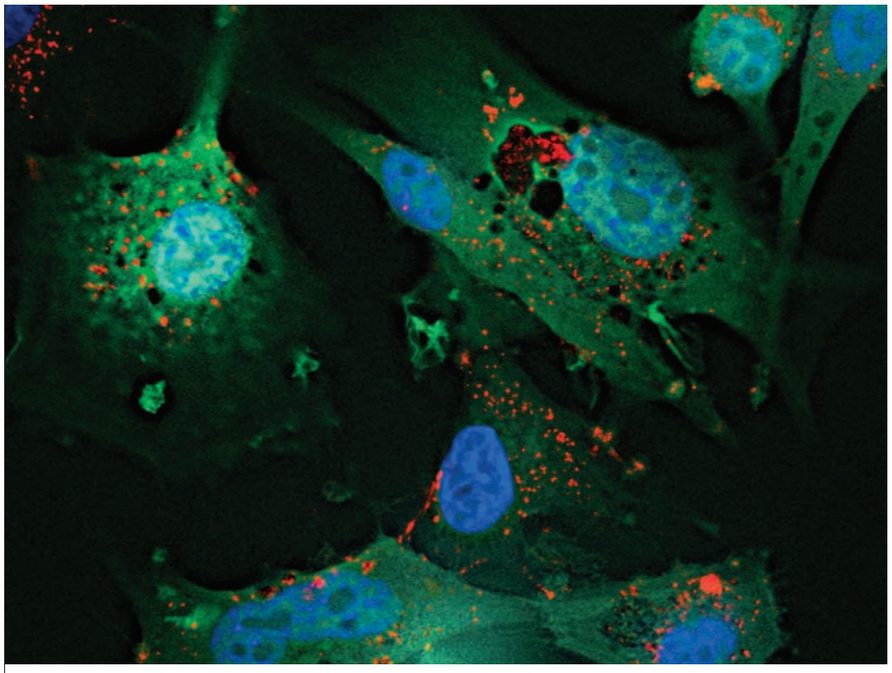


Dr. Alexander Gray/Wellcome Trust Medical Photographic Library

Endocytosis in cancer cells (confocal micrograph). The red spots are fluorescent spheres used to follow the process of endocytosis; some of the spheres have been taken up by cells.

Study Plan

6 Membranes and Transport

Why It Matters

All organisms encounter environmental factors that could disrupt their water content and internal concentrations of ions and molecules, but some species face dramatic challenges. Consider the striped bass *(Morone saxatilis)*, which migrates between the ocean and freshwater streams in North America **(Figure 6.1).** Seawater is more salty than the fluids inside the fish. In this situation, water tends to leave the body of the fish and enter the seawater, and salt ions from the water tend to enter the fish. When the bass migrates into freshwater streams, now the inside of the fish is more salty than the surrounding freshwater, and its cells must keep its ions in and excess water out. If the cellular systems that regulate the balance fail in either situation, death is likely.

The challenge is not unique to organisms migrating between freshwater and the oceans—all living things must constantly bring in some molecules and ions and keep out others to maintain their internal environment. The **plasma membrane**—the exceedingly thin layer of lipids and proteins that covers the surface of all cells—makes this possible.

The plasma membrane is the primary zone of contact between a cell and its environment. It forms a barrier that keeps the cell con-

Andrew Martinez/Photo Researchers, Inc.

Figure 6.1
A striped bass, an organism that tolerates both saltwater and freshwater environments.

tents from mixing freely with molecules outside the cell. Only selected ions can move across the barrier to enter or leave the cytoplasm. Within eukaryotic cells, membranes surrounding internal organelles play similar roles, creating environments that differ from the surrounding cytoplasm.

The structure and function of biological membranes are the focus of this chapter. We first consider the structure of membranes and then examine how membranes selectively transport substances in and out of cells and organelles. Other roles of membranes, including recognition of molecules on other cells, adherence to other cells or extracellular materials, and reception of molecular signals such as hormones, are the subjects of Chapters 7, 40, and 43 in this book.

6.1 Membrane Structure

A watery fluid medium—or aqueous solution—bathes both surfaces of all biological membranes. The membranes are also fluid, but they are kept separate from their surroundings by the properties of the lipid and protein molecules from which they are formed.

Biological Membranes Contain Both Lipid and Protein Molecules

Biological membranes consist of lipids and proteins assembled into a thin film. The proportions of lipid and protein molecules in membranes vary, depending on the functions of the membranes in the cells.

Membrane Lipids. *Phospholipids* and *sterols* are the two major types of lipids in membranes (see Section 3.4). Phospholipids have nonpolar fatty acid chains at one end; at the other end, phospholipids have a phosphate group linked to one of several alcohols or amino acids, making this end polar **(Figure 6.2a).** The polar end is hydrophilic—it "prefers" being in an aqueous environment—and the nonpolar end is hydrophobic—it "prefers" being in an environment from which water is excluded. In other words, phospholipids have dual solubility properties.

In an aqueous medium, phospholipid molecules satisfy their dual solubility characteristics by assembling into a **bilayer**—a layer two molecules thick **(Figure 6.2b).** In a bilayer, the polar ends of the phospholipid molecules are located at the surfaces, where

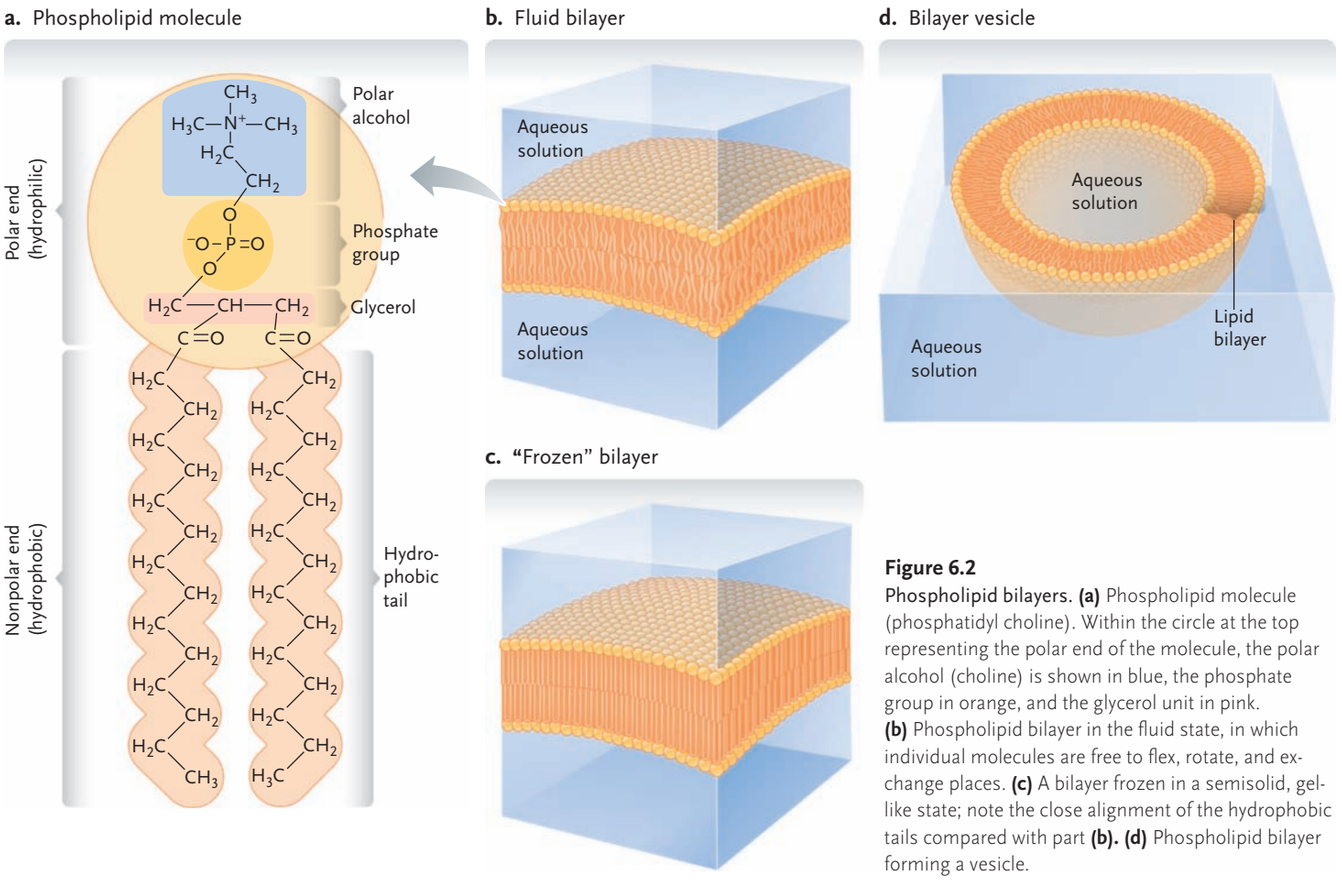


Figure 6.2
Phospholipid bilayers. **(a)** Phospholipid molecule (phosphatidyl choline). Within the circle at the top representing the polar end of the molecule, the polar alcohol (choline) is shown in blue, the phosphate group in orange, and the glycerol unit in pink. **(b)** Phospholipid bilayer in the fluid state, in which individual molecules are free to flex, rotate, and exchange places. **(c)** A bilayer frozen in a semisolid, gel-like state; note the close alignment of the hydrophobic tails compared with part **(b). (d)** Phospholipid bilayer forming a vesicle.

they face the surrounding aqueous medium. The nonpolar fatty acid chains arrange themselves end to end in the membrane interior, in a nonpolar region that excludes water. At low temperatures, the phospholipid bilayer becomes frozen to produce a semisolid, gel-like state **(Figure 6.2c).** When a phospholipid bilayer sheet is shaken in water, it breaks and spontaneously forms small *vesicles* **(Figure 6.2d).** Vesicles consist of a spherical shell of phospholipid bilayer enclosing a small droplet of water.

Membrane sterols also have dual solubility characteristics. As explained in Section 3.4, these molecules have nonpolar carbon rings with a nonpolar side chain at one end and a single polar group (an —OH group) at the other end. In biological membranes, sterols pack into membranes alongside the phospholipid hydrocarbon chains, with only the polar end extending into the polar membrane surface **(Figure 6.3).** The predominant sterol of animal cell membranes is **cholesterol**, which is important for maintaining membrane fluidity. A variety of sterols, called *phytosterols,* is found in plants.

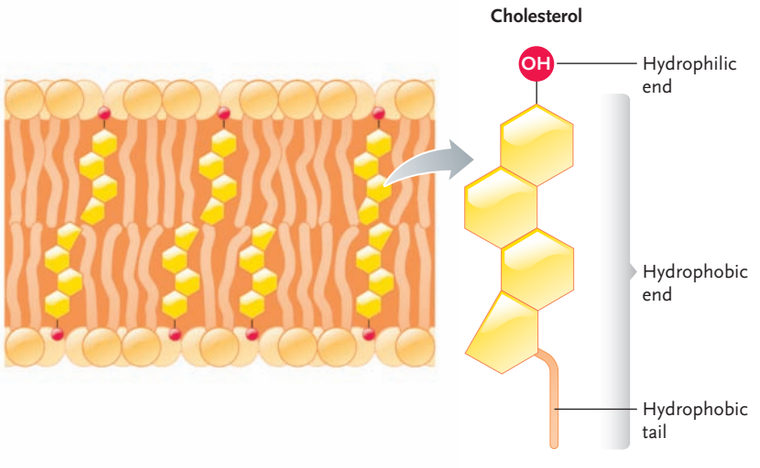
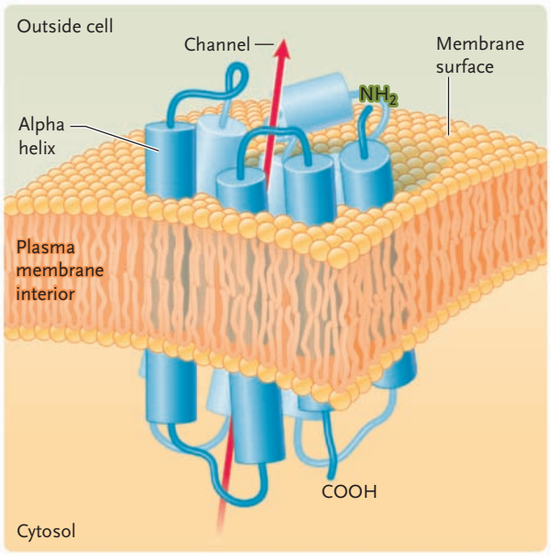


Figure 6.3
The position taken by cholesterol in bilayers. The hydrophilic —OH group at one end of the molecule extends into the polar regions of the bilayer; the ring structure extends into the nonpolar membrane interior.

