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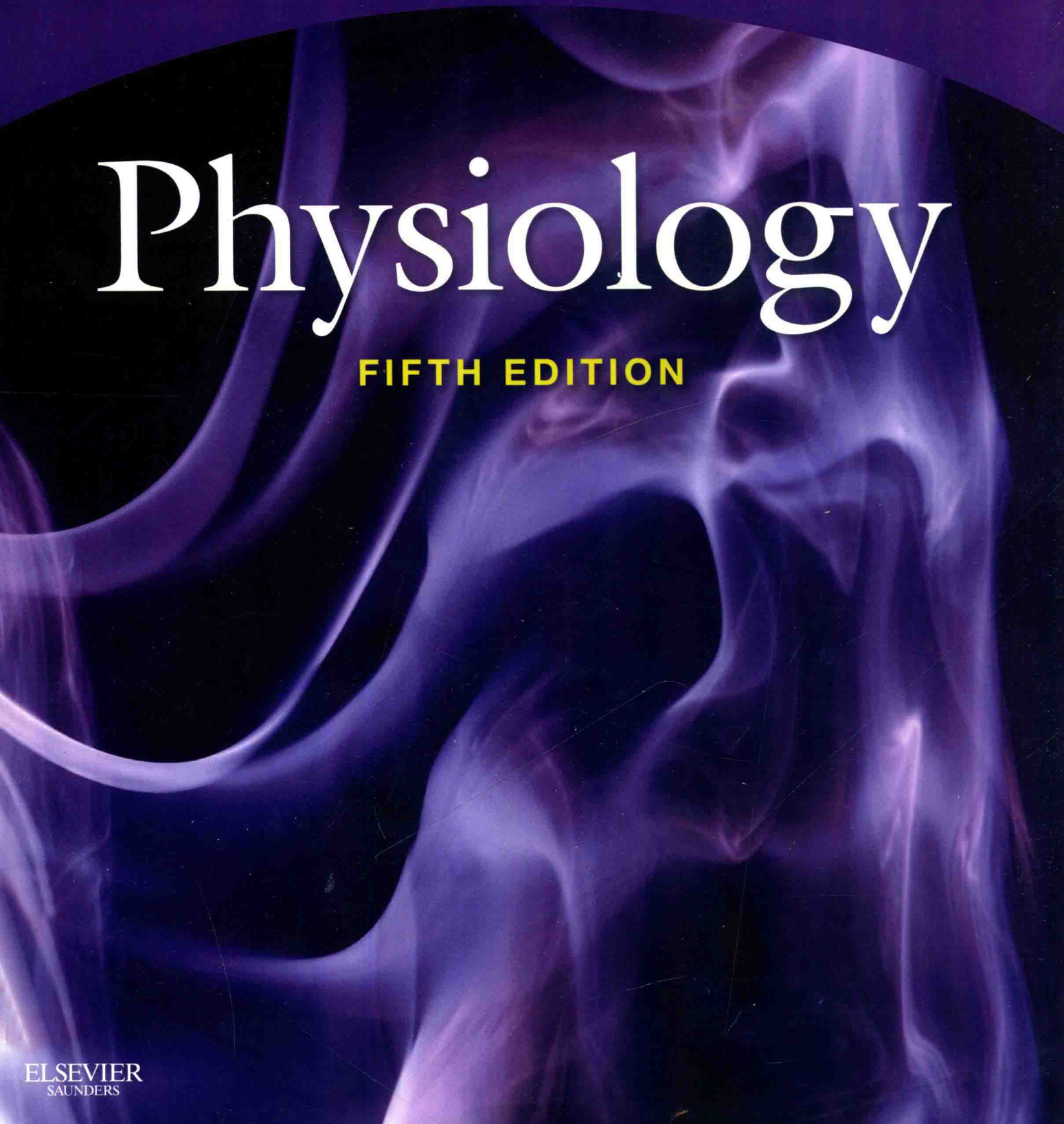
LINDA S. COSTANZO

# Physiology

FIFTH EDITION



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To

**Heinz Valtin** and **Arthur C. Guyton,**

who have written so well for students of physiology

**Richard, Dan, Rebecca, Sheila, Elise,** and **Max,**

who make everything worthwhile

# *Preface*

Physiology is the foundation of medical practice. A firm grasp of its principles is essential for the medical student and the practicing physician. This book is intended for students of medicine and related disciplines who are engaged in the study of physiology. It can be used either as a companion to lectures and syllabi in discipline-based curricula or as a primary source in integrated or problem-based curricula. For advanced students, the book can serve as a reference in pathophysiology courses and in clinical clerkships.

In the fifth edition of this book, as in the previous editions, the important concepts in physiology are covered at the organ system and cellular levels. Chapters 1 and 2 present the underlying principles of cellular physiology and the autonomic nervous system. Chapters 3 through 10 present the major organ systems: neurophysiology and cardiovascular, respiratory, renal, acid-base, gastrointestinal, endocrine, and reproductive physiology. The relationships between organ systems are emphasized to underscore the integrative mechanisms for homeostasis.

This edition includes the following features designed to facilitate the study of physiology:

- **Text** that is easy to read and concise: Clear headings orient the student to the organization and hierarchy of the material. Complex physiologic information is presented systematically, logically, and step-wise. When a process occurs in a specific sequence, the steps are numbered in the text and often correlate with numbers shown in a figure. Bullets are used to separate and highlight the features of a process. Rhetorical questions are posed throughout the text to anticipate the questions that students may be asking; by first contemplating and then answering these questions, students learn to explain difficult concepts and rationalize unexpected or paradoxical findings. References at the end of each chapter direct the student to monographs, texts, review articles, and classic papers that offer further detail or historical perspective. Chapter summaries provide a brief overview.
- **Tables and illustrations** that can be used in concert with the text or, because they are designed to stand alone, as a review: The tables summarize, organize, and make comparisons. Examples are (1) a table that compares the gastrointestinal hormones with respect to hormone family, site of and stimuli for secretion, and hormone actions; (2) a table that compares the pathophysiologic features of disorders of $Ca^{2+}$ homeostasis; and (3) a table that compares the features of the action potential in different cardiac tissues. The illustrations are clearly labeled, often with main headings, and include simple diagrams, complex diagrams with numbered steps, and flow charts.
- **Equations and sample problems** that are integrated into the text: All terms and units in equations are defined, and each equation is restated in words to place it in a physiologic context. Sample problems are followed by complete numerical solutions and explanations that guide the student through the proper steps in reasoning; by

following the steps provided, students acquire the skills and confidence to solve similar or related problems.

