Nicotine Addiction and Cell Biology

Receptors and Reception

In the United States, about 23% of adults and 30% of adolescents smoke cigarettes. In many nations, these figures are even higher. Yet the effects of smoking on health—such as greatly increased risks of developing heart disease, cancer, stroke, and lung disease—are well known. Why, then, do so many people smoke?

The answer is that they are addicted to the nicotine in cigarettes. Cell biology can explain how an enjoyable habit becomes a physical dependency.

Tobacco used for smoking comes from the plant *Nicotiniana tabacum* and has been linked to cancer since the mid-1700s. Recognition of smoking tobacco as an addictive behavior is more recent. A 1964 Surgeon General's report distinguished between "addicting" and "habituating" drugs and defined "addiction" as causing intoxication. On this basis, cigarette smoking was considered merely habituating, a definition that tobacco companies promoted for years. The 1964 report also linked smoking to cancer and lung disease, which frightened some of the 40% of the population that then smoked into quitting. On a worldwide basis, even today, cigarette smoking directly or indirectly causes about 20% of all deaths.

More recent Surgeon General's reports reflect accumulating scientific evidence on the dangers of smoking. The 1988 report stated clearly that nicotine causes addiction, and the 1994 report calls smoking a "totally preventable public health tragedy." It was also in 1994 that the Food and Drug Administration began investigating the possibility of regulating tobacco as a drug, because of its ability to addict. Today, the director of the National Institute on Drug Abuse calls all drug addiction, including nicotine addiction, "a chronic, relapsing brain disorder characterized by compulsive drug seeking." That's a far cry from the billboards depicting happy smokers that once boasted, "Alive with pleasure!"

According to the Diagnostic and Statistical Manual of Mental Disorders, a person addicted to tobacco:

1. must smoke more to attain the same effects (tolerance) over time;
2. experiences withdrawal symptoms when smoking stops, including weight gain, difficulty concentrating, insomnia, restlessness, anxiety, depression, slowed metabolism, and lowered heart rate;
3. smokes more often and for longer than intended;

To increase sales, cigarette companies used ads to suggest smoking was actually good for you.

The cycle of nicotine addiction

- Cigarette smoke inhaled.
- Nicotine reaches brain cells (neurons).
- Nicotine binds to receptors on neurons' cell membranes.
- Positive ions can travel through receptors into the neurons.
- Ion influx leads to dopamine release.
- Dopamine causes feelings of pleasure...
- ...and suppresses withdrawal symptoms.
- Drug-seeking behavior reinforced.

Nicotine is addictive because of effects at the surface of cells. Those effects produce a cycle of nicotine addiction.
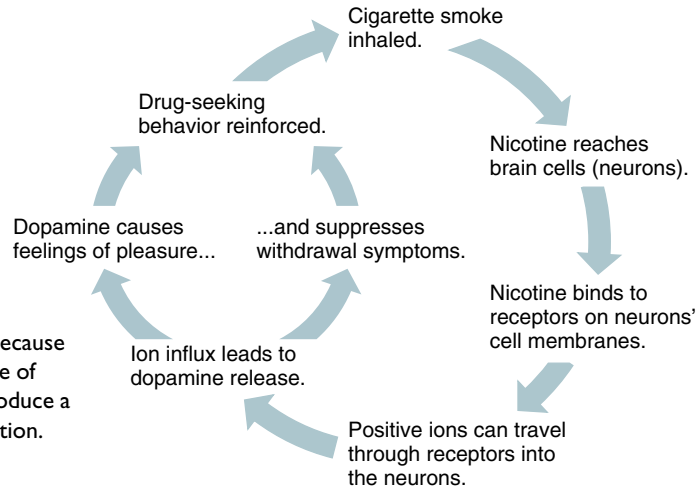
4. spends considerable time obtaining cigarettes, and feels compelled to do so;
5. devotes less time to other activities;
6. continues to smoke despite knowing the dangers;
7. wants to stop, but cannot easily do so.

Cigarette smoke contains about 4,000 different chemicals, including carbon monoxide and cyanide. It is the nicotine that causes the addiction, and the addiction supplies enough of the other chemicals to gradually destroy health. Nicotine reaches the brain within seconds of the first inhalation, as it also speeds heart rate and constricts blood vessels, raising blood pressure.

Tracing nicotine's effects on brain cells (neurons) introduces several concepts discussed in this chapter. An activated form of nicotine binds to proteins that form structures called nicotinic receptors that are parts of the cell membranes of certain neurons. These neurons are in a brain region called the nucleus accumbens. The receptors normally bind the neurotransmitter acetylcholine. When sufficient nicotine binds, a channel within the receptor opens and admits positively charged ions into the neuron.

When a certain number of ions enter, the neuron is stimulated to release the neurotransmitter dopamine from its other end. Dopamine provides the pleasurable feelings associated with smoking. Addiction stems from two sources—seeking the good feelings of releasing all that dopamine, and avoiding painful withdrawal symptoms.

Binding nicotinic receptors isn't the only effect of nicotine on the brain. When a smoker increases the number of cigarettes smoked, the number of nicotinic receptors on the brain cells increases. This happens because the way that the nicotine binds impairs the recycling of receptor proteins, so that new receptors are produced faster than they are taken apart. However, after a period of steady nicotine exposure, many of the receptors malfunction and no longer admit the positive ions that trigger nerve transmission. This may be why as time goes on it takes more nicotine to produce the same physical effects.

Cigarette smoke contains about 4,000 different chemicals, including carbon monoxide and cyanide.

Experiments with mice demonstrate that it is nicotine's binding to these receptors that reinforces drug-seeking behavior, reinforcing addiction. Mice that lack these receptors (but are otherwise normal) do not push a lever that administers nicotine intravenously to them, as will mice that have the receptors.

Many questions remain concerning the biological effects of tobacco smoking. Why don't lab animals experience withdrawal? Why do people who have successfully stopped smoking often start again 6 months later, even though withdrawal symptoms ease within 3 weeks of quitting? Why do some people become addicted easily, yet others smoke only a few cigarettes a day and can stop anytime?

While scientists try to answer these questions, society must deal with questions of rights and responsibilities that cigarette smoking causes.

How Does the Cell Membrane Control Cell Function?

Cells must regulate what enters and leaves them; maintain their specific shapes; and interact with other cells. The cell membrane and underlying cytoskeleton make these functions possible.

The 2-year-old's health appeared to be returning mere hours after the liver transplant. Yet, cells of the immune system had already detected the new organ and, interpreting it as "foreign," began to produce molecules to attack it. Even though the donor's liver was carefully "matched" to the little girl—the pattern and types of molecules on the surfaces of its cells was very similar to that on the cells of her own liver cells—the match was not perfect. A rejection reaction would soon destroy the liver and the little girl would need another transplant to survive.

Rejection of a transplanted organ illustrates the importance of cell surfaces in the coordinated functioning of a multicellular organism. The cell surface is one component of a cellular architecture of sorts. It includes structures that give a cell its particular three-dimensional shape and topography, help determine the locations and movements of organelles and biochemicals within the cell, and participate in the cell's interactions with other cells and the extracellular environment.

The cellular architecture consists of surface molecules embedded in the cell membrane, which is the outer covering of a cell. Just beneath the cell membrane protein fibers form part of the cell's interior scaffolding, or **cytoskeleton.** Together, the cell surface and cytoskeleton form a dynamic structural framework that helps to distinguish one cell from another and provide the means for a cell to perform its unique functions (fig. 4.1). The

FIGURE 4.1
Cellular Architecture.
A white blood cell's inner skeleton and surface features enable it to move in the body and to recognize "foreign" cell surfaces—such as those of transplanted tissue. This T lymphocyte rejects foreign tissue.
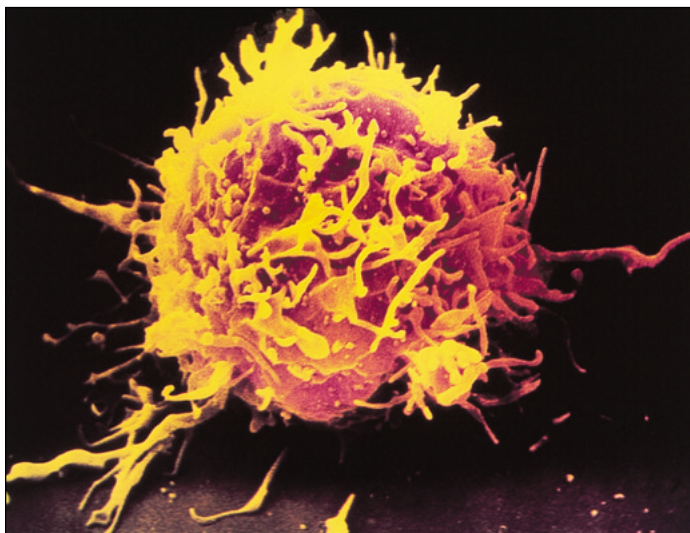
various components of the cellular architecture must communicate and interact for the cell to carry out the processes of life.

At a conference where most participants do not know one another, name tags are often used to identify people. All cells also have name tags in the form of carbohydrates, lipids, and proteins that protrude from their surfaces. Some surface molecules distinguish cells of different species, like company affiliations on name tags. Other surface structures distinguish individuals within a species.

Surface structures also distinctively mark cells of different tissues in an individual, so that a bone cell's surface is different from that of a nerve cell or a muscle cell. Surface differences between cell types are particularly important during the development of an embryo, when different cells sort and grow into specific tissues and organs.

The special characteristics of different cell types are shaped in part by the substances that enter and leave them. The cell membrane monitors the movements of molecules in and out of the cell. The chemical characteristics and the pattern of molecules that are part of a cell membrane determine which substances can cross it. Archaean cells have interior membranes, and in eukaryotic cells, membranes form organelles.
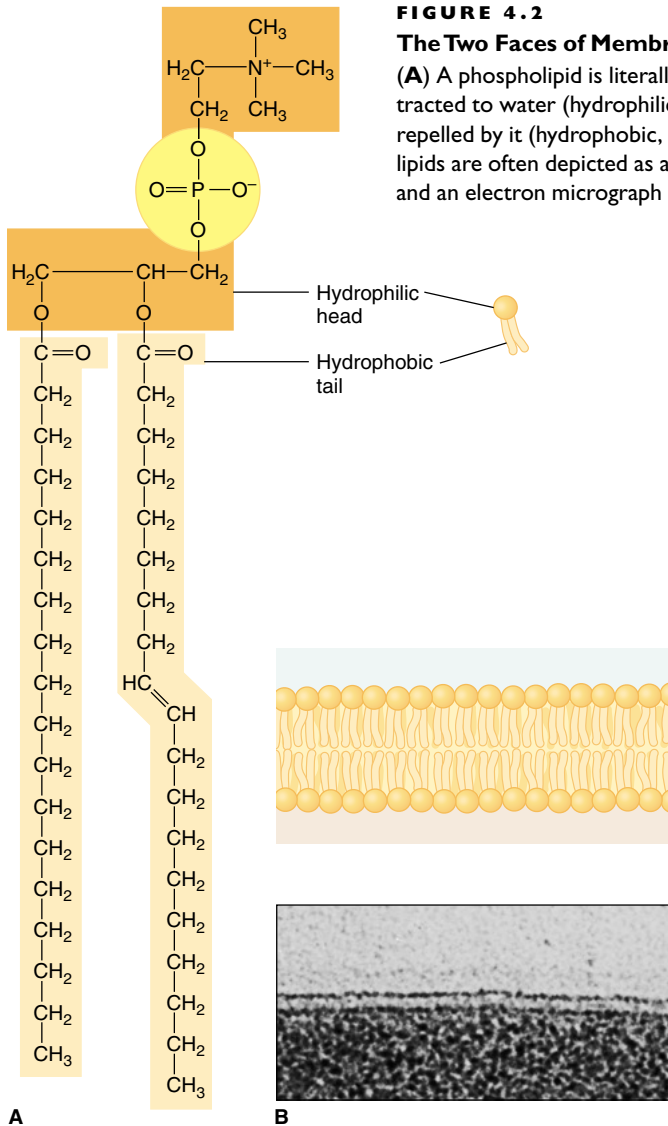
What Is the Structure of a Cell Membrane?

The structure of a biological membrane is possible because of a chemical property of the phospholipid molecules that compose it. **Phospholipids** are lipid molecules bonded to phosphate groups (PO_4, a phosphorus atom bonded to four oxygen atoms). The phosphate end of a phospholipid molecule is attracted to water (hydrophilic, or "water-loving"); the other end, consisting of two fatty acid chains, is repelled by water (hydrophobic, or "water-fearing"). Because of these water preferences, phospholipid molecules in water spontaneously arrange into the most energy-efficient organization, a **phospholipid bilayer.** In this two-layered, sandwichlike structure, the hydrophilic surfaces are on the outsides of the "sandwich," exposed to the watery medium outside and inside the cell. The hydrophobic surfaces face each other on the inside of the "sandwich," away from water (fig. 4.2).

Cell membranes consist of phospholipid bilayers and the proteins and other molecules embedded in them and extending from them (fig. 4.3). The hydrophobic interior keeps out most substances dissolved in water. However, some proteins embedded in the phospholipid bilayer create passageways through which water-soluble molecules and ions pass. Other proteins are carriers, transporting substances across the membrane.