Membrane Proteins. Membrane proteins also have hydrophilic and hydrophobic regions that give them dual solubility properties. The hydrophobic regions of membrane proteins are formed by segments of the amino acid chain with hydrophobic side groups. These hydrophobic segments are often wound into alpha helices, which span the membrane bilayer **(Figure 6.4).** The hydrophobic segments are connected by loops of hydrophilic amino acids that extend into the polar regions at the membrane surfaces (for example, see Figure 6.4).

Each type of membrane has a characteristic group of proteins that is responsible for its specialized functions. **Transport proteins** form channels that allow selected polar molecules and ions to pass across a membrane. **Recognition proteins** in the plasma membrane identify a cell as part of the same individual or as foreign. **Receptor proteins** recognize and bind molecules from other cells that act as chemical signals, such as the peptide hormone insulin in animals. **Cell adhesion proteins** bind cells together by recognizing and binding receptors or chemical groups on other cells or on the extracellular

a. Typical membrane protein



b. Hydrophilic and hydrophobic surfaces

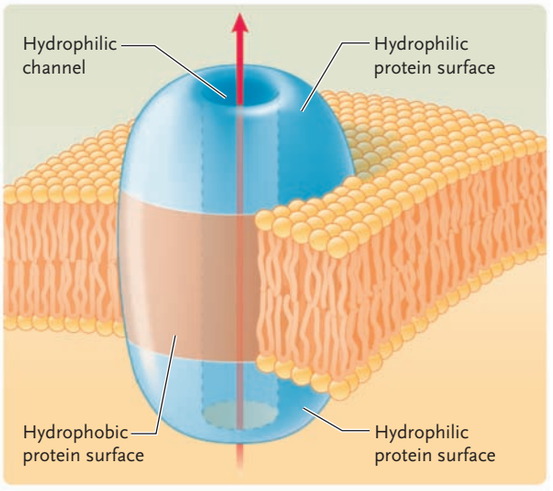


Figure 6.4
Structure of membrane proteins. **(a)** Typical membrane protein, bacteriorhodopsin, showing the membrane-spanning alpha-helical segments (blue cylinders), connected by flexible loops of the amino acid chain at the membrane surfaces. **(b)** The same protein as in **(a)** in a diagram that shows hydrophilic (blue) and hydrophobic (orange) surfaces and the membrane-spanning channel created by this protein. Bacteriorhodopsin absorbs light energy in plasma membranes of photosynthetic archaeans.

matrix. Still other proteins are enzymes that speed chemical reactions carried out by membranes, such as the reactions in mitochondria that create ATP.

Membrane Glycolipids and Glycoproteins. Many of the phospholipids and proteins in membranes have carbohydrate groups linked to them, forming glycolipids and glycoproteins **(Figure 6.5).** In the plasma membrane, the carbohydrate groups, which are polar, are attached covalently to parts of membrane lipid and protein molecules that face the exterior membrane surface. They are so abundant on the exterior surface that they give cells a "sugar coating" or **glycocalyx** (*glykys* = sweet; *calyx* = cup or vessel).

The Fluid Mosaic Model Explains Membrane Structure

The current view of membrane structure is based on the fluid mosaic model (see Figure 6.5). S. Jonathan Singer and Garth L. Nicolson at the University of California, San Diego, advanced this model in 1972. The **fluid mosaic model** proposes that the membrane consists of a fluid phospholipid bilayer in which proteins are embedded and float freely.

The "fluid" part of the fluid mosaic model refers to the phospholipid molecules, which vibrate, flex back and forth, spin around their long axis, move sideways, and exchange places within the same bilayer half. Only rarely does a phospholipid flip-flop between the two layers. Phospholipids exchange places within a layer millions of times a second, making the phospholipid molecules in the membrane highly dynamic. Membrane fluidity is critical to the functions of membrane proteins and allows membranes to accommodate, for example, cell growth, motility, and surface stresses.

Membranes remain fluid at a relatively wide range of temperatures. Low temperatures can be detrimental to membrane structure, and therefore membrane function, because at a sufficiently low temperature the phospholipid molecules become closely packed and the membrane becomes a nonfluid gel. A common modification that helps keep membranes fluid at low temperatures is increasing the proportion of unsaturated fatty acid chains in membrane phospholipids. The double bonds in the unsaturated fatty acid chains produce physical kinks in the chain that interfere with the packing of the phospholipids at low temperatures, thereby reducing the temperature at which the bilayer becomes a nonfluid gel. In a paradoxical way, cholesterol also helps protect against the adverse effects of low temperatures. Cholesterol in the membrane decreases membrane fluidity at moderate to high temperatures because of

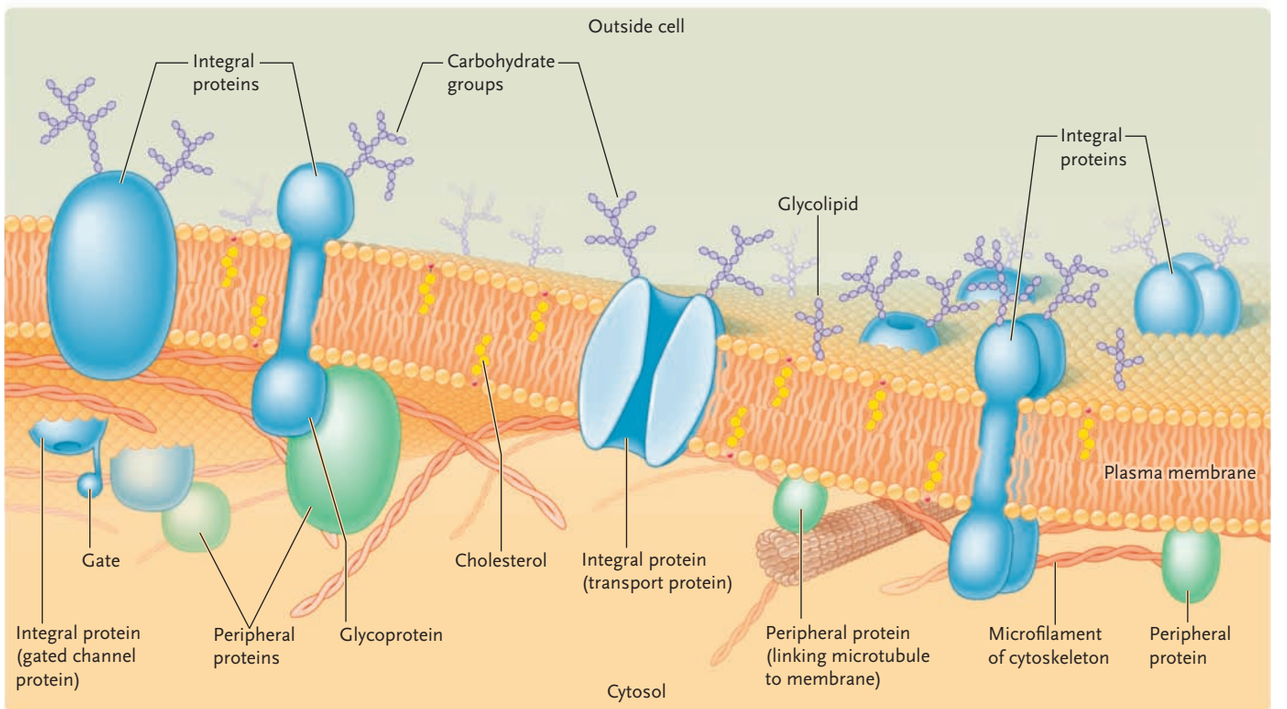


Figure 6.5
Membrane structure according to the fluid mosaic model, in which integral membrane proteins are suspended individually in a fluid bilayer. Peripheral proteins are attached to integral proteins or membrane lipids mostly on the cytoplasmic side of the membrane (shown only on the inner surface in the figure). In the plasma membrane, carbohydrate groups of membrane glycoproteins and glycolipids face the cell exterior.

Focus on Research

Basic Research: Keeping Membranes Fluid at Cold Temperatures

The fluid state of biological membranes is critical to membrane function and absolutely vital to cellular life. When membranes freeze, researchers have shown that the phospholipids form a semisolid gel in which they are unable to move (see Figure 6.2c), and proteins become locked in place. Freezing can kill cells by impeding vital membrane functions such as transport.

Many eukaryotic organisms, including algae, higher plants, protozoa, and animals, adapt to colder temperatures by changing membrane lipids. Experiments comparing membrane composition have shown that, in animals with body temperatures that fluctuate with environmental temperature, such as fish, amphibians, and reptiles, both the proportion of double bonds in membrane phospholipids and the cholesterol content are increased at lower temperatures. How do these changes affect membrane fluidity? Double bonds in unsaturated fatty acids introduce "kinks" in their hydrocarbon chain (see Figure 3.12); the kinks help bilayers stay fluid at lower temperatures by interfering with packing of the hydrocarbons. Cholesterol depresses the freezing point by interfering with close packing of membrane phospholipids.

All of these membrane changes also occur in mammals that enter hibernation in cold climates. When mammals enter hibernation, their body temperature may fall to as low as 5°C without freezing their membranes. The resistance to freezing allows the nerve cells of a hibernating mammal to remain active so that the animal can maintain basic body functions and respond, although sluggishly, to external stimuli. In active, nonhibernating mammals, membranes freeze into the gel state at about 15°C.

interactions between the rigid cholesterol rings and the membrane phospholipids (see Figure 6.3). However, at the high concentrations found in eukaryotic membranes, the disruption of the ordered packing of phospholipids by cholesterol helps slow the transition of the membrane to the nonfluid gel state when temperatures drop. (See *Focus on Research* for a description of other strategies that organisms use to keep their membranes from freezing at low temperatures.)

At high temperatures, membranes can become too fluid and will become leaky, allowing ions to cross in an uncontrolled manner. This leaking disrupts the function of the cell; thus, it is likely to die. As described previously, cholesterol reduces membrane fluidity at high temperatures, thereby providing some protection.

The "mosaic" part of the fluid mosaic model refers to the membrane proteins, most of which float individually in the fluid lipid bilayer, like icebergs in the sea. Membrane proteins are larger than membrane lipids, and those that move do so much more slowly than do lipids. A number of membrane proteins are attached to the cytoskeleton. These proteins either are immobile or move in a directed fashion, perhaps along cytoskeletal filaments.

Membrane proteins are oriented across the membrane so that particular functional groups and active sites face either the inside or the outside membrane surface. The inside and outside halves of the bilayer also contain different mixtures of phospholipids. These differences make biological membranes *asymmetric* and give their inside and outside surfaces different functions.