- **Clinical physiology** presented in boxes: Each box features a fictitious patient with a classic disorder. The clinical findings and proposed treatment are explained in terms of underlying physiologic principles. An integrative approach to the patient is used to emphasize the relationships between organ systems. For example, the case of type I diabetes mellitus involves a disorder not only of the endocrine system but also of the renal, acid-base, respiratory, and cardiovascular systems.
- **Practice questions** in "Challenge Yourself" sections at the end of each chapter: Practice questions, which are designed for short answers (a word, a phrase, or a numerical solution), challenge the student to apply principles and concepts in problem solving rather than to recall isolated facts. The questions are posed in varying formats and are given in random order. They will be most helpful when used as a tool after studying each chapter and without referring to the text. In that way, the student can confirm his or her understanding of the material and can determine areas of weakness. Answers are provided at the end of the book.
- **Abbreviations and normal values** presented in appendices. As students refer to and use these common abbreviations and values throughout the book, they will find that they become second nature.

This book embodies three beliefs that I hold about teaching: (1) even complex information can be transmitted clearly if the presentation is systematic, logical, and presented step-wise; (2) the presentation can be just as effective in print as in person; and (3) beginning medical students wish for nonreference teaching materials that are accurate and didactically strong but without the details that primarily concern experts. In essence, a book can "teach" if the teacher's voice is present, if the material is carefully selected to include essential information, and if great care is paid to logic and sequence. This text offers a down-to-earth and professional presentation written *to* students and *for* students.

I hope that the readers of this book enjoy their study of physiology. Those who learn its principles well will be rewarded throughout their professional careers!

*Linda S. Costanzo*

# *Acknowledgments*

I gratefully acknowledge the contributions of Elyse O'Grady, Andrea Vosburgh, and John Casey at Elsevier in preparing the fifth edition of *Physiology*. The artist, Matthew Chansky, revised existing figures and created new figures—all of which beautifully complement the text.

Colleagues at Virginia Commonwealth University have faithfully answered my questions, especially Drs. Clive Baumgarten, Diomedes Logothetis, Roland Pittman, and Raphael Witorsch. Sincere thanks also go to the medical students worldwide who have generously written to me about their experiences with earlier editions of the book.

My husband, Richard, our children, Dan and Rebecca, our daughter-in-law, Sheila, and our grandchildren, Elise and Max, have provided enthusiastic support and unqualified love, which give the book its spirit.

# Contents

# Cellular Physiology

Understanding the functions of the organ systems requires profound knowledge of basic cellular mechanisms. Although each organ system differs in its overall function, all are undergirded by a common set of physiologic principles.

The following basic principles of physiology are introduced in this chapter: body fluids, with particular emphasis on the differences in composition of intracellular fluid and extracellular fluid; creation of these concentration differences by transport processes in cell membranes; the origin of the electrical potential difference across cell membranes, particularly in excitable cells such as nerve and muscle; generation of action potentials and their propagation in excitable cells; transmission of information between cells across synapses and the role of neurotransmitters; and the mechanisms that couple the action potentials to contraction in muscle cells.

These principles of cellular physiology constitute a set of recurring and interlocking themes. Once these principles are understood, they can be applied and integrated into the function of each organ system.



## VOLUME AND COMPOSITION OF BODY FLUIDS

### Distribution of Water in the Body Fluid Compartments

In the human body, water constitutes a high proportion of body weight. The total amount of fluid or water is called **total body water,** which accounts for 50% to 70% of body weight. For example, a 70-kilogram (kg) man whose total body water is 65% of his body weight has 45.5 kg or 45.5 liters (L) of water (1 kg water ≈ 1 L water). In general, total body water correlates inversely with body fat. Thus, total body water is a higher percentage of body weight when body fat is low and a lower percentage when body fat is high. Because females have a higher percentage of adipose tissue than males, they tend to have less body water. The distribution of water among body fluid compartments is described briefly in this chapter and in greater detail in Chapter 6.

Total body water is distributed between two major body fluid compartments: intracellular fluid (ICF) and extracellular fluid (ECF) (Fig. 1-1). The **ICF** is contained within the cells and is two thirds of total body water; the **ECF** is outside the cells and is one third of total body water. ICF and ECF are separated by the cell membranes.

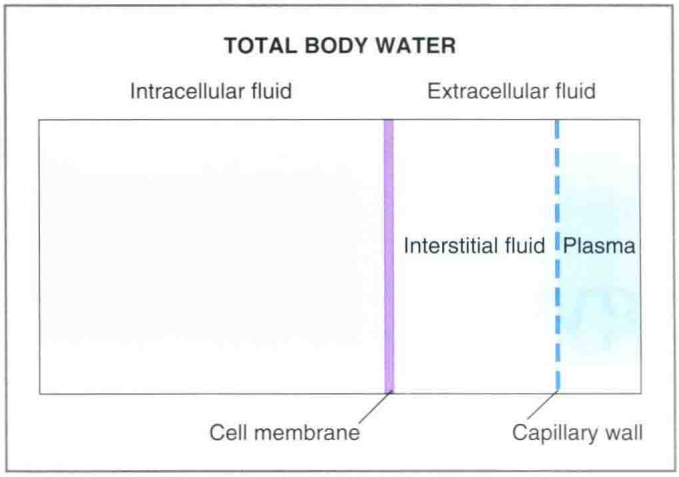


**Figure 1–1** Body fluid compartments.

ECF is further divided into two compartments: plasma and interstitial fluid. **Plasma** is the fluid circulating in the blood vessels and is the smaller of the two ECF subcompartments. **Interstitial fluid** is the fluid that actually bathes the cells and is the larger of the two subcompartments. Plasma and interstitial fluid are separated by the capillary wall. Interstitial fluid is an **ultrafiltrate** of plasma, formed by filtration processes across the capillary wall. Because the capillary wall is virtually impermeable to large molecules such as plasma proteins, interstitial fluid contains little, if any, protein.

The method for estimating the volume of the body fluid compartments is presented in Chapter 6.

## Composition of Body Fluid Compartments

The composition of the body fluids is not uniform. ICF and ECF have vastly different concentrations of various solutes. There are also certain predictable differences in solute concentrations between plasma and interstitial fluid that occur as a result of the exclusion of protein from interstitial fluid.

### *Units for Measuring Solute Concentrations*

Typically, **amounts** of solute are expressed in moles, equivalents, or osmoles. Likewise, **concentrations** of solutes are expressed in moles per liter (mol/L), equivalents per liter (Eq/L), or osmoles per liter (Osm/L). In biologic solutions, concentrations of solutes are usually quite low and are expressed in *milli*moles per liter (mmol/L), *milli*equivalents per liter (mEq/L), or *milli*osmoles per liter (mOsm/L).