Proteins within the oily phospholipid bilayer can move laterally within the layer, sometimes at remarkable speed. Because of this movement, the protein-phospholipid bilayer is often called a fluid mosaic.

One way to classify membrane proteins is by their location in the phospholipid bilayer. Membrane proteins may lie completely within the phospholipid bilayer or traverse the membrane to extend out of one or both sides. In animal cells, some membrane proteins, called glycoproteins, contain branchlike carbohydrate molecules which protrude from the membrane's outer surface.

FIGURE 4.2

The Two Faces of Membrane Phospholipids.

(**A**) A phospholipid is literally a two-faced molecule, with one end attracted to water (hydrophilic, or "water-loving") and the other repelled by it (hydrophobic, or "water-fearing"). Membrane phospholipids are often depicted as a circle with two tails. (**B**) A depiction and an electron micrograph of a phospholipid bilayer.

A

B

The proteins and glycoproteins that jut from the cell membrane contribute to the surface characteristics that are so important to a cell's interactions with other cells.

The functions of membrane proteins are related to their locations within the phospholipid bilayer. We saw in the case of transplant rejection that one function of cell membrane proteins is to establish a cell's surface as "self." Some membrane proteins exposed on the outer face of the membrane are receptors, binding outside molecules and triggering cascades of chemical reactions in the cell that lead to a specific response. Other membrane proteins enable specific cell types to stick to each other, making cell-to-cell interactions possible. Table 4.1 lists functions of membrane proteins.

TABLE 4.1   Types of Membrane Proteins

PROTEIN TYPE	FUNCTION
Transport proteins	Move substances across membranes
Cell surface proteins	Establish self
Cellular adhesion molecules	Enable cells to stick to each other
Receptor proteins	Receive and transmit messages into a cell

FIGURE 4.3

Anatomy of a Cell Membrane.

In a cell membrane, mobile proteins are embedded throughout a phospholipid bilayer, producing a somewhat fluid structure. An underlying mesh of protein fibers supports the cell membrane. Jutting from the animal cell membrane's outer face are carbohydrate molecules linked to proteins (glycoproteins) and lipids (glycolipids). The typical plant cell is surrounded by a cell wall, a network of cellulose fibers.
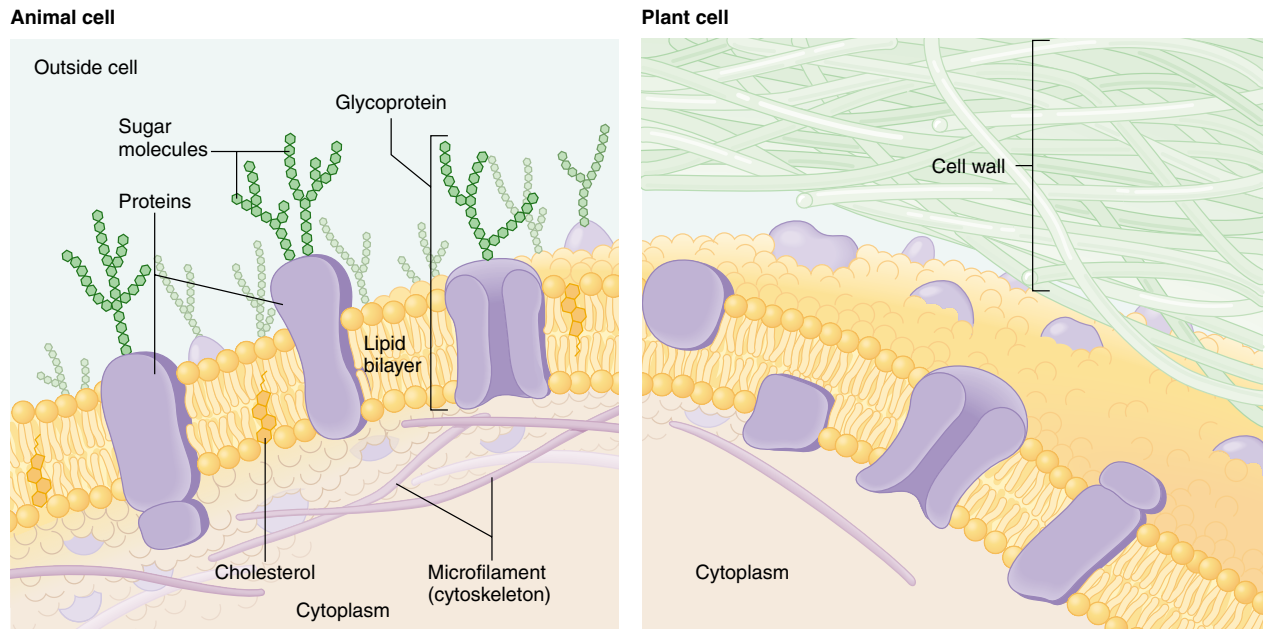
Cell membranes have specific protein/phospholipid ratios, and disruption of the ratio can affect health. For example, the cell membranes of certain cells that support nerve cells are about three-quarters myelin, a lipid. The cells enfold nerve cells in tight layers, wrapping their fatty cell membranes into a sheath that provides the insulation that speeds nerve impulse transmission. In multiple sclerosis, the cells coating the nerves that lead to certain muscles lack myelin. The resulting blocked neural messages to muscles impair vision and movement and cause numbness and tremor. In Tay-Sachs disease, the reverse happens. Cell membranes accumulate excess lipid, and nerve cells cannot transmit messages to each other and to muscle cells. An affected child gradually loses the ability to see, hear, and move.

4.1 MASTERING CONCEPTS

1. What are some functions of the cell surface?
2. What types of molecules make up a cell membrane?
3. How are the components of a cell membrane organized?
4. How do the locations of membrane proteins determine their functions?
5. How do membranes differ in different cell types?

OLC

How Do Substances Cross Membranes?

Specialized cells function as they do only if certain molecules and ions are maintained at certain levels inside and outside of them. The cell membrane oversees these vital concentration differences. Before considering how cells control which substances enter and leave, recall that an **aqueous solution** is a homogeneous mixture of a substance dissolved in water. The dissolved material is the **solute,** and the liquid in which it is dissolved is the **solvent.** Concentration refers to the relative number of one kind of molecule compared to the total number of molecules present, and it is usually given in terms of the solute. When solute concentration is high, the proportion of solvent (water) present is low, and the solution is concentrated. When solute concentration is low, solvent is proportionately high, and the solution is dilute.

Diffusion Moves Substances from High to Low Concentration   The cell membrane is choosy, or selectively permeable—that is, some molecules can pass freely through the membrane (either between the molecules of the phospholipid bilayer or through protein-lined channels), while others cannot. For example, oxygen (O_2), carbon dioxide (CO_2), and water (H_2O) freely cross cell and other biological membranes. They do so by a process called **diffusion,** which is the movement of a substance from a region where it is more concentrated to a region where it is less concentrated, without using energy (fig 4.4). Diffusion occurs because molecules are in constant motion, and they move so that two regions of differing concentration tend to become equal. Heat increases diffusion by increasing the rate of colli-

sions between molecules. An easy way to observe diffusion is to place a tea bag in a cup of hot water. Compounds in the tea leaves dissolve gradually and diffuse throughout the cup. The tea is at first concentrated near the bag, but the brownish color eventually spreads to create a uniform brew.

The natural tendency of a substance to move from where it is highly concentrated to where it is less so is called "moving down" or "following" its **concentration gradient.** A gradient is a general term that refers to a difference in some quality between two neighboring regions. Gradients may be created by concentration, electrical, pH, and pressure differences. Ions such as sodium (Na^+) and potassium (K^+) establish electrical gradients.

Molecules crossing a membrane because of this natural tendency to travel from higher to lower concentration is called simple diffusion because it does not require energy or a carrier molecule. Simple diffusion eventually reaches a point where the concentration of the substance is the same on both sides of the membrane. After this, molecules of the substance continue to flow randomly back and forth across the membrane at the same rate, so that the concentration remains equal on both sides. This point of equal movement back and forth is called **dynamic equilibrium.**

To envision dynamic equilibrium, picture a party taking place in two rooms. Everyone has arrived, and no one has yet left. People walk between the rooms in a way that maintains the same number of partiers in each room, but the specific occupants change. The party is in dynamic equilibrium.

The Movement of Water Is Osmosis   The fluids that continually bathe cells of multicellular organisms consist of molecules and ions dissolved in water. Because cells are constantly exposed to water, it is important to understand how a cell regulates water entry. If too much water enters a cell, it swells; if too much water leaves, it shrinks. Either response may affect a cell's ability to function. Movement of water across biological membranes by simple diffusion is called **osmosis.** The concentration of dissolved substances inside and outside the cell determines the direction and intensity of movement.

In osmosis, water is driven to move because the membrane is impermeable to the solute, and the solute concentrations differ on each side of the membrane (fig. 4.5). Water moves across the

FIGURE 4.4
Diffusion.
Molecules and atoms collide with each other, spreading out to have the same volume of space around each one. Diffusion always results in molecules or atoms moving from regions of high concentration toward low until equilibrium is reached.
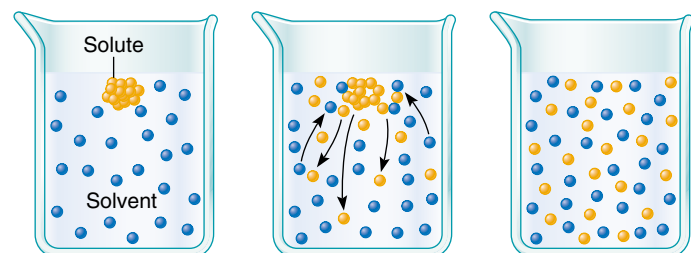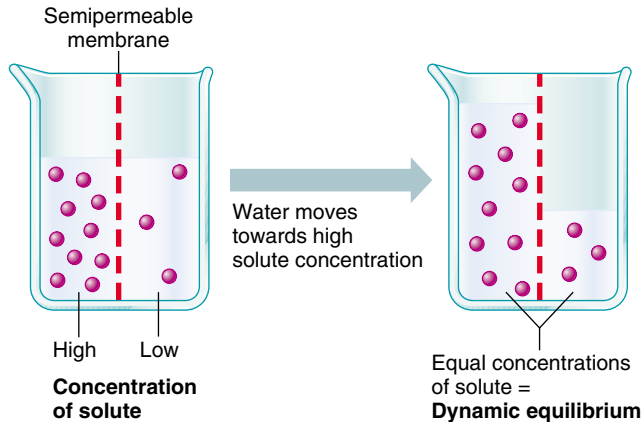
FIGURE 4.5
Osmosis.

An artificial membrane dividing a beaker demonstrates osmosis by permitting water to pass from one chamber to another, but preventing large salt molecules from doing the same. Water will flow from an area of low salt (solute) concentration towards an area of high salt concentration. Eventually, the volume on each side of the membrane will be different, but the final concentrations (amount of solute per unit of volume) will be the same. Dynamic equilibrium is reached when there is no tendency for water to flow in either direction.

FIGURE 4.6
Diffusion Affects Cell Shape.

A red blood cell changes shape in response to changing plasma solute concentrations. (**A**) A human red blood cell is normally isotonic to the surrounding plasma. When water enters and leaves the cell at the same rate, the cell maintains its shape. (**B**) When the salt concentration of the plasma increases, water leaves the cells to dilute the outside solute faster than water enters the cell. The cell shrinks. (**C**) When the salt concentration of the plasma decreases relative to the salt concentration inside the cell, water flows into the cell faster than it leaves. The cell swells, and may even burst.

membrane in the direction that dilutes the solute on the side where it is more concentrated.

Variants of the word "tonicity" are used to describe osmosis in relative terms. Tonicity refers to the differences in solute concentration in two compartments separated by a semipermeable membrane. A cell interior is **isotonic** to the surrounding fluid when solute concentrations are the same within and outside the cell. In this situation, there is no net flow of water, a cell's shape does not change, and salt concentration is ideal for enzyme activity.
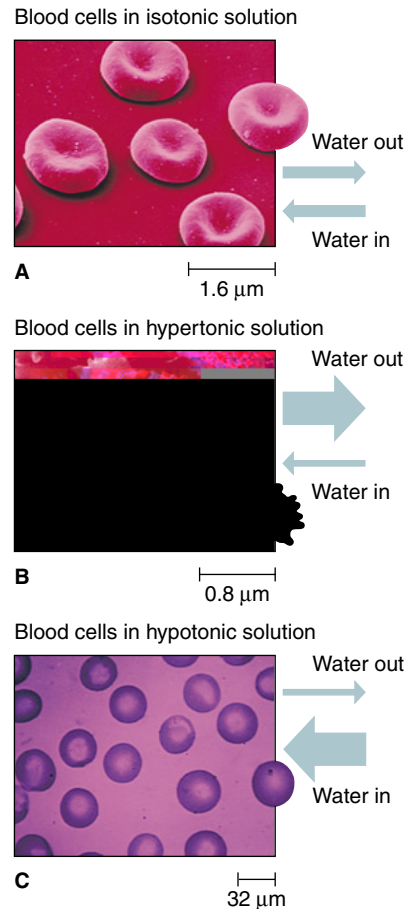
Disrupting a cell's isotonic state changes its internal environment and shape as water rushes in or leaks out. If a cell is placed in a solution in which the concentration of solute is lower than it is inside the cell, water enters the cell to dilute the higher solute concentration there. In this situation, the solution outside the cell is **hypotonic** to the inside of the cell. The cell swells. In the opposite situation, if a cell is placed in a solution in which the solute concentration is higher than it is inside the cell, water leaves the cell to dilute the higher solute concentration outside. In this case, the outside is **hypertonic** to the inside. This cell shrinks.