Proteins that are embedded in the phospholipid bilayer are termed **integral proteins** (see Figure 6.5). Essentially all transport, receptor, recognition, and cell adhesion proteins that give membranes their specific functions are integral membrane proteins.

Other proteins, called **peripheral proteins** (see Figure 6.5), are held to membrane surfaces by noncovalent bonds—hydrogen bonds and ionic bonds—formed with the polar parts of integral membrane proteins or membrane lipids. Most peripheral proteins are on the cytoplasmic side of the membrane. Some peripheral proteins are parts of the cytoskeleton, such as microtubules, microfilaments, or intermediate filaments, or proteins that link the cytoskeleton together. These structures hold some integral membrane proteins in place. For example, this anchoring constrains many types of receptors to the sides of cells that face body surfaces, cavities, or tubes.

The Fluid Mosaic Model Is Fully Supported by Experimental Evidence

The novel ideas of a fluid membrane and a flexible mosaic arrangement of proteins and lipids challenged an accepted model in which a relatively rigid, stable membrane was coated on both sides with proteins arranged like jam on bread. Researchers tested the new model with an intensive burst of research. The experimental evidence from that research completely supports every major hypothesis of the model: that membrane lipids are arranged in a bilayer, that the bilayer is fluid, that proteins are suspended individually in the bilayer, and that the arrangement of both membrane lipids and proteins is asymmetric.

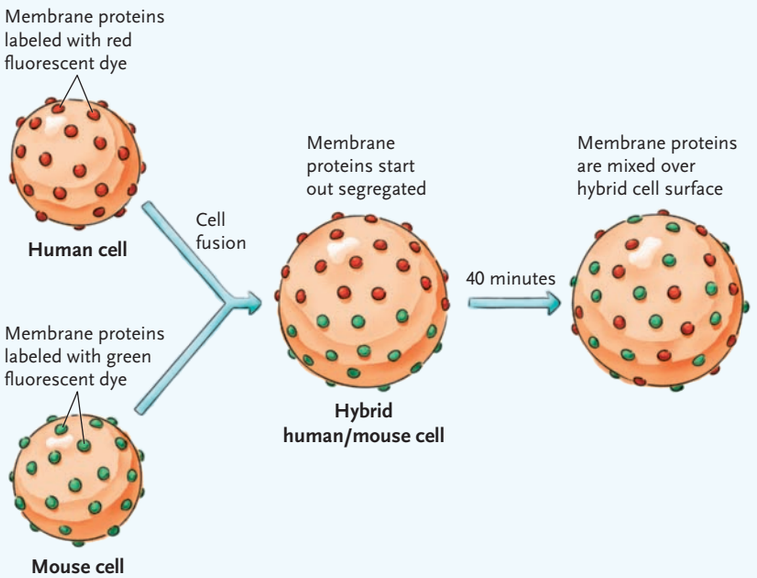
Evidence That Membranes Are Fluid. In a now-classic study carried out in 1970, L. David Frye and Michael A. Edidin grew human cells and mouse cells separately in tissue culture. Then they added antibodies that bound to either human or mouse membrane proteins **(Figure 6.6).** The anti-human antibodies were

Figure 6.6 Experimental Research

The Frye-Edidin Experiment Demonstrating That the Phospholipid Bilayer Is Fluid

QUESTION: Do membrane proteins move in the phospholipid bilayer?

EXPERIMENT: Frye and Edidin labeled membrane proteins on cultured human and mouse cells with fluorescent dyes, red for human proteins and green for mouse proteins. Human and mouse cells were then fused and the pattern of fluorescence was followed under a microscope.



CONCLUSION: The rapid mixing of membrane proteins in the hybrid human/mouse cells showed that membrane proteins move in the phospholipid bilayer, indicating that the membrane is fluid.

attached to dye molecules that fluoresce with a red color under ultraviolet light; the anti-mouse antibodies were linked to dye molecules that fluoresce green. Next, they fused the human and mouse cells. Immediately after fusion, the cells were half red and half green, with a clear dividing line between the colors. Within a few minutes, the colors began to mix along the dividing line. In 40 minutes, the colors were completely intermixed on fused cells, indicating the mouse and human proteins had moved around in the fused membranes. In other words, the experiment showed that membrane proteins move in membranes; this movement occurs because the membranes are fluid.

Based on the measured rates at which molecules mix in biological membranes, the membrane bilayer appears to be about as fluid as light machine oil, such as the lubricants you might use around the house to oil a door hinge, the wheels of a skateboard, or a bicycle.

Evidence for Membrane Asymmetry and Individual Suspension of Proteins. An experiment that used membranes prepared for electron microscopy by the **freeze-fracture technique** confirmed that the membrane is a bilayer with proteins suspended in it individually and that the arrangement of membrane lipids and proteins is asymmetric **(Figure 6.7).** In this technique, experimenters freeze a block of cells rapidly by dipping it in, for example, liquid nitrogen. Then they fracture the block by giving it a blow from a microscopically sharp knife edge. Often, the fracture splits bilayers into inner and outer halves, exposing the hydrophobic membrane interior. In the electron microscope, the split membranes appear as smooth layers in which individual particles the size of proteins are embedded (see Figure 6.7c).

Study Break

1. Describe the fluid mosaic model for membrane structure.
2. Give two examples each of integral proteins and peripheral proteins.

6.2 Functions of Membranes in Transport: Passive Transport

The primary function of cellular membranes is **transport**, the controlled movement of ions and molecules from one side of a membrane to the other. The membrane proteins are the molecules responsible for transport. The movement is typically *directional;* that is, some ions and molecules consistently move into cells, whereas others move out of cells. Transport is also *specific;* that is, only certain ions and molecules move directionally across membranes. Transport is critical to the ionic and molecular organization of cells, and with it, the maintenance of cellular life.

Transport occurs by two mechanisms. The first mechanism, **passive transport,** depends on concentration differences on the two sides of a membrane (concentration = number of molecules or ions per unit volume). In this mechanism, ions and molecules move across the membrane from the side with the higher concentration to the side with the lower concentration (that is, *with* the gradient). The difference in concentration provides the energy for this form of transport.

The second mechanism, **active transport,** moves ions or molecules *against* the concentration gradient; that is, from the side with the lower concentration to the side with the higher concentration. Active transport

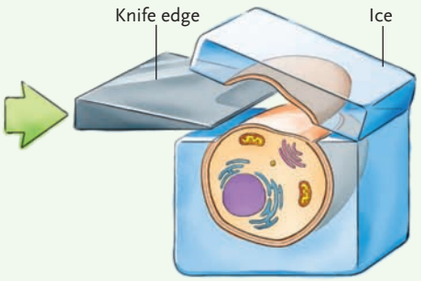
Figure 6.7 Research Method

Freeze Fracture

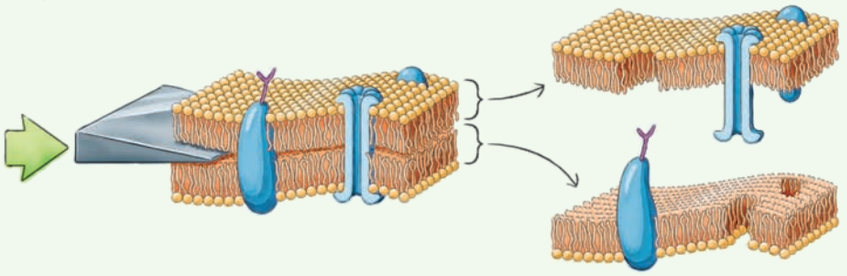
PURPOSE: Quick-frozen cells are fractured to split apart lipid bilayers for analysis of the membrane interior.

PROTOCOL:

1. The specimen is frozen quickly in liquid nitrogen and then fractured by a sharp blow by a knife edge.



2. The fracture may travel over membrane surfaces as it passes through the specimen, or it may split membrane bilayers into inner and outer halves as shown here.



INTERPRETING THE RESULTS: The image of a freeze-fractured plasma membrane is visualized using the electron microscope. The particles visible in the exposed membrane interior are integral membrane proteins.

Don W. Fawcett/Photo Researchers, Inc.

uses energy directly or indirectly obtained by breaking down ATP. The properties of passive and active transport are compared in **Table 6.1.**

Passive Transport Is Based on Diffusion

Passive transport is a form of **diffusion**, the net movement of ions or molecules from a region of higher concentration to a region of lower concentration. If you add a drop of food dye to a container of clear water, the dye molecules, and therefore the color, will spread or *diffuse* from their initial center of high concentration until they are distributed evenly. At this point, the water has an even color. Diffusion depends on the constant motion of ions or molecules at temperatures above absolute zero (−273°C). The constant motion gradually mixes the dye molecules and water molecules until they are distributed uniformly.

The concentration difference that drives diffusion, a **concentration gradient**, is a form of potential energy. At the initial state, when molecules are more concentrated in one region of a solution, as when a dye is dropped into one side of a container of water, the molecules are highly organized and at a state of minimum entropy. In the final state, when they are distributed evenly throughout the solution, they are less organized and at a state of maximum entropy. As the distribution proceeds to the state of maximum dis-

Table 6.1 Characteristics of Transport Mechanisms

Characteristic	Passive Transport		Active Transport
	Simple Diffusion	Facilitated Diffusion	
Membrane component responsible for transport	Lipids	Proteins	Proteins
Binding of transported substance	No	Yes	Yes
Energy source	Concentration gradients	Concentration gradients	ATP hydrolysis or concentration gradients
Direction of transport	With gradient of transported substance	With gradient of transported substance	Against gradient of transported substance
Specificity for molecules or molecular classes	Nonspecific	Specific	Specific
Saturation at high concentrations of transported molecules	No	Yes	Yes

order, the molecules release free energy that can accomplish work (see Section 4.1 for a discussion of entropy and free energy).

Diffusion involves a *net* movement of molecules or ions. Molecules and ions actually move in all directions at all times in a solution. But when molecules or ions exist in a concentration gradient, more of them move from the area of higher concentration to areas of lower concentration than in the opposite direction. Even after their concentration is the same in all regions, there is still constant movement of molecules or ions from one space to another, but there is no net change in concentration on either side. This condition is an example of a *dynamic equilibrium.*

Substances Move Passively through Membranes by Simple or Facilitated Diffusion

Hydrophobic (nonpolar) molecules are able to dissolve in the lipid bilayer of a membrane and move through it freely. By contrast, hydrophilic molecules such as ions and polar molecules are impeded in their movement through the membrane by the hydrophobic core; thus, their passage is slow. Charged atoms and molecules are mostly blocked from moving through the membrane because of the hydrophobic core. Membranes that affect diffusion in this way are said to be **selectively permeable.**

Transport by Simple Diffusion. A few small substances diffuse through the lipid part of a biological membrane. With one major exception—water—these substances are nonpolar inorganic gases such as O_2, N_2, and CO_2 and nonpolar organic molecules such as steroid hormones. This type of transport, which depends solely on molecular size and lipid solubility, is **simple diffusion** (see Table 6.1).

Water is a strongly polar molecule. Nevertheless, water molecules are small enough to slip through momentary spaces created between the hydrocarbon tails of phospholipid molecules as they flex and move in a fluid bilayer. However, this type of water movement across the membrane is relatively slow.

Transport by Facilitated Diffusion. Many polar and charged molecules such as water, amino acids, sugars, and ions diffuse across membranes with the help of transport proteins, a mechanism termed **facilitated diffusion.** In essence, the transport proteins enable polar and charged molecules to avoid interaction with the hydrophobic lipid bilayer (see Table 6.1).

Facilitated diffusion is specific: the membrane proteins involved transport certain polar and charged molecules, but not others. Facilitated diffusion is also dependent on concentration gradients: proteins aid the transport of polar and charged molecules through membranes, but a favorable concentration gradient provides the energy for transport. Transport stops if the gradient falls to zero.

Two Groups of Transport Proteins Carry Out Facilitated Diffusion

The proteins that carry out facilitated diffusion are integral membrane proteins that extend entirely through the membrane. There are two types of transport proteins involved in facilitated diffusion. One type, **channel proteins,** forms hydrophilic channels in the membrane through which water and ions can pass **(Figure 6.8a).** The channel "facilitates" the diffusion of molecules through the membrane by providing an avenue. For example, facilitated diffusion of water through membranes occurs through specialized water channels called **aquaporins** (see Figure 6.8a). A billion molecules of water per second can move through an aquaporin channel. How the molecules move is fascinating. Each water molecule is severed from its hydrogen-bonded neighbors as it is handed off to a succession of hydrogen-bonding sites on the aquaporin protein in the channel.

Other channel proteins facilitate the transport of ions such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chlorine (Cl^-). Most of these ion transporters, which occur in all eukaryotes, are **gated channels;** that is, they switch between open, closed, or intermediate states. The gates may be opened or closed by changes in voltage across the membrane, for instance, or by binding signal molecules. In animals, voltage-gated ion channels are used in nerve conduction and the control of muscle contraction. *Insights from the Molecular Revolution* describes molecular experiments showing the conformational changes that open channel gates.

Gated ion channels perform functions that are vital to survival, as illustrated by the effects of hereditary defects in the channels. For example, the hereditary disease *cystic fibrosis* results from a fault in a gated Cl^- channel. The faulty channel allows unusually high levels of Cl^-, as well as Na^+, to pass into extracellular fluids and from sweat glands. Abnormally sticky mucus accumulates in the respiratory tract leading to chronic lung infections that, with other effects of the Cl^- transport deficiency, are typically fatal by age 30 for persons born with the disease.

Carrier proteins are the second type of transport proteins; they also form passageways through the lipid bilayer **(Figure 6.8b).** Carrier proteins each bind a specific single solute, such as glucose or an amino acid, and transport it across the lipid bilayer (glucose is also transported by active transport, as described in the next section). Because a single solute is transferred in this carrier-mediated fashion, the transfer is called *uniport transport.* In performing the transport step, the carrier

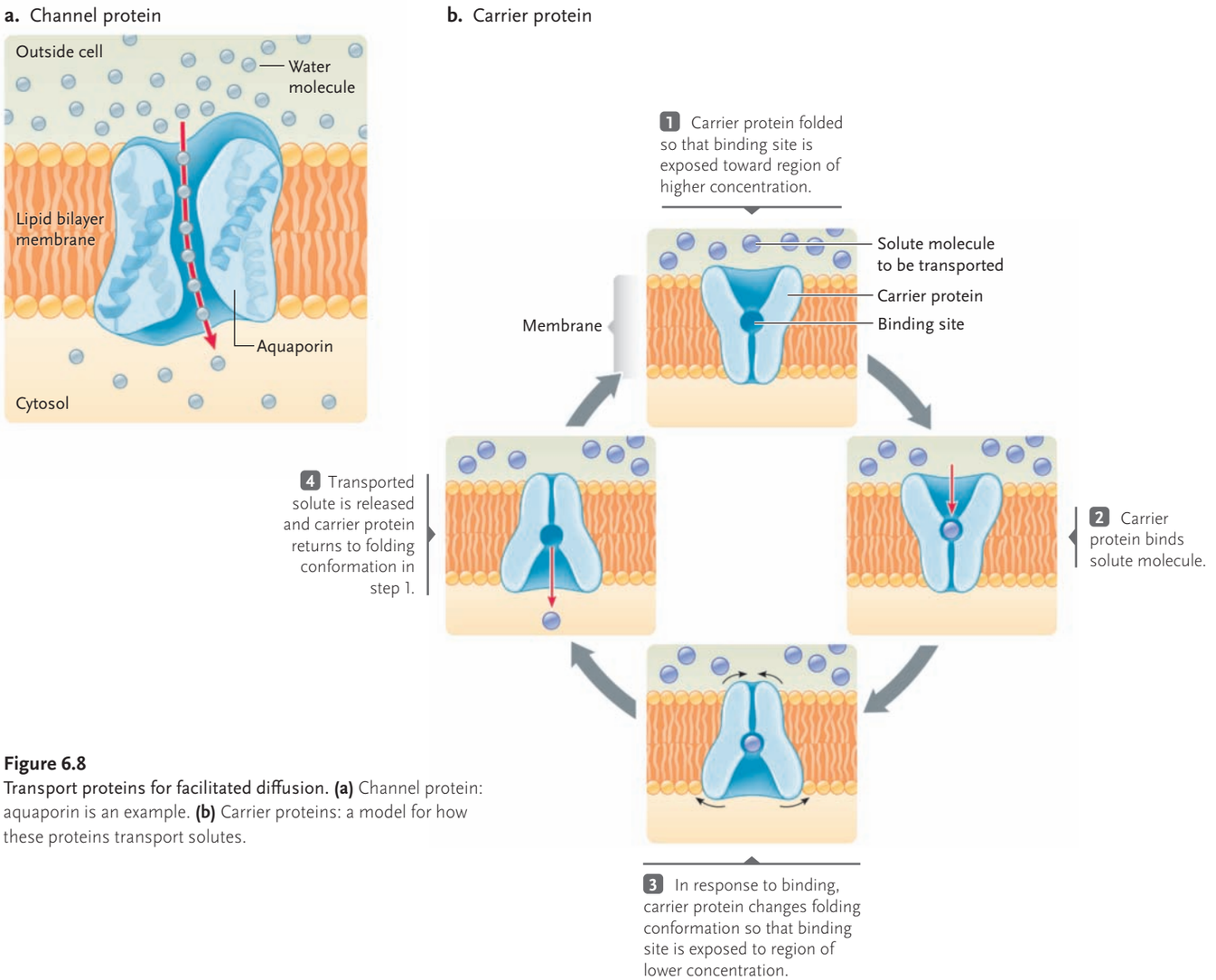


Figure 6.8
Transport proteins for facilitated diffusion. **(a)** Channel protein: aquaporin is an example. **(b)** Carrier proteins: a model for how these proteins transport solutes.

protein undergoes conformational changes that progressively move the solute-binding site from one side of the membrane to the other, thereby transporting the solute. This property distinguishes carrier protein function from channel protein function.

Facilitated diffusion by carrier proteins can become *saturated* when there are not enough transport proteins to handle all the solute molecules. For example, if glucose is added at higher and higher concentrations to the solution that surrounds an animal cell, the rate at which it passes through the membrane at first increases proportionately with the increase in concentration. However, at some point, as the glucose concentration is increased still further, the increase in the rate of transport slows. Eventually, further increases in concentration cause no additional rise in the rate of transport—the transport mechanism is saturated. By contrast, saturation does not occur for simple diffusion.

Because the proteins that perform facilitated diffusion are specific, cells can control the kinds of molecules and ions that pass through their membranes by regulating the types of transport proteins in their membranes. As a result, each type of cellular membrane, and each type of cell, has its own group of transport proteins and passes a characteristic group of substances by facilitated diffusion. The kinds of transport proteins present in a cell ultimately depend on the activity of genes in the cell nucleus.

Study Break

1. What is the difference between passive and active transport?
2. What is the difference between simple and facilitated diffusion?

Insights from the Molecular Revolution

Tracking Gating Movements in a Channel Protein

Passive transport of ions often occurs through gated channels, and in animals, such channels operate to generate nerve signals and to stimulate muscle contraction. Knowledge of the structures of the gates and how each structural component plays a role in its function is required to understand this type of transport mechanism. For instance, researchers have studied voltage-gated ion transport proteins in nerve cells to determine such structure–function relations. As part of nerve transmission, a gated sodium channel opens to allow sodium ions to flow inward and a gated potassium channel opens to allow potassium ions to flow outward, both with their concentration gradients. The proteins of both channels have six alpha-helical segments, designated S1 to S6, that zigzag back and forth across the plasma membrane and form the passage through which ions move when the channel opens. Do these segments also participate in opening and closing the channels? To answer this question, scientists investigated whether any of the six helices responds to the voltage changes that stimulate opening and closing of the channels, and whether the helix moves as part of the gating.

Several experiments had implicated S4 as the critical helix. For example, in one experiment, the researchers substituted one amino acid for another at different sites in the channel proteins; of these substitutions, those in S4 had the greatest effect on the ability of the channels to respond to voltage changes in the membrane.

Lidia M. Mannuzzu, Mario M. Morrone, and Ehud Y. Isacoff of the University of California at Berkeley performed an experiment that confirmed that movement of S4 is the first step in voltage gating. The investigators tagged S4 with a dye molecule so they could trace movements of the helix in voltage-gated potassium channels in the plasma membranes of egg cells of the African clawed frog, *Xenopus laevis*.

Mannuzzu and her colleagues used molecular techniques to make five different versions of the potassium channel, each with the amino acid cysteine substituted at a different position in helix S4. They combined the cysteine with a particular dye that fluoresces—emits light—with a different wavelength (color) when it is in a nonpolar or polar environment.

Before the voltage change was made, all the different versions of the channel protein emitted light at the wavelength characteristic of a nonpolar environment. This result indicated that, before the channel opens, S4 is buried in the nonpolar interior of the plasma membrane. Immediately after the voltage change, the emitted light wavelength changed to that of a polar environment, indicating that S4 moves from the channel interior to the polar membrane surface as the channel gate opens.

The investigators were even able to find out whether S4 moves to the outside or the inside of the plasma membrane by applying a substance to the outside of the membrane that would "quench" emission of the fluorescent dye. Since quenching did occur, they concluded that helix S4 moves to the outside surface of the plasma membrane when the channel gate opens.

Taken together, the results of the experiments show that, in the first response of the gated channel to a change in membrane voltage, S4 moves from the interior to the external surface of the channel protein, and the channel gates open. This result provides the first direct confirmation that S4 actually moves as a part of the response. The techniques used in the experiments also provide a new way to track further gating changes that, until now, had been invisible to scientists investigating membrane channels.

6.3 Passive Water Transport and Osmosis

As discussed earlier, water can also follow concentration gradients and diffuse passively across membranes in response. It diffuses both directly through the membrane and through aquaporins. The passive transport of water, called **osmosis**, occurs constantly in living cells. Inward or outward movement of water by osmosis develops forces that can cause cells to swell and burst or shrink and shrivel up. Much of the energy budget of many cell types, particularly in animals, is spent counteracting the inward or outward movement of water by osmosis.

