3

Cells: The Living Units

Just as bricks and timbers are the structural units of a house, **cells** are the structural units of all living things, from one-celled "generalists" like amoebas to complex multicellular organisms such as humans, dogs, and trees. The human body has 50 to 100 trillion of these tiny building blocks.

This chapter focuses on structures and functions shared by all cells. We address specialized cells and their unique functions in later chapters.

The Cellular Basis of Life

✓ Define cell.

✓ List the three major regions of a generalized cell and their functions.

The English scientist Robert Hooke first observed plant cells with a crude microscope in the late 1600s. Then, in the 1830s two German scientists, Matthias Schleiden and Theodor Schwann, proposed that all living things are composed of cells. German pathologist Rudolf Virchow extended this idea by contending that cells arise only from other cells.

Since the late 1800s, cell research has been exceptionally fruitful and provided us with four concepts collectively known as the **cell theory**:

- A *cell* is the basic structural and functional unit of living organisms. When you define cell properties, you define the properties of life.
- The activity of an organism depends on both the individual and the collective activities of its cells.
- According to the *principle of complementarity of structure and function*, the biochemical activities of cells are dictated by their shapes or forms, and by the relative number of their specific subcellular structures.
- Continuity of life from one generation to another has a cellular basis.

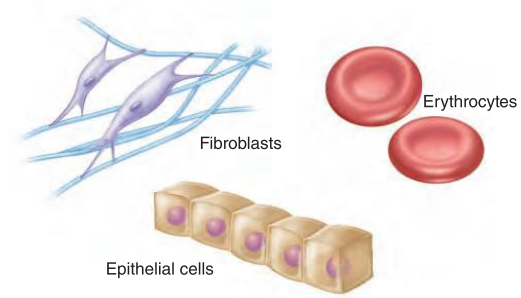
We will expand on all of these concepts as we progress. Let us begin with the idea that the cell is the smallest living unit. Whatever its form, however it behaves, the cell is the microscopic package that contains all the parts necessary to survive in an ever-changing world. It follows then that loss of cellular homeostasis underlies virtually every disease.

The trillions of cells in the human body include over 200 different cell types that vary greatly in shape, size, and function **(Figure 3.1)**. The disc-shaped red blood cells, branching nerve cells, and cubelike cells of kidney tubules are just a few examples of the shapes cells take. Cells also vary in length—ranging from 2 micrometers (1/12,000 of an inch) in the smallest cells to over a meter in the nerve cells that cause you to wiggle your toes. A cell's shape reflects its function. For example, the flat, tilelike epithelial cells that line the inside of your cheek fit closely together, forming a living barrier that protects underlying tissues from bacterial invasion.

Regardless of type, all cells are composed chiefly of carbon, hydrogen, nitrogen, oxygen, and trace amounts of several other elements. In addition, all cells have the same basic parts and some common functions. For this reason, it is possible to speak of a **generalized**, or **composite**, **cell (Figure 3.2)**.

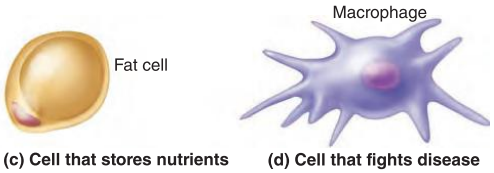
A human cell has three main parts:

- The *plasma membrane*: the outer boundary of the cell.
- The *cytoplasm* (si′to-plazm): the intracellular fluid packed with *organelles*, small structures that perform specific cell functions.
- The *nucleus* (nu′kle-us): an organelle that controls cellular activities. Typically the nucleus lies near the cell's center.

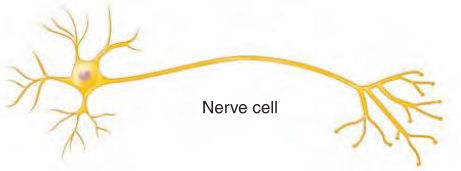


(a) Cells that connect body parts, form linings, or transport gases

(b) Cells that move organs and body parts



(c) Cell that stores nutrients **(d) Cell that fights disease**



(e) Cell that gathers information and controls body functions

(f) Cell of reproduction

Figure 3.1 Cell diversity. (Note that cells are not drawn to the same scale.)

Check Your Understanding

1. Summarize the four key points of the cell theory.
2. How would you explain the meaning of a "generalized cell" to a classmate?

For answers, see Appendix H.

Next, let's examine the three main parts of the cell in greater detail.