One **mole** is $6 \times 10^{23}$ molecules of a substance. One **millimole** is 1/1000 or $10^{-3}$ moles. A glucose concentration of 1 mmol/L has $1 \times 10^{-3}$ moles of glucose in 1 L of solution.

An **equivalent** is used to describe the amount of charged (ionized) solute and is the number of moles of the solute multiplied by its valence. For example, one mole of potassium chloride (KCl) in solution dissociates into one equivalent of potassium ($K^+$) and one equivalent of chloride ($Cl^-$). Likewise, one mole of calcium chloride ($CaCl_2$) in solution dissociates into *two* equivalents of calcium ($Ca^{2+}$) and *two* equivalents of chloride ($Cl^-$); accordingly, a $Ca^{2+}$ concentration of 1 mmol/L corresponds to 2 mEq/L.

One **osmole** is the number of particles into which a solute dissociates in solution. **Osmolarity** is the concentration of particles in solution expressed as osmoles per liter. If a solute does not dissociate in solution (e.g., glucose), then its osmolarity is equal to its molarity. If a solute dissociates into more than one particle in solution (e.g., NaCl), then its osmolarity equals the molarity multiplied by the number of particles in solution. For example, a solution containing 1 mmol/L NaCl is 2 mOsm/L because NaCl dissociates into two particles.

**pH** is a logarithmic term that is used to express hydrogen ($H^+$) concentration. Because the $H^+$ concentration of body fluids is very low (e.g., $40 \times 10^{-9}$ Eq/L in arterial blood), it is more conveniently expressed as a logarithmic term, pH. The negative sign means that pH decreases as the concentration of $H^+$ increases, and pH increases as the concentration of $H^+$ decreases. Thus,

$$pH = -\log_{10}[H^+]$$

**SAMPLE PROBLEM.** Two men, Subject A and Subject B, have disorders that cause excessive acid production in the body. The laboratory reports the acidity of Subject A's blood in terms of $[H^+]$ and the acidity of Subject B's blood in terms of pH. Subject A has an arterial $[H^+]$ of $65 \times 10^{-9}$ Eq/L, and Subject B has an arterial pH of 7.3. *Which subject has the higher concentration of $H^+$ in his blood?*

**SOLUTION.** To compare the acidity of the blood of each subject, convert the $[H^+]$ for Subject A to pH as follows:

$$\begin{aligned} pH &= -\log_{10}[H^+] \\ &= -\log_{10}(65 \times 10^{-9}\ \text{Eq/L}) \\ &= -\log_{10}(6.5 \times 10^{-8}\ \text{Eq/L}) \end{aligned}$$

$$\log_{10} 6.5 = 0.81$$

$$\log_{10} 10^{-8} = -8.0$$

$$\log_{10} 6.5 \times 10^{-8} = 0.81 + (-8.0) = -7.19$$

$$pH = -(-7.19) = 7.19$$

Thus, Subject A has a blood pH of 7.19 computed from the $[H^+]$, and Subject B has a reported blood pH of 7.3. Subject A has a lower blood pH, reflecting a higher $[H^+]$ and a more acidic condition.

### Electroneutrality of Body Fluid Compartments

Each body fluid compartment must obey the **principle of macroscopic electroneutrality;** that is, each compartment must have the same concentration, in mEq/L, of positive charges (**cations**) as of negative charges (**anions**). There can be no more cations than anions, or vice versa. Even when there is a potential difference across the cell membrane, charge balance still is maintained in the bulk (macroscopic) solutions. Because potential differences are created by the separation of just a few charges adjacent to the membrane, this small separation of charges is not enough to measurably change bulk concentrations.

### Composition of Intracellular Fluid and Extracellular Fluid

The compositions of ICF and ECF are strikingly different, as shown in Table 1-1. The major cation in **ECF** is sodium ($Na^+$), and the balancing anions are chloride ($Cl^-$) and bicarbonate ($HCO_3^-$). The major cations in **ICF** are potassium ($K^+$) and magnesium ($Mg^{2+}$), and the balancing anions are proteins and organic phosphates. Other notable differences in composition involve $Ca^{2+}$ and pH. Typically, ICF has a very low concentration of ionized $Ca^{2+}$ ($\approx 10^{-7}$ mol/L), whereas the $Ca^{2+}$ concentration in ECF is higher by approximately four orders of magnitude. ICF is more acidic (has a lower pH) than ECF. Thus, substances found in high concentration in ECF are found in low concentration in ICF, and vice versa.

Remarkably, given all of the concentration differences for individual solutes, the total solute concentration (**osmolarity**) is the same in ICF and ECF. This equality is achieved because water flows freely across cell membranes. Any transient differences in osmolarity that occur between ICF and ECF are quickly dissipated by water movement into or out of cells to reestablish the equality.

**Table 1–1** Approximate Compositions of Extracellular and Intracellular Fluids

| Substance and Units | Extracellular Fluid | Intracellular Fluid* |
|---|---|---|
| $Na^+$ (mEq/L) | 140 | 14 |
| $K^+$ (mEq/L) | 4 | 120 |
| $Ca^{2+}$, ionized (mEq/L) | 2.5† | $1 \times 10^{-4}$ |
| $Cl^-$ (mEq/L) | 105 | 10 |
| $HCO_3^-$ (mEq/L) | 24 | 10 |
| pH‡ | 7.4 | 7.1 |
| Osmolarity (mOsm/L) | 290 | 290 |

*The major anions of intracellular fluid are proteins and organic phosphates.
†The corresponding total [$Ca^{2+}$] in extracellular fluid is 5 mEq/L or 10 mg/dL.
‡pH is $-\log_{10}$ of the [$H^+$]; pH 7.4 corresponds to [$H^+$] of $40 \times 10^{-9}$ Eq/L.

### Creation of Concentration Differences across Cell Membranes

The differences in solute concentration across cell membranes are created and maintained by energy-consuming transport mechanisms in the cell membranes.

The best known of these transport mechanisms is the $Na^+$-$K^+$ ATPase ($Na^+$-$K^+$ pump), which transports $Na^+$ from ICF to ECF and simultaneously transports $K^+$ from ECF to ICF. Both $Na^+$ and $K^+$ are transported against their respective electrochemical gradients; therefore, an energy source, adenosine triphosphate (ATP), is required. The $Na^+$-$K^+$ ATPase is responsible for creating the large concentration gradients for $Na^+$ and $K^+$ that exist across cell membranes (i.e., the low intracellular $Na^+$ concentration and the high intracellular $K^+$ concentration).

