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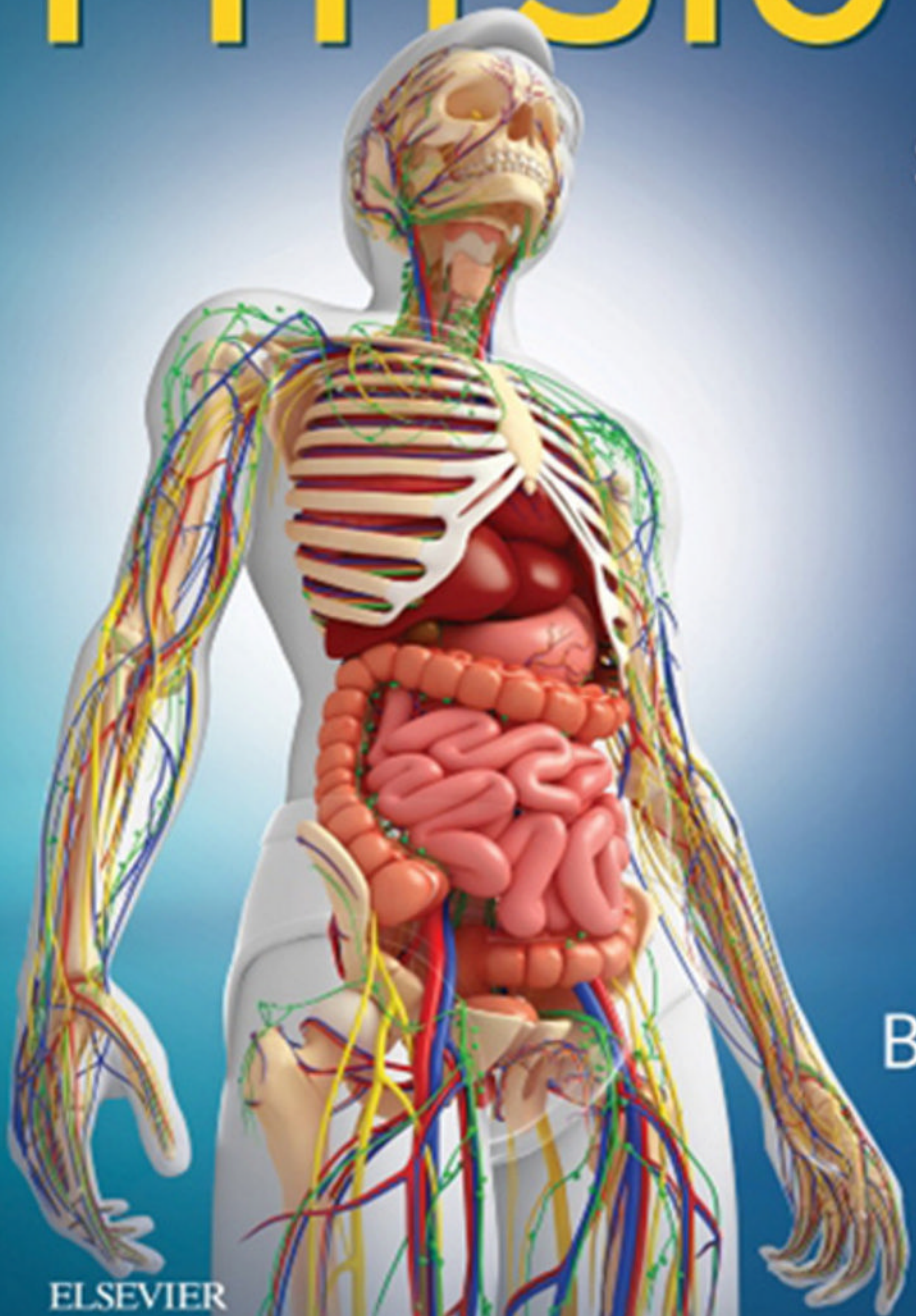

Bruce M. **Koeppen**
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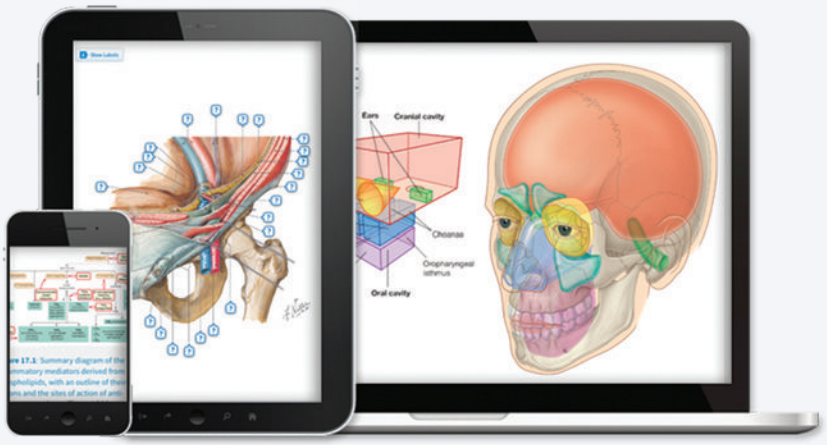

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This seventh edition of Physiology *is dedicated to the many students who have used this textbook to learn and understand the function of the human body.*

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Preface

We are pleased that the following section authors have continued as members of the seventh edition team: Drs. Kalman Rubinson and Eric Lang (nervous system), Dr. James Watras (muscle), Dr. Achilles Pappano (cardiovascular system), Drs. Michelle Cloutier and Roger Thrall (respiratory system), Drs. Kim Barrett and Helen Raybould (gastrointestinal system), and Dr. Bruce White (endocrine and reproductive systems). We also welcome the following authors: Dr. Withrow Gil Wier (cardiovascular system), and Dr. John Harrison (endocrine and reproduction systems).

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 has been written to make the text as lucid, accurate, and current as possible. We have included both clinical and molecular information in each section, as feedback on these features has indicated that this information serves to provide clinical context and new insights into physiologic phenomena at the cellular and molecular levels. New to this edition is a list of sources that the reader can consult for further information on the topics covered in each chapter. We hope that you find this a valuable addition to the book.

The human body consists of billions of cells that are organized into tissues (e.g., muscle, epithelia, and nervous tissue) and organ systems (e.g., nervous, cardiovascular, respiratory, renal, gastrointestinal, endocrine, and reproductive). For these tissues and organ systems to function properly and thus allow humans to live and carry out daily activities, several general conditions must be met. First and foremost, the cells within the body must survive. Survival requires adequate cellular energy supplies, maintenance of an appropriate intracellular milieu, and defense against a hostile external environment. Once cell survival is ensured, the cell can then perform its designated or specialized function (e.g., contraction by skeletal muscle cells). Ultimately, the function of cells, tissues, and organs must be coordinated and regulated. All of these functions are the essence of the discipline of physiology and are presented throughout this book. What follows is a brief introduction to these general concepts.

Cells need a constant supply of energy. This energy is derived from the hydrolysis of **adenosine triphosphate** (**ATP**). If not replenished, the cellular ATP supply would be depleted in most cells in less than 1 minute. Thus, ATP must be continuously synthesized. This in turn requires a steady supply of cellular fuels. However, the cellular fuels (e.g., glucose, fatty acids, and ketoacids) are present in the blood at levels that can support cellular metabolism only for a few minutes. The blood levels of these cellular fuels are maintained through the ingestion of precursors (i.e., carbohydrates, proteins, and fats). In addition, these fuels can be stored and then mobilized when ingestion of the precursors is not possible. The storage forms of these fuels are triglycerides (stored in adipose tissue), glycogen (stored in the liver and skeletal muscle), and protein. The maintenance of adequate levels of cellular fuels in the blood is a complex process involving the following tissues, organs, and organ systems:

- *Liver*: Converts precursors into fuel storage forms (e.g., glucose → glycogen) when food is ingested, and converts storage forms to cellular fuels during fasting (e.g., glycogen → glucose and amino acids → glucose).
- *Skeletal muscle*: Like the liver, stores fuel (glycogen and protein) and converts glycogen and protein to fuels (e.g., glucose) or fuel intermediates (e.g., protein → amino acids) during fasting.
- *Gastrointestinal tract*: Digests and absorbs fuel precursors.
- *Adipose tissue*: Stores fuel during feeding (e.g., fatty acids → triglycerides) and releases the fuels during fasting.
- *Cardiovascular system*: Delivers the fuels to the cells and to and from their storage sites.
- *Endocrine system*: Maintains the blood levels of the cellular fuels by controlling and regulating their storage and their release from storage (e.g., insulin and glucagons).
- *Nervous system*: Monitors oxygen levels and nutrient content in the blood and, in response, modulates the cardiovascular, pulmonary, and endocrine systems and induces feeding and drinking behaviors.

In addition to energy metabolism, the cells of the body must maintain a relatively constant intracellular environment to survive. This includes the uptake of fuels needed to produce ATP, the export from the cell of cellular wastes, the maintenance of an appropriate intracellular ionic environment, the establishment of a resting membrane potential, and the maintenance of a constant cellular volume. All of these functions are carried out by specific membrane transport proteins.

The composition of the extracellular fluid (ECF) that bathes the cells must also be maintained relatively constant. In addition, the volume and temperature of the ECF must be regulated. Epithelial cells in the lungs, gastrointestinal tract, and kidneys are responsible for maintaining the volume and composition of the ECF, while the skin plays a major role in temperature regulation. On a daily basis, H_2O and food are ingested, and essential components are absorbed across the epithelial cells of the gastrointestinal tract. This daily intake of solutes and water must be matched by excretion from the body, thus maintaining **steady-state balance**. The kidneys are critically involved in the maintenance of steady-state balance for water and many components of the ECF (e.g., Na^+, K^+, HCO_3^-, pH, Ca^{++}, organic solutes). The lungs ensure an adequate supply of O_2 to "burn" the cellular fuels for the production of ATP and excrete the major waste product of this process (i.e., CO_2). Because CO_2 can affect the pH of the ECF, the lungs work with the kidneys to maintain ECF pH.

Because humans inhabit many different environments and often move between environments, the body must be able to rapidly adapt to the challenges imposed by changes in ambient temperature and availability of food and water. Such adaptation requires coordination of the function of cells in different tissues and organs as well as their regulation. The nervous and endocrine systems coordinate and regulate cell, tissue, and organ function. The regulation of function can occur rapidly (seconds to minutes), as is the case for levels of cellular fuels in the blood, or over much longer periods of time (days to weeks), as is the case for acclimatization when an individual moves from a cool to a hot environment or changes from a high-salt to a low-salt diet.

The function of the human body represents complex processes at multiple levels. This book explains what is currently known about these processes. Although the emphasis is on the normal function of the human body, discussion of disease and abnormal function is also appropriate, as these often illustrate physiologic processes and principles at the extremes.

The authors for 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.

Bruce M. Koeppen, MD, PhD
Bruce A. Stanton, PhD

Contents

SECTION 1

Cellular Physiology

BRUCE M. KOEPPEN AND BRUCE A. STANTON

1

Principles of Cell and Membrane Function

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What organelles are found in a typical eukaryotic cell, and what is their function?
2. What is the composition of the plasma membrane?
3. What are the major classes of membrane transport proteins, and how do they transport biologically important molecules and ions across the plasma membrane?
4. What is the electrochemical gradient, and how it is used to determine whether the transport of a molecule or ion across the plasma membrane is active or passive?
5. What are the driving forces for movement of water across cell membrane and the capillary wall?

In addition, the student should be able to define and understand the following properties of physiologically important solutions and fluids:

- Molarity and equivalence
- Osmotic pressure
- Osmolarity and osmolality
- Oncotic pressure
- Tonicity

The human body is composed of billions of cells. Although cells can perform different functions, they share certain common elements. This chapter provides an overview of these common elements and focuses on the important function of the transport of molecules and water into and out of the cell across its plasma membrane.

Overview of Eukaryotic Cells

Eukaryotic cells are distinguished from prokaryotic cells by the presence of a membrane-delimited nucleus. With the exception of mature human red blood cells and cells within the lens of the eye, all cells within the human body contain a nucleus. The cell is therefore effectively divided into two compartments: the nucleus and the cytoplasm. The cytoplasm is an aqueous solution containing numerous organic molecules, ions, cytoskeletal elements, and a number of organelles. Many of the organelles are membrane-enclosed compartments that carry out specific cellular function. An idealized eukaryotic cell is depicted in Fig. 1.1, and the primary function of some components and compartments of the cell are summarized in Table 1-1. Readers who desire a more in-depth presentation of this material are encouraged to consult one of the many textbooks on cell and molecular biology that are currently available.

The Plasma Membrane

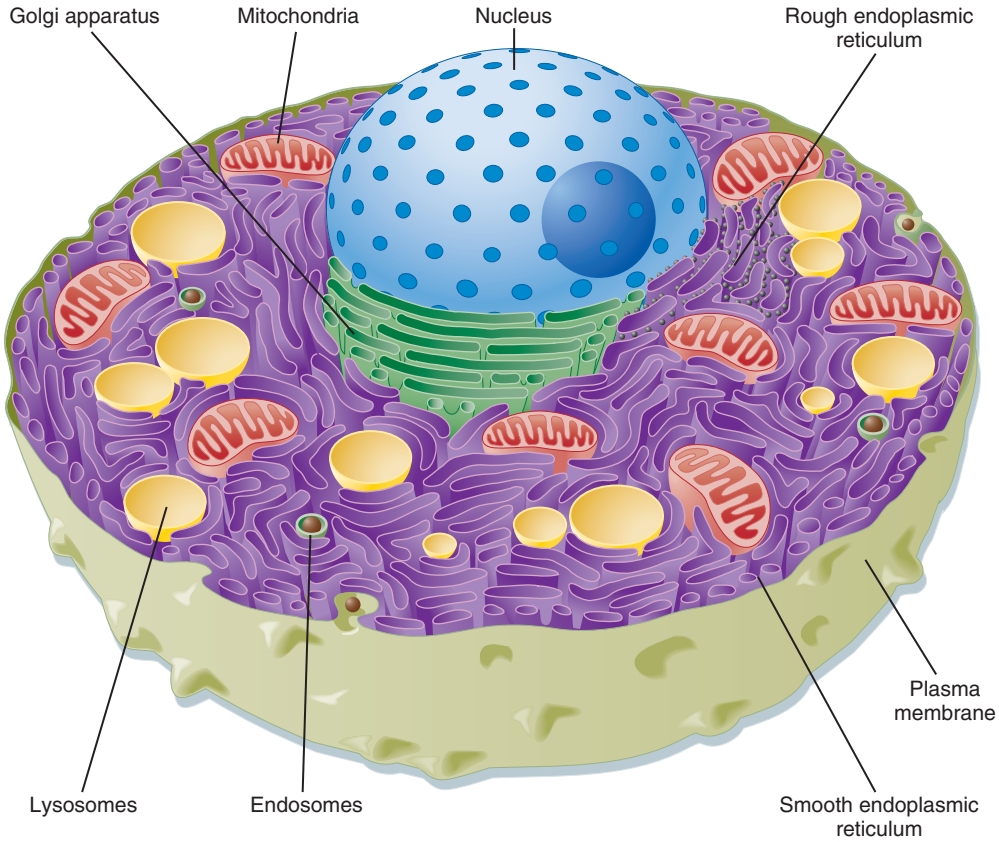
The cells within the body are surrounded by a plasma membrane that separates the intracellular contents from the extracellular environment. Because of the properties of this membrane and, in particular, the presence of specific membrane proteins, the plasma membrane is involved in a number of important cellular functions, including the following:

- Selective transport of molecules into and out of the cell. A function carried out by membrane transport proteins.
- Cell recognition through the use of cell surface antigens.
- Cell communication through neurotransmitter and hormone receptors and through signal transduction pathways.
- Tissue organization, such as temporary and permanent cell junctions, and interaction with the extracellular matrix, with the use of a variety of cell adhesion molecules.
- Membrane-dependent enzymatic activity.
- Determination of cell shape by linkage of the cytoskeleton to the plasma membrane.

In this chapter, the structure and function of the plasma membrane of eukaryotic cells are considered. More specifically, the chapter focuses on the transport of molecules and water across the plasma membrane. Only the principles of membrane transport are presented here. Additional details that relate to specific cells are presented in the various sections and chapters of this book.

Structure and Composition

The plasma membrane of eukaryotic cells consists of a 5-nm-thick lipid bilayer with associated proteins (Fig. 1.2). Some of the membrane-associated proteins are integrated into the lipid bilayer; others are more loosely attached to the



• **Fig. 1.1** Schematic drawing of a eukaryotic cell. The top portion of the cell is omitted to illustrate the nucleus and various intracellular organelles. See text for details.

TABLE 1.1 Primary Functions of Some Eukaryotic Cellular Components and Compartments

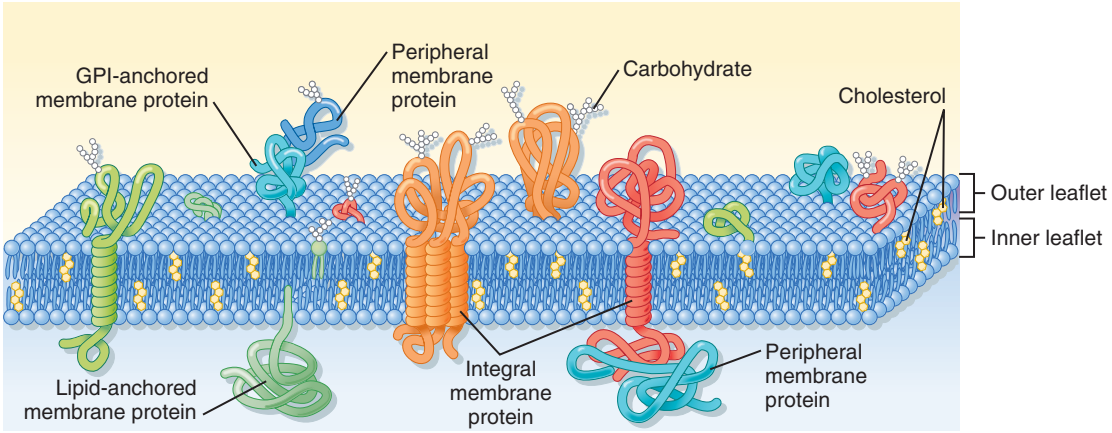
Component	Primary Function
Cytosol	Metabolism, protein synthesis (free ribosomes)
Cytoskeleton	Cell shape and movement, intracellular transport
Nucleus	Genome (22 autosomes and 2 sex chromosomes), DNA and RNA synthesis
Mitochondria	ATP synthesis by oxidative phosphorylation, Ca^{2+} storage
Smooth endoplasmic reticulum	Synthesis of lipids, Ca^{2+} storage
Free ribosomes	Translation of mRNA into cytosolic proteins
Rough endoplasmic reticulum	Translation of mRNA into membrane associated proteins or for secretion out of the cell
Lysosome	Intracellular degradation
Endosome	Cellular uptake of cholesterol, removal of receptors from the plasma membrane, uptake of small molecules and water into the cell, internalization of large particles (e.g., bacteria, cell debris)
Golgi apparatus	Modification, sorting, and packaging of proteins and lipids for delivery to other organelles within the cell or for secretion out of the cell
Proteosome	Degradation of intracellular proteins
Peroxisome	Detoxification of substances

ATP, adenosine triphosphate; mRNA, messenger RNA.

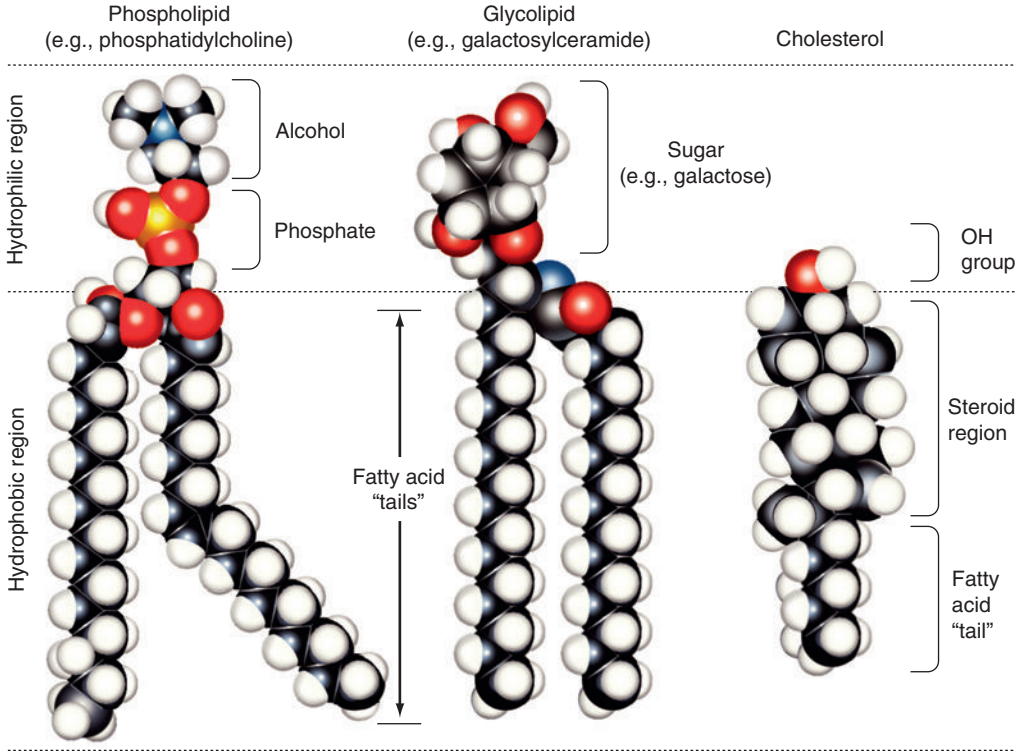
inner or outer surfaces of the membrane, often by binding to the integral membrane proteins.

Membrane Lipids

The major lipids of the plasma membrane are **phospholipids** and **phosphoglycerides.** Phospholipids are amphipathic molecules that contain a charged (or polar) hydrophilic head and two (nonpolar) hydrophobic fatty acyl chains (Fig. 1.3). The amphipathic nature of the phospholipid molecule is critical for the formation of the bilayer: The hydrophobic fatty acyl chains form the core of the bilayer, and the polar head groups are exposed on the surface.



• **Fig. 1.2** Schematic diagram of the cell plasma membrane. Not shown are lipid rafts. See text for details. (Modified from Cooper GM. *The Cell—A Molecular Approach.* 2nd ed. Washington, DC: Sinauer; 2000, Fig. 12.3.)



• **Fig. 1.3** Models of the major classes of plasma membrane lipids, depicting the hydrophilic and hydrophobic regions of the molecules. The molecules are arranged as they exist in one leaflet of the bilayer. The opposing leaflet is not shown. One of the fatty acyl chains in the phospholipid molecule is unsaturated. The presence of this double bond produces a "kink" in the fatty acyl chain, which prevents tight packing of membrane lipids and increases membrane fluidity. (Modified from Hansen JT, Koeppen BM: *Netter's Atlas of Human Physiology.* Teterboro, NJ: Icon Learning Systems; 2002.)

The majority of membrane phospholipids have a glycerol "backbone" to which are attached the fatty acyl chains, and an alcohol is linked to glycerol via a phosphate group. The common alcohols are choline, ethanolamine, serine, inositol, and glycerol. Another important phospholipid, sphingomyelin, has the amino alcohol sphingosine as its "backbone" instead of glycerol. Table 1-2 lists these common phospholipids. The fatty acyl chains are usually 14 to 20 carbons in length and may be saturated or unsaturated (i.e., contain one or more double bonds).

The phospholipid composition of the membrane varies among different cell types and even between the bilayer leaflets. For example, in the erythrocyte plasma membrane, phosphatidylcholine and sphingomyelin are found predominantly in the outer leaflet of the membrane, whereas phosphatidylethanolamine, phosphatidylserine,

TABLE 1.2 Plasma Membrane Lipids

Phospholipid	Primary Location in Membrane
Phosphatidylcholine	Outer leaflet
Sphingomyelin	Outer leaflet
Phospatidylethanolamine	Inner leaflet
Phosphatidylserine	Inner leaflet
Phosphatidylinositol*	Inner leaflet

*Involved in signal transduction.

and phosphatidylinositol are found in the inner leaflet. As described in detail in Chapter 3, phosphatidylinositol plays an important role in signal transduction, and its location in the inner leaflet of the membrane facilitates this signaling role.

The sterol molecule **cholesterol** is also a critical component of the bilayer (see Fig. 1.3). It is found in both leaflets and serves to stabilize the membrane at normal body temperature (37°C). As much as 50% of the lipids found in the membrane can be cholesterol. A minor lipid component of the plasma membrane is **glycolipids.** These lipids, as their name indicates, consist of two fatty acyl chains linked to polar head groups that consist of carbohydrates (see Fig. 1.3). As discussed in the section on membrane proteins, one glycolipid, glycosylphosphatylinositol (GPI), plays an important role in anchoring proteins to the outer leaflet of the membrane. Both cholesterol and glycolipids, like the phospholipids, are amphipathic, and they are oriented with their polar groups on the outer surface of the leaflet in which they are located. Their hydrophobic portion is thus located within the interior of the bilayer.

The lipid bilayer is not a static structure. The lipids and associated proteins can diffuse within the plane of the membrane. The fluidity of the membrane is determined by temperature and by its lipid composition. As temperature increases, the fluidity of the membrane increases. The presence of unsaturated fatty acyl chains in the phospholipids and glycolipids also increases membrane fluidity. If a fatty acyl chain is unsaturated, the presence of a double bond introduces a "kink" in the molecule (see Fig. 1.3). This kink prevents the molecule from associating closely with surrounding lipids, and, as a result, membrane fluidity is increased. Although the lipid bilayer is "fluid," movement of proteins in the membrane can be constrained or limited. For example, membrane proteins can be anchored to components of the intracellular cytoskeleton, which limits their movement. Membrane domains can also be isolated from one another. An important example of this can be found in epithelial tissues. Junctional complexes (e.g., tight junctions) separate the plasma membrane of epithelial cells into two domains: apical and basolateral (see Chapter 2). The targeted localization of membrane proteins into one or other of these domains allows epithelial cells to carry out vectorial transport of substances from one side of the epithelium to the opposite side. The ability to carry out vectorial transport is crucial for the functioning of several organ systems (e.g., the gastrointestinal tract and kidneys). In addition, some regions of the membrane contain lipids (e.g., sphingomyelin and cholesterol) that aggregate into what are called **lipid rafts.** These lipid rafts often have an association with specific proteins, which diffuse in the plane of the membrane as a discrete unit. Lipid rafts appear to serve a number of functions. One important function of these rafts is to segregate signaling molecules.

Membrane Proteins

As much as 50% of the plasma membrane is composed of proteins. These membrane proteins are classified as integral, lipid-anchored, or peripheral.

Integral membrane proteins are imbedded in the lipid bilayer, where hydrophobic amino acid residues are associated with the hydrophobic fatty acyl chains of the membrane lipids. Many integral membrane proteins span the bilayer; such proteins are termed **transmembrane proteins.** Transmembrane proteins have both hydrophobic and hydrophilic regions. The hydrophobic region, often in the form of an α helix, spans the membrane. Hydrophilic amino acid residues are then exposed to the aqueous environment on either side of the membrane. Transmembrane proteins may pass through the membrane multiple times.

AT THE CELLULAR LEVEL

There is a superfamily of membrane proteins that serve as receptors for many hormones, neurotransmitters, and numerous drugs. These receptors are coupled to heterotrimeric G proteins and are termed *G protein–coupled receptors* (see Chapter 3). These proteins span the membrane with seven α-helical domains. The binding site of each ligand is either on the extracellular portion of the protein (large ligands) or in the membrane-spanning portion (small ligands), whereas the cytoplasmic portion binds to the G protein. This superfamily of membrane proteins makes up the third largest family of genes in humans. Nearly half of all nonantibiotic prescription drugs are targeted toward G protein–coupled receptors.

A protein can also be attached to the membrane via **lipid anchors.** The protein is covalently attached to a lipid molecule, which is then embedded in one leaflet of the bilayer. Glycosylphosphatidylinositol (GPI) anchors proteins to the outer leaflet of the membrane. Proteins can be attached to the inner leaflet via their amino-terminus by fatty acids (e.g., myristate or palmitate) or via their carboxyl-terminus by prenyl anchors (e.g., farnesyl or geranylgeranyl).

Peripheral proteins may be associated with the polar head groups of the membrane lipids, but they more commonly bind to integral or lipid-anchored proteins.

In many cells, some of the outer leaflet lipids, as well as many of the proteins exposed on the outer surface of the

membrane, are glycosylated (i.e., have short chains of sugars, called *oligosaccharides,* attached to them). Collectively, these glycolipids and glycoproteins form what is called the glycocalyx. Depending on the cell these glycolipids and glycoproteins may be involved in cell recognition (e.g., cell surface antigens) and formation of cell-cell interactions (e.g., attachment of neutrophils to vascular endothelial cells).

Membrane Transport

Although plasma membrane proteins perform many important cellular functions, as noted previously, the remainder of this chapter focuses on one group of plasma membrane proteins: the membrane transport proteins, or transporters. It has been estimated that approximately 10% of human genes (≈2000) code for transporters. They are also targets for numerous drugs.

The normal function of cells requires the continuous movement of water and solutes into and out of the cell. The intracellular and extracellular fluids are composed primarily of H_2O, in which solutes (e.g., ions, glucose, amino acids) are dissolved. The plasma membrane, with its hydrophobic core, is an effective barrier to the movement of virtually all of these biologically important solutes. It also restricts the movement of water across the membrane. The presence of specific membrane transporters in the membrane is responsible for the movement of these solutes and water across the membrane.

Membrane Transport Proteins

Membrane transporters have been classified in several different ways. In this chapter, the transporters are divided into four general groups: water channels, ion channels, solute carriers, and adenosine triphosphate (ATP)–dependent transporters. Table 1-3 lists these groups of membrane transporters, their modes of transport, and estimates of the rates at which they transport molecules or ions across the membrane.

Water Channels

Water channels, or **aquaporins (AQPs),** are the main routes for water movement into and out of the cell. They are widely distributed throughout the body (e.g., the brain, lungs, kidneys, salivary glands, gastrointestinal tract, and liver). Cells express different AQP isoforms, and some cells even express multiple isoforms. For example, cells in the collecting ducts of the kidneys express AQP3 and AQP4 in their basolateral membrane and AQP2 in their apical membrane. Moreover, the abundance of AQP2 in the apical membrane is regulated by antidiuretic hormone (also called arginine vasopressin), which is crucial for the ability of the kidneys to concentrate the urine (see Chapter 35).

Although all AQP isoforms allow the passive movement of H_2O across the membrane, some isoforms also provide a pathway for other molecules such as glycerol, urea, mannitol, purines, pyrimidines, CO_2, and NH_3 to cross the membrane. Because glycerol was one of the first molecules identified as crossing the membrane via some AQPs, this group of AQPs is collectively called *aquaglyceroporins* (see also Chapter 34). Regulation of the amount of H_2O that can enter or leave the cell via AQPs occurs primarily by altering the number of AQPs in the membrane.

TABLE 1.3 Major Classes of Plasma Membrane Transporters

Class	Transport Mode	Transport Rate
Pore*	Open (not gated)	Up to 10^9 molecules/sec
Channel	Gated	10^6-10^8 molecules/sec
Solute carrier	Cycle	10^2-10^4 molecules/sec
ATP-dependent	Cycle	10^2-10^4 molecules/sec

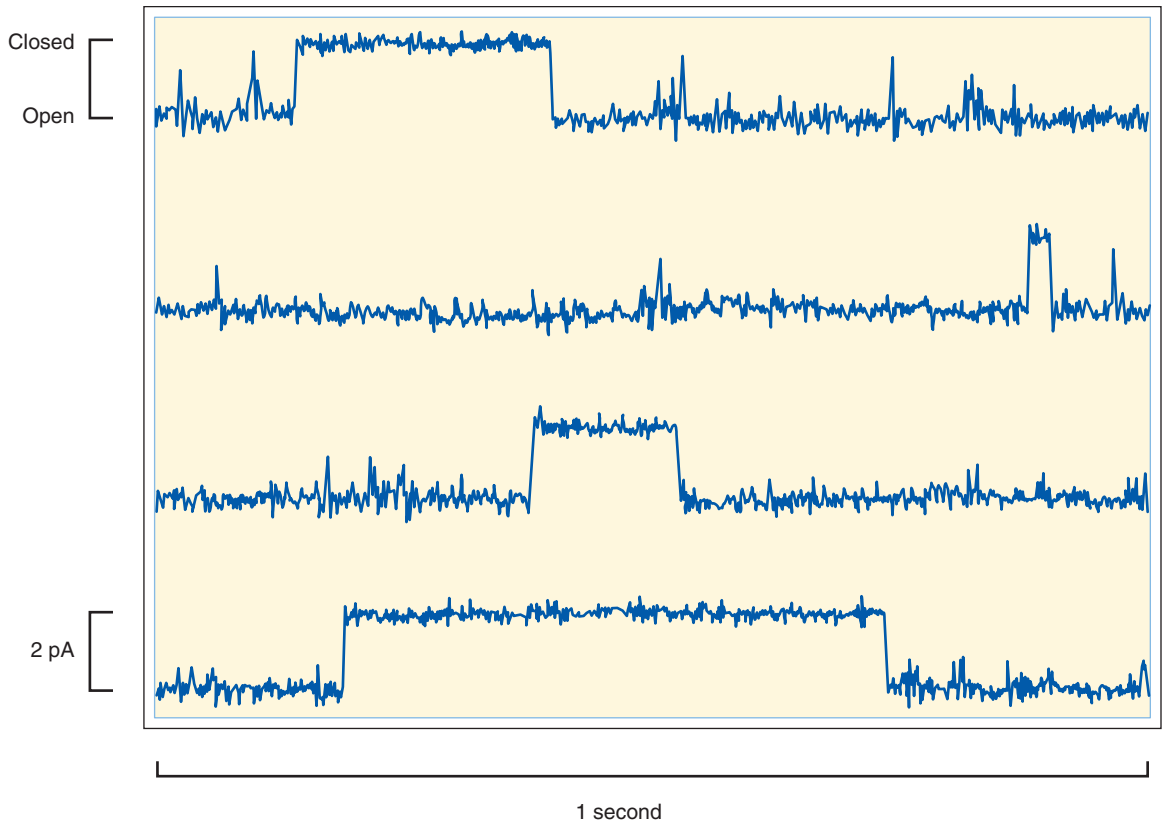
*Examples include porins that are found in the outer membrane of mitochondria, and water channels (i.e., aquaporins) that function as a pore.
ATP, adenosine triphosphate.

AT THE CELLULAR LEVEL

Each AQP molecule consists of six membrane-spanning domains and a central water-transporting pore. Four AQP monomers assemble to form a homotetramer in the plasma membrane, with each monomer functioning as a water channel.

Ion Channels

Ion channels are found in all cells, and are especially important for the function of excitable cells (e.g., neurons and muscle cells). Ion channels are classified by their selectivity, conductance and mechanism of channel gating (i.e., opening and closing). *Selectivity* is defined as the nature of the ions that pass through the channel. At one extreme, ion channels can be highly selective, in that they allow only a specific ion through. At the other extreme, they may be nonselective, allowing all or a group of cations or anions through. *Channel conductance* refers to the number of ions that pass through the channel and is typically expressed in picosiemens (pS). The range of conductance is considerable: Some channels have a conductance of only 1 to 2 pS, whereas others have a conductance of more than 100 pS. For some channels, the conductance varies, depending on the direction in which the ion is moving. For example, if the channel has a larger conductance when ions are moving into the cell than when they are moving out of the cell, the channel is said to be an *inward rectifier.* Moreover, ion channels fluctuate between an open state or a closed state, a process called *gating* (Fig. 1.4). Factors that can control gating include membrane voltage, extracellular agonists or antagonists (e.g., acetylcholine is an extracellular agonist that controls the gating of a cation-selective channel in the motor end plate of skeletal muscle cells; see Chapter 6), intracellular messengers (e.g., Ca^{++}, ATP, cyclic guanosine



● **Fig. 1.4** Recording of current flow through a single ion channel. The channel spontaneously fluctuates between an open state and a closed state. The amplitude of the current is approximately 2 pA (2×10^{-12} amps); that is, 12.5 million ions/second cross the membrane.

monophosphate), and mechanical stretch of the plasma membrane. Ion channels can be regulated by a change in the number of channels in the membrane or by gating of the channels.

Solute Carriers

Solute carriers (denoted *SLCs* by the HUGO Gene Nomenclature Committee) represent a large group of membrane transporters categorized into more than 50 families; almost 400 specific transporters have been identified to date. These carriers can be divided into three groups according to their mode of transport. One group, **uniporters** (or **facilitated transporters**), transports a single molecule across the membrane. The transporter that brings glucose into the cell (glucose transporter 1 [GLUT-1], or SLC2A1) is an important member of this group. The second group, **symporters** (or **cotransporters**), couples the movement of two or more molecules/ions across the membrane. As the name implies, the molecules/ions are transported in the same direction. The Na^+,K^+,$2Cl^-$ (NKCC) symporter found in the kidney (NKCC2, or SLC12A1), which is crucial for diluting and concentrating the urine (see Chapter 34), is a member of this group. The third group, **antiporters** (or **exchange transporters**), also couples the movement of two or more molecules/ions across the membrane; in this case, however, the molecules/ions are transported in opposite directions. The Na^+-H^+ antiporter is a member of this group of solute carriers. One isoform of this antiporter (NHE-1, or SLC9A1) is found in all cells and plays an important role in regulating intracellular pH.

Adenosine Triphosphate–Dependent Transporters

The ATP-dependent transporters, as their name implies, use the energy in ATP to drive the movement of molecules/ions across the membrane. There are two groups of ATP-dependent transporters: the **ATPase ion transporters** and the **ATP-binding cassette (ABC) transporters.** The ATPase ion transporters are subdivided into P-type ATPases and V-type ATPases.[a] The P-type ATPases are phosphorylated during the transport cycle. Na^+,K^+-ATPase is an important example of a P-type ATPase. With the hydrolysis of each ATP molecule, it transports three Na^+ ions out of the cell and two K^+ ions into the cell. Na^+,K^+-ATPase is present in all cells and plays a critical role in establishing cellular ion and electrical gradients, as well as maintaining cell volume (see Chapter 2).

V-type H^+-ATPases are found in the membranes of several intracellular organelles (e.g., endosomes, lysosomes); as a result, they are also referred to as *vacuolar H^+-ATPases.* The

[a]Another type of ATPases, F-type ATPases, is found in the mitochondria, and they are responsible for ATP synthesis. They are not considered in this chapter.

AT THE CELLULAR LEVEL

Na^+,K^+-ATPase (also called the *Na^+,K^+-pump* or just the *Na^+-pump*) is found in all cells and is responsible for establishing the gradients of Na^+ and K^+ across the plasma membrane. These gradients in turn provide energy for several essential cell functions (see Chapter 2). Na^+,K^+-ATPase is composed of three subunits (α, β, and γ), and the protein exists in the membrane with a stoichiometric composition of 1α, 1β, 1γ. The α subunit contains binding sites for Na^+,K^+ and ATP. It is also the subunit that binds cardiac glycosides (e.g., ouabain), which specifically inhibit the enzyme. It has a transmembrane domain and three intracellular domains: phosphorylation (P-domain), nucleotide binding (N-domain), and actuator (A-domain). Although the α subunit is the functional subunit of the enzyme (i.e., it hydrolyzes ATP, binds Na^+ and K^+, and translocates them across the membrane), it cannot function without the β subunit. The β subunit is responsible for targeting the α subunit to the membrane and also appears to modulate the affinity of the Na^+,K^+-ATPase for Na^+ and K^+. The α and β subunits can carry out Na^+ and K^+ transport in the absence of the γ subunit. However, the γ subunit appears to play a regulatory role. The γ subunit is a member of a family of proteins called **FXYD proteins** (so named for the FXYD amino acid sequence found in the protein).

IN THE CLINIC

Cystic fibrosis is an autosomal recessive disease characterized by chronic lung infections, pancreatic insufficiency, and infertility in boys and men. Death usually occurs because of respiratory failure. It is most prevalent in white people and is the most common lethal genetic disease in this population, occurring in 1 per 3000 live births. It is a result of mutations in a gene on chromosome 7 that codes for an ABC transporter. To date, more than 1000 mutations in the gene have been identified. The most common mutation is a deletion of a phenylalanine at position 508 (F508del). Because of this deletion, degradation of the protein by the endoplasmic reticulum in enhanced, and, as a result, the transporter does not reach the plasma membrane. This transporter, called **cystic fibrosis transmembrane conductance regulator (CFTR),** normally functions as a Cl^- channel and also regulates other membrane transporters (e.g., the epithelial Na^+ channel [ENaC]). Thus in individuals with cystic fibrosis, epithelial transport is defective, which is responsible for the pathophysiologic process. For example, in patients not affected by cystic fibrosis, the epithelial cells that line the airway of the lung are covered with a layer of mucus that entraps inhaled particulates and bacteria. Cilia on the epithelial cells then transport the entrapped material out of the lung, a process termed *mucociliary transport* (see Chapter 26 for more details). In patients with cystic fibrosis, the inability to secrete Cl^-, Na^+, and H_2O results in an increase in the viscosity of the airway surface mucus; thus the cilia cannot transport the entrapped bacteria and other pathogens out of the lung. This in turn leads to recurrent and chronic lung infections. The inflammatory process that accompanies these infections ultimately destroys the lung tissue, causing respiratory failure and death. In 2015, the U.S. Food and Drug Administration approved lumacaftor/ivacaftor (Orkambi), a drug that increases the amount of F508del CFTR in the plasma membrane of lung epithelial cells.

H^+-ATPase in the plasma membrane plays an important role in urinary acidification (see Chapter 37).

ABC transporters represent a large group of membrane transporters. They are found in both prokaryotic and eukaryotic cells, and they have amino acid domains that bind ATP (i.e., ABC domains). Seven subgroups of ABC transporters in humans and more than 40 specific transporters have been identified to date. They transport a diverse group of molecules/ions, including Cl^-, cholesterol, bile acids, drugs, iron, and organic anions.

Because biologically important molecules enter and leave cells through membrane transporters, membrane transport is specific and regulated. Although some membrane transporters are ubiquitously expressed in all cells (e.g., Na^+,K^+-ATPase), the expression of many other transporters is limited to specific cell types. This specificity of expression tailors the function of the cell to the organ system in which it is located (e.g., the sodium-glucose–linked transporters SGLT-1 and SGLT-2 in the epithelial cells of the intestines and renal proximal tubules). In addition, the amount of a molecule being transported across the membrane can be regulated. Such regulation can take place through altering the number of transporters in the membrane or altering the rate or kinetics of individual transporters (e.g., the time an ion channel stays in the open versus closed state), or both.

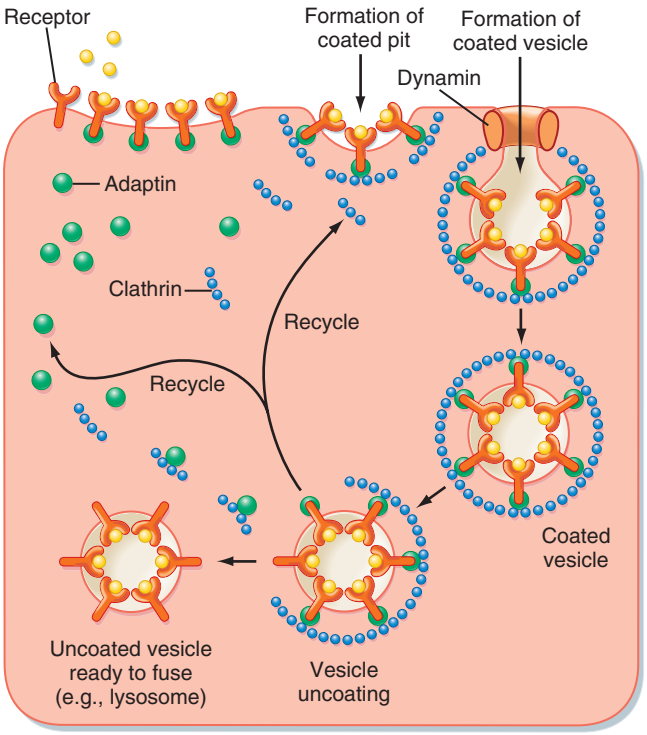
Vesicular Transport

Solute and water can be brought into the cell through a process of **endocytosis** and released from the cell through the process of **exocytosis.** Endocytosis is the process whereby a piece of the plasma membrane pinches off and is internalized into the cell interior, and exocytosis is the process whereby vesicles inside the cell fuse with the plasma membrane. In both of these processes, the integrity of the plasma membrane is maintained, and the vesicles allow for the transfer of the contents among cellular compartments. In some cells (e.g., the epithelial cells lining the gastrointestinal tract), endocytosis across one membrane of the cell is followed by exocytosis across the opposite membrane. This allows the transport of substances inside the vesicles across the epithelium, a process termed **transcytosis.**

Endocytosis occurs in three mechanisms. The first is **pinocytosis,** which consists of the nonspecific uptake of small molecules and water into the cell. Pinocytosis is a prominent feature of the endothelial cells that line capillaries and is responsible for a portion of the fluid exchange that occurs across these vessels. The second form of endocytosis, **phagocytosis,** allows for the cellular internalization of large particles (e.g., bacteria, cell debris). This process is an important characteristic of cells in the immune system (e.g., neutrophils and macrophages). Often, but not always, phagocytosis is a receptor-mediated process. For example,

AT THE CELLULAR LEVEL

Proteins within the plasma membrane of cells are constantly being removed and replaced with newly synthesized proteins. As a result, membrane proteins are constantly being replaced. One mechanism by which membrane proteins are "tagged" for replacement is by the attachment of ubiquitin to the cytoplasmic portion of the protein. Ubiquitin is a 76–amino acid protein that is covalently attached to the membrane protein (usually to lysine) by a class of enzymes called *ubiquitin protein ligases.* One important group of these ligases is the developmentally downregulated protein 4 (Nedd4)/Nedd4-like family. Once a membrane protein is ubiquitinated, it undergoes endocytosis and is degraded either by lysosomes or by the proteosome. Cells also contain deubiquitinating enzymes (DUBs). Thus the amount of time a protein stays in the plasma membrane depends on the rate that ubiquitin groups are added by the ligases versus the rate that they are removed by the DUBs. For example, Na^+ reabsorption by the collecting ducts of the kidneys is stimulated by the adrenal hormone aldosterone (see Chapters 34 and 35). One of the actions of aldosterone is to inhibit Nedd4-2. This prevents ubiquitination of ENaC in the apical membrane of epithelial cells. Thus the channels are retained for a longer period of time in the membrane, and as a result, more Na^+ enters the cell and is thereby reabsorbed.



• **Fig. 1.5** Receptor-mediated endocytosis. Receptors on the surface of the cell bind the ligand. A clathrin-coated pit is formed with adaptin linking the receptor molecules to clathrin. Dynamin, a guanosine triphosphatase (GTPase), assists in separation of the endocytic vesicle from the membrane. Once inside the cell, the clathrin and adaptin molecules dissociate and are recycled. The uncoated vesicle is then ready to fuse with other organelles in the cell (e.g., lysosomes). (Adapted from Ross MH, Pawlina W: *Histology.* 5th ed. Baltimore: Lippincott Williams & Wilkins; 2006.)

macrophages have receptors on their surface that bind the Fc portion of immunoglobulins. When bacteria invade the body they are often coated with antibody, a process called opsonization. These bacteria then attach to the membrane of macrophages via the fragment crystallizable (Fc) portion of the immunoglobulin, undergo phagocytosis, and are destroyed inside the cell. The third mechanism of endocytosis is **receptor-mediated endocytosis,** which allows the uptake of specific molecules into the cell. In this form of endocytosis, molecules bind to receptors on the surface of the cell. Endocytosis involves a number of accessory proteins, including adaptin, clathrin, and the GTPase dynamin (Fig. 1.5).

Exocytosis can be either constitutive or regulated. Constitutive secretion occurs, for example, in plasma cells that are secreting immunoglobulin or in fibroblasts secreting collagen. Regulated secretion occurs in endocrine cells, neurons, and exocrine glandular cells (e.g., pancreatic acinar cells). In these cells, the secretory product (e.g., hormone, neurotransmitter, or digestive enzyme), after synthesis and processing in the rough endoplasmic reticulum and Golgi apparatus, is stored in the cytoplasm in secretory granules until an appropriate signal for secretion is received. These signals may be hormonal or neural. Once the cell receives the appropriate stimulus, the secretory vesicle fuses with the plasma membrane and releases its contents into the extracellular fluid. Fusion of the vesicle with the membrane is mediated by a number of accessory proteins. One important group is the SNARE (**s**oluble *N*-ethylmaleimide sensitive fusion protein [**N**SF] **a**ttachment protein **re**ceptors) proteins. These membrane proteins help target the secretory

IN THE CLINIC

Cholesterol is an important component of cells (e.g., it is a key component of membranes). However, most cells are unable to synthesize cholesterol and therefore must obtain it from the blood. Normally, cholesterol is ingested in the diet, and it is transported through the blood in association with lipoproteins. Low-density lipoproteins (LDLs) in the blood carry cholesterol to cells, where they bind to LDL receptors in the plasma membrane. After the receptors bind LDL, they collect into "coated pits" and undergo endocytosis as clathrin-coated vesicles. Once inside the cell, the endosomes release LDL and then recycle the LDL receptors back to the cell surface. Inside the cell, LDL is then degraded in lysosomes, and the cholesterol is made available to the cell. Defects in the LDL receptor prevent cellular uptake of LDL. Individuals with this defect have elevated levels of blood LDL, often called "bad cholesterol," because it is associated with the development of cholesterol-containing plaques in the smooth muscle layer of arteries. This process, atherosclerosis, is associated with an increased risk for heart attacks as a result of occlusion of the coronary arteries.