framework for its presentation of contemporary cellular neurophysiology. Substantial attention has been directed toward the sensory and motor systems, because of their clinical relevance. Analysis of the fundamental principles common to the various sensory systems facilitates the comprehension of the various components of that system.

In section III, **(Muscle),** we have described the basic mechanisms of contraction in skeletal, smooth, and cardiac muscles. The characteristics of skeletal and smooth muscle are presented in detail in this section, but the description of cardiac muscle performance is divided between Sections III and IV.

In section IV, **(The Cardiovascular System),** we have dissected the system initially into its major components. One such component, namely blood composition and function, has been condensed and included as an introductory chapter in the cardiovascular section. In the subsequent chapters related to the heart and vasculature, we have first examined the functions of the individual cardiovascular components. Subsequently, we have analyzed how the various parts of the closed loop circulatory system interact under various physiological and pathological conditions.

Section V, **(The Respiratory Section)** emphasizes the physical principles that underlie the mechanics of breathing and the exchange of gas between the blood and the alveoli, and between the blood and the peripheral tissues. Furthermore, the neural and chemical processes that regulate respiration, the role of the lungs in immune defense, and certain non-respiratory functions of the lungs have been described in detail.

Section VI, **(The Gastrointestinal System),** presents first the processes of motility and secretion in the gastrointestinal tract, and then explains how these functions are integrated by neural, endocrine, and paracrine mechanisms. Furthermore, the role of ion transporters in the absorption and secretion of electrolytes in the gastrointestinal tract have been described. Subsequently, certain critical mechanisms are shown to account for the pathogenesis of various gastrointestinal disturbances.

In Section VII, **(The Kidneys),** the mechanisms by which the kidneys handle water and certain important solutes have

been described in detail. The regulation of body fluid osmolality and volume, and of acid-base balance, has also been explained.

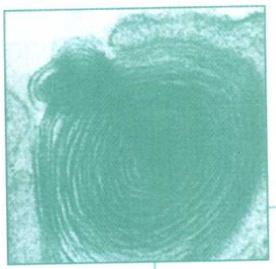
In Section VIII, **(The Endocrine System),** similarities in the functioning of the various endocrine glands are emphasized. Major new insights into the mechanisms of hormone action, the regulation of energy storage and turnover, and the processes of reproduction are presented. Discussions of the male 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.

The authors of each section have presented what they believe to be the most likely mechanisms responsible for the phenomena under consideration. We have adopted this compromise to achieve brevity, clarity, and simplicity. We have not cited the specific sources for each of the assertions that appear throughout the book, but we have listed references at the end of each chapter. These references provide a current and comprehensive review of the topic.