Similarly, the intracellular $Ca^{2+}$ concentration is maintained at a level much lower than the extracellular $Ca^{2+}$ concentration. This concentration difference is established, in part, by a cell membrane $Ca^{2+}$ ATPase that pumps $Ca^{2+}$ against its electrochemical gradient. Like the $Na^+$-$K^+$ ATPase, the $Ca^{2+}$ ATPase uses ATP as a direct energy source.

In addition to the transporters that use ATP directly, other transporters establish concentration differences across the cell membrane by utilizing the transmembrane $Na^+$ concentration gradient (established by the $Na^+$-$K^+$ ATPase) as an energy source. These transporters create concentration gradients for glucose, amino acids, $Ca^{2+}$, and $H^+$ without the direct utilization of ATP.

Clearly, cell membranes have the machinery to establish large concentration gradients. However, if cell membranes were freely permeable to all solutes, these gradients would quickly dissipate. Thus, it is critically important that cell membranes are *not* freely permeable to all substances but, rather, have selective permeabilities that maintain the concentration gradients established by energy-consuming transport processes.

Directly or indirectly, the differences in composition between ICF and ECF underlie every important physiologic function, as the following examples illustrate: (1) The resting membrane potential of nerve and muscle critically depends on the difference in concentration of $K^+$ across the cell membrane; (2) The upstroke of the action potential of these same excitable cells depends on the differences in $Na^+$ concentration across the cell membrane; (3) Excitation-contraction coupling in muscle cells depends on the differences in $Ca^{2+}$ concentration across the cell membrane and the membrane

of the sarcoplasmic reticulum; and (4) Absorption of essential nutrients depends on the transmembrane $Na^+$ concentration gradient (e.g., glucose absorption in the small intestine or glucose reabsorption in the renal proximal tubule).

### Concentration Differences between Plasma and Interstitial Fluids

As previously discussed, ECF consists of two subcompartments: interstitial fluid and plasma. The most significant difference in composition between these two compartments is the presence of proteins (e.g., albumin) in the plasma compartment. Plasma proteins do not readily cross capillary walls because of their large molecular size and, therefore, are excluded from interstitial fluid.

The exclusion of proteins from interstitial fluid has secondary consequences. The plasma proteins are negatively charged, and this negative charge causes a redistribution of small, permeant cations and anions across the capillary wall, called a **Gibbs-Donnan equilibrium.** The redistribution can be explained as follows: The plasma compartment contains the impermeant, negatively charged proteins. Because of the requirement for electroneutrality, the plasma compartment must have a slightly lower concentration of small anions (e.g., $Cl^-$) and a slightly higher concentration of small cations (e.g., $Na^+$ and $K^+$) than that of interstitial fluid. The small concentration difference for permeant ions is expressed in the **Gibbs-Donnan ratio,** which gives the plasma concentration relative to the interstitial fluid concentration for anions and interstitial fluid relative to plasma for cations. For example, the $Cl^-$ concentration in plasma is slightly less than the $Cl^-$ concentration in interstitial fluid (due to the effect of the impermeant plasma proteins); the Gibbs-Donnan ratio for $Cl^-$ is 0.95, meaning that $[Cl^-]_{plasma}/[Cl^-]_{interstitial\ fluid}$ equals 0.95. For $Na^+$, the Gibbs-Donnan ratio is also 0.95, but $Na^+$, being positively charged, is oriented the opposite way, and $[Na^+]_{interstitial\ fluid}/[Na^+]_{plasma}$ equals 0.95. Generally, these minor differences in concentration for small cations and anions are ignored.

## CHARACTERISTICS OF CELL MEMBRANES

Cell membranes are composed primarily of lipids and proteins. The lipid component consists of phospholipids, cholesterol, and glycolipids and is responsible for the high permeability of cell membranes to lipid-soluble substances such as carbon dioxide, oxygen, fatty acids, and steroid hormones. The lipid component of cell membranes is also responsible for the low permeability of cell membranes to water-soluble substances such as ions, glucose, and amino acids. The protein component of the membrane consists of transporters, enzymes, hormone receptors, cell-surface antigens, and ion and water channels.

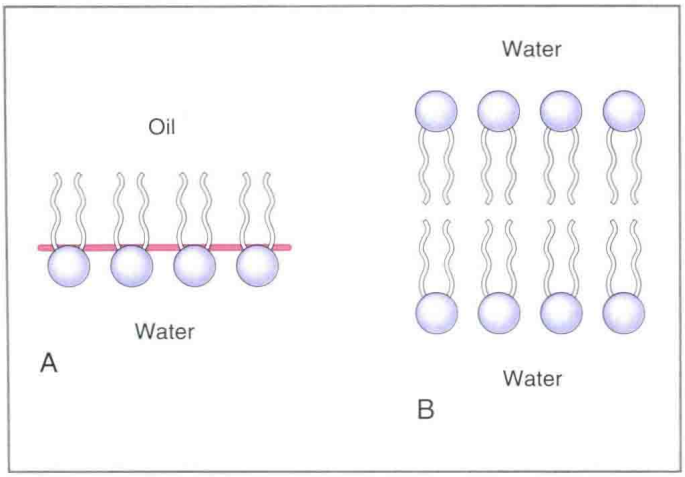


**Figure 1–2 Orientation of phospholipid molecules at oil and water interfaces.** Depicted are the orientation of phospholipid at an oil-water interface **(A)** and the orientation of phospholipid in a bilayer, as occurs in the cell membrane **(B).**

### Phospholipid Component of Cell Membranes

Phospholipids consist of a phosphorylated glycerol backbone ("head") and two fatty acid "tails" (Fig. 1-2). The glycerol backbone is **hydrophilic** (water soluble), and the fatty acid tails are **hydrophobic** (water insoluble). Thus, phospholipid molecules have both hydrophilic and hydrophobic properties and are called **amphipathic.** At an oil-water interface (see Fig. 1-2*A*), molecules of phospholipids form a monolayer and orient themselves so that the glycerol backbone dissolves in the water phase and the fatty acid tails dissolve in the oil phase. In cell membranes (see Fig. 1-2*B*), phospholipids orient so that the lipid-soluble fatty acid tails face each other and the water-soluble glycerol heads point away from each other, dissolving in the aqueous solutions of the ICF or ECF. This orientation creates a **lipid bilayer.**

### Protein Component of Cell Membranes

Proteins in cell membranes may be either integral or peripheral, depending on whether they span the membrane or whether they are present on only one side. The distribution of proteins in a phospholipid bilayer is illustrated in the **fluid mosaic model,** shown in Figure 1-3.