Osmosis Can Be Demonstrated in a Purely Physical System

The apparatus shown in **Figure 6.9a** is a favorite laboratory demonstration of osmosis. It consists of an inverted thistle tube (so named because its shape resembles a thistle flower) tightly sealed at its lower end by a sheet of cellophane. The tube is filled with a solution of glucose molecules in water and is suspended in a beaker of distilled water. The cellophane film acts as a selectively permeable membrane because its pores are large enough to admit water molecules but not glucose. At the start of the experiment, the position of the tube is set so the level of the liquid in the tube is at same level as the distilled water in the beaker. Almost

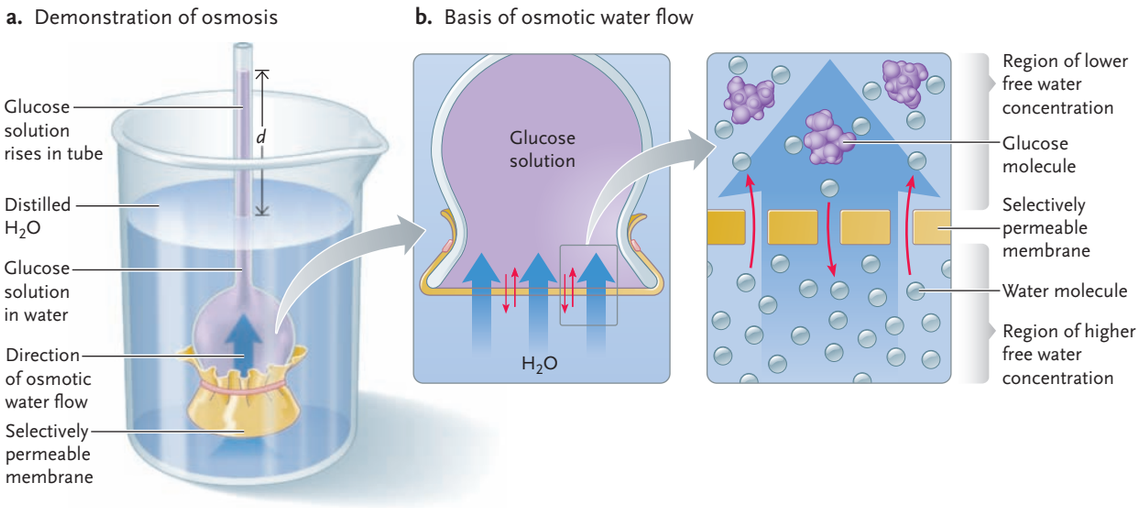


Figure 6.9
Osmosis. **(a)** An apparatus demonstrating osmosis. The fluid in the tube rises due to the osmotic flow of water through the cellophane membrane, which is permeable to water but not to glucose molecules. Osmotic flow continues until the weight of the water in column *d* develops enough pressure to counterbalance the movement of water molecules into the tube. **(b)** The basis of osmotic water flow. The pure water solution on the left is separated from the glucose solution on the right by a membrane permeable to water but not to glucose. The free water concentration on the glucose side is lower than on the water-only side because water molecules are associated with the glucose molecules. That is, water molecules are in greater concentration on the bottom than on the top. Although water molecules move in both directions across the membrane (small red arrows), there is a net upward movement of water (blue arrows), with the water's concentration gradient.

immediately, the level of the solution in the tube begins to rise, eventually reaching a maximum height above the liquid in the beaker.

The liquid rises in the tube because water moves by osmosis from the beaker into the thistle tube. The movement occurs passively, in response to a concentration gradient in which the water molecules are higher in concentration in the beaker than inside the thistle tube. The basis for the gradient is shown in **Figure 6.9b.** The glucose molecules are more concentrated on one side of the selectively permeable membrane. On this side, association of water molecules with those solute molecules reduces the amount of water available to cross the membrane. Thus, although initially there is an equal apparent water concentration on each side of the membrane, there is a difference in the *free water* concentration—that is, the water available to move across the membrane. Specifically, the concentration of free water molecules is lower on the glucose side than on the pure water side. In response, a net movement of water occurs from the pure water side to the glucose solution side. Osmosis is the net diffusion of water molecules through a selectively permeable membrane in response to a gradient of this type.

The solution stops rising in the tube when the pressure created by the weight of the raised solution exactly balances the tendency of water molecules to move from the beaker into the tube in response to the concentration gradient. This pressure is the **osmotic pressure** of the solution in the tube. At this point, the system is in a state of dynamic equilibrium and no further net movement of water molecules occurs.

A formal definition for osmosis is *the net movement of water molecules across a selectively permeable membrane by passive diffusion, from a solution of lesser solute concentration to a solution of greater solute concentration* (the *solute* is the substance dissolved in water). For osmosis to occur, the selectively permeable membrane must allow water molecules, but not molecules of the solute, to pass. Pure water does not need to be on one side of the membrane; osmotic water movement also occurs if a solute is at different concentrations on the two sides. Because osmosis occurs in response to a concentration gradient, it releases free energy and can accomplish work.

The Free Energy Released by Osmosis May Work for or against Cellular Life

Osmosis occurs in cells because they contain a solution of proteins and other molecules that are retained in the cytoplasm by a membrane impermeable to them but freely permeable to water. The resulting osmotic movement of water is used as an energy source for some of the activities of life. However, it can also create a disturbance that cells must counteract by ex-

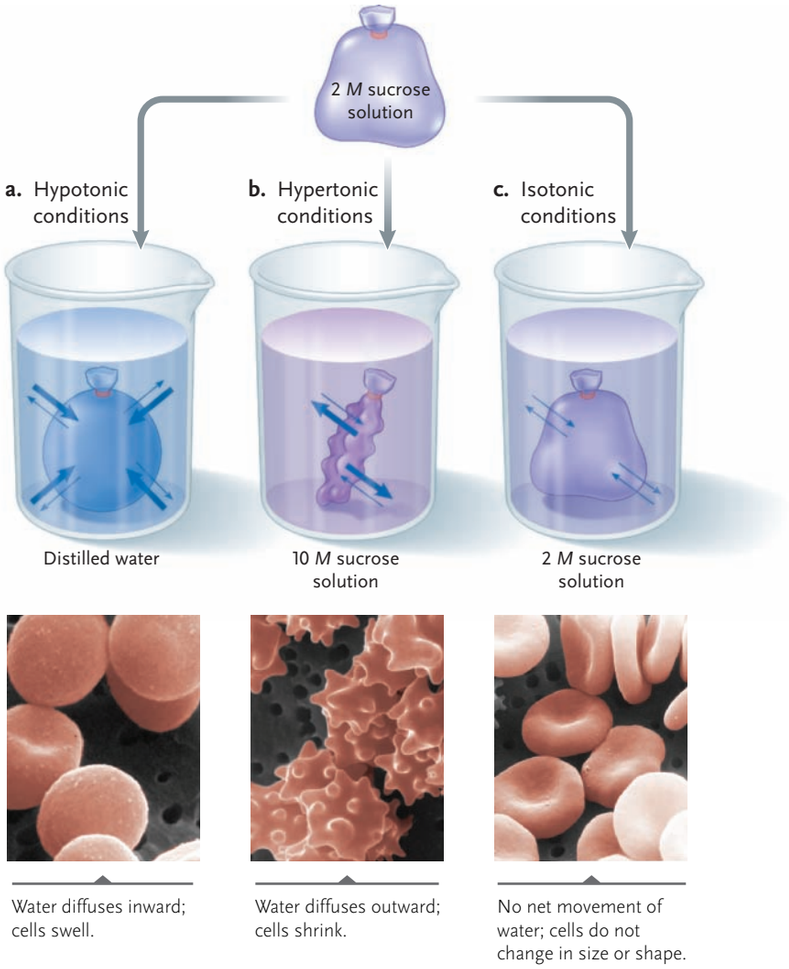


Figure 6.10

Tonicity and osmotic water movement. The diagrams show what happens when a cellophane bag filled with a 2 *M* sucrose solution is placed in a **(a)** hypotonic, **(b)** hypertonic, or **(c)** isotonic solution. The cellophane is permeable to water but not to sucrose molecules. The width of the arrows shows the amount of water movement. In the first beaker, the distilled water is hypotonic to the solution in the bag; net movement of water is into the bag. In the second beaker, the 10 *M* solution is hypertonic to the solution in the bag; net movement of water is out of the bag. In the third beaker, the solutions inside and outside the bag are isotonic; there is no net movement of water in or out of the bag. The animal cell micrographs show the corresponding effects on red blood cells placed in **(a)** hypotonic, **(b)** hypertonic, or **(c)** isotonic solutions.

(Micrographs, M. Sheetz, R. Painter, and S. Singer. *Journal of Cell Biology*, 70:493, 1976. By permission of Rockefeller University Press.)

pending energy. If the solution that surrounds a cell contains dissolved substances at lower concentrations than the cell, the solution is said to be **hypotonic** to the cell (*hypo* = under or below; *tonos* = tension or tone). When a cell is in a hypotonic solution, water enters by osmosis and the cell tends to swell **(Figure 6.10a).** Animal cells in a hypotonic solution may actually swell to the point of bursting. However, in most plant cells, strong walls prevent the cells from bursting in a hypotonic solution. In most land plants, the cells at the surfaces of roots are surrounded by almost pure water, which is hypotonic to the cells and tissues of the root. As a result, water flows from the surrounding soil into the root cells by osmosis. The osmotic pressure developed by the inward flow contributes part of the force required to raise water from the roots to the leaves of the plant. Water also normally moves into cells of the stems and leaves of plants by osmosis. The resulting osmotic pressure, called **turgor pressure**, pushes the cells tightly against their walls and supports the softer tissues against the force of gravity **(Figure 6.11a).**

Organisms living in surroundings that contain salts or other molecules at higher concentrations than their own bodies must constantly expend energy to replace water lost by osmosis. In this situation, the outside solution is said to be **hypertonic** to the cells (*hyper* = over or above; see **Figure 6.10b**). If the outward osmotic movement exceeds the capacity of cells to replace the lost water, both animal and plant cells will shrink. In plants, the shrinkage and loss of internal osmotic pressure under these conditions causes stems and leaves to wilt. In extreme cases, plant cells shrink so much that they retract from their walls, a condition known as **plasmolysis (Figure 6.11b).**

In animals, ions, proteins, and other molecules are concentrated in extracellular fluids, as well as inside cells, so that the concentration of water inside and outside cells is usually equal or **isotonic** (*iso* = the same; see **Figure 6.10c**). To keep fluids on either side of the plasma membrane isotonic, animal cells must constantly use energy to pump Na^+ from inside to outside by active transport (see Section 6.4); otherwise, water would move inward by osmosis and cause the cells to burst. For animal cells, an isotonic solution is usually optimal, whereas for plant cells, an isotonic solution results in some loss of turgor **(Figure 6.11c).** The mechanisms by which animals balance their water content by regulating osmosis are discussed in Chapter 46.

Passive transport, driven by concentration gradients, accounts for much of the movement of water, ions, and many types of molecules into or out of cells. In addition, all cells transport some ions and molecules against their concentration gradients by active transport (see the next section).

Study Break

1. What conditions are required for osmosis to occur?
2. Explain the effect of a hypertonic solution that surrounds animal cells.

6.4 Active Transport

Many substances are pushed across membranes against their concentration gradients by active transport "pumps." Active transport concentrates molecules such as sugars and amino acids inside cells and pushes ions in or out of cells. Ion transport may contribute to a voltage difference across a membrane, called a *membrane potential*. It may also control osmotic pressures.

Active Transport Requires a Direct or Indirect Input of Energy Derived from ATP Hydrolysis

There are two kinds of active transport: primary and secondary. In **primary active transport**, the same protein that transports a substance also hydrolyzes ATP to power the transport directly. In **secondary active transport,** the transport is indirectly driven by ATP hydrolysis. That is, the transport proteins do not break down ATP; instead, the transporters use a favorable concentration gradient of ions, built up by primary active transport, as their energy source for active transport of a different ion or molecule.

Other features of active transport resemble facilitated diffusion (listed in Table 6.1). Both processes depend on membrane transport proteins, both are specific, and both can be saturated. The transport proteins are carrier proteins that change their conformation as they function.

Primary Active Transport Moves Positively Charged Ions across Membranes

The primary active transport pumps all move positively charged ions—H^+, Ca^{2+}, Na^+, and K^+—across membranes **(Figure 6.12).** The gradients of positive ions established by primary active transport pumps underlie functions that are absolutely essential for cellular life. For example, **H^+ pumps** (also called **proton pumps**) move hydrogen ions across membranes and push hydrogen ions across the plasma membrane from the cytoplasm to the cell exterior. The pumps of the plasma membrane (see Figure 6.12) temporarily bind a phosphate group removed from ATP during the pumping cycle. Proton pumps are not common in animals.