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

The Editors

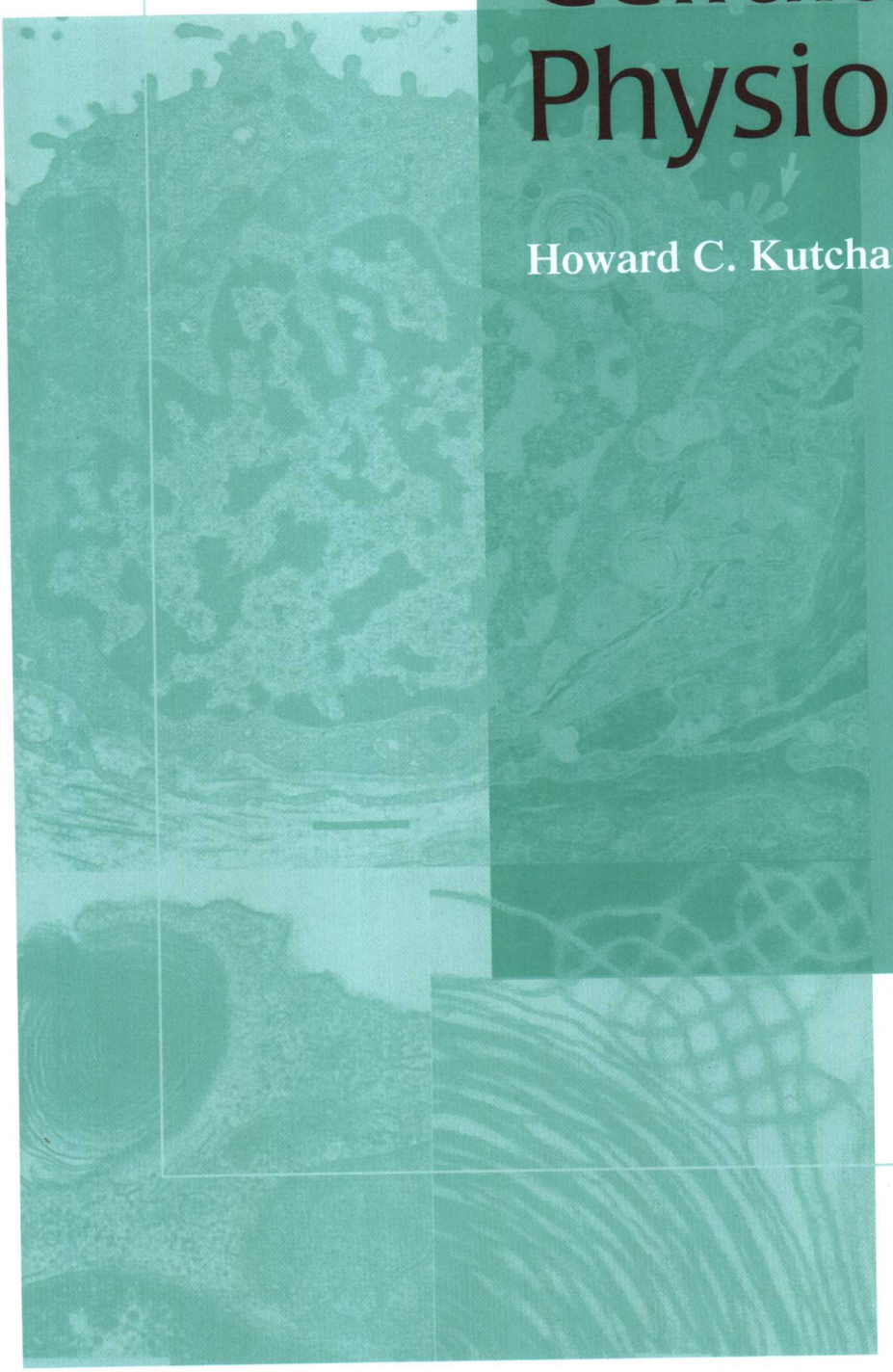
Contents

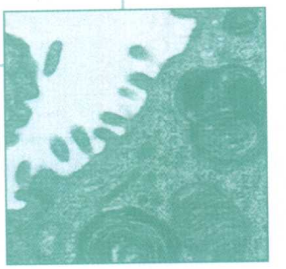


section one

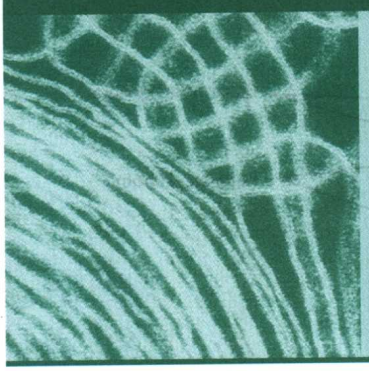
Cellular Physiology

Howard C. Kutchai





chapter one



Cellular Membranes and Transmembrane Transport of Solutes and Water

CELLULAR MEMBRANES

Membranes are important components 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 the extracellular matrix, 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 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.

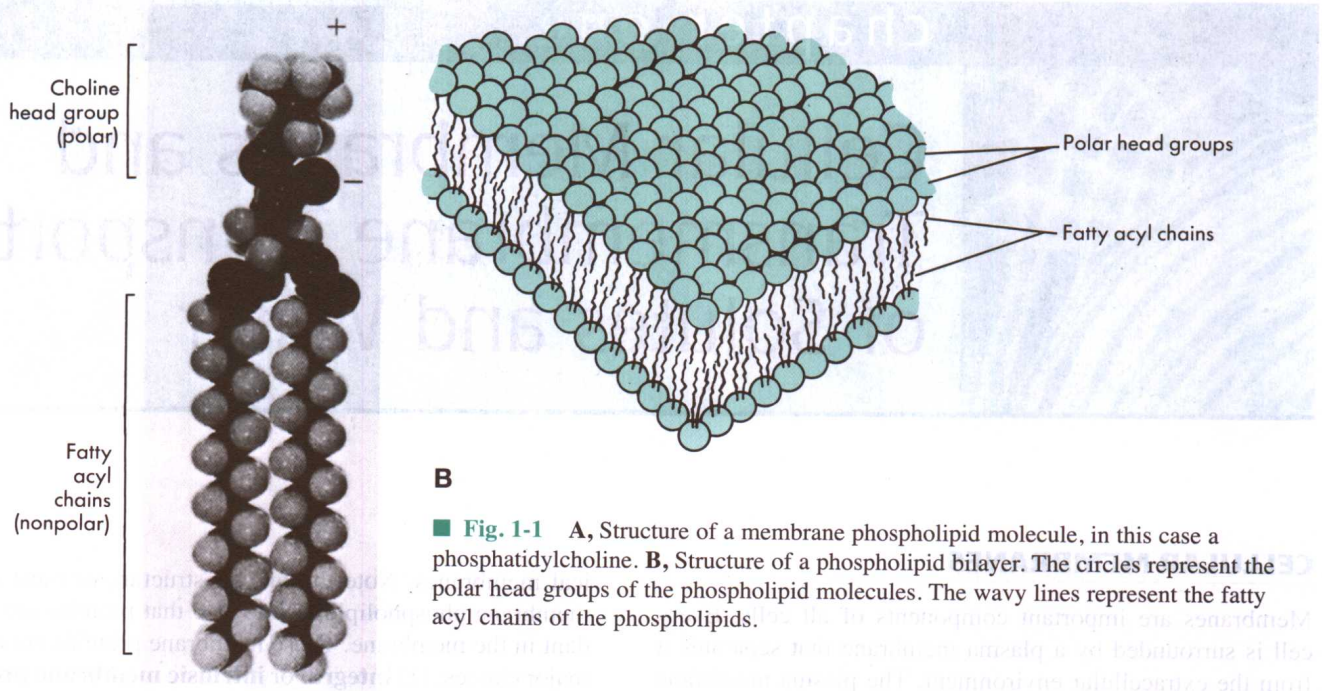
MEMBRANE STRUCTURE

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. These hydrophobic interactions can be disrupted by 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, acetylcholine receptors (integral membrane proteins) are sequestered at the motor end plate of skeletal muscle. Other proteins and certain lipids may be enriched in regions or domains in the membrane. Different membrane proteins are confined to the apical and basolateral plasma membranes of epithelial cells. In some cells, the 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.**



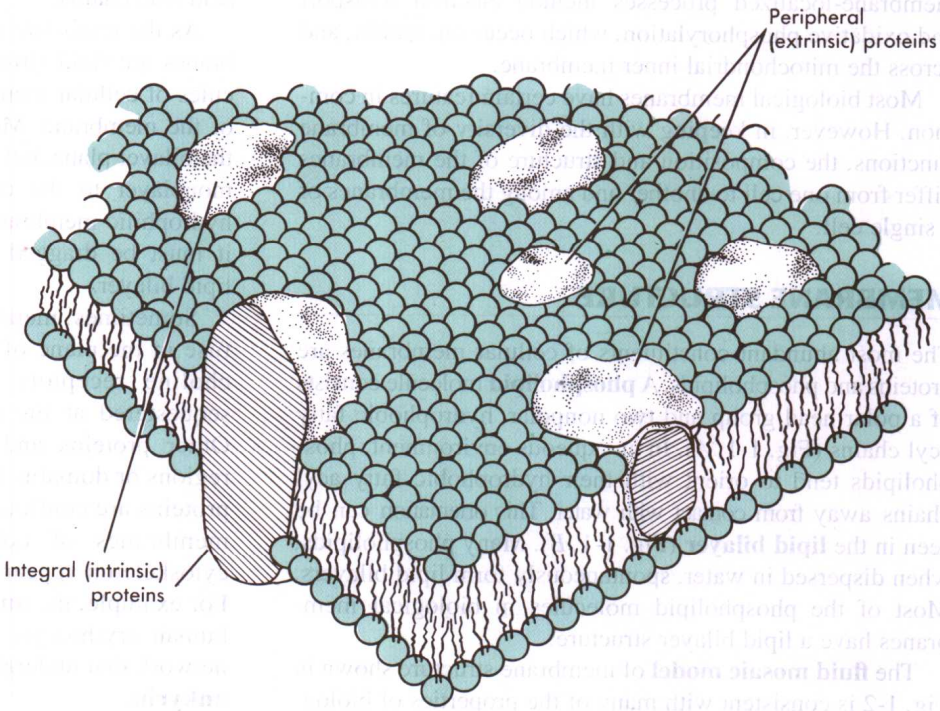
■ **Fig. 1-1** **A,** Structure of a membrane phospholipid molecule, in this case a phosphatidylcholine. **B,** Structure of a phospholipid bilayer. The circles represent the polar head groups of the phospholipid molecules. The wavy lines represent the fatty acyl chains of the phospholipids.

If the motor nerve that innervates a skeletal muscle is accidentally severed, the acetylcholine receptors are no longer sequestered at the motor end plate. 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)



■ **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.

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.** IP3 is released into the cytosol, where it acts on receptors in the endoplasmic reticulum to cause release of stored Ca^{2+}, which affects a wide variety of cellular processes. Diacylglycerol remains in the plasma membrane, where it participates, along with Ca^{2+}, 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** is the carbohydrate moiety of a particular glycolipid, ganglioside (G_{M1}). The A and B blood group antigens (Chapter 14) are the carbohydrate moieties of other gangliosides on the human erythrocyte membrane.

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.

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^{2+}-ATPase (also called the Ca^{2+}-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^{2+}-ATPase actively pumps Ca^{2+} into the sarcoplasmic reticulum. In the ion-transporting ATPases, the domains that bind and hydrolyze ATP face the cytosolic side of the membrane exclusively.

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 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 differences in concentration 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 this 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