Hypotonic and hypertonic are relative terms and can refer to the surrounding solution or to the solution inside the cell. It may help to remember that *hyper* means "over," *hypo* means "under," and *iso* means "the same." A solution in one region may be hypotonic or hypertonic to a solution in another region.

The effects of immersing a cell in a hypertonic or hypotonic solution can be demonstrated with a human red blood cell, which is normally suspended in an isotonic solution called plasma (fig. 4.6). In this state, the cell is doughnut-shaped, with a central indentation. Placing a red blood cell in a hypertonic solution draws water out of the cell, and it shrinks. Placing the cell in a hypotonic solution has the opposite effect. Because

there are more solutes inside the cell, water flows into the cell, causing it to swell. Size changes caused by osmosis in plant cells are less dramatic because of the cell wall.

Because shrinking and swelling cells may not function normally, unicellular organisms can regulate osmosis to maintain their shapes. Many cells alter membrane transport activities, changing the concentrations of different solutes on either side of the cell membrane, in a way that drives osmosis in a direction that maintains the cell's shape. This enables some single-celled organisms that live in the ocean to remain isotonic to their salty environment, keeping their shapes. In contrast, the paramecium, a single-celled organism that lives in ponds, must work to maintain its oblong form. A paramecium contains more concentrated solutes than the pond, so water tends to flow into the organism. A

FIGURE 4.7
Aquatic Organisms Must Pump Water.
Paramecia keep their shapes with contractile vacuoles that fill and then pump excess water out of the cells across the cell membrane (**A**). The contractile vacuole moves near the cell membrane as it fills (**B**), and then releases the water to the outside. The organelle then resumes its empty shape (**C**) and moves back to the interior of the cell.

Water diffuses through cell membrane

Contractile vacuole

A

Vacuole pumps out water

Contractile vacuole (full)

Contractile vacuole (empty)

B   100 μm   **C**   100 μm

FIGURE 4.8
Plant Cells Keep Their Shapes by Regulating Diffusion.
Like paramecia, plant cells usually contain more concentrated solutes than their surroundings, drawing more water into the cell. (**A**) In a hypotonic solution, water enters the cell and collects in vacuoles. The cell swells against its rigid, restraining cell wall, generating turgor pressure. (**B**) When a plant cell is placed in a hypertonic environment (so that solutes are more concentrated outside the cells), water flows out of the vacuoles, and the cell shrinks. Turgor pressure is low, and the plant wilts.

Vacuole   Cytoplasm
         Cell wall
A

Vacuole   Cytoplasm
         Cell wall
B

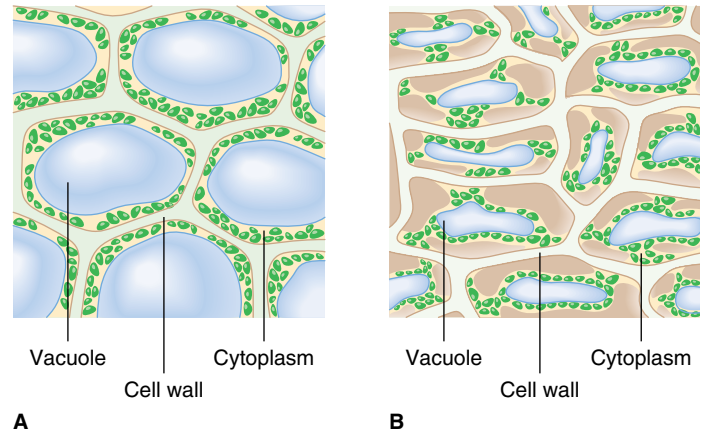special organelle called a contractile vacuole pumps the extra water out (fig. 4.7).

Plant cells also face the challenge of maintaining their shapes even with a concentrated interior. Instead of expelling the extra water that rushes in, as the paramecium does, plant cells expand until their cell walls restrain their cell membranes. The resulting rigidity, caused by the force of water against the cell wall, is called **turgor pressure** (fig. 4.8). A piece of wilted lettuce demonstrates the effect of losing turgor pressure. When placed in water, the leaf becomes crisp, as the individual cells expand like inflated balloons.

In the human body, osmosis influences the concentration of urine. Brain cells called osmoreceptors shrink when body fluids are too concentrated, which signals the pituitary gland to release antidiuretic hormone (ADH). The bloodstream transports ADH to cells lining the kidney tubules, where it alters their permeabilities so that water exits the tubules and enters capillaries (microscopic blood vessels) that entwine about the tubules. This conserves water. Without ADH's action, this water would remain in the kidney tubules and leave the body in dilute urine. Instead, it returns to the bloodstream, precisely where it's needed (see chapter 38).

Transport Proteins Move Molecules and Ions   The phospholipid bilayer keeps many ions and polar molecules from diffusing across cell membranes. However, such substances can still cross cell membranes with the help of transport proteins. These proteins are abundant and diverse. They typically span the membrane, and come in three varieties—channels, carriers, and pumps (fig. 4.9).

A channel transport protein, as its name implies, forms a pore through which a solute passes. The size of the pore and the charges that line its interior surface determine which molecules or ions can pass through. The transported substance may or may not bind to the protein. Some of these proteins have parts that form gatelike structures that control flow through them under certain conditions. Transport through a channel protein is fast—some 100 million ions or molecules a second may enter or exit the cell.

A carrier protein binds a specific ion or molecule, which contorts the protein in a way that moves the cargo to the other face of the membrane, where it exits. Carrier proteins provide **passive transport** if energy is not expended, or **active transport** if energy drives the movement. Passive transport using a carrier protein is also called facilitated diffusion, because the substance being moved travels down its concentration gradient. The basis of facilitated diffusion is that on the side of the membrane where the substance is more highly concentrated, more molecules contact the carrier protein. Eventually, dynamic equilibrium results, unless some other activity interferes, such as the cell's producing or consuming the substance being transported. Facilitated diffusion can move 100 to 1,000 ions or molecules a second.

Active transport enables a cell to admit a substance that is more concentrated inside than outside. This requires an input of energy. Returning to the party analogy, active transport is like a guest elbowing her way into a room that is already crowded with the majority of the partygoers. Energy for active transport often comes from adenosine triphosphate (ATP), which is discussed further in the next chapter. When a phosphate group is split from ATP, it releases energy that is harnessed to help drive a cellular
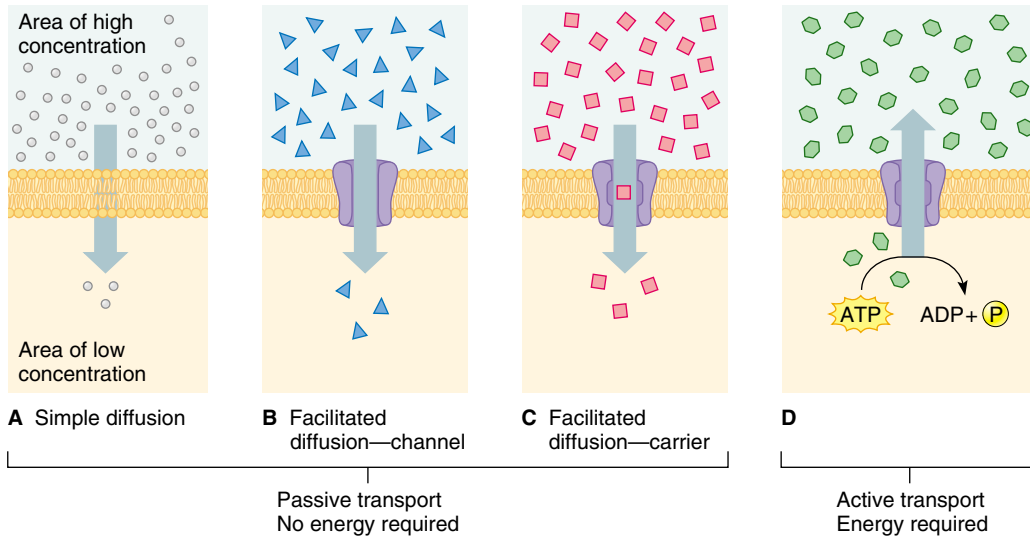
A Simple diffusion

B Facilitated diffusion—channel

C Facilitated diffusion—carrier

D

Passive transport
No energy required

Active transport
Energy required

FIGURE 4.9

Transport Moves Substances.
Simple diffusion, facilitated diffusion, and active transport move ions and molecules across cell membranes. In passive transport, molecules move down their concentration gradients by themselves by squeezing through the membrane components (**A**), through a channel protein (**B**), or aboard a carrier protein (**C**), without direct energy input. In active transport (**D**), a molecule or ion crosses a membrane against its concentration gradient, using energy and carrier proteins that function as pumps.
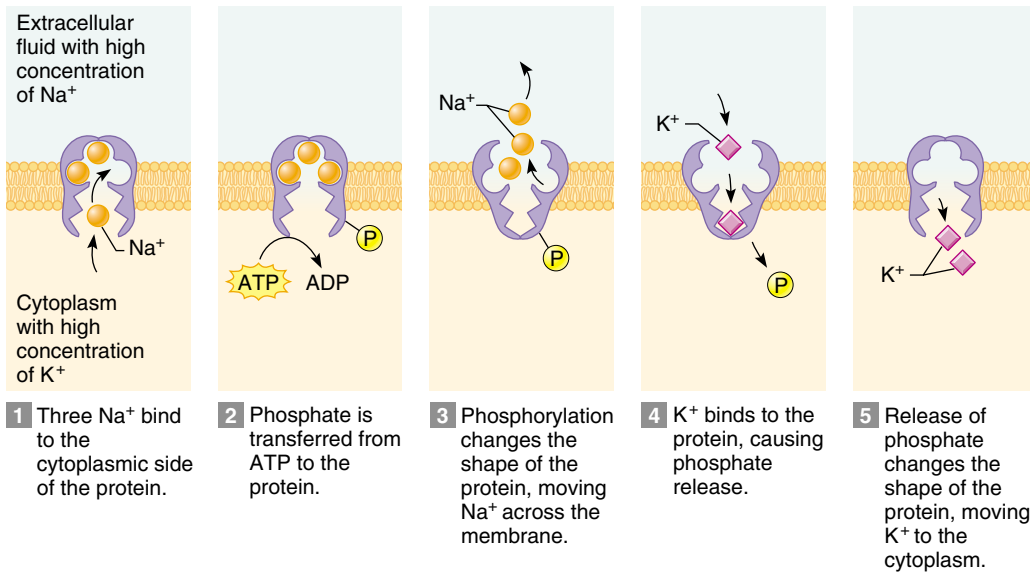

1 Three Na^+ bind to the cytoplasmic side of the protein.

2 Phosphate is transferred from ATP to the protein.

3 Phosphorylation changes the shape of the protein, moving Na^+ across the membrane.

4 K^+ binds to the protein, causing phosphate release.

5 Release of phosphate changes the shape of the protein, moving K^+ to the cytoplasm.

FIGURE 4.10

The Sodium-Potassium Pump.
This "pump," actually a carrier protein embedded in the cell membrane, uses energy (ATP) to move potassium ions (K^+) into the cell and sodium ions (Na^+) out of the cell. The pump first binds Na^+ on the inside face of the membrane (*1*). ATP is split to ADP and a phosphate group is transferred to the carrier or pump. (*2*) This binding alters the conformation of the pump and causes it to release the Na^+ to the outside. The altered pump can now take up K^+ from outside the cell (*3*). Next, the pump releases the bound phosphate (*4*), which again alters the conformation of the carrier protein. This change in shape releases K^+ to the cell's interior (*5*). The pump is also back in the proper shape to bind intracellular Na^+.

function, such as moving a molecule through a membrane against its concentration gradient.

The first active transport system discovered was a carrier protein called the **sodium-potassium pump** found in the cell membranes of most animal cells. Cells must contain high concentrations of potassium ions (K^+) and low concentrations of sodium ions (Na^+) to perform such basic functions as maintaining their volume and synthesizing protein, as well as to conduct more specific activities, such as transmitting nerve impulses and enabling the lungs and kidneys to function.

The sodium-potassium pump contains binding sites for both Na^+ and K^+. A pumping cycle begins with the binding of three Na^+ on the inside of the cell (fig. 4.10). The terminal phosphate of ATP is then transferred to the protein, causing it to change shape and expose the sodium ions to the outside of the cell. Since the sodium ion concentration is lower outside the cell,

the ions diffuse away from the pump. This exposes two binding sites for K^+ ions, which are immediately filled. When the pump has bound two K^+ ions, the phosphate is released, causing the pump to return to its original shape. This exposes the K^+ ions to the cytoplasm, where they diffuse away from the pump. The cycle is ready to begin again. The entire process takes only a fraction of a second.

Yet another way to move molecules across membranes is **co-transport,** in which a protein carries one substance as it ferries a different substance down its concentration gradient. Often active transport indirectly powers cotransport. A good example is the process of "sucrose loading" that sends the sugar into certain tissues in plants. An ATP-driven pump in the cell membrane sends hydrogen ions (protons) out of the cell. The protons accumulate in the cell walls that surround the cell membranes, building up energy like a wound spring. Then the protons move down their

FIGURE 4.11

Cotransport.

Energy from ATP is used to pump hydrogen ions out of the plant cell, creating a concentration gradient. The flow of hydrogen ions back into the cell is coupled to the transport of sucrose into a cell by means of a symporter protein channel. The energy of the gradient fuels the active transport.
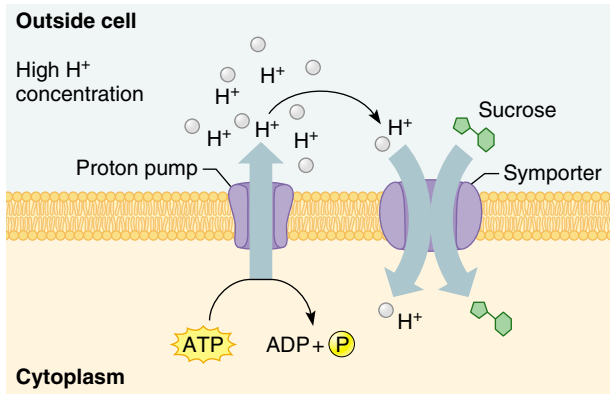
concentration gradient back into the cell aboard a protein called a symporter, using the energy of the gradient to also transport sucrose (fig. 4.11).

4.1 MASTERING CONCEPTS

1. What is diffusion?
2. How do differing concentrations of solutes in neighboring aqueous solutions drive the movement of water molecules?
3. How do facilitated diffusion and active transport differ from each other and from simple diffusion?
4. Describe the mechanisms of passive transport and active transport.

OLC

Exocytosis, Endocytosis, and Transcytosis Most molecules dissolved in water are small, and they can cross cell membranes by simple diffusion, facilitated diffusion, or active transport. Large molecules (and even bacteria) can also enter and leave cells, with the help of vesicles that form from cell membranes.

Exocytosis transports large particles out of cells, such as some components of milk (see fig. 3.11). Inside a cell, a vesicle made of a phospholipid bilayer is filled with substances to be ejected. The vesicle moves to the cell membrane and joins with it, releasing the substance outside the membrane (fig. 4.12). For example, exocytosis in the front tip of a sperm cell releases enzymes that enable the tiny cell to penetrate the much larger egg cell.
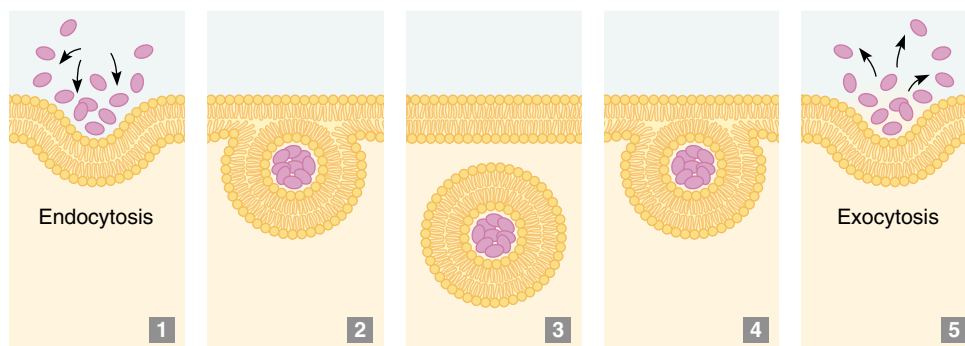
Endocytosis allows a cell to capture large molecules on its external surface in a nonspecific way and bring them into the cell. Protein molecules just inside the cell membrane join, forming a vesicle that traps whatever is outside the membrane. The vesicle pinches off and moves into the cell. At times, all that is captured are solutes and water in a process known as pinocytosis (fig. 4.13A).

Phagocytosis is another form of endocytosis that some cells use to capture and destroy debris or smaller organisms such as bacteria (fig. 4.13B). If the substance brought into the cell must be digested for the cell to use it, the vesicle fuses with a lysosome, creating an **endosome** and activating the enzymes within. Once digested, the contents of the vesicle are pumped out of the vesicle and into the cytoplasm for the cell to use. Endosome formation is one way that a cell can capture raw materials. The components of the vesicle, along with the membrane proteins, are cycled back to the cell membrane, and waste is removed by exocytosis. Some cells use specialized forms of endocytosis and exocytosis, such as nerve cells that release and recover signaling molecules.

When biologists first viewed endocytosis in white blood cells in the 1930s, they thought a cell would gulp in anything at its surface. We now recognize a more specific form of the process called **receptor-mediated endocytosis.** A receptor protein on a cell's surface binds a particular biochemical, called a **ligand;** the cell membrane then indents, embracing the ligand and drawing it into the cell (fig. 4.13C).

FIGURE 4.12

Endocytosis and Exocytosis.

Endocytosis brings large particles and even bacteria into a cell. A small portion of the cell membrane buds inward (*1*), entrapping the particles (*2*), and a vesicle forms, which brings the substances into the cell. Biochemicals and particles exit cells by exocytosis. Vesicles surround or take up the structures to be exported (*3*), then move to the cell membrane (*4*) and merge with it, releasing the particles to the outside (*5*).
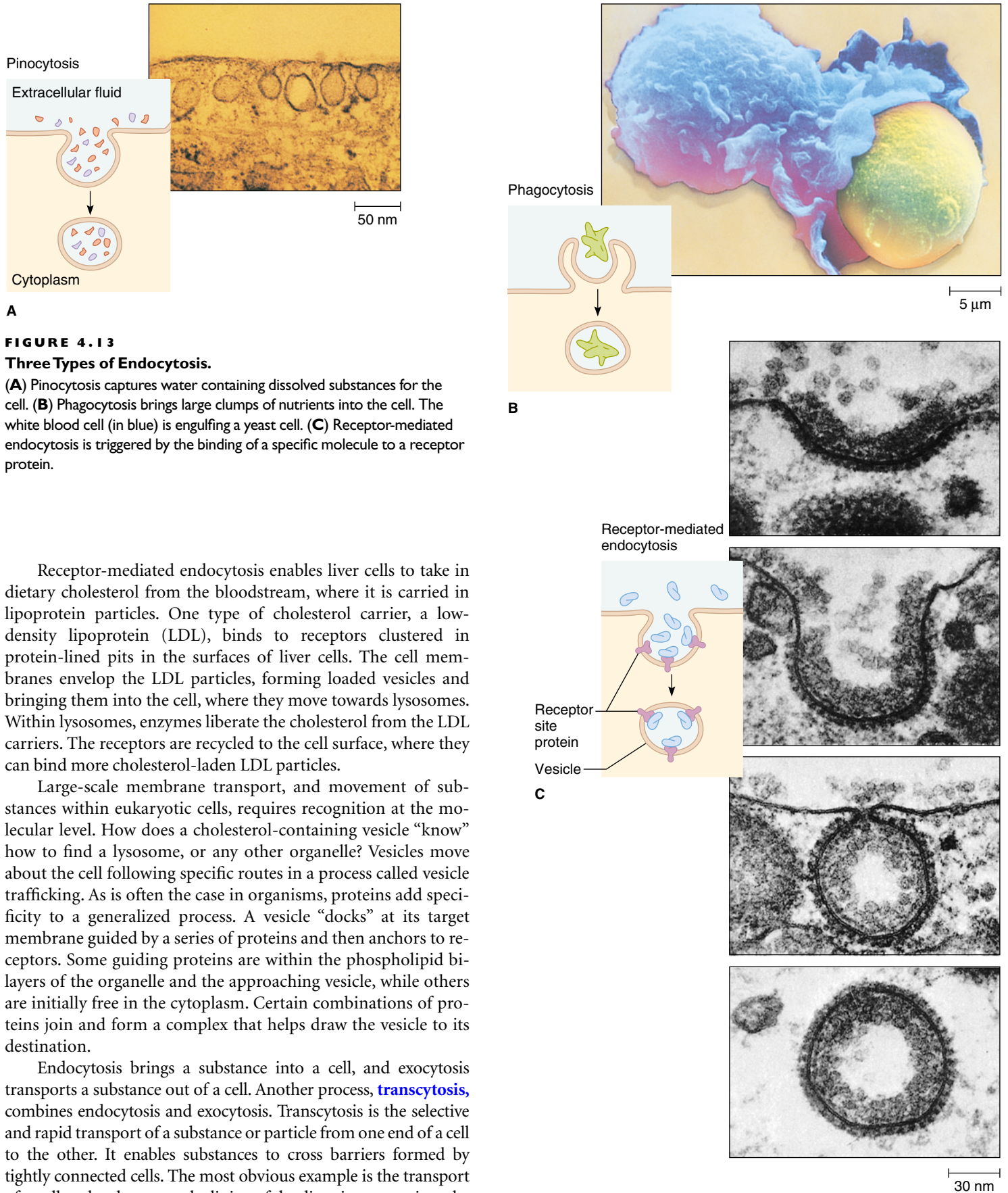
Pinocytosis

Extracellular fluid

Cytoplasm

A

50 nm

FIGURE 4.13
Three Types of Endocytosis.
(**A**) Pinocytosis captures water containing dissolved substances for the cell. (**B**) Phagocytosis brings large clumps of nutrients into the cell. The white blood cell (in blue) is engulfing a yeast cell. (**C**) Receptor-mediated endocytosis is triggered by the binding of a specific molecule to a receptor protein.

Phagocytosis

B

5 μm

Receptor-mediated endocytosis

Receptor site protein

Vesicle

C

30 nm

Receptor-mediated endocytosis enables liver cells to take in dietary cholesterol from the bloodstream, where it is carried in lipoprotein particles. One type of cholesterol carrier, a low-density lipoprotein (LDL), binds to receptors clustered in protein-lined pits in the surfaces of liver cells. The cell membranes envelop the LDL particles, forming loaded vesicles and bringing them into the cell, where they move towards lysosomes. Within lysosomes, enzymes liberate the cholesterol from the LDL carriers. The receptors are recycled to the cell surface, where they can bind more cholesterol-laden LDL particles.

Large-scale membrane transport, and movement of substances within eukaryotic cells, requires recognition at the molecular level. How does a cholesterol-containing vesicle "know" how to find a lysosome, or any other organelle? Vesicles move about the cell following specific routes in a process called vesicle trafficking. As is often the case in organisms, proteins add specificity to a generalized process. A vesicle "docks" at its target membrane guided by a series of proteins and then anchors to receptors. Some guiding proteins are within the phospholipid bilayers of the organelle and the approaching vesicle, while others are initially free in the cytoplasm. Certain combinations of proteins join and form a complex that helps draw the vesicle to its destination.

Endocytosis brings a substance into a cell, and exocytosis transports a substance out of a cell. Another process, **transcytosis,** combines endocytosis and exocytosis. Transcytosis is the selective and rapid transport of a substance or particle from one end of a cell to the other. It enables substances to cross barriers formed by tightly connected cells. The most obvious example is the transport of small molecules across the lining of the digestive system into the bloodstream. The digestive system breaks down macromolecules

TABLE 4.2   Movement Across Membranes

MECHANISM	CHARACTERISTICS	EXAMPLE
Diffusion	Follows concentration gradient	Oxygen diffuses from lung into capillaries
Osmosis	Diffusion of water	Water reabsorbed from kidney tubules
Facilitated diffusion	Follows concentration gradient, assisted by carrier protein	Glucose diffuses into red blood cells
Active transport	Moves against concentration gradient, assisted by carrier protein and energy, usually ATP	Salts reabsorbed from kidney tubules
Cotransport	Movement of one substance is coupled to movement of a second substance down its concentration gradient, often countering a proton pump	Sucrose transport into phloem cells
Exocytosis	Membrane-bounded vesicle fuses with cell membrane, releasing its contents outside of cell	Nerve cells release neurotransmitters
Endocytosis	Membrane engulfs substance and draws it into cell in membrane-bounded vesicle	White blood cells ingest bacteria
Transcytosis	Combines endocytosis and exocytosis	Products of the digestive system entering the bloodstream

to monomers. These monomers are transported across the cell membrane of cells (endocytosis), across the cytoplasm to the other side of the cells (trancytosis), and released into the bloodstream (exocytosis).

Table 4.2 summarizes the transport mechanisms that move substances across membranes.

4.1 MASTERING CONCEPTS

1. How do exocytosis and endocytosis transport large particles across cell membranes?
2. How can endocytosis become specialized?
3. Which structures guide vesicles inside a cell?
4. How does transcytosis combine exocytosis and endocytosis?

OLC

4.2   How Does the Cytoskeleton Support a Cell?

Within cells, a vast network of tubules and filaments guides organelle movement, provides overall shape, and establishes vital links to specific molecules that are part of the cell membrane.

The cytoskeleton is a meshwork of tiny protein rods and tubules that molds the distinctive structures of eukaryotic cells, positioning organelles and providing characteristic overall three-dimensional shapes. The protein girders of the cytoskeleton are dynamic structures that are broken down and built up as a cell performs specific activities. Some cytoskeletal elements function as rails, forming conduits for cellular contents on the move; other components of the cytoskeleton, called motor molecules, power the movement of organelles along these rails by converting chemical energy to mechanical energy.

The cytoskeleton includes three major types of elements—**microtubules, microfilaments,** and **intermediate filaments** (fig. 4.14). They are distinguished by protein type, diameter, and

FIGURE 4.14

The Cytoskeleton Is Made of Protein Rods and Tubules.
The three major components of the cytoskeleton are microtubules, intermediate filaments, and microfilaments. Through special staining, the cytoskeleton in this cell glows yellow under the microscope.
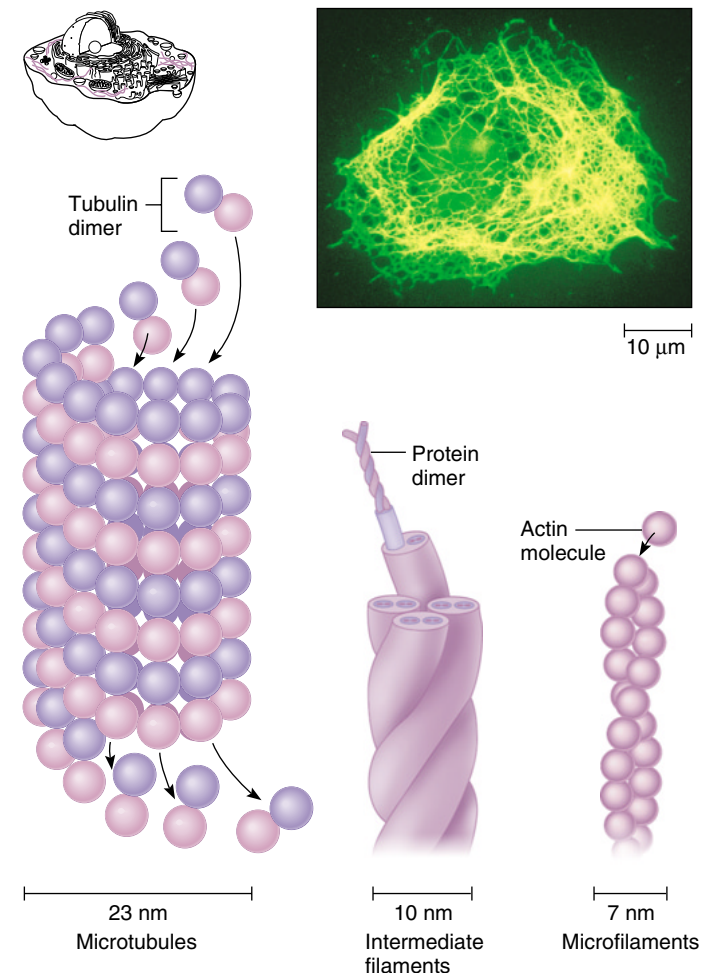

10 μm

Tubulin dimer

Protein dimer

Actin molecule

23 nm
Microtubules

10 nm
Intermediate filaments

7 nm
Microfilaments

TABLE 4.3   Functions of the Cytoskeleton

1. Moving chromosomes apart during cell division
2. Controlling vesicle trafficking
3. Building organelles by helping to transport their components
4. Enabling cellular appendages and cells themselves to move
5. Connecting cells to each other
6. Secreting and taking up neurotransmitters in nerve cells

how they aggregate into larger structures. Other proteins connect these components to each other, creating the meshwork that provides the cell's strength and ability to resist forces, which maintains shape. Table 4.3 lists some functions of the cytoskeleton, and the following sections discuss the three major components.

Microtubules Are Built of Tubulin

All eukaryotic cells contain long, hollow microtubules that provide many cellular movements. A microtubule is composed of pairs (dimers) of a protein, called tubulin, assembled into a hollow tube 25 nanometers in diameter (fig. 4.14). The cell can change the length of the tubule by adding or removing tubulin molecules.

Cells contain both formed microtubules and individual tubulin molecules. When the cell requires microtubules to carry out a spe-

cific function—dividing, for example—the free tubulin dimers self-assemble into more tubules. After the cell divides, some of the microtubules dissociate into individual tubulin dimers. This replenishes the cell's supply of building blocks. Cells are in a perpetual state of flux, building up and breaking down microtubules. Some drugs used to treat cancer affect the microtubules that pull a cell's duplicated chromosomes apart, either by preventing tubulin from assembling into microtubules, or by preventing microtubules from breaking down into free tubulin dimers. In each case, cell division stops.

Microtubules also form locomotor organelles, which move or enable cells to move. The two types of locomotor organelles are **cilia** and **flagella** (fig. 4.15). Cilia are hairlike structures that move in a coordinated fashion, producing a wavelike motion extending from the surface of the cell (fig. 4.16). An individual cilium is constructed of nine microtubule pairs that surround a central, separated pair and form a pattern described as "9 + 2." A type of motor protein called **dynein** connects the outer microtubule pairs and also links them to the central pair. Dynein molecules use energy from ATP to shift in a way that slides adjacent microtubules against each other. This movement bends the cilium (or flagellum). Coordinated movement of these cellular extensions sets up a wave that moves the cell or propels substances along its surface.

Cilia have many vital functions in animal cells. They beat particles up and out of respiratory tubules, and move egg cells in the female reproductive tract. Some single-celled organisms may have thousands of individual cilia, enabling them to "swim" through water.
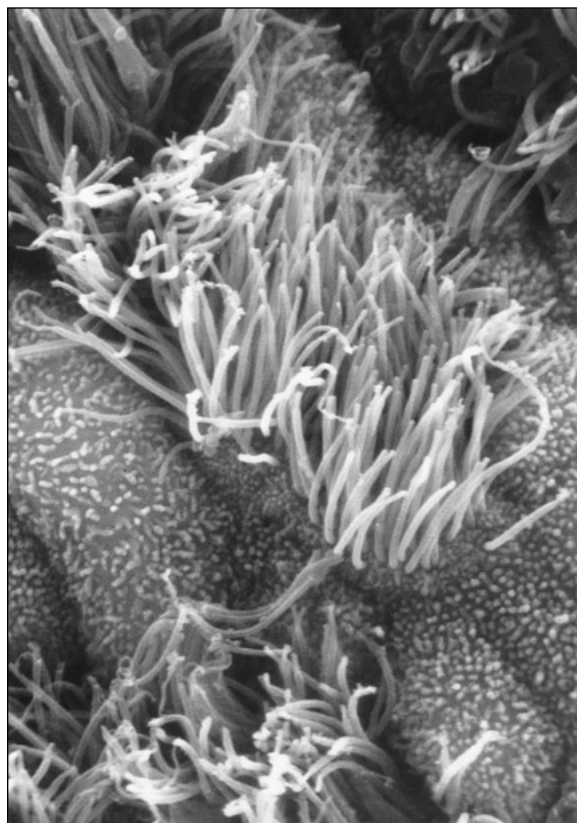
A   4 μm

FIGURE 4.15
Cilia and Flagella.
The cilia in (**A**) line the human respiratory tract, where their coordinated movements propel dust particles upward so the person can expel them. The flagella on human sperm cells (**B**) enable them to swim.

B   8 μm
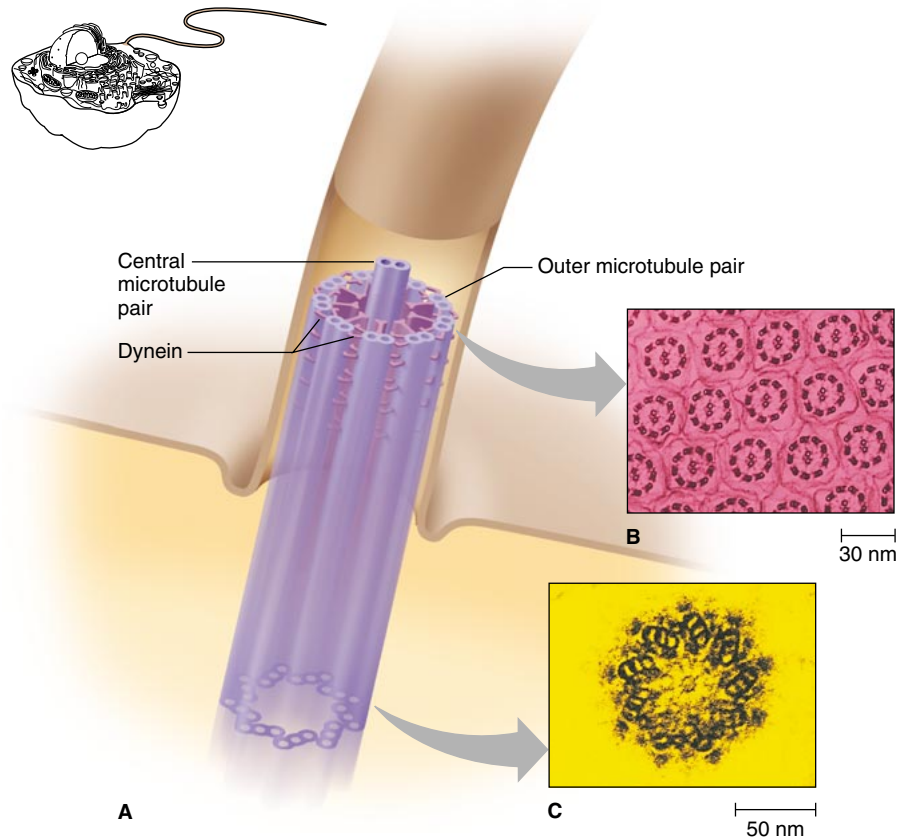
FIGURE 4.16
Microtubules Move Cells.
The microtubules that form cilia and the cytoskeletons of flagella have a characteristic "9 + 2" organization.
(**A**) Dynein joins the outer microtubule doublets to each other and to the central pair of microtubules.
(**B**) A transmission electron micrograph showing a cross section of a group of flagella.
(**C**) A structure called a basal body anchors the flagellum to the cell.

Cilia tend to be short and numerous, like a fringe. A flagellum, also built of a 9 + 2 microtubule array, is much longer. Flagella are more like tails, and their whiplike movement enables cells to move. Sperm cells in many species have prominent flagella (see fig. 4.15B). A human sperm cell has only one flagellum, but a sperm cell of a cycad (a type of tree) has thousands of flagella.

Microfilaments Are Built of Actin

Another component of the cytoskeleton is the microfilament (fig. 4.17), which is a long, thin rod composed of the protein actin. In contrast to the microtubules, microfilaments are not hollow and are only about 7 nm in diameter. Microfilaments are vital in providing strength for cells to survive the stretching and compression that often occurs in multicellular organisms. They also help to anchor one cell to another and provide many other functions within the cell through proteins that interact with actin.

One of the best-understood actin-binding proteins is myosin, which uses energy from ATP to move actin filaments. Bundles of myosin slide microfilaments toward each other in muscle cells, generating the motion of muscle contraction (figs. 4.17 and 34.15). Other varieties of myosin-actin interactions move components within the cytoplasm, help cells to move, and distribute the cytoplasm during cell division.

FIGURE 4.17
Muscle Acts by Protein Interactions.
Actin microfilaments are interspersed with thicker myosin filaments in muscle tissue. The binding of myosin to actin, followed by a change in the shape of myosin, provides the force behind muscle movement.

Minor mechanical stress

Blister
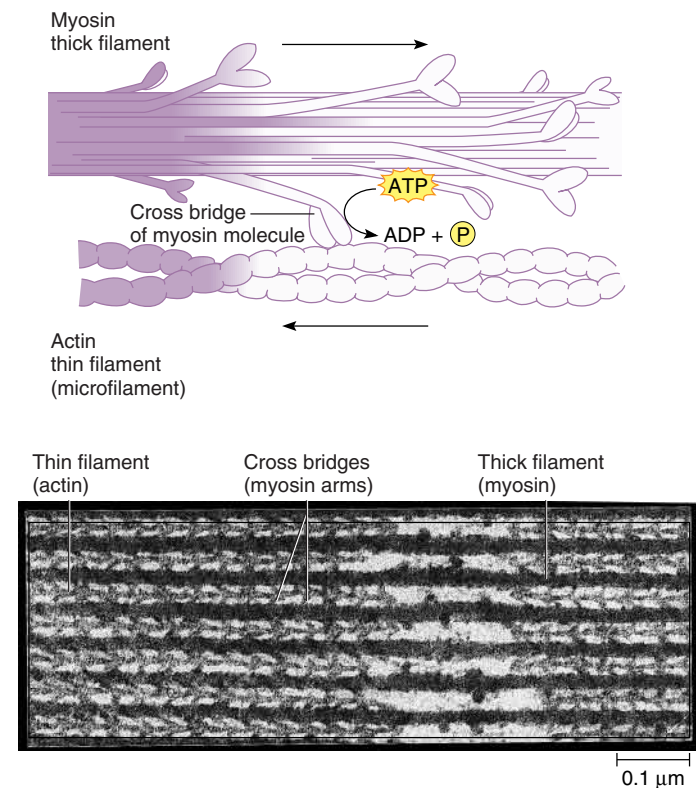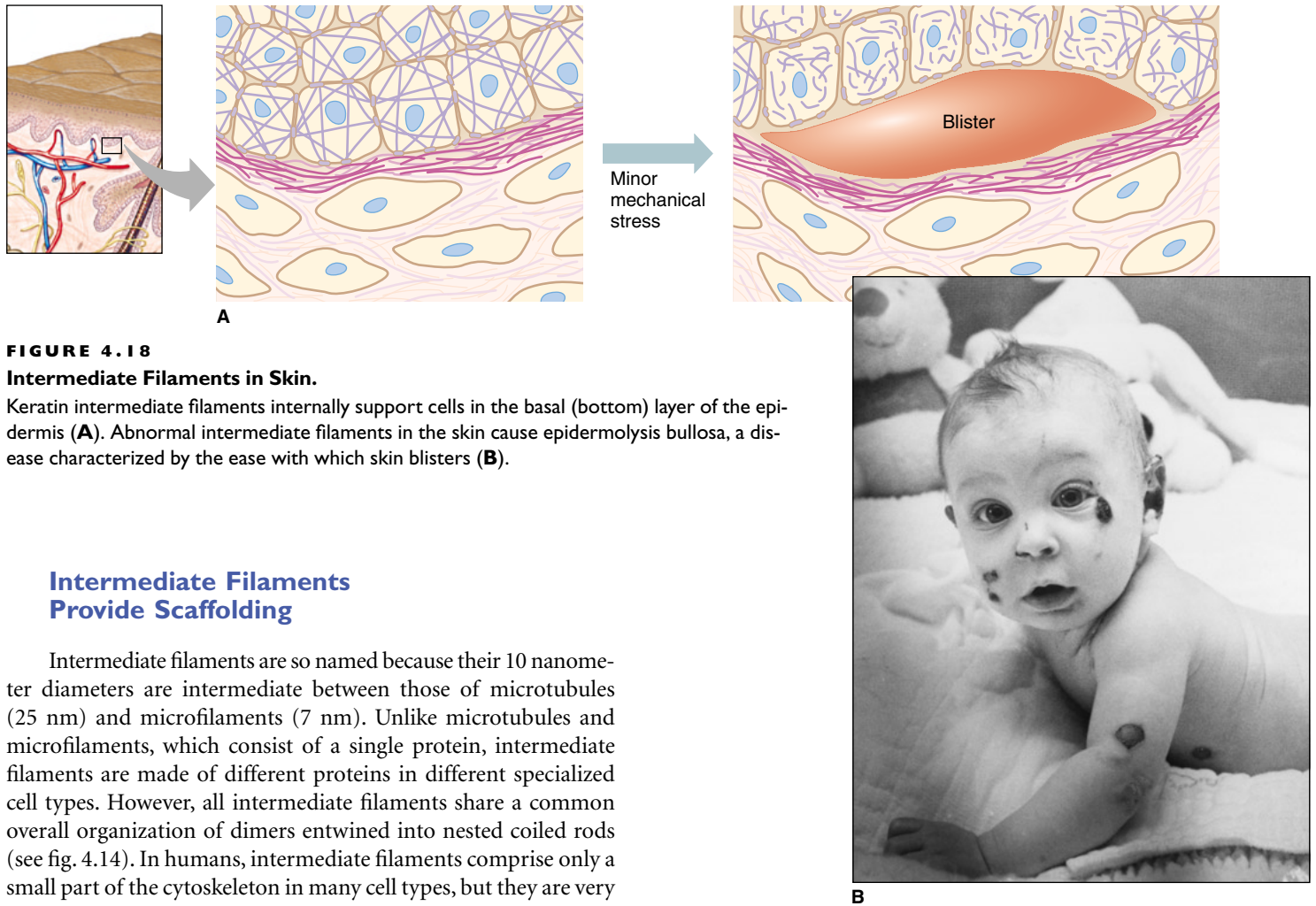
FIGURE 4.18

Intermediate Filaments in Skin.
Keratin intermediate filaments internally support cells in the basal (bottom) layer of the epidermis (**A**). Abnormal intermediate filaments in the skin cause epidermolysis bullosa, a disease characterized by the ease with which skin blisters (**B**).

Intermediate Filaments Provide Scaffolding

Intermediate filaments are so named because their 10 nanometer diameters are intermediate between those of microtubules (25 nm) and microfilaments (7 nm). Unlike microtubules and microfilaments, which consist of a single protein, intermediate filaments are made of different proteins in different specialized cell types. However, all intermediate filaments share a common overall organization of dimers entwined into nested coiled rods (see fig. 4.14). In humans, intermediate filaments comprise only a small part of the cytoskeleton in many cell types, but they are very abundant in skin cells and nerve cells. They form an internal scaffold in the cytoplasm and resist mechanical stress, both functions that maintain a cell's shape.

Intermediate filaments in actively dividing skin cells in the bottommost layer of the epidermis form a strong inner framework (fig. 4.18). It maintains the cells' shapes and firmly attaches them to each other and to the underlying tissue, which is important as this tissue forms a barrier. In an inherited condition called epidermolysis bullosa, keratin intermediate filaments are abnormal, causing the skin to blister easily as tissue layers separate. Intermediate filaments in nerve cells, called neurofilaments, consist of different types of proteins. They surround microtubules and bridge them to each other, stabilizing the extensions of these cells in specific positions, which is important for nerve conduction. The neurofilaments establish and maintain particular diameters of these extensions.

The different components of the cytoskeleton intimately interact through dozens of proteins that interconnect all parts of the cytoskeleton. In multicellular organisms, the cytoskeleton is also important in fostering interactions with noncellular material outside a cell and to other cells. Health 4.1 discusses how the cytoskeleton contributes to the specialized functions of red blood cells, which traverse an endless network of conduits, and muscle cells, which are part of a densely packed, highly active tissue.

B

4.2 MASTERING CONCEPTS

1. What are some functions of the cytoskeleton?
2. What are the major components of the cytoskeleton?
3. How do the components of the cytoskeleton interact?

OLC

4.3 How Do Cells Interact and Respond to Signals?

Cells must permanently attach to one another to build most tissues; transiently attach to carry out certain functions; and send and receive biochemical messages and respond to them.

All organisms can detect and respond to changes in their environment. A unicellular organism may move toward or away from a particular stimulus. When life became multicellular, about a billion years ago, cell-to-cell communication became crucial too. Such cells "talk" to each other and make contact in thousands of ways. We look now at the structures that join the

A Disrupted Cytoskeleton Affects Health

Red Blood Cells

Much of what we know about the cohesion between the cell membrane and the cytoskeleton comes from studies of human red blood cells. The doughnut shapes of these cells enable them to squeeze through the narrowest blood vessels on their 300-mile (483-kilometer), 120-day journey through the circulatory system.

A red blood cell's strength derives from rods of proteins called spectrin that form a meshwork beneath the cell membrane (fig. 4.A). Proteins called ankyrins attach the spectrin rods to the membrane. Spectrin molecules are like the steel girders of the red blood cell architecture, and the ankyrins are like the nuts and bolts. If either is absent, the cell's structural support collapses. Abnormal ankyrin in red blood cells causes anemia (too few red blood cells) because the cells balloon out and block circulation and then die. Researchers expect to find defective ankyrin behind problems in other cell types, because it seems to be a key protein in establishing contact between the components of the cell's architecture.

Muscle Cells

Red blood cells and muscle cells are similar in that each must maintain its integrity and shape in the face of great physical force. The red blood cell can dissipate some of the force

FIGURE 4.A
The Red Blood Cell Membrane.
Red blood cells must withstand great turbulent force in the circulation. The cytoskeleton beneath the cell membrane enables these cells to retain their shapes, which are adapted to movement. A protein called ankyrin binds spectrin from the cytoskeleton to the interior face of the cell membrane. On its other end, ankyrin binds a large glycoprotein that helps transport ions across the cell membrane. Abnormal ankyrin causes the cell membrane to collapse—a problem for a cell whose function depends upon its shape.
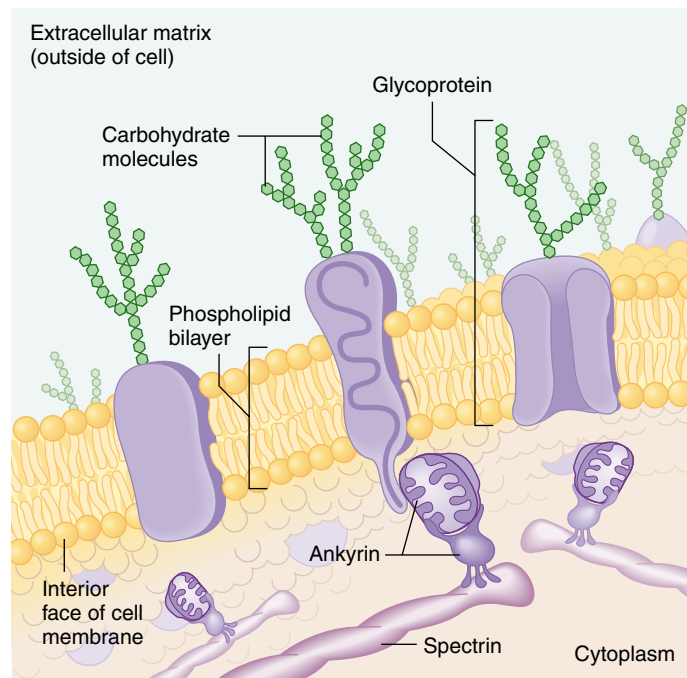
cells of multicellular organisms, and then consider two broad types of interactions between cells—cell adhesion and signal transduction.

Animal Cell Junctions Are of Several Types

Animal cells have several types of intercellular junctions (fig. 4.19). In a **tight junction,** the cell membranes of adjacent cells fuse at a localized point. The area of fusion surrounds the two cells like a belt, closing the space between them and ensuring that substances must pass through cells to reach the tissues beyond. Tight junctions join cells into sheets, such as those that line the inside of the human digestive tract.

Extensive tight junctions firmly attach the endothelial cells that form microscopic blood vessels (capillaries) in the human brain, creating some 400 miles of a "blood-brain barrier." This barrier prevents chemical fluctuations, which can damage delicate brain tissue.

The blood-brain barrier readily admits lipid-soluble drugs, because the cell membranes of the endothelium are lipid-rich. The drugs heroin, valium, nicotine, cocaine, and alcohol are lipid-soluble and cross the barrier, which is why they can act so rapidly. Oxygen also enters the brain by directly crossing endothelial cell membranes. Water-soluble molecules must take other routes across the barrier. Insulin moves through the cell by transcytosis. Glucose, amino acids, and iron cross the barrier with the aid of carrier molecules, providing the brain with a constant supply of these nutrients.

because it moves within a fluid. Muscle cells, in contrast, are held within a larger structure—a muscle—where they must withstand powerful forces of contraction, as well as rapid shape changes.

A muscle cell is filled with tiny filaments of actin and myosin, the proteins that slide past one another, providing contraction. A far less abundant protein in muscle cells, dystrophin, is also very important. Dystrophin is critical to muscle cell structure. It physically links actin in the cytoskeleton to glycoproteins that are part of the cell membrane (fig. 4.B). Some of the glycoproteins, in turn, bind to laminin, a cross-shaped protein that is anchored in non-cellular material surrounding the muscle cell, called extracellular matrix. By holding together the cytoskeleton, cell membrane, and extracellular matrix, dystrophin and the associated glycoproteins greatly strengthen the muscle cell, which enables it to maintain its structure and function during repeated rounds of contraction. The muscle weakness disorders called muscular dystrophies result from missing or abnormal dystrophin or the glycoproteins it binds to. ✛

FIGURE 4.B
Cells Need Anchors.
Dystrophin is a membrane protein that stabilizes muscle cell structure by linking the cytoskeleton to the cell membrane. (Actin is present in the cytoskeleton of all cells and is also one of the two major contractile proteins of muscle.)
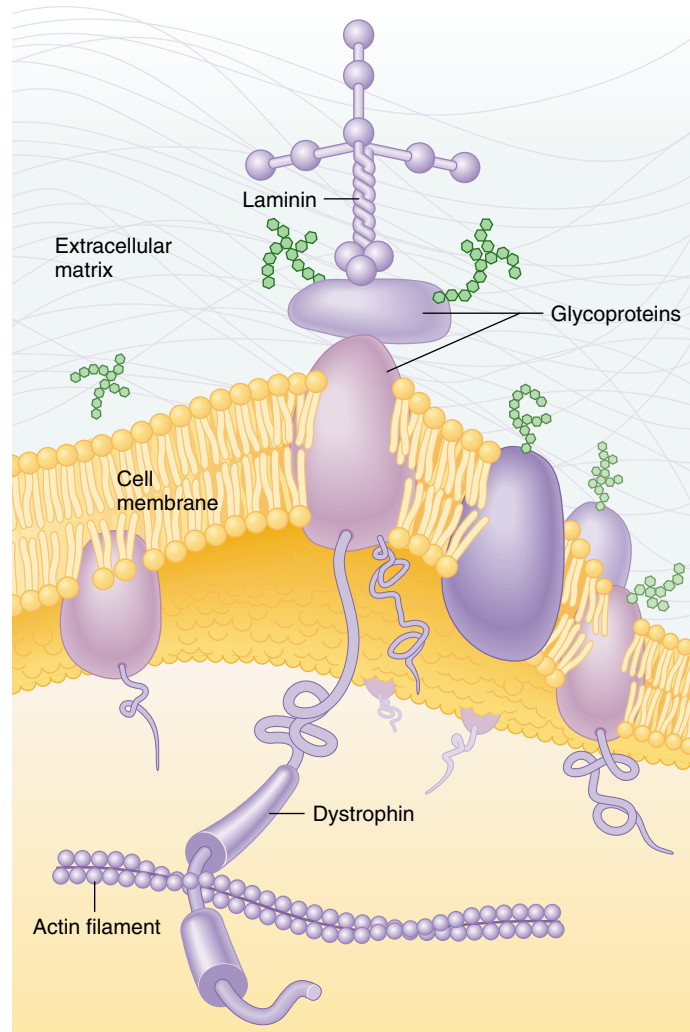
Another type of intercellular junction in animal cells, called a **desmosome,** links intermediate filaments in adjacent cells in a single spot on both cells (fig. 4.19). Desmosomes hold skin cells in place. A type of connection called a **gap junction** links the cytoplasm of adjacent cells, allowing exchange of ions, nutrients, and other small molecules. Gap junctions join heart muscle cells as well as muscle cells that line the digestive tract.
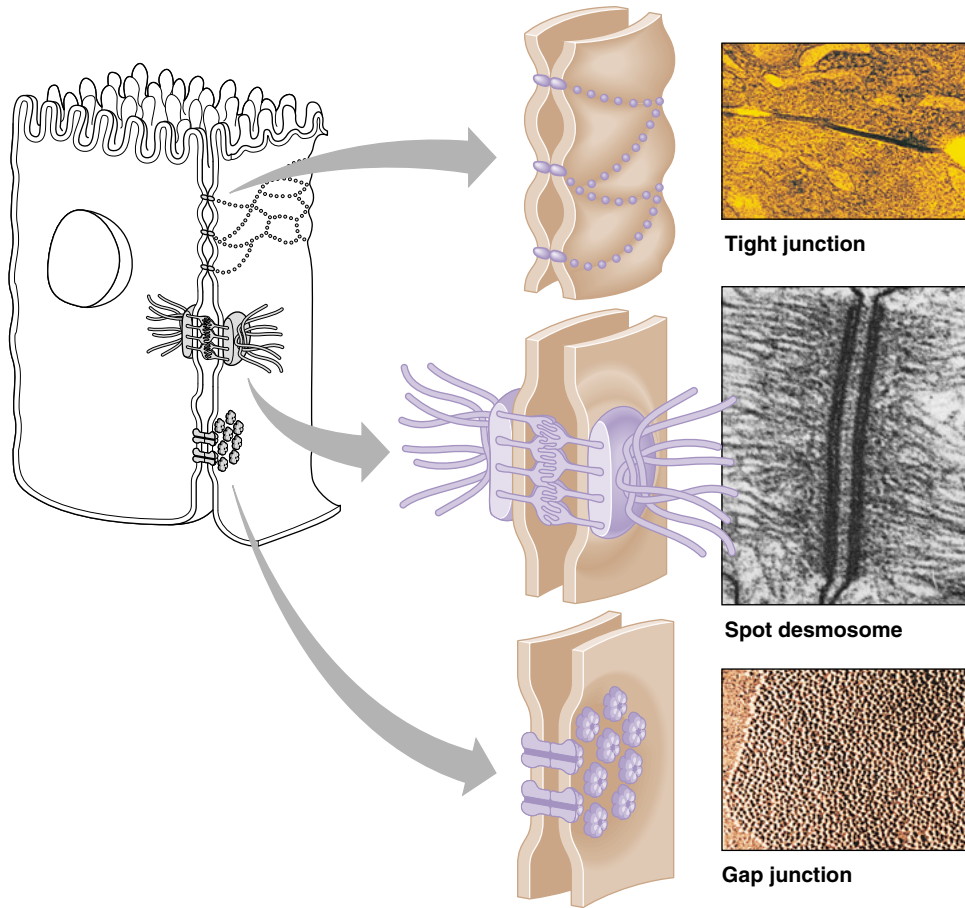
Cell Walls Are Dynamic Structures

Cell walls surround the cell membranes of nearly all bacteria, archaea, fungi, algae, and plants. Their name is misleading—they are not just barriers that serve only to outline the cells within. Cell walls do impart shape and regulate cell volume, but they also in-

teract with other molecules, helping to determine how a cell in a complex organism specializes.

Cell walls are built of different components in different types of organisms, and may also vary in composition in different parts of the same cell, or at different times in development. Much of the plant cell wall consists of cellulose molecules aligned to form microfibrils that are 10 to 25 nanometers in diameter. Recall that cellulose is a glucose polymer (see fig. 2.15). The microfibrils, in turn, aggregate and twist to form macrofibrils, with diameters of 0.5 micrometers. This fibrous organization imparts great strength, which is increased by molecules of hemicellulose, another polysaccharide, that forms hydrogen bonds to the cellulose microfibrils. Another type of polysaccharide, called pectin, absorbs and holds water, which adds flexibility to the overall

FIGURE 4.19
Animal Cell Connections.
Tight junctions fuse neighboring cell membranes, desmosomes form "spot welds," and gap junctions allow small molecules to move between the cytoplasm of adjacent cells.

Tight junction

Spot desmosome

Gap junction

or leaf depends upon which cell walls it touches, revealing that a wall affects cells other than the one that it surrounds. Cell walls may therefore help to control the cell-cell interactions that determine how some multicellular organisms develop.

Table 4.4 summarizes intercellular junctions.
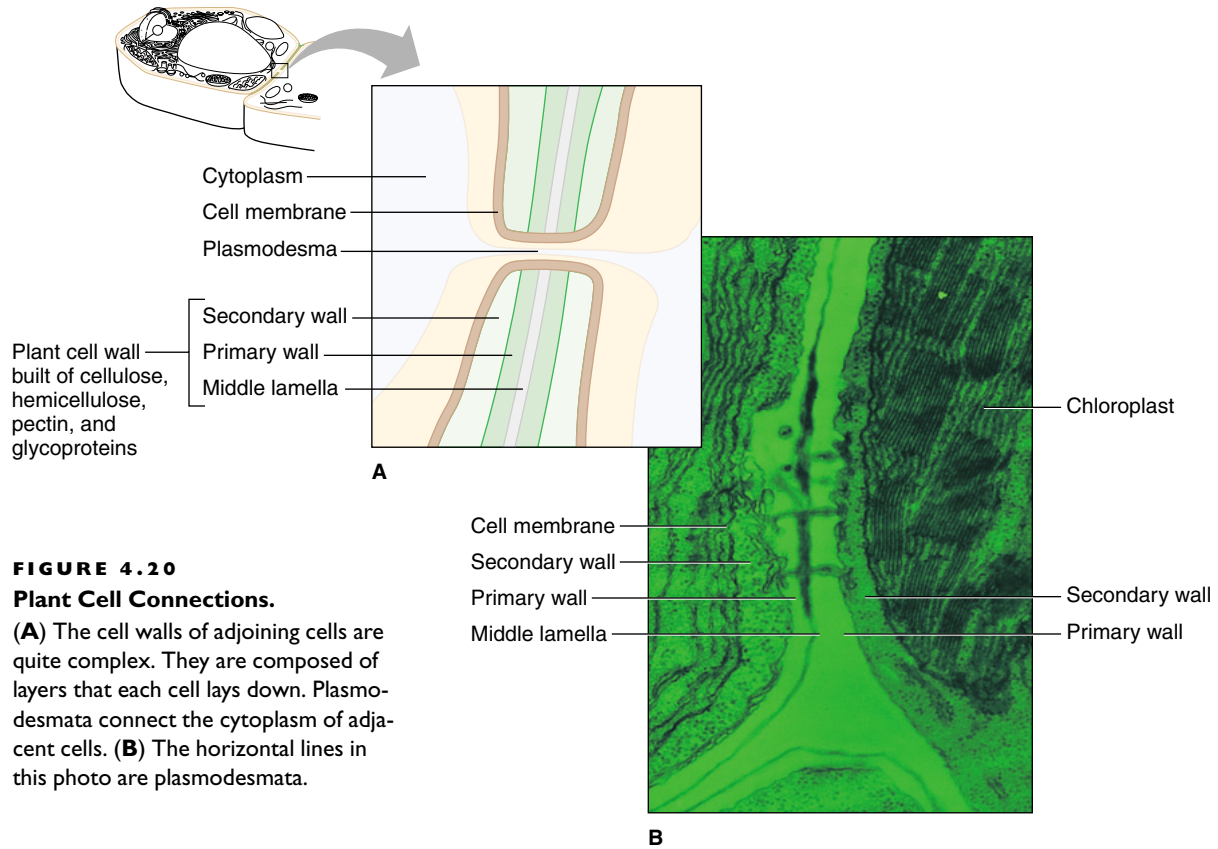
Cell Adhesion Directs Cell Movements

Cells stick to each other through a process called adhesion, which is a precise sequence of interactions between proteins that bring cells into contact. One well-studied example of cell adhesion is inflammation—the painful, red swelling at a site of injury or infection. In inflammation, white blood cells move from the circulation to an endangered body part, where they squeeze between the cells of the blood vessel walls to reach the site of injury or infection.

Cellular adhesion molecules (CAMs) help guide white blood cells. Different types of CAMs act in sequence (fig. 4.21). First, CAMs called **selectins** slow the white blood cell they cling to by also binding to carbohydrates on the capillary wall. This has the effect of slowing the cell

from moving at 2,500 micrometers per second to a more leisurely 50 micrometers per second. Next, clotting blood, bacteria, or decaying tissue release chemicals that signal the white blood cell to stay and also activate a second type of CAM, called an **integrin.** An integrin links the white blood cell to a third type of CAM, called an **adhesion receptor protein,** that extends from the capillary wall at the injury site. Both types of CAMs then pull the white blood cell between the blood vessel lining cells to the other side, where the damage is.

Cell adhesion is critical to many functions. CAMs guide cells surrounding an embryo to grow toward maternal cells and form the placenta, the supportive organ linking a pregnant woman to the fetus. Sequences of CAMs help establish the connections between nerve cells that underlie learning and memory.

Defects in cell adhesion affect health. Consider the plight of a young woman named Brooke Blanton. She first experienced the effects of faulty cell adhesion as an infant, when her teething sores did not heal. These and other small wounds never accumulated pus, which consists of bacteria, cellular debris, and white blood cells and is a sign of the body fighting infection. Doctors eventually diagnosed Brooke with a newly recognized disorder called leukocyte-adhesion deficiency. Her body lacks the CAMs that

structure and adheres adjacent cells to each other (fig. 4.20). Cell walls also contain glycoproteins, enzymes, and many other proteins that have not yet been identified.

A plant cell secretes many of the components of its wall, so the older layer of a cell wall is on the exterior of the cell, whereas newer layers hug the cell membrane. Some cells have secondary cell walls beneath the initial ones. The region where the walls of adjacent cells meet is called the **middle lamella.** To facilitate cell-to-cell communication and coordination of function, connections of the cell membrane, called **plasmodesmata,** link plant cells. Plasmodesmata form "tunnels" through which the cytoplasm and some of the organelles of one plant cell can interact with those of another (fig. 4.20). They are particularly plentiful in parts of plants that conduct water or nutrients and in cells that secrete oils and nectars.

Experiments reveal the important role of the cell wall in determining cell specialization. Consider a simple organism, the brown alga *Fucus*. It has two cell types that form two tissues: a rootlike rhizoid, and fronds. If the wall is stripped from a *Fucus* cell, it can specialize as either rhizoid or frond, as if its developmental fate has been reset. A cell with its wall intact can become only one type. In plants, whether a cell specializes as root, shoot,

Cytoplasm
Cell membrane
Plasmodesma

Secondary wall
Primary wall
Plant cell wall built of cellulose, hemicellulose, pectin, and glycoproteins
Middle lamella

A

Chloroplast

Cell membrane
Secondary wall
Primary wall
Middle lamella

Secondary wall
Primary wall

B

FIGURE 4.20
Plant Cell Connections.
(**A**) The cell walls of adjoining cells are quite complex. They are composed of layers that each cell lays down. Plasmodesmata connect the cytoplasm of adjacent cells. (**B**) The horizontal lines in this photo are plasmodesmata.

enable white blood cells to stick to blood vessel walls. As a result, her blood cells move right past wounds. Brooke must avoid injury and infection, and receive antiinfective treatments for even the slightest wound. More common disorders may reflect abnormal cell adhesion. Lack of cell adhesion eases the journey of cancer cells from one part of the body to another. Arthritis may occur when white blood cells are reined in by the wrong adhesion molecules and inflame a joint where there isn't an injury.

Signal Transduction Mediates Messages

The process by which cells receive information from the outside, amplify it, and then respond, is generally called **signal transduction.** It is an ancient process, because all organisms do it, and many use the same molecules. Plants, fungi, and animals, for example, all use nitric oxide (NO) as one of many signaling molecules (see chapter 2 opening essay).

Organisms of all complexities receive and respond to signals. Bacteria move toward or away from changes in light intensity or the concentration of a particular chemical. A bacterium can de-

tect the presence of a nutrient, and then produce the enzymes required to tap its energy. Environmental extremes can stimulate a bacterium to encase itself in a protective spore, until better conditions arise. Signal transduction in the slime mold *Dictyostelium discoidium,* a protist, provides a glimpse into one way that life may have evolved from the unicellular to the multicellular. When its bacterial food is abundant, the organism exists as single cells. When food becomes scarce, the single cells begin producing cyclic adenosine monophosphate (cAMP), which causes the cells to stream toward each other, and aggregate to form a slug, which can move, possibly finding food (see chapter 21).

The cell membrane is the key site of the chemical interactions that underlie signal transduction. Proteins embedded in the membrane that extend from one or both faces are crucial to the process. The first type of protein in the signal transduction cascade is a receptor, which directly binds to a specific ligand molecule, which is known as the first messenger. The responding receptor contacts a nearby protein, called a regulator, which is the second protein in the pathway. Next, the regulator protein activates a nearby enzyme. The product of the reaction that the

TABLE 4.4   Intercellular Junctions

TYPE	FUNCTION	LOCATION
Tight junctions	Close spaces between animal cells by fusing cell membranes	Inside lining of small intestine
Desmosomes	Spot weld adjacent animal cell membranes	Outer skin layer
Gap junctions	Form channels between animal cells, allowing exchange of substances	Muscle cells in heart and digestive tract
Plasmodesmata	Allow substances to move between plant cells	Weakened areas of cell walls

enzyme catalyzes is called the second messenger, and it lies at the crux of the entire process. The second messenger triggers the cell's response, typically by activating certain genes or enzymes. cAMP is a very common second messenger that mediates many types of messages in cells. Because a single stimulus can trigger production of many second messenger molecules, signal transduction amplifies the incoming information.

Viagra, a drug used to treat erectile dysfunction (impotence), works by altering signal transduction. The drug binds to cyclic guanosine monophosphate (cGMP), a second messenger similar to cAMP. Viagra blocks binding of an enzyme that normally breaks down cGMP. With cGMP around longer, its effect of relaxing the muscle layer of blood vessels in the penis is sustained. The organ remains filled with blood longer.

Cell signaling coordinates the activation of dozens of related processes within a cell by producing groups of molecules that turn on and amplify the effects of other molecules. Signal transduction is extremely complex, with many steps and variants. Figure 4.22 presents a generalized view of the process.
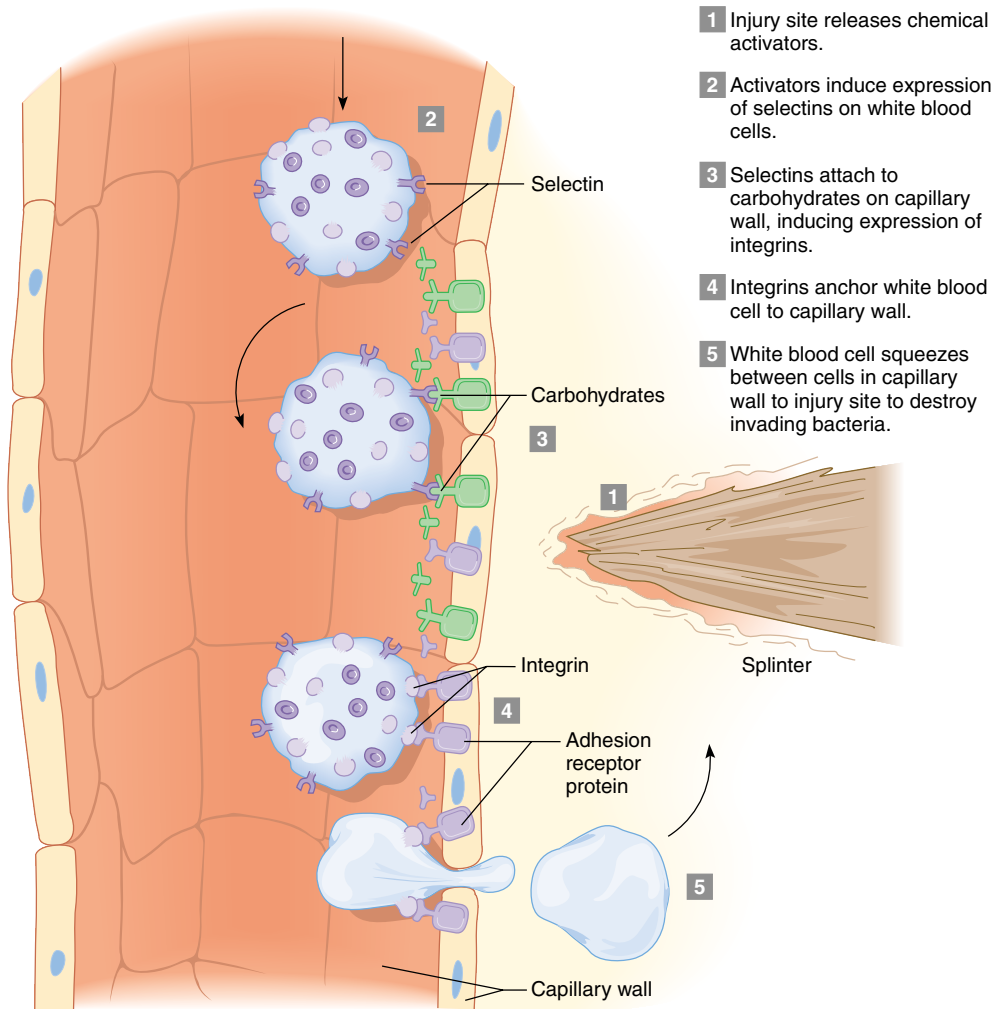

1 Injury site releases chemical activators.

2 Activators induce expression of selectins on white blood cells.

3 Selectins attach to carbohydrates on capillary wall, inducing expression of integrins.

4 Integrins anchor white blood cell to capillary wall.

5 White blood cell squeezes between cells in capillary wall to injury site to destroy invading bacteria.

FIGURE 4.21
Adhesion Aids in Defenses.
Cellular adhesion molecules (CAMs), including selectin, integrin, and receptors, direct white blood cells to injury sites.

4.3 MASTERING CONCEPTS

1. What types of structures link cells in animals?
2. What is the composition of a plant cell wall?
3. What functions do cell walls provide?
4. How do cellular adhesion molecules direct a white blood cell to an injury site?
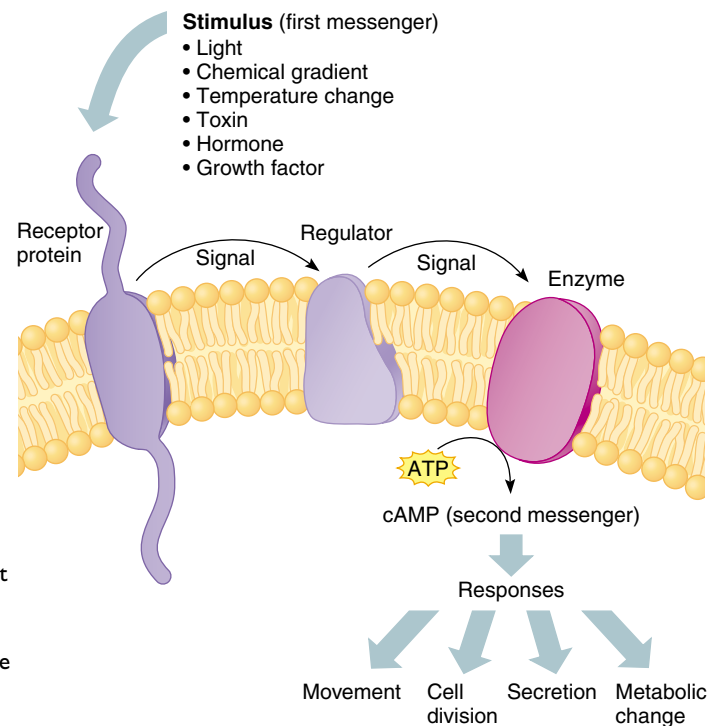5. How do cells transduce signals?

OLC

Stimulus (first messenger)
• Light
• Chemical gradient
• Temperature change
• Toxin
• Hormone
• Growth factor

Receptor protein   Regulator   Enzyme
Signal   Signal

ATP

cAMP (second messenger)

Responses

Movement   Cell division   Secretion   Metabolic change

FIGURE 4.22
Signal Transduction.
A first messenger binds a receptor, triggering a cascade of biochemical activity at the cell's surface. An enzyme, adenylate cyclase, catalyzes a reaction inside the cell that circularizes ATP to cyclic AMP, the second messenger. cAMP stimulates various responses, such as cell division, secretion, metabolic changes, and muscle contraction. The splitting of ATP also provides energy.

Chapter Summary

4.1 How Does the Cell Membrane Control Cell Function?

1. The cell surface is a selective interface between the cell and the outside environment. It receives and transmits incoming messages, controls which substances enter and leave the cell, and mediates attachments to and interactions with other cells and extracellular material.

2. The features of a cell's surface identify it as belonging to a particular species, individual, and tissue. The surface consists of molecules embedded in and extending from the cell membrane.

3. A biological membrane consists of a **phospholipid bilayer** embedded with movable proteins, glycoproteins, and glycolipids. The percentage and distribution of membrane proteins varies in different cell types. Membrane proteins carry out a variety of functions.

4. Substances cross cell membranes in several ways. In **diffusion,** a molecule passes through openings in a membrane following its **concentration gradient. Osmosis** is the simple diffusion of water across a semipermeable membrane. Terms describing **tonicity (isotonic, hypotonic, hypertonic)** predict whether cells will swell or shrink when the surroundings change. Cells are adapted to maintain shape when solute concentration changes.

5. A carrier protein transports a substance passively (without energy) or actively (with energy). In **cotransport,** a protein carries one substance down its concentration gradient, as well as a second substance.

6. In **exocytosis,** vesicles inside the cell carry substances to the cell membrane, where they fuse with the membrane and release the cargo outside. In **endocytosis,** molecules are brought into the cell by a vesicle in the cell membrane. **Endosomes** are vesicles that shuttle substances within cells. **Receptor-mediated endocytosis** is more specific. Within cells, proteins guide vesicles to particular organelles. Substances cross cells, entering by endocytosis and exiting by exocytosis, in **transcytosis.**

4.2 How Does the Cytoskeleton Support a Cell?

7. The **cytoskeleton** is a network of rods and tubules that provides cells with form, support, and the ability to move.

8. **Microtubules** self-assemble from hollow **tubulin** subunits to form **cilia, flagella,** and the spindle fibers that separate chromosomes during cell division. Some microtubules have a characteristic 9 + 2 configuration. **Dynein** causes adjacent microtubules to slide, which moves the overall structure.

9. **Microfilaments** are solid and smaller than microtubules. They are composed of the protein **actin** and provide contractile motion when they interact with **myosin.**

10. **Intermediate filaments** are intermediate in diameter between microtubules and microfilaments. They consist of entwined dimers of various proteins. They strengthen the cytoskeleton.

4.3 How Do Cells Interact and Respond to Signals?

11. Junctions connecting animal cells include **tight junctions, desmosomes,** and **gap junctions.** Tight junctions create a seal between adjacent cells. Desmosomes anchor cells in place. Gap junctions allow adjacent cells to exchange cytoplasmic material.

12. Most organisms other than animals have cell walls, which provide shape and mediate signals. Plant cell walls consist of cellulose fibrils connected by hemicellulose, plus pectin and various proteins. **Plasmodesmata** are continuations of cell membranes between cells through thinned parts of the cell wall.

13. **Cellular adhesion molecules** enable cells to contact each other in precise steps that carry out a particular function.

14. In **signal transduction,** receptors in the cell membrane receive input from **first messengers** and transmit the messages through a series of membrane proteins. Eventually this signaling activates a **second messenger,** which stimulates the cell to carry out a specific function.

Testing Your Knowledge

1. Why are some substances able to cross a cell membrane easily, and some not?
2. What types of chemicals comprise cell membranes?
3. Explain the differences among diffusion, facilitated diffusion, active transport, and endocytosis.
4. List five functions of the cytoskeleton.
5. List two functions of
   a. microtubules
   b. microfilaments
   c. intermediate filaments
6. Describe how cells use junctions in different ways.
7. Why are CAMs important?
8. What is signal transduction?

Thinking Scientifically

1. How does each of the following processes illustrate the interaction of cell components?
   a. maintaining the integrity of the red blood cell membrane
   b. the ability of muscle cells to withstand the force of contraction
   c. signal transduction
   d. cell adhesion in leukocyte trafficking
2. Describe how dynein and dystrophin are vital for the functioning of certain cells, even though they are not very abundant.
3. Liver cells are packed with glucose. What mechanism could be used to transport more glucose into a liver cell? Why would only this mode of transport work?
4. A drop of a 5% salt (NaCl) solution is added to a leaf of the aquatic plant *Elodea*. When the leaf is viewed under a microscope, colorless regions appear at the edges of each cell as the cell membranes shrink from the cell walls. What is happening to these cells?
5. Would a substance that destroys the integrity of the blood-brain barrier be dangerous? Why or why not?

References and Resources

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