The **Ca^{2+} pump** (or **calcium pump**) is distributed widely among eukaryotes. It pushes Ca^{2+} from the cytoplasm to the cell exterior, and also from the cytosol into the vesicles of the endoplasmic reticulum (ER). As a result, Ca^{2+} concentration is typically high outside cells and inside ER vesicles and low in the cytoplasmic solution. This Ca^{2+} gradient is used universally among eukaryotes as a regulatory control of cellular activities as diverse as secretion, microtubule assembly, and muscle contraction; the latter is discussed further in Chapters 7 and 41.

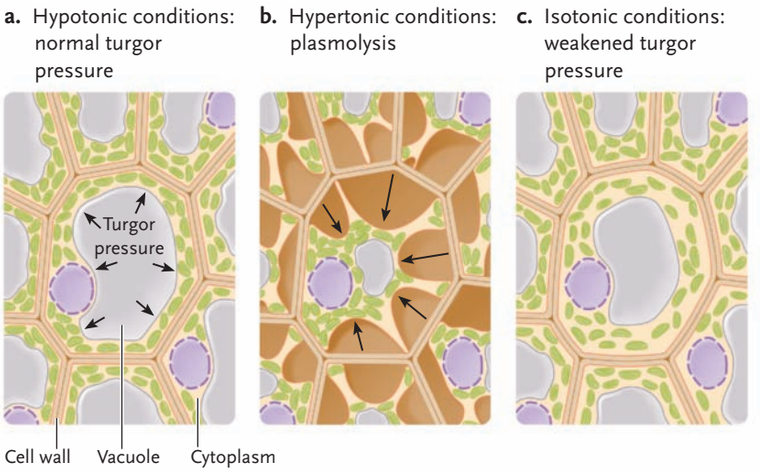


Figure 6.11
Effects of turgor pressure and plasmolysis in plants. **(a)** Plant cells developing normal turgor pressure, which keeps the cytoplasmic contents pressed against the cell walls. The pressure is developed by osmotic water flow into the large central vacuole. **(b)** Plant cells in plasmolysis, in which the cells have lost so much water due to outward osmotic flow that they have shrunk away from their walls. **(c)** Plant cells in an isotonic solution, which results in decreased water flow into the cell, shrinkage of the central vacuole, and some loss of turgor.

The **Na^+/K^+ pump** (or **sodium-potassium pump**), located in the plasma membrane, pushes 3 Na^+ out of the cell and 2 K^+ into the cell in the same pumping cycle. As a result, positive charges accumulate in excess outside the membrane, and the inside of the cell becomes negatively charged with respect to the outside. Voltage—an electrical potential difference—across the plasma membrane results in part from this difference in charge. It also results from the unequal distribution of ions across the membrane created by passive transport. The voltage across a membrane is called a **membrane potential;** it measures from about −50 to −200 millivolts (mV; 1 millivolt = 1/1000th of a volt), with the minus sign indicating that the charge inside the cell is negative versus the outside. In summary, there is both a concentration difference (of the ions) and an electrical charge difference on the two sides of the membrane, constituting what is called an **electrochemical gradient.** Electrochemical gradients store energy that is used for other transport mechanisms. For instance, the electrochemical gradient across the membrane is involved with the movement of ions associated with nerve impulse transmission (see Chapter 37).

Secondary Active Transport Moves Both Ions and Organic Molecules across Membranes

As noted earlier, secondary active transport pumps use the concentration gradient of an ion established by a primary pump as their energy source. For example, the

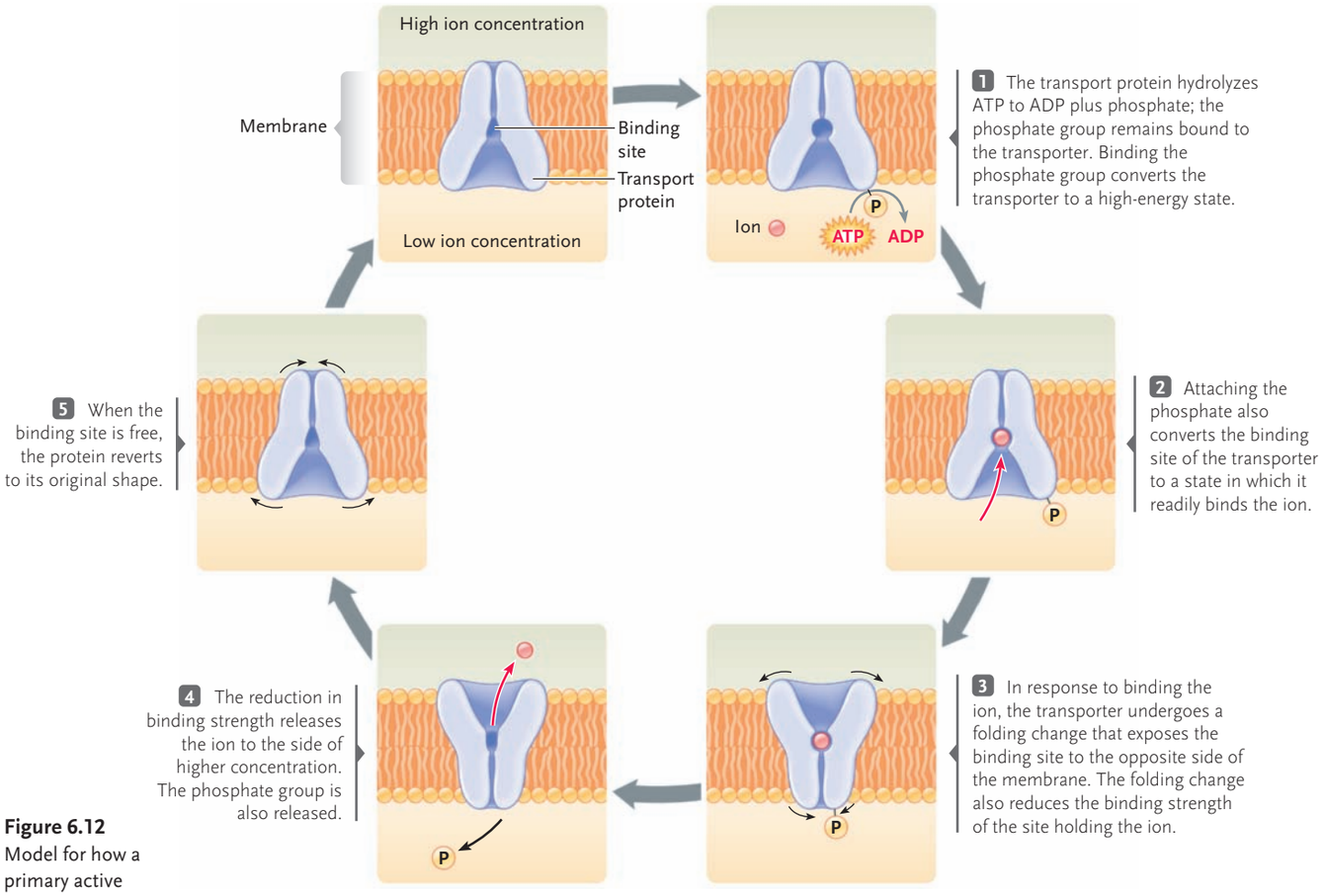


Figure 6.12
Model for how a primary active transport pump operates.

driving force for most secondary active transport in animal cells is the high outside/low inside Na^+ gradient created by the Na^+/K^+ pump. Also, in secondary active transport, the transfer of the solute across the membrane always occurs coupled with transfer of the ion that supplies the driving force.

Secondary active transport occurs by two mechanisms known as *symport* and *antiport* **(Figure 6.13).** In **symport** (also called **cotransport**), the solute moves through the membrane channel in the same direction as the driving ion. Sugars, such as glucose, and amino acids are examples of molecules actively transported into cells by symport. In **antiport** (also known as **exchange diffusion**), the driving ion moves through the membrane channel in one direction, providing the energy for the active transport of another molecule through the membrane in the opposite direction. In many cases, ions are exchanged by antiport. For example, in red blood cells, antiport is the mechanism used for the coupled movement of chloride and bicarbonate ions through a membrane channel; depending on the conditions, either chloride ions enter and bicarbonate ions leave the cells, or bicarbonate ions enter and chloride ions leave.

Active and passive transport move ions and smaller hydrophilic molecules across cellular membranes. Cells can also move much larger molecules or aggregates of molecules from inside to outside, or in the reverse direction, by including them in the inward or outward vesicle traffic of the cell. The mechanisms that carry out this movement—exocytosis and endocytosis—are discussed in the next section.

Study Break

1. What is active transport? What is the difference between primary and secondary active transport?
2. How is a membrane potential generated?

6.5 Exocytosis and Endocytosis

The largest molecules transported through cellular membranes by passive and active transport are in the size range of amino acids or monosaccharides such as

glucose. Eukaryotic cells import and export larger molecules by exocytosis and endocytosis (introduced in Section 5.3). The export of materials by exocytosis primarily carries secretory proteins and some waste materials from the cytoplasm to the cell exterior. Import by endocytosis may carry proteins, larger aggregates of molecules, or even whole cells from the outside into the cytoplasm. Exocytosis and endocytosis also contribute to the back-and-forth flow of membranes between the endomembrane system and the plasma membrane. Both exocytosis and endocytosis require energy; thus, both processes stop if the ability of a cell to make ATP is inhibited.

Exocytosis Releases Molecules to the Outside by Means of Secretory Vesicles

In exocytosis, secretory vesicles move through the cytoplasm and contact the plasma membrane **(Figure 6.14a).** The vesicle membrane fuses with the plasma membrane, releasing the contents of the vesicle to the cell exterior.

All eukaryotic cells secrete materials to the outside through exocytosis. For example, in animals, glandular cells secrete peptide hormones or milk proteins, and cells that line the digestive tract secrete mucus and digestive enzymes. Plant cells secrete carbohydrates by exocytosis to build a strong cell wall.

Endocytosis Brings Materials into Cells in Endocytic Vesicles

In endocytosis, proteins and other substances are trapped in pitlike depressions that bulge inward from the plasma membrane. The depression then pinches off as an endocytic vesicle. Endocytosis occurs in most eukaryotic cells by one of two distinct but related pathways. In the simplest of these mechanisms, **bulk-phase endocytosis** (sometimes called **pinocytosis,** meaning "cell drinking"), extracellular water is taken in together with any molecules that happen to be in solution in the water **(Figure 6.14b).** No binding by surface receptors occurs.

In the second endocytic pathway, **receptor-mediated endocytosis,** the target molecules to be taken in are bound to the outer cell surface by receptor proteins **(Figure 6.14c, d).** The receptors, which are integral proteins of the plasma membrane, recognize and bind only certain molecules—primarily proteins or other molecules carried by proteins—from the solution that surrounds the cell. After binding their target molecules, the receptors collect into a depression in the plasma membrane; this depression is called a **coated pit** because of the network of proteins (called **clathrin**) that coat and reinforce the cytoplasmic side. With the target molecules attached, the pits deepen and pinch free of the plasma membrane to form endocytic vesicles. Once in the cytoplasm, an endocytic vesicle rapidly loses its clathrin coat and may fuse with a lysosome. The enzymes within the lysosome then digest the contents of the vesicle, breaking them down into smaller molecules useful to the cell. These molecular products—for example, amino acids and monosaccharides—enter the cytoplasm by crossing the vesicle membrane via transport proteins. The membrane proteins are recycled to the plasma membrane.

Mammalian cells take in many substances by receptor-mediated endocytosis, including peptide hormones, antibodies, and blood proteins. The receptors that bind these substances to the plasma membrane are present in thousands to hundreds of thousands of copies. For example, a mammalian cell plasma membrane has about 20,000 receptors for *low-density lipoprotein (LDL)*. LDL, a complex of lipids and proteins, is the way cholesterol moves through the bloodstream. When LDL binds to its receptor on the membrane, it is taken into the cell by receptor-mediated endocytosis; then, by the steps described earlier, the LDL is broken down within the cell and cholesterol is released into the cytoplasm.

Some cells, such as certain white blood cells *(phagocytes)* in the bloodstream, or protists such as *Amoeba proteus,* can take in large aggregates of molecules, cell parts, or even whole cells by a process related to receptor-mediated endocytosis. The process, called **phagocytosis** (meaning "cell eating"), begins when surface receptors bind molecules on the substances to be

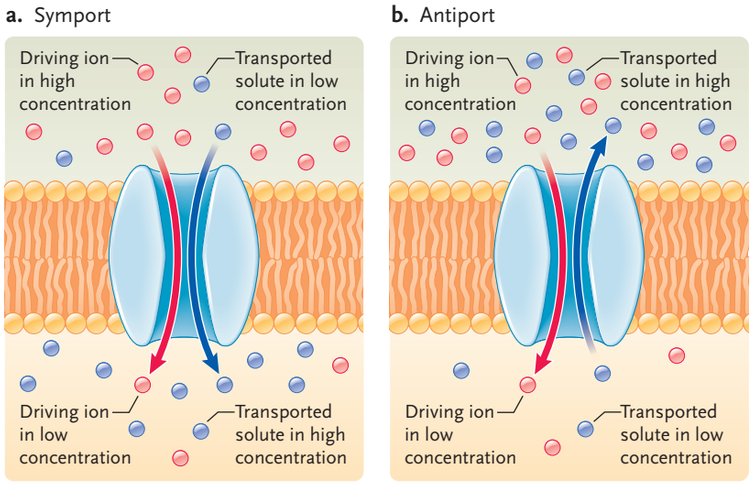
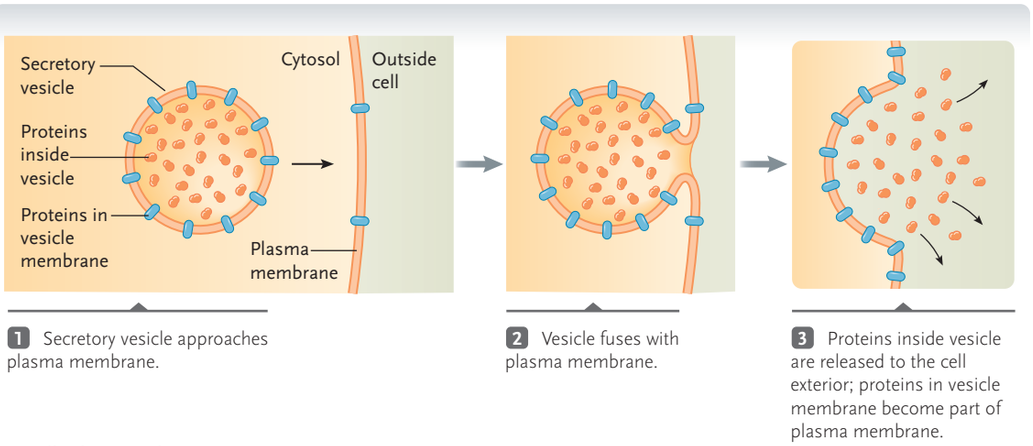


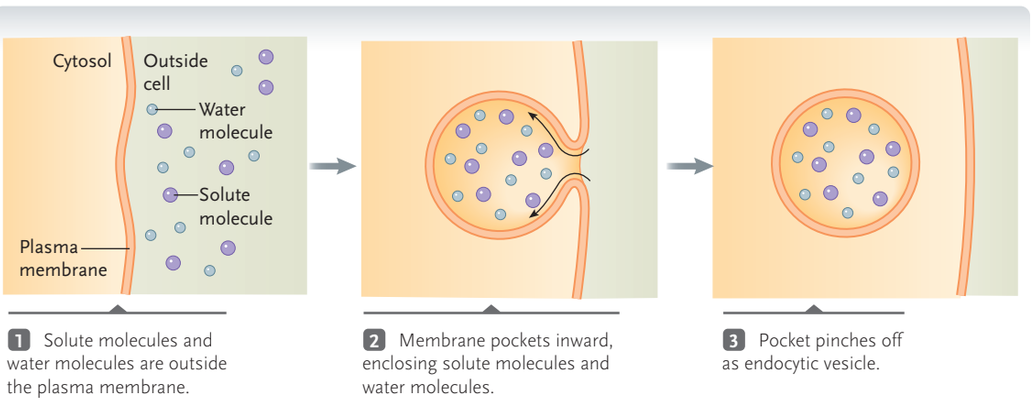
Figure 6.13
Secondary active transport, in which a concentration gradient of an ion is used as the energy source for active transport of a solute. **(a)** In symport, the transported solute moves in the same direction as the gradient of the driving ion. **(b)** In antiport, the transported solute moves in the direction opposite from the gradient of the driving ion.

Figure 6.14
Exocytosis and endocytosis. **(a)** Exocytosis. **(b)** Bulk-phase endocytosis. **(c)** Diagram and **(d)** electron micrographs of receptor-mediated endocytosis.

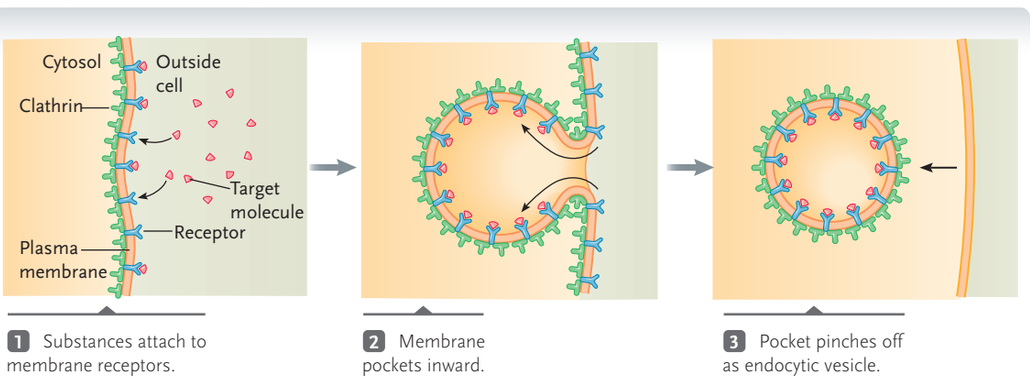
a. Exocytosis



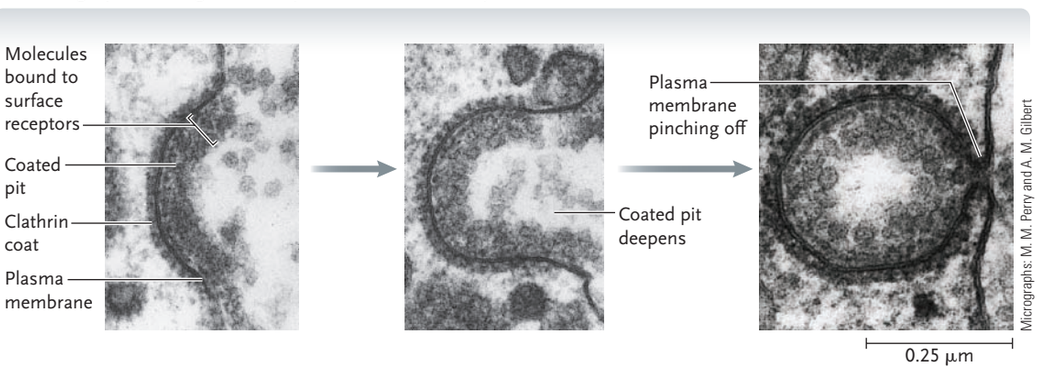
b. Bulk-phase endocytosis (pinocytosis)

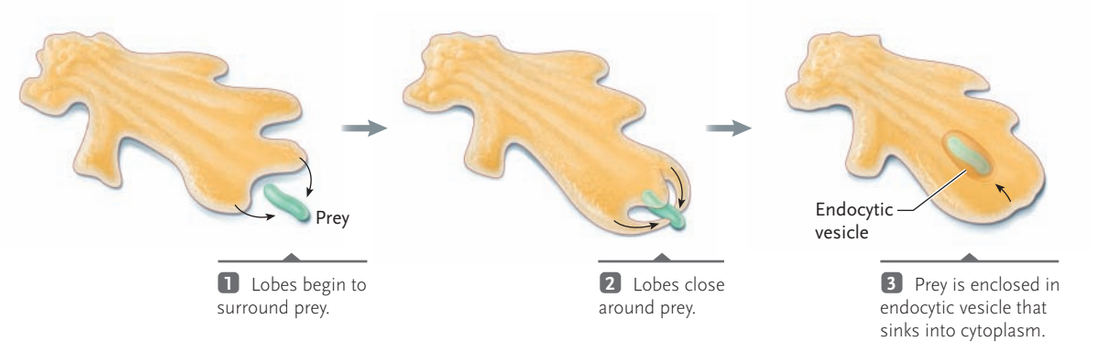


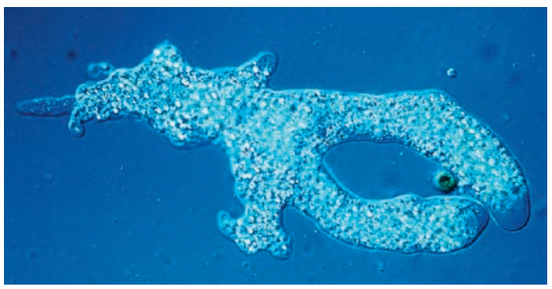
c. Receptor-mediated endocytosis



d. Micrographs of stages of receptor-mediated endocytosis shown in **c**







Mike Abbey/Visuals Unlimited

Figure 6.15
Phagocytosis, in which lobes of the cytoplasm extend outward and surround a cell targeted as prey. The micrograph shows the protist *Chaos carolinense* engulfing a single-celled alga *(Pandorina)* by phagocytosis (corresponding to step 2 in the diagram); white blood cells called phagocytes carry out a similar process in mammals.

taken in **(Figure 6.15).** Cytoplasmic lobes then extend, surround, and engulf the materials, forming a pit that pinches off and sinks into the cytoplasm as a large endocytic vesicle. The materials then are digested within the cell as in receptor-mediated endocytosis, and any remaining residues are sequestered permanently into storage vesicles or are expelled from cells by exocytosis as wastes.

The combined workings of exocytosis and endocytosis constantly cycle membrane segments between the internal cytoplasm and the cell surface. The balance of the two mechanisms maintains the surface area of the plasma membrane at controlled levels.

Thus, through the combined mechanisms of passive transport, active transport, exocytosis, and endocytosis, cells maintain their internal concentrations of ions and molecules and exchange larger molecules such as proteins with their surroundings. The next chapter explores cell communication through intercellular chemical messengers. Many of these messengers act through binding to specific proteins embedded in the plasma membrane.

Study Break

1. What is the mechanism of exocytosis?
2. What is the difference between bulk-phase endocytosis and receptor-mediated endocytosis?

Unanswered Questions

Research continues into the structure and assembly of membranes and the transport of substances across membranes by various mechanisms.

How do aquaporin channels function?

Peter Agre at Johns Hopkins University School of Medicine in Baltimore received a Nobel Prize in 2003 for his discovery of aquaporins. Aquaporins are specific channels for water transport across cell membranes. Problems with aquaporin function are associated with various human diseases, such as congenital cataracts, a form of diabetes, congestive heart failure, and brain edema (swelling caused by excess fluid). Therefore, a better understanding of aquaporin function could help facilitate the development of drugs to treat those diseases.

The ability to absorb or release water varies considerably among cells and tissues of an organism and between organisms. Since Agre's discovery, more than 200 different aquaporins have been identified in tissues from mammals, nonmammalian vertebrates, invertebrates, plants, and various microorganisms. Variation in aquaporin structure among these forms is likely responsible for their differences in function. Agre's research group is pursuing this issue by characterizing the structures of various aquaporins from humans, yeast, and bacteria to produce high-resolution models. Such models will be informative for designing experiments to further our understanding of the function of these channel molecules. Agre's group is also studying the regulation of the aquaporin genes to characterize tissue-specific production of aquaporins. The results of this line of investigation will provide a valuable piece of the puzzle concerning variation in water uptake.

Can endocytosis of nanotubes deliver therapeutic agents into cells?

The goal of many research groups has been the use of endocytosis to deliver therapeutic agents to diseased cells, such as cancer cells. There are many possible ways to deliver therapeutic agents to cells. Hongjie Dai, a physical chemist at Stanford University in California, has been working with carbon nanotubes, which are cylindrical carbon molecules with a diameter of just a few nanometers (about 50,000 times smaller than the width of a human hair) and up to several centimeters in length.

Dai's research team has shown that carbon nanotubes can carry proteins and DNA into cells. How are the carbon nanotubes taken into the cells? Knowing the route is important for determining what kinds of chemical bonds will be needed to attach therapeutic agents to the carbon nanotubes. For example, endocytosis produces vesicles that can fuse with lysosomes. Therefore, if carbon nanotubes are taken up by endocytosis, then the drug or DNA being delivered could be attached to the nanotubes by disulfide bonds because those bonds would readily be broken by the acidic environment of the lysosome, thereby releasing the agent.

Dai's group has evidence that carbon nanotubes are taken into cells by endocytosis. Endocytosis requires energy in the form of either ATP or heat, and when they cooled the cell cultures or treated them with an inhibitor that stopped ATP production, the cells could no longer take in carbon nanotubes.

Future research will focus on use of carbon nanotubes to deliver anticancer agents specifically to cancer cells in tissue culture. Undoubtedly, much work will be needed to produce an efficient method for that delivery, as well as an effective way to release and activate the anticancer agent within the cell. If success is forthcoming with tissue culture systems, the protocols will be moved to model organisms for cancer and eventually to humans for clinical trials.

Peter J. Russell

Review

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6.1 Membrane Structure

- Both membrane phospholipids and membrane proteins have hydrophobic and hydrophilic regions, giving them dual solubility properties.
- Membranes are based on a fluid phospholipid bilayer, in which the polar regions of the phospholipids lie at the surfaces of the bilayer and their nonpolar tails associate together in the interior (Figures 6.2–6.5).
- Membrane proteins are suspended individually in the bilayer, with their hydrophilic regions at the membrane surfaces and their hydrophobic regions in the interior (Figures 6.4 and 6.5).
- The lipid bilayer forms the structural framework of membranes and serves as a barrier that prevents the passage of most water-soluble molecules.
- Proteins embedded in the phospholipid bilayer perform most membrane functions, including transport of selected hydrophilic substances, recognition, signal reception, cell adhesion, and metabolism.
- Integral membrane proteins are embedded deeply in the bilayer and cannot be removed without dispersing the bilayer. Peripheral membrane proteins associate with membrane surfaces (Figure 6.5).
- Membranes are asymmetric—that is, different proportions of phospholipid types occur in the two bilayer halves.

Animation: Lipid bilayer organization

Animation: Cell membranes

6.2 Functions of Membranes in Transport: Passive Transport

- Passive transport depends on diffusion, the net movement of molecules with a concentration gradient, from a region of higher concentration to a region of lower concentration. Passive transport does not require cells to expend energy (Table 6.1).
- Simple diffusion is the passive transport of substances across the lipid portion of cellular membranes with their concentration gradients. It proceeds most rapidly for small molecules that are soluble in lipids (Table 6.1).

- Facilitated diffusion is the passive transport of substances at rates higher than predicted from their lipid solubility. It depends on membrane proteins, follows concentration gradients, is specific for certain substances, and becomes saturated at high concentrations of the transported substance (Figure 6.8 and Table 6.1).
- Most proteins that carry out facilitated diffusion of ions are controlled by "gates" that open or close their transport channels (Figure 6.8).

Interaction: Selective permeability

Animation: Passive transport

6.3 Passive Water Transport and Osmosis

- Osmosis is the net diffusion of water molecules across a selectively permeable membrane in response to differences in the concentration of solute molecules (Figure 6.9). Water moves from hypotonic (lower concentrations of solute molecules) to hypertonic solutions (higher concentrations of solute molecules). When the solutions on each side are isotonic, there is no net osmotic movement of water in either direction (Figure 6.10).

Animation: Solute concentration and osmosis

Interaction: Tonicity and water movement

6.4 Active Transport

- Active transport moves substances against their concentration gradients and requires cells to expend energy. It depends on membrane proteins, is specific for certain substances, and becomes saturated at high concentrations of the transported substance (Table 6.1).
- Active transport proteins are either primary transport pumps, which directly use ATP as their energy source, or secondary transport pumps, which use favorable concentration gradients of positively charged ions, created by primary transport pumps, as their energy source for transport (Figure 6.12).
- Secondary active transport may occur by symport, in which the transported substance moves in the same direction as the concentration gradient used as the energy source, or by antiport, in which the transported substance moves in the direction opposite to the concentration gradient used as the energy source (Figure 6.13).

Animation: Active transport

6.5 Exocytosis and Endocytosis

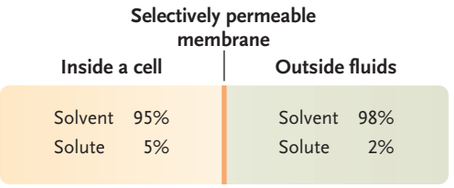
- Large molecules and particles are moved out of and into cells by exocytosis and endocytosis. The mechanisms allow substances to leave and enter cells without directly passing through the plasma membrane (Figure 6.14).
- In exocytosis, a vesicle carrying secreted materials contacts and fuses with the plasma membrane on its cytoplasmic side. The fusion introduces the vesicle membrane into the plasma membrane and releases the vesicle contents to the cell exterior (Figure 6.14a).
- In endocytosis, materials on the cell exterior are enclosed in a segment of the plasma membrane that pockets inward and pinches off on the cytoplasmic side as an endocytic vesicle. Endocytosis occurs in two overall forms, bulk-phase (pinocytosis) and receptor-mediated endocytosis. Most of the materials that enter cells are digested into molecular subunits small enough to be transported across the vesicle membranes (Figures 6.14b–d).

Animation: Phagocytosis

Questions

Self-Test Questions

1. In the fluid mosaic model:
   a. plasma membrane proteins orient their hydrophilic sides toward the internal bilayer.
   b. phospholipids often flip-flop between the inner and outer layers.
   c. the mosaic refers to proteins attached to the underlying cytoskeleton.
   d. the fluid refers to the phospholipid bilayer.
   e. the mosaic refers to the symmetry of the internal membrane proteins and sterols.
2. Which of the following statements is *false*? Proteins in the plasma membrane can:
   a. transport proteins.
   b. synthesize polypeptides.
   c. recognize self versus foreign molecules.
   d. allow adhesion between the same tissue cells or cells of different tissues.
   e. combine with lipids or sugars to form complex macromolecules.
3. The freeze-fracture technique demonstrated:
   a. that the plasma membrane is a bilayer with individual proteins suspended in it.
   b. that the plasma membrane is fluid.
   c. the different functions of membrane proteins.
   d. that proteins are bound to the cytoplasmic side but not embedded in the lipid bilayer.
   e. the direction of movement of solutes through the membrane.
4. In the following diagram, assume that the setup was left unattended. Which of the following statements is correct?



   a. The relation of the cell to its environment is isotonic.
   b. The cell is in a hypertonic environment.
   c. The net flow of solvent is into the cell.
   d. The cell will soon shrink.
   e. Diffusion can occur here but not osmosis.
5. Which of the following statements is true for the diagram in question 4?
   a. The net movement of solutes is into the cell.
   b. There is no concentration gradient.
   c. There is a potential for plasmolysis.
   d. The solvent will move against its concentration gradient.
   e. If this were a plant cell, turgor pressure would be maintained.
6. Using the principle of diffusion, a dialysis machine removes waste solutes from a patient's blood. Imagine blood runs through a cylinder wherein diffusion can occur across an artificial selectively permeable membrane to a saline solution

on the other side. Which of the following statements is correct?
   a. Solutes move from lower to higher concentration.
   b. The concentration gradient is lower in the patient's blood than in the saline solution wash.
   c. The solutes are transported through a symport in the blood cell membrane.
   d. The saline solution has a lower concentration gradient of solute than the blood.
   e. The waste solutes are actively transported from the blood.

7. A characteristic of carrier molecules in a primary active transport pump is that:
   a. they cannot transport a substance and also hydrolyze ATP.
   b. they retain their same shape as they perform different roles.
   c. their primary role is to move negatively charged ions across membranes.
   d. they move Na^+ into a neural cell and K^+ out of the same cell.
   e. They act to establish an electrochemical gradient.

8. A driving ion moving through a membrane channel in one direction gives energy to actively transport another molecule in the opposite direction. What is this process called?
   a. facilitated diffusion
   b. exchange diffusion
   c. symport transport
   d. primary active transport pump
   e. cotransport

9. Phagocytosis illustrates which phenomenon?
   a. receptor-mediated endocytosis
   b. bulk-phase endocytosis
   c. exocytosis
   d. pinocytosis
   e. cotransport

10. Place in order the following events of receptor-mediated endocytosis.
   (1) Clathrin coat disappears.
   (2) Receptors collect in a coated pit covered with clathrin on the cytoplasmic side.
   (3) Receptors recognize and bind specific molecules.
   (4) Endocytic vesicle may fuse with lysosome while receptors are recycled to the cell surface.
   (5) Pits deepen and pinch free of plasma membrane to form endocytic vesicles.
   a. 4, 1, 2, 5, 3
   b. 2, 1, 3, 5, 4
   c. 3, 2, 5, 1, 4
   d. 4, 1, 5, 2, 3
   e. 3, 1, 2, 4, 5

Questions for Discussion

1. The bacterium *Vibrio cholerae* causes cholera, a disease characterized by severe diarrhea that may cause infected people to lose up to 20 *L* of fluid in a day. The bacterium enters the body when someone drinks contaminated water. It adheres to the intestinal lining, where it causes cells of the lining to release sodium and chloride ions. Explain how this release is related to the massive fluid loss.
2. Irrigation is widely used in dryer areas of the United States to support agriculture. In those regions, the water evaporates and leaves behind deposits of salt. What problems might these salt deposits cause for plants?
3. In hospitals, solutions of glucose with a concentration of 0.3 *M* can be introduced directly into the bloodstream of patients without tissue damage by osmotic water movement. The same is true of NaCl solutions, but these must be adjusted to 0.15 *M* to be introduced without damage. Explain why one solution is introduced at 0.3 *M* and the other at 0.15 *M*.

Experimental Analysis

Design an experiment to determine the concentration of NaCl (table salt) in water that is isotonic to potato cells. Use only the following materials: a knife, small cookie cutters, and a balance.

Evolution Link

What evidence would convince you that membranes and active transport mechanisms evolved from an ancestor common to both prokaryotes and eukaryotes?

How Would You Vote?

The ability to detect mutant genes that cause severe disorders raises bioethical questions. Should we encourage the mass screening of prospective parents for mutant genes that cause cystic fibrosis? Should society encourage women to give birth only if their child will not develop severe medical problems? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.