- **Integral membrane proteins** are embedded in, and anchored to, the cell membrane by **hydrophobic**

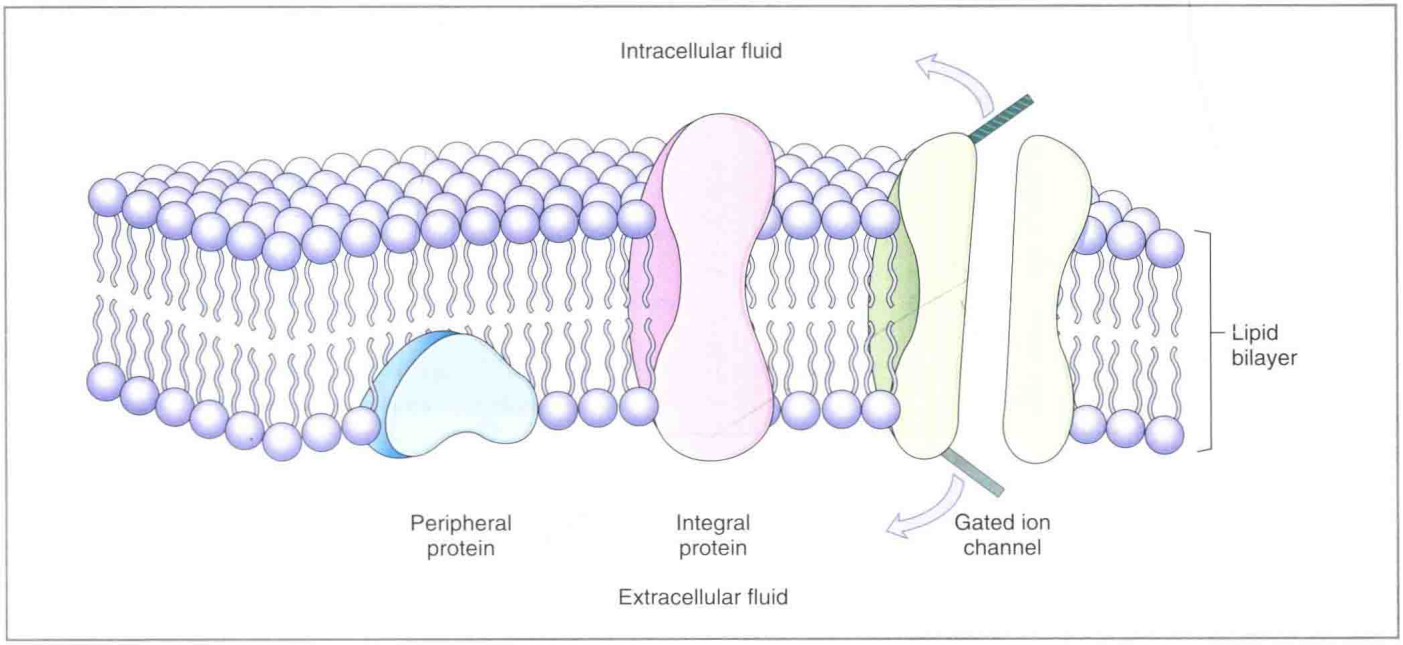


**Figure 1-3** Fluid mosaic model for cell membranes.

**interactions.** To remove an integral protein from the cell membrane, its attachments to the lipid bilayer must be disrupted (e.g., by detergents). Some integral proteins are **transmembrane proteins,** meaning they span the lipid bilayer one or more times; thus, transmembrane proteins are in contact with both ECF and ICF. Examples of transmembrane integral proteins are ligand-binding receptors (e.g., for hormones or neurotransmitters), transport proteins (e.g., $Na^+$-$K^+$ ATPase), pores, ion channels, cell adhesion molecules, and GTP-binding proteins (G proteins). Other integral proteins are embedded in the membrane but do not span it.

- **Peripheral membrane proteins** are *not* embedded in the membrane and are *not* covalently bound to cell membrane components. They are loosely attached to either the intracellular or extracellular side of the cell membrane by **electrostatic interactions** (e.g., with integral proteins) and can be removed with mild treatments that disrupt ionic or hydrogen bonds. One example of a peripheral membrane protein is **ankyrin,** which "anchors" the cytoskeleton of red blood cells to an integral membrane transport protein, the $Cl^-$-$HCO_3^-$ exchanger (also called band 3 protein).

## TRANSPORT ACROSS CELL MEMBRANES

Several types of mechanisms are responsible for transport of substances across cell membranes (Table 1-2).

Substances may be transported down an electrochemical gradient (downhill) or against an electrochemical gradient (uphill). **Downhill** transport occurs by diffusion, either simple or facilitated, and requires no input of metabolic energy. **Uphill** transport occurs by active transport, which may be primary or secondary. Primary and secondary active transport processes are distinguished by their energy source. Primary active transport requires a *direct* input of metabolic energy; secondary active transport utilizes an *indirect* input of metabolic energy.

Further distinctions among transport mechanisms are based on whether the process involves a protein carrier. Simple diffusion is the only form of transport that is *not* carrier mediated. Facilitated diffusion, primary active transport, and secondary active transport all involve integral membrane proteins and are called **carrier-mediated transport.** All forms of carrier-mediated transport share the following three features: saturation, stereospecificity, and competition.

- **Saturation.** Saturability is based on the concept that carrier proteins have a limited number of binding sites for the solute. Figure 1-4 shows the relationship between the rate of carrier-mediated transport and solute concentration. At low solute concentrations, many binding sites are available and the rate of transport increases steeply as the concentration increases. However, at high solute concentrations, the available binding sites become scarce and the rate of transport levels off. Finally, when all of the binding sites are occupied, saturation is achieved at a point called the **transport maximum,** or $T_m$. The

**Table 1–2** Summary of Membrane Transport

| Type of Transport | Active or Passive | Carrier-Mediated | Uses Metabolic Energy | Dependent on $Na^+$ Gradient |
|---|---|---|---|---|
| Simple diffusion | Passive; downhill | No | No | No |
| Facilitated diffusion | Passive; downhill | Yes | No | No |
| Primary active transport | Active; uphill | Yes | Yes; direct | No |
| Cotransport | Secondary active* | Yes | Yes; indirect | Yes (solutes move in same direction as $Na^+$ across cell membrane) |
| Countertransport | Secondary active* | Yes | Yes; indirect | Yes (solutes move in opposite direction as $Na^+$ across cell membrane) |

*$Na^+$ is transported downhill and one or more solutes are transported uphill.

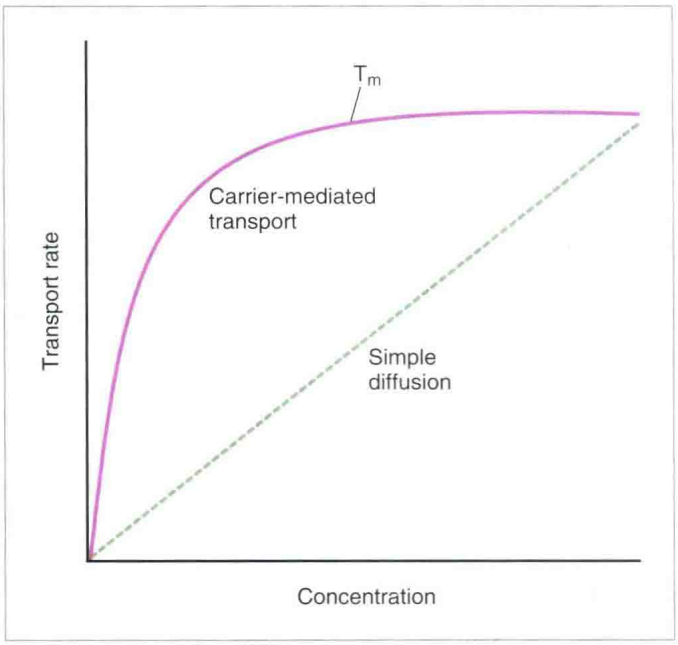


**Figure 1–4 Kinetics of carrier-mediated transport.** $T_m$, Transport maximum.

kinetics of carrier-mediated transport are similar to Michaelis-Menten enzyme kinetics—both involve proteins with a limited number of binding sites. (The $T_m$ is analogous to the $V_{max}$ of enzyme kinetics.) $T_m$-limited glucose transport in the proximal tubule of the kidney is an example of saturable transport.

- **Stereospecificity.** The binding sites for solute on the transport proteins are stereospecific. For example, the transporter for glucose in the renal proximal tubule recognizes and transports the natural isomer D-glucose, but it does not recognize or transport the unnatural isomer L-glucose. In contrast, simple diffusion does not distinguish between the two glucose isomers because no protein carrier is involved.
- **Competition.** Although the binding sites for transported solutes are quite specific, they may recognize, bind, and even transport chemically related solutes. For example, the transporter for glucose is specific for D-glucose, but it also recognizes and transports a closely related sugar, D-galactose. Therefore, the presence of D-galactose inhibits the transport of D-glucose by occupying some of the binding sites and making them unavailable for glucose.

## Simple Diffusion

### *Diffusion of Nonelectrolytes*

Simple diffusion occurs as a result of the random thermal motion of molecules, as shown in Figure 1-5. Two solutions, A and B, are separated by a membrane that is permeable to the solute. The solute concentration in A is initially twice that of B. The solute molecules are in constant motion, with equal probability that a given molecule will cross the membrane to the other solution. However, because there are twice as many solute molecules in Solution A as in Solution B, there will be greater movement of molecules from A to B than from B to A. In other words, there will be **net diffusion** of the solute from A to B, which will continue until the solute concentrations of the two solutions become equal (although the random movement of molecules will go on forever).

Net diffusion of the solute is called **flux,** or **flow** (**J**), and depends on the following variables: size of the concentration gradient, partition coefficient, diffusion coefficient, thickness of the membrane, and surface area available for diffusion.

#### CONCENTRATION GRADIENT ($C_A - C_B$)

The concentration gradient across the membrane is the driving force for net diffusion. The larger the difference in solute concentration between Solution A and

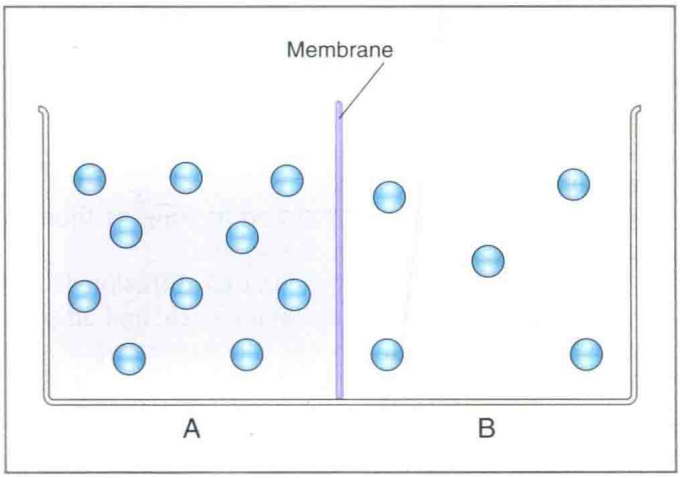


**Figure 1–5 Simple diffusion.** The two solutions, **A** and **B**, are separated by a membrane, which is permeable to the solute (*circles*). Solution A initially contains a higher concentration of the solute than does Solution B.

Solution B, the greater the driving force and the greater the net diffusion. It also follows that, if the concentrations in the two solutions are equal, there is no driving force and no net diffusion.

#### PARTITION COEFFICIENT (K)

The partition coefficient, by definition, describes the solubility of a solute in oil relative to its solubility in water. The greater the relative solubility in oil, the higher the partition coefficient and the more easily the solute can dissolve in the cell membrane's lipid bilayer. Nonpolar solutes tend to be soluble in oil and have high values for partition coefficient, whereas polar solutes tend to be insoluble in oil and have low values for partition coefficient. The partition coefficient can be measured by adding the solute to a mixture of olive oil and water and then measuring its concentration in the oil phase relative to its concentration in the water phase. Thus,

$$K = \frac{\text{Concentration in olive oil}}{\text{Concentration in water}}$$

#### DIFFUSION COEFFICIENT (D)

The diffusion coefficient depends on such characteristics as size of the solute molecule and the viscosity of the medium. It is defined by the Stokes-Einstein equation (see later). The diffusion coefficient correlates *inversely* with the molecular radius of the solute and the viscosity of the medium. Thus, small solutes in nonviscous solutions have the largest diffusion coefficients and diffuse most readily; large solutes in viscous solutions have the smallest diffusion coefficients and diffuse least readily. Thus,

$$D = \frac{KT}{6\pi r\eta}$$

where

D = Diffusion coefficient
K = Boltzmann's constant
T = Absolute temperature (K)
r = Molecular radius
$\eta$ = Viscosity of the medium

#### THICKNESS OF THE MEMBRANE ($\Delta X$)

The thicker the cell membrane, the greater the distance the solute must diffuse and the lower the rate of diffusion.

#### SURFACE AREA (A)

The greater the surface area of membrane available, the higher the rate of diffusion. For example, lipid-soluble gases such as oxygen and carbon dioxide have particularly high rates of diffusion across cell membranes. These high rates can be attributed to the large surface area for diffusion provided by the lipid component of the membrane.

To simplify the description of diffusion, several of the previously cited characteristics can be combined into a single term called **permeability (P).** Permeability includes the partition coefficient, the diffusion coefficient, and the membrane thickness. Thus,

$$P = \frac{KD}{\Delta x}$$

By combining several variables into permeability, the rate of net diffusion is simplified to the following expression:

$$J = PA(C_A - C_B)$$

where

J = Net rate of diffusion (mmol/sec)
P = Permeability (cm/sec)
A = Surface area for diffusion ($cm^2$)
$C_A$ = Concentration in Solution A (mmol/L)
$C_B$ = Concentration in Solution B (mmol/L)

### *Diffusion of Electrolytes*

Thus far, the discussion concerning diffusion has assumed that the solute is a nonelectrolyte (i.e., it is uncharged). However, if the diffusing solute is an **ion** or an **electrolyte,** there are two additional consequences of the presence of charge on the solute.

First, if there is a potential difference across the membrane, that potential difference will alter the net rate of diffusion of a charged solute. (A potential difference does not alter the rate of diffusion of a nonelectrolyte.) For example, the diffusion of $K^+$ ions will be

**SAMPLE PROBLEM.** Solution A and Solution B are separated by a membrane whose permeability to urea is $2 \times 10^{-5}$ cm/sec and whose surface area is 1 $cm^2$. The concentration of urea in A is 10 mg/mL, and the concentration of urea in B is 1 mg/mL. The partition coefficient for urea is $10^{-3}$, as measured in an oil-water mixture. *What are the initial rate and direction of net diffusion of urea?*

**SOLUTION.** Note that the partition coefficient is extraneous information because the value for permeability, which already includes the partition coefficient, is given. Net flux can be calculated by substituting the following values in the equation for net diffusion: Assume that 1 mL of water = 1 $cm^3$. Thus,

$$J = PA(C_A - C_B)$$

where

$$J = 2 \times 10^{-5} \text{ cm/sec} \times 1 \text{ cm}^2 \times (10 \text{ mg/mL} - 1 \text{ mg/mL})$$

$$J = 2 \times 10^{-5} \text{ cm/sec} \times 1 \text{ cm}^2 \times (10 \text{ mg/cm}^3 - 1 \text{ mg/cm}^3)$$
$$= 1.8 \times 10^{-4} \text{ mg/sec}$$

The *magnitude* of net flux has been calculated as $1.8 \times 10^{-4}$ mg/sec. The *direction* of net flux can be determined intuitively because net flux will occur from the area of high concentration (Solution A) to the area of low concentration (Solution B). Net diffusion will continue until the urea concentrations of the two solutions become equal, at which point the driving force will be zero.

slowed if $K^+$ is diffusing into an area of positive charge, and it will be accelerated if $K^+$ is diffusing into an area of negative charge. This effect of potential difference can either add to or negate the effects of differences in concentrations, depending on the orientation of the potential difference and the charge on the diffusing ion. If the concentration gradient and the charge effect are oriented in the same direction across the membrane, they will combine; if they are oriented in opposite directions, they may cancel each other out.

Second, when a charged solute diffuses down a concentration gradient, that diffusion can *itself* generate a potential difference across a membrane called a **diffusion potential.** The concept of diffusion potential will be discussed more fully in a following section.

## Facilitated Diffusion

Like simple diffusion, facilitated diffusion occurs down an electrochemical potential gradient; thus, it requires no input of metabolic energy. Unlike simple diffusion, however, facilitated diffusion uses a membrane carrier and exhibits all the characteristics of carrier-mediated transport: saturation, stereospecificity, and competition. At low solute concentration, facilitated diffusion typically proceeds faster than simple diffusion (i.e., is facilitated) because of the function of the carrier. However, at higher concentrations, the carriers will become saturated and facilitated diffusion will level off. (In contrast, simple diffusion will proceed as long as there is a concentration gradient for the solute.)

An excellent example of facilitated diffusion is the transport of **D-glucose** into skeletal muscle and adipose cells by the **GLUT4** transporter. Glucose transport can proceed as long as the blood concentration of glucose is higher than the intracellular concentration of glucose and as long as the carriers are not saturated. Other monosaccharides such as D-galactose, 3-*O*-methyl glucose, and phlorizin competitively inhibit the transport of glucose because they bind to transport sites on the carrier. The competitive solute may itself be transported (e.g., D-galactose), or it may simply occupy the binding sites and prevent the attachment of glucose (e.g., phlorizin). As noted previously, the nonphysiologic stereoisomer, L-glucose, is not recognized by the carrier for facilitated diffusion and, therefore, is not bound or transported.

## Primary Active Transport

In active transport, one or more solutes are moved against an electrochemical potential gradient (uphill). In other words, solute is moved from an area of low concentration (or low electrochemical potential) to an area of high concentration (or high electrochemical potential). Because movement of a solute *uphill* is work, metabolic energy in the form of ATP must be provided. In the process, ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate ($P_i$), releasing energy from the terminal high-energy phosphate bond of ATP. When the terminal phosphate is released, it is transferred to the transport protein, initiating a cycle of phosphorylation and dephosphorylation. When the ATP energy source is directly coupled to the transport process, it is called *primary* active transport. Three examples of primary active transport in physiologic systems are the $Na^+$-$K^+$ ATPase present in all cell membranes, the $Ca^{2+}$ ATPase present in sarcoplasmic and endoplasmic reticulum, and the $H^+$-$K^+$ ATPase present in gastric parietal cells.

### $Na^+$-$K^+$ ATPase ($Na^+$-$K^+$ Pump)

$Na^+$-$K^+$ ATPase is present in the membranes of all cells. It pumps $Na^+$ from ICF to ECF and $K^+$ from ECF to ICF (Fig. 1-6). Each ion moves against its respective electrochemical gradient. The stoichiometry can vary but, typically, for every three $Na^+$ ions pumped out of the cell, two $K^+$ ions are pumped into the cell. This stoichiometry of three $Na^+$ ions per two $K^+$ ions means that,

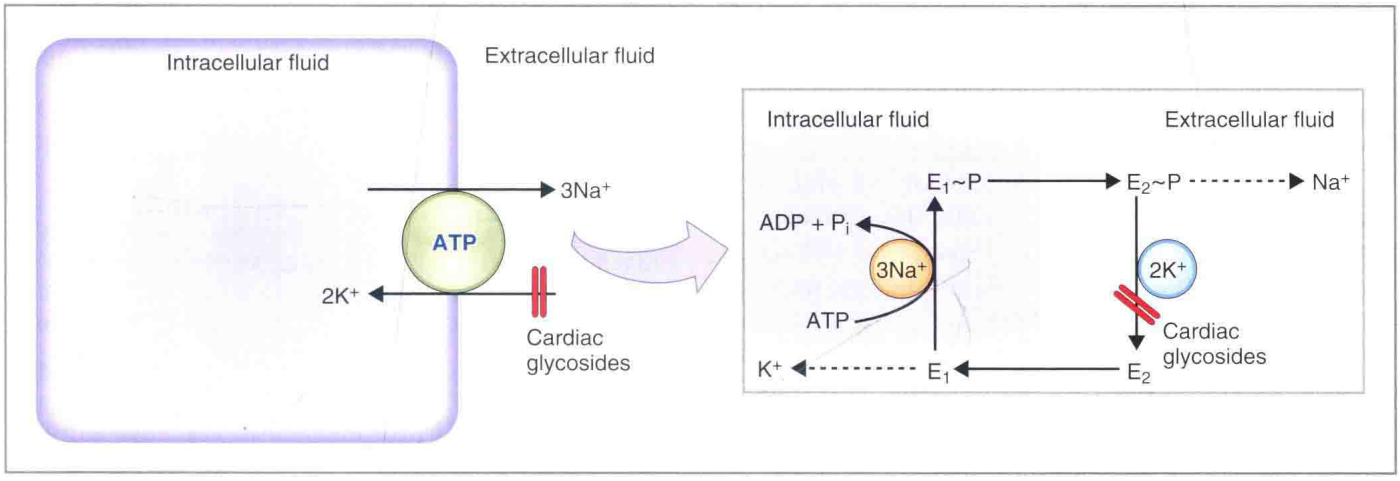


**Figure 1–6 $Na^+$-$K^+$ pump of cell membranes.** ADP, Adenosine diphosphate; ATP, adenosine triphosphate; E, $Na^+$-$K^+$ ATPase; E ~ P, phosphorylated $Na^+$-$K^+$ ATPase; $P_i$, inorganic phosphate.

for each cycle of the $Na^+$-$K^+$ ATPase, more positive charge is pumped out of the cell than is pumped into the cell. Thus, the process is termed **electrogenic** because it creates a charge separation and a potential difference. The $Na^+$-$K^+$ ATPase is responsible for maintaining concentration gradients for both $Na^+$ and $K^+$ across cell membranes, keeping the intracellular $Na^+$ concentration low and the intracellular $K^+$ concentration high.

The $Na^+$-$K^+$ ATPase consists of α and β subunits. The α subunit contains the ATPase activity, as well as the binding sites for the transported ions, $Na^+$ and $K^+$. The $Na^+$-$K^+$ ATPase switches between two major conformational states, $E_1$ and $E_2$. In the **$E_1$ state,** the binding sites for $Na^+$ and $K^+$ face the intracellular fluid and the enzyme has a high affinity for $Na^+$. In the **$E_2$ state,** the binding sites for $Na^+$ and $K^+$ face the extracellular fluid and the enzyme has a high affinity for $K^+$. The enzyme's ion-transporting function (i.e., pumping $Na^+$ out of the cell and $K^+$ into the cell) is based on cycling between the $E_1$ and $E_2$ states and is powered by ATP hydrolysis.

The **transport cycle** is illustrated in Figure 1-6. The cycle begins with the enzyme in the $E_1$ state, bound to ATP. In the $E_1$ state, the ion-binding sites face the intracellular fluid, and the enzyme has a high affinity for $Na^+$; three $Na^+$ ions bind, ATP is hydrolyzed, and the terminal phosphate of ATP is transferred to the enzyme, producing a high-energy state, $E_1 \sim P$. Now, a major conformational change occurs, and the enzyme switches from $E_1 \sim P$ to $E_2 \sim P$. In the $E_2$ state, the ion-binding sites face the extracellular fluid, the affinity for $Na^+$ is low, and the affinity for $K^+$ is high. The three $Na^+$ ions are released from the enzyme to extracellular fluid, two $K^+$ ions are bound, and inorganic phosphate is released from $E_2$. The enzyme now binds intracellular ATP, and another major conformational change occurs that returns the enzyme to the $E_1$ state; the two $K^+$ ions are released to intracellular fluid, and the enzyme is ready for another cycle.

**Cardiac glycosides** (e.g., **ouabain** and **digitalis**) are a class of drugs that inhibits $Na^+$-$K^+$ ATPase. Treatment with this class of drugs causes certain predictable changes in intracellular ionic concentration: The intracellular $Na^+$ concentration will increase, and the intracellular $K^+$ concentration will decrease. Cardiac glycosides inhibit the $Na^+$-$K^+$ATPase by binding to the $E_2 \sim P$ form near the $K^+$-binding site on the extracellular side, thereby preventing the conversion of $E_2 \sim P$ back to $E_1$. By disrupting the cycle of phosphorylation-dephosphorylation, these drugs disrupt the entire enzyme cycle and its transport functions.

### *$Ca^{2+}$ ATPase ($Ca^{2+}$ Pump)*

Most **cell** (**plasma**) **membranes** contain a $Ca^{2+}$ ATPase, or plasma-membrane $Ca^{2+}$ ATPase (**PMCA**), whose function is to extrude $Ca^{2+}$ from the cell against an electrochemical gradient; one $Ca^{2+}$ ion is extruded for each ATP hydrolyzed. PMCA is responsible, in part, for maintaining the very low intracellular $Ca^{2+}$ concentration. In addition, the **sarcoplasmic reticulum** of muscle cells and the **endoplasmic reticulum** of other cells contain variants of $Ca^{2+}$ ATPase that pump two $Ca^{2+}$ ions (for each ATP hydrolyzed) from intracellular fluid into the interior of the sarcoplasmic or endoplasmic reticulum (i.e., $Ca^{2+}$ sequestration). These variants are called sarcoplasmic and endoplasmic reticulum $Ca^{2+}$ ATPase (**SERCA**). $Ca^{2+}$ ATPase functions similarly to $Na^+$-$K^+$ ATPase, with $E_1$ and $E_2$ states that have, respectively, high and low affinities for $Ca^{2+}$. For PMCA, the $E_1$ state binds $Ca^{2+}$ on the intracellular side, a conformational change to the $E_2$ state occurs, and the $E_2$ state releases $Ca^{2+}$ to extracellular fluid. For SERCA, the $E_1$ state binds $Ca^{2+}$ on the intracellular side and the $E_2$ state releases $Ca^{2+}$ to the lumen of the sarcoplasmic or endoplasmic reticulum.