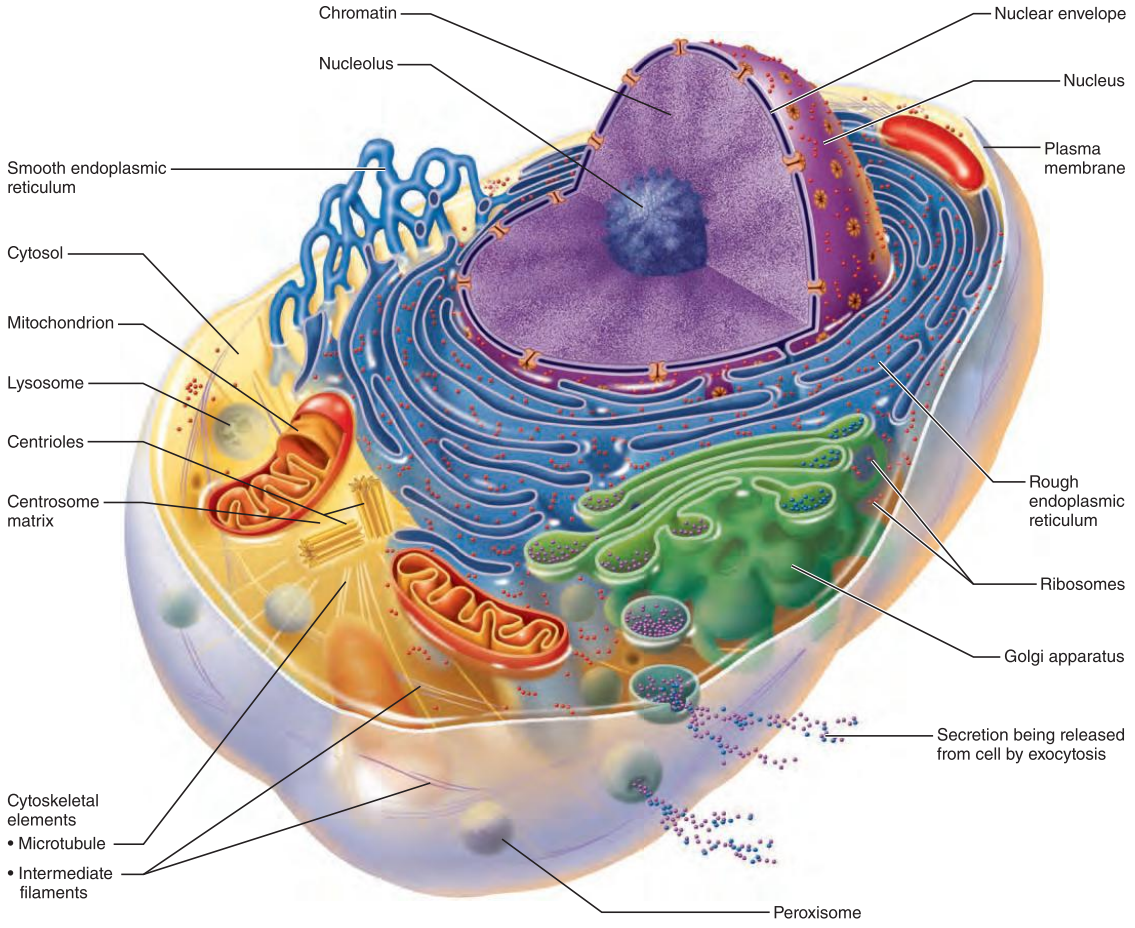


Figure 3.2 Structure of the generalized cell. No cell is exactly like this one, but this composite illustrates features common to many human cells. Note that not all of the organelles are drawn to the same scale in this illustration.

The Plasma Membrane: Structure

- ✓ Describe the chemical composition of the plasma membrane and relate it to membrane functions.
- ✓ Compare the structure and function of tight junctions, desmosomes, and gap junctions.

The flexible **plasma membrane** defines the extent of a cell, thereby separating two of the body's major fluid compartments—the *intracellular* fluid within cells and the *extracellular* fluid (ECF) outside cells. The term *cell membrane* is commonly used as a synonym for plasma membrane, but because nearly all cellular organelles are enclosed in a membrane, in this book we will always refer to the cell's surface, or outer limiting membrane, as the plasma membrane. The plasma membrane is much more than a passive envelope. As you will see, its unique structure allows it to play a dynamic role in cellular activities.

The Fluid Mosaic Model

The **fluid mosaic model** of membrane structure depicts the plasma membrane as an exceedingly thin (7–10 nm) structure composed of a double layer, or bilayer, of lipid molecules with protein molecules "plugged into" or dispersed in it **(Figure 3.3)**. The proteins, many of which float in the fluid *lipid bilayer*, form a constantly changing mosaic pattern. The model is named for this characteristic.

Membrane Lipids

The lipid bilayer forms the basic "fabric" of the membrane. It is constructed largely of *phospholipids*, with smaller amounts of *glycolipids*, *cholesterol*, and areas called *lipid rafts*.

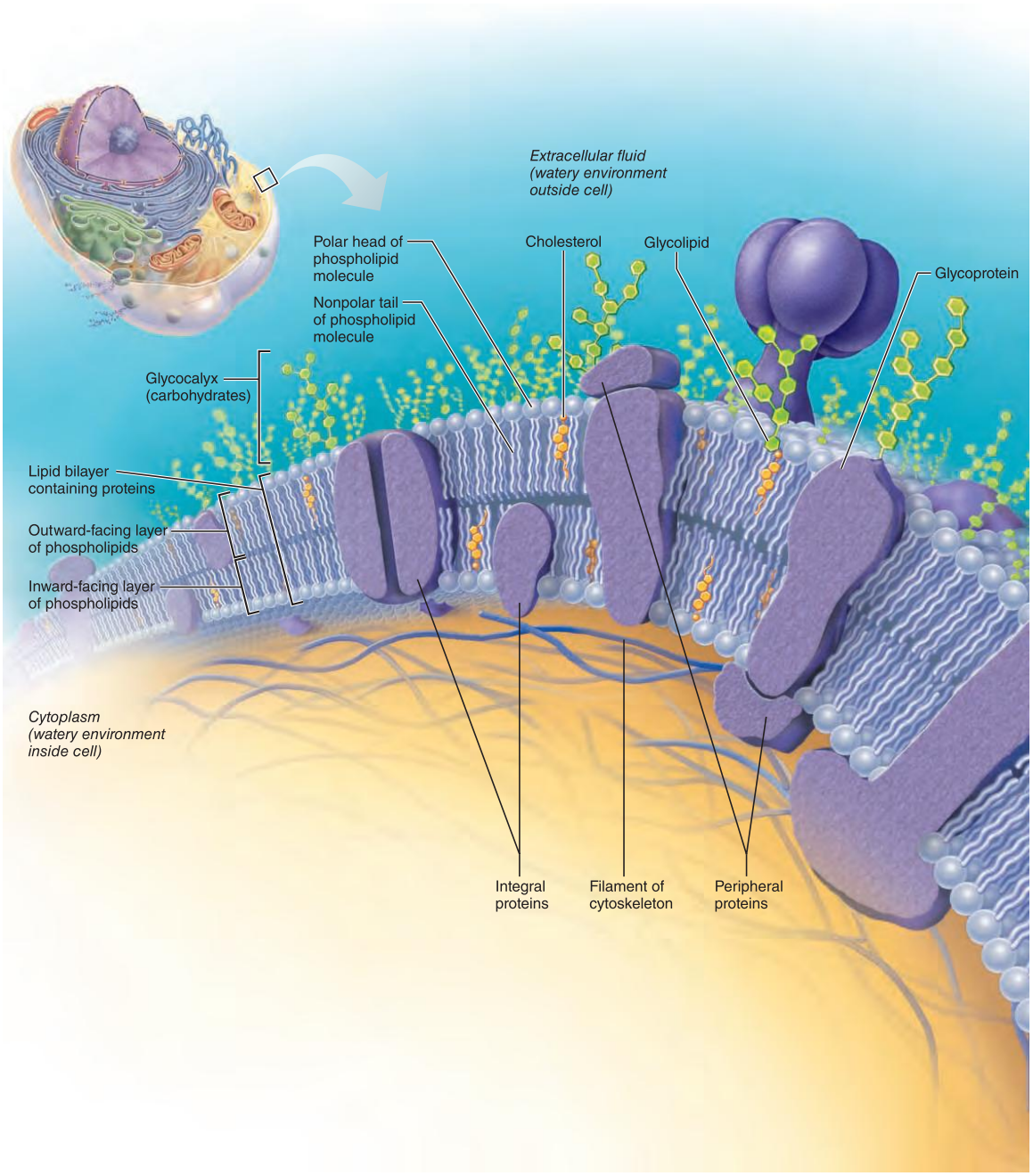


Figure 3.3 The plasma membrane. The lipid bilayer forms the basic structure of the membrane. The associated proteins are involved in membrane functions such as membrane transport, catalysis, and cell-to-cell recognition.

Phospholipids Each lollipop-shaped phospholipid molecule has a polar "head" that is charged and is **hydrophilic** (*hydro* = water, *philic* = loving), and an uncharged, nonpolar "tail" that is made of two fatty acid chains and is **hydrophobic** (*phobia* = fear). The polar heads are attracted to water—the main constituent of both the intracellular and extracellular fluids—and so they lie on both the inner and outer surfaces of the membrane. The nonpolar tails, being hydrophobic, avoid water and line up in the center of the membrane.

The result is that all plasma membranes, indeed all biological membranes, share a sandwich-like structure: They are composed of two parallel sheets of phospholipid molecules lying tail to tail, with their polar heads exposed to water on either side of the membrane or organelle. This self-orienting property of phospholipids encourages biological membranes to self-assemble into closed, generally spherical, structures and to reseal themselves when torn.

With a consistency similar to olive oil, the plasma membrane is a dynamic fluid structure in constant flux. Its lipid molecules move freely from side to side, parallel to the membrane surface, but their polar-nonpolar interactions prevent them from flip-flopping or moving from one half of the bilayer to the other half. The inward-facing and outward-facing surfaces of the plasma membrane differ in the kinds and amounts of lipids they contain, and these variations are important in determining local membrane structure and function. Most membrane phospholipids are unsaturated, a condition which kinks their tails (increasing the space between them) and increases membrane fluidity. (See the illustration of phosphatidylcholine in Figure 2.16b, p. 45.)

Glycolipids **Glycolipids** (gli″ko-lip′idz) are lipids with attached sugar groups. Found only on the outer plasma membrane surface, glycolipids account for about 5% of total membrane lipids. Their sugar groups, like the phosphate-containing groups of phospholipids, make that end of the glycolipid molecule polar, whereas the fatty acid tails are nonpolar.

Cholesterol Some 20% of membrane lipid is cholesterol. Like phospholipids, cholesterol has a polar region (its hydroxyl group) and a nonpolar region (its fused ring system). It wedges its platelike hydrocarbon rings between the phospholipid tails, stabilizing the membrane, while decreasing the mobility of the phospholipids and the fluidity of the membrane.

Membrane Proteins

A cell's plasma membrane bristles with proteins that allow it to communicate with its environment. Proteins make up about half of the plasma membrane by mass and are responsible for most of the specialized membrane functions. Some membrane proteins float freely. Others are "tethered" to intracellular structures that make up the *cytoskeleton* and are restricted in their movement.

There are two distinct populations of membrane proteins, integral and peripheral (Figure 3.3).

Integral Proteins **Integral proteins** are firmly inserted into the lipid bilayer. Some protrude from one membrane face only, but most are *transmembrane proteins* that span the entire membrane and protrude on both sides. Whether transmembrane or not, all integral proteins have both hydrophobic and hydrophilic regions. This structural feature allows them to interact with both the nonpolar lipid tails buried in the membrane and the water inside and outside the cell.

Some transmembrane proteins are involved in transport, and cluster together to form *channels*, or pores, through which small, water-soluble molecules or ions can move, thus bypassing the lipid part of the membrane. Others act as *carriers* that bind to a substance and then move it through the membrane **(Figure 3.4a)**. Some transmembrane proteins are enzymes (Figure 3.4d). Still others are receptors for hormones or other chemical messengers and relay messages to the cell interior—a process called *signal transduction* (Figure 3.4b).

Peripheral Proteins Unlike integral proteins, **peripheral proteins** (Figure 3.3) are not embedded in the lipid bilayer. Instead, they attach loosely to integral proteins and are easily removed without disrupting the membrane. Peripheral proteins include a network of filaments that helps support the membrane from its cytoplasmic side (Figure 3.4c). Some peripheral proteins are enzymes. Others are motor proteins involved in mechanical functions, such as changing cell shape during cell division and muscle cell contraction. Still others link cells together.

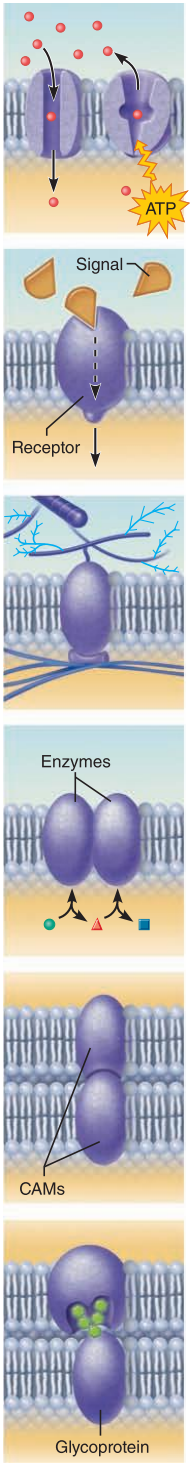
Lipid Rafts

About 20% of the outer membrane surface contains **lipid rafts**, dynamic assemblies of saturated phospholipids (which pack together tightly) associated with unique lipids called sphingolipids and lots of cholesterol. The quiltlike lipid rafts are more stable and less fluid than the rest of the membrane, and they can include or exclude specific proteins to various extents. Because of these qualities, lipid rafts are assumed to be concentrating platforms for certain receptor molecules or for protein molecules needed for cell signaling (discussed on p. 81), membrane invagination (see endocytosis, p. 77), or other functions.

The Glycocalyx

Many of the proteins that abut the extracellular fluid are glycoproteins with branching sugar groups. The term **glycocalyx** (gli″ko-kal′iks; "sugar covering") describes the fuzzy, sticky, carbohydrate-rich area at the cell surface. Quite honestly, you can think of your cells as sugar-coated. The glycocalyx on each cell's surface is enriched both by glycolipids and by glycoproteins secreted by the cell.

Because every cell type has a different pattern of sugars in its glycocalyx, the glycocalyx provides highly specific biological markers by which approaching cells recognize each other (Figure 3.4f). For example, a sperm recognizes an ovum (egg cell) by the ovum's unique glycocalyx. Cells of the immune system identify a bacterium by binding to certain membrane glycoproteins in the bacterial glycocalyx.



(a) Transport

- A protein (left) that spans the membrane may provide a hydrophilic channel across the membrane that is selective for a particular solute.
- Some transport proteins (right) hydrolyze ATP as an energy source to actively pump substances across the membrane.

(b) Receptors for signal transduction

- A membrane protein exposed to the outside of the cell may have a binding site that fits the shape of a specific chemical messenger, such as a hormone.
- When bound, the chemical messenger may cause a change in shape in the protein that initiates a chain of chemical reactions in the cell.

(c) Attachment to the cytoskeleton and extracellular matrix

- Elements of the cytoskeleton (cell's internal supports) and the extracellular matrix (fibers and other substances outside the cell) may anchor to membrane proteins, which helps maintain cell shape and fix the location of certain membrane proteins.
- Others play a role in cell movement or bind adjacent cells together.

(d) Enzymatic activity

- A membrane protein may be an enzyme with its active site exposed to substances in the adjacent solution.
- A team of several enzymes in a membrane may catalyze sequential steps of a metabolic pathway as indicated (left to right) here.

(e) Intercellular joining

- Membrane proteins of adjacent cells may be hooked together in various kinds of intercellular junctions.
- Some membrane proteins (cell adhesion molecules or CAMs) of this group provide temporary binding sites that guide cell migration and other cell-to-cell interactions.

(f) Cell-cell recognition

- Some glycoproteins (proteins bonded to short chains of sugars) serve as identification tags that are specifically recognized by other cells.

Figure 3.4 Membrane proteins perform many tasks. A single protein may perform a combination of these functions.

Homeostatic Imbalance 3.1

Definite changes occur in the glycocalyx of a cell that is becoming cancerous. In fact, a cancer cell's glycocalyx may change almost continuously, allowing it to keep ahead of immune system recognition mechanisms and avoid destruction. (Cancer is discussed on pp. 145–146.) ✚

Check Your Understanding

3. What basic structure do all cellular membranes share?
4. Why do phospholipids, which form the greater part of membranes, organize into a bilayer—tail-to-tail—in a watery environment?
5. What is the importance of the glycocalyx in cell interactions?

For answers, see Appendix H.

Cell Junctions

Although certain cell types—blood cells, sperm cells, and some immune system cells—are "footloose" in the body, many other types are knit into tight communities. Typically, three factors act to bind cells together:

- Glycoproteins in the glycocalyx act as an adhesive.
- Wavy contours of the membranes of adjacent cells fit together in a tongue-and-groove fashion.
- Special cell junctions form **(Figure 3.5)**.

Because junctions are the most important factor securing cells together, let's look more closely at the various types.

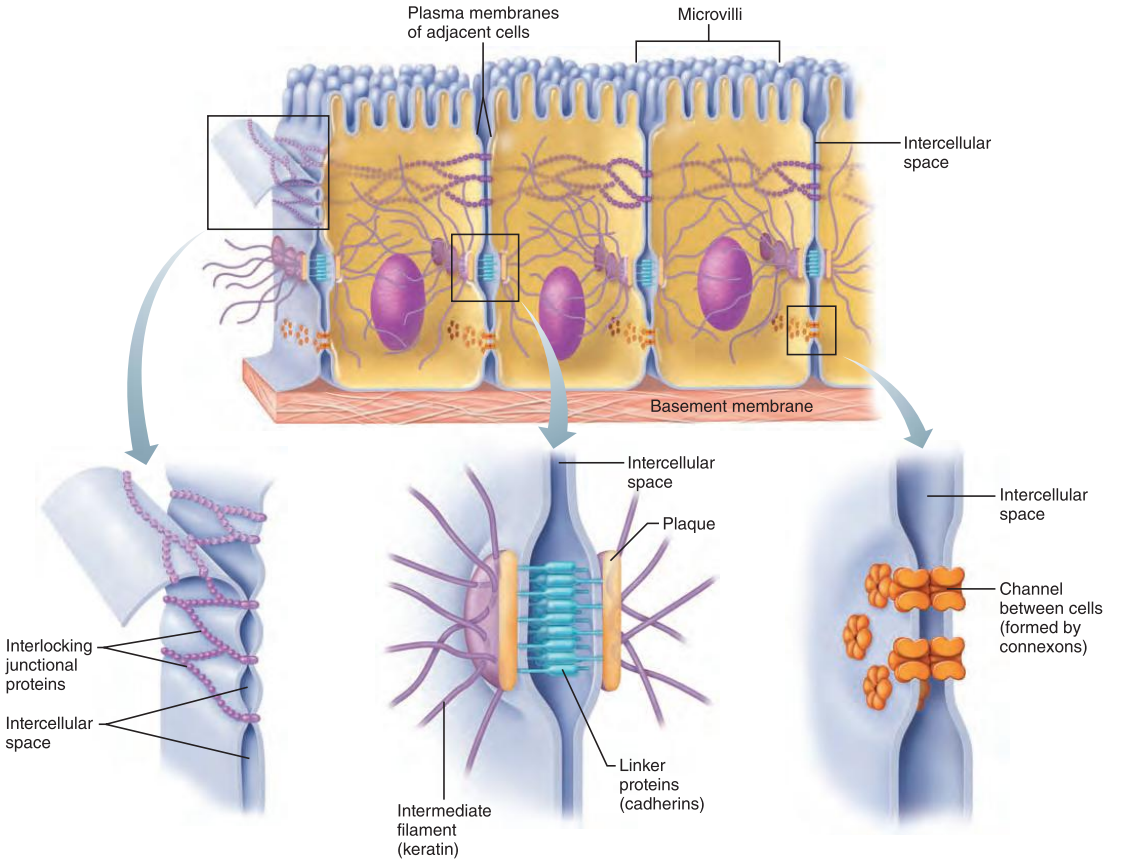
Tight Junctions

In a **tight junction**, a series of integral protein molecules in the plasma membranes of adjacent cells fuse together, forming an *impermeable junction* that encircles the cell (Figure 3.5a). Tight junctions help prevent molecules from passing through the extracellular space between adjacent cells. For example, tight junctions between epithelial cells lining the digestive tract keep digestive enzymes and microorganisms in the intestine from seeping into the bloodstream. (Although called "impermeable" junctions, some tight junctions are leaky and may allow certain ions to pass.)

Desmosomes

Desmosomes (des′muh-sōmz; "binding bodies") are *anchoring junctions*—mechanical couplings scattered like rivets along the sides of abutting cells to prevent their separation (Figure 3.5b). On the cytoplasmic face of each plasma membrane is a buttonlike thickening called a *plaque*. Adjacent cells are held together by thin linker protein filaments (cadherins) that extend from the plaques and fit together like the teeth of a zipper in the intercellular space. Thicker keratin filaments (intermediate filaments, which form part of the cytoskeleton) extend from the cytoplasmic side of the plaque across the width of the cell to anchor to the plaque on the cell's opposite side. In this way, desmosomes bind neighboring cells together and also contribute to a continuous internal network of strong "guy-wires."

This arrangement distributes tension throughout a cellular sheet and reduces the chance of tearing when it is subjected to



(a) Tight junctions: Impermeable junctions prevent molecules from passing through the intercellular space.

(b) Desmosomes: Anchoring junctions bind adjacent cells together like a molecular "Velcro" and help form an internal tension-reducing network of fibers.

(c) Gap junctions: Communicating junctions allow ions and small molecules to pass for intercellular communication.

Figure 3.5 Cell junctions. An epithelial cell is shown joined to adjacent cells by three common types of cell junctions. (Note: Except for epithelia, it is unlikely that a single cell will have all three junction types.)

pulling forces. Desmosomes are abundant in tissues subjected to great mechanical stress, such as skin and heart muscle.

Gap Junctions

A **gap junction**, or *nexus* (nek′sus; "bond"), is a communicating junction between adjacent cells. At gap junctions the adjacent plasma membranes are very close, and the cells are connected by hollow cylinders called *connexons* (kŏ-nek′sonz), composed of transmembrane proteins. The many different types of connexon proteins vary the selectivity of the gap junction channels. Ions, simple sugars, and other small molecules pass through these water-filled channels from one cell to the next (Figure 3.5c).

Gap junctions are present in electrically excitable tissues, such as the heart and smooth muscle, where ion passage from cell to cell helps synchronize their electrical activity and contraction.

Check Your Understanding

6. Which two types of cell junctions would you expect to find between muscle cells of the heart?

For answer, see Appendix H.

The Plasma Membrane: Membrane Transport

- Relate plasma membrane structure to active and passive transport processes.
- Compare and contrast simple diffusion, facilitated diffusion, and osmosis relative to substances transported, direction, and mechanism.

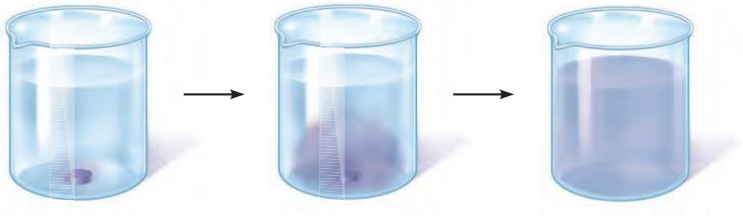


Figure 3.6 Diffusion. Molecules in solution move continuously and collide constantly with other molecules, causing them to move away from areas of their highest concentration and become evenly distributed. From left to right, molecules from a dye pellet diffuse into the surrounding water down their concentration gradient.

Our cells are bathed in an extracellular fluid called **interstitial fluid** (in″ter-stish′al) that is derived from the blood. Like a rich, nutritious "soup," interstitial fluid contains thousands of ingredients, including amino acids, sugars, fatty acids, vitamins, regulatory substances such as hormones and neurotransmitters, salts, and waste products. To remain healthy, each cell must extract from this mix the exact amounts of the substances it needs at specific times.

Although there is continuous traffic across the plasma membrane, it is a **selectively**, or **differentially**, **permeable** barrier: It allows some substances to pass while excluding others. It allows nutrients to enter the cell, but keeps many undesirable substances out. At the same time, it keeps valuable cell proteins and other necessary substances in the cell, but allows wastes to exit.

Substances move through the plasma membrane in essentially two ways—passively or actively. In **passive processes**, substances cross the membrane without any energy input from the cell. In **active processes**, the cell provides the metabolic energy (usually ATP) needed to move substances across the membrane. Table 3.1 on p. 72 summarizes passive transport processes, and Table 3.2 on p. 78 summarizes active transport.

Homeostatic Imbalance 3.2

Selective permeability is a characteristic of healthy, intact cells. When a cell (or its plasma membrane) is severely damaged, the membrane becomes permeable to virtually everything, and substances flow into and out of the cell freely. This phenomenon is evident when someone has been severely burned. Precious fluids, proteins, and ions "weep" from the damaged cells. ✚

Passive Processes

The two main types of passive transport are *diffusion* (dĭ-fu′zhun) and *filtration*. Diffusion is an important means of passive membrane transport for every cell of the body. Because filtration generally occurs only across capillary walls, we will discuss it later in conjunction with capillary transport.

Diffusion

Diffusion is the tendency of molecules or ions to move from an area where they are in higher concentration to an area where they are in lower concentration, that is, down or along their **concentration gradient**. The constant random and high-speed motion of molecules and ions (a result of their intrinsic kinetic energy) results in collisions. With each collision, the particles ricochet off one another and change direction. The overall effect of this erratic movement is to scatter or disperse the particles throughout the environment **(Figure 3.6)**. The greater the difference in concentration of the diffusing molecules and ions between the two areas, the more collisions occur and the faster the net diffusion of the particles.

Because the driving force for diffusion is the kinetic energy of the molecules themselves, the speed of diffusion is influenced by molecular *size* (the smaller, the faster) and by *temperature* (the warmer, the faster). In a closed container, diffusion eventually produces a uniform mixture of molecules. In other words, the system reaches equilibrium, with molecules moving equally in all directions (no *net* movement).

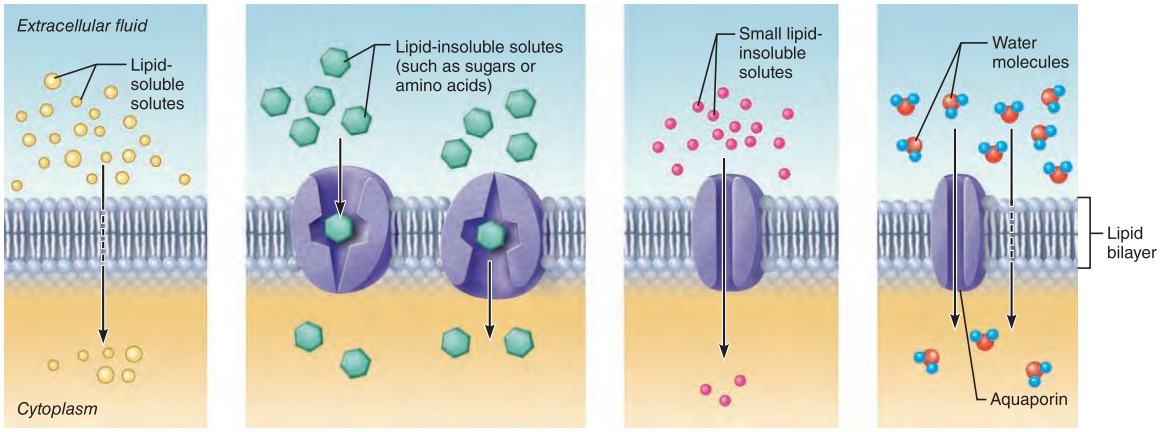
Diffusion is immensely important in physiological systems and it occurs rapidly because the distances molecules are moving are very short, perhaps 1/1000 (or less) the thickness of this page! Examples include the movement of ions across cell membranes and the movement of neurotransmitters between two nerve cells.

The plasma membrane is a physical barrier to free diffusion because of its hydrophobic core. However, a molecule or ion *will* diffuse through the membrane if the molecule is (1) lipid soluble, (2) small enough to pass through membrane channels, or (3) assisted by a carrier molecule.

The unassisted diffusion of lipid-soluble or very small particles is called *simple diffusion*. Assisted diffusion is known as *facilitated diffusion*. A special name, *osmosis*, is given to the diffusion of a solvent (usually water) through a membrane.

Simple Diffusion In **simple diffusion**, nonpolar and lipid-soluble substances diffuse directly through the lipid bilayer **(Figure 3.7a)**. Such substances include oxygen, carbon dioxide, and fat-soluble vitamins. Because oxygen concentration is always higher in the blood than in tissue cells, oxygen continuously diffuses from the blood into the cells. Carbon dioxide, on the other hand, is in higher concentration within the cells, so it diffuses from tissue cells into the blood.

Facilitated Diffusion Certain molecules, notably glucose and other sugars, some amino acids, and ions are transported



(a) Simple diffusion of fat-soluble molecules directly through the phospholipid bilayer

(b) Carrier-mediated facilitated diffusion via protein carrier specific for one chemical; binding of substrate causes transport protein to change shape

(c) Channel-mediated facilitated diffusion through a channel protein; mostly ions selected on basis of size and charge

(d) Osmosis, diffusion of a solvent such as water through a specific channel protein (aquaporin) or through the lipid bilayer

Figure 3.7 Diffusion through the plasma membrane.

passively even though they are unable to pass through the lipid bilayer. Instead they move through the membrane by a passive transport process called **facilitated diffusion** in which the transported substance either (1) binds to protein carriers in the membrane and is ferried across or (2) moves through water-filled protein channels.

- **Carrier-mediated facilitated diffusion. Carriers** are transmembrane integral proteins that are specific for transporting certain polar molecules or classes of molecules, such as sugars and amino acids, that are too large to pass through membrane channels. Alterations in the shape of the carrier allow it to first envelop and then release the transported substance, shielding it en route from the nonpolar regions of the membrane. Essentially, changes in the conformation of the carrier protein move the binding site from one face of the membrane to the other (Figure 3.7b and Table 3.1).

  Note that a substance transported by carrier-mediated facilitated diffusion, such as glucose, moves down its concentration gradient, just as in simple diffusion. Glucose is normally in higher concentrations in the blood than in the cells, where it is rapidly used for ATP synthesis. So, glucose transport within the body is *typically* unidirectional—into the cells. However, carrier-mediated transport is limited by the number of protein carriers present. For example, when all the glucose carriers are "engaged," they are said to be *saturated*, and glucose transport is occurring at its maximum rate.
- **Channel-mediated facilitated diffusion. Channels** are transmembrane proteins that transport substances, usually ions or water, through aqueous channels from one side of the membrane to the other (Figure 3.7c and d). Channels are selective due to pore size and the charges of the amino acids lining the channel. *Leakage channels* are always open and simply allow ions or water to move according to concentration gradients. *Gated channels* are controlled (opened or closed) by chemical or electrical signals.

  Like carriers, many channels can be inhibited by certain molecules, show saturation, and tend to be specific. Substances moving through them also follow the concentration gradient (always moving down the gradient). When a substance crosses the membrane by simple diffusion, the rate of diffusion is not controllable because the lipid solubility of the membrane is not immediately changeable. By contrast, the rate of facilitated diffusion *is* controllable because the permeability of the membrane can be altered by regulating the activity or number of individual carriers or channels.

Oxygen, water, glucose, and various ions are vitally important to cellular homeostasis. Their passive transport by diffusion (either simple or facilitated) represents a tremendous saving of cellular energy. Indeed, if these substances had to be transported actively, cell expenditures of ATP would increase exponentially!

Osmosis The diffusion of a solvent, such as water, through a selectively permeable membrane is **osmosis** (oz-mo′sis; *osmos* = pushing). Even though water is highly polar, it passes via osmosis through the lipid bilayer (Figure 3.7d). This is surprising because you'd expect water to be repelled by the hydrophobic lipid tails. One hypothesis is that random movements of the membrane lipids open small gaps between their wiggling tails, allowing water to slip and slide its way through the membrane by moving from gap to gap.

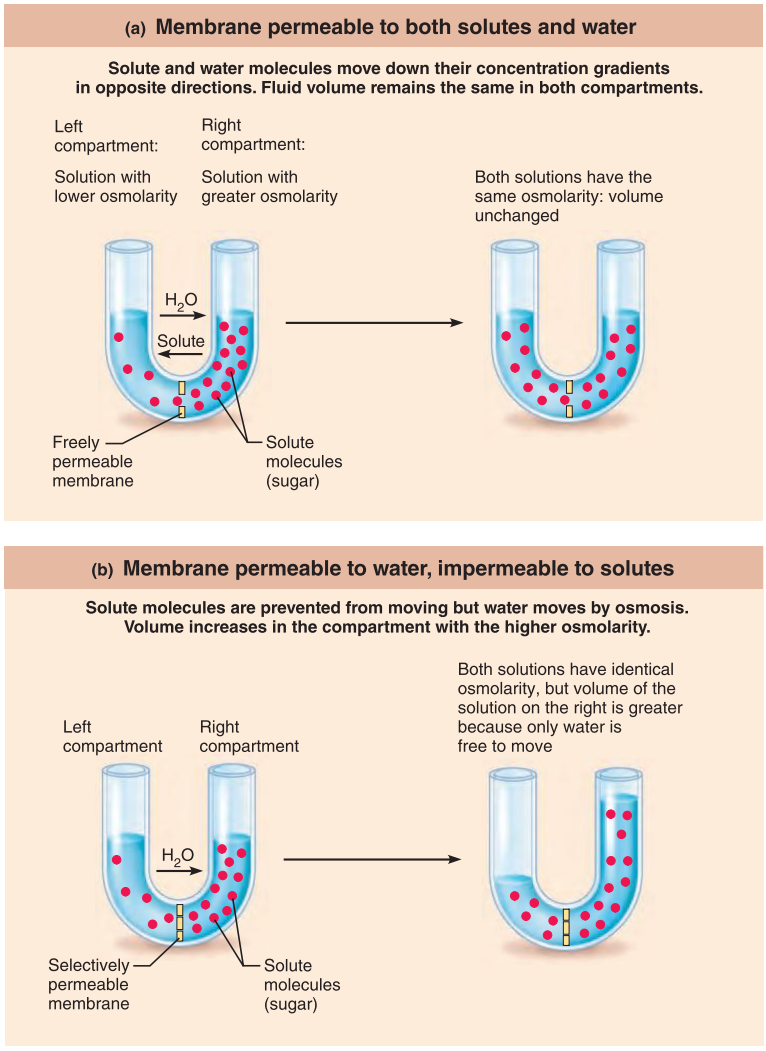


Figure 3.8 **Influence of membrane permeability on diffusion and osmosis.**

Water also moves freely and reversibly through water-specific channels constructed by transmembrane proteins called **aquaporins (AQPs)**, which allow single-file diffusion of water molecules. Although water-filled aquaporin channels are believed to be present in all cell types, they are particularly abundant in red blood cells and in cells involved in water balance such as kidney tubule cells.

Osmosis occurs whenever the water concentration differs on the two sides of a membrane. If distilled water is present on both sides of a selectively permeable membrane, no *net* osmosis occurs, even though water molecules move in both directions through the membrane. If the solute concentration on the two sides of the membrane differs, water concentration differs as well (as solute concentration increases, water concentration decreases).

The extent to which solutes decrease water's concentration depends on the *number*—not the *type*—of solute particles, because one molecule or one ion of solute (theoretically) displaces one water molecule. The total concentration of all solute particles in a solution is referred to as the solution's **osmolarity** (oz″mo-lar′ĭ-te). When equal volumes of aqueous solutions of different osmolarity are separated by a membrane that is *permeable to all molecules* in the system, net diffusion of both solute

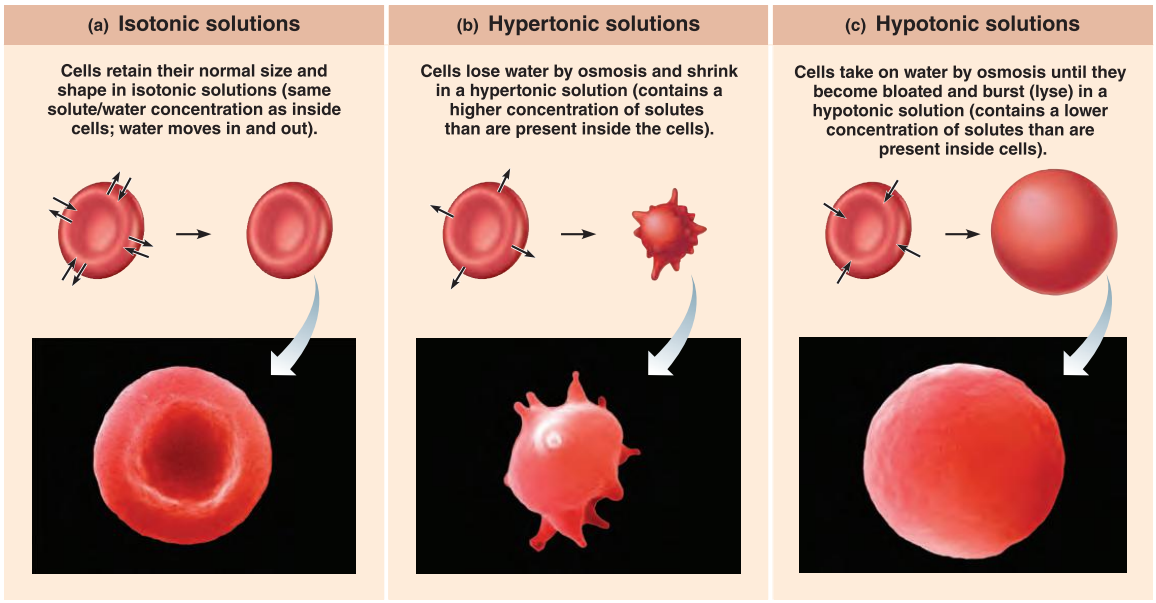


Figure 3.9 **The effect of solutions of varying tonicities on living red blood cells.**

and water occurs, each moving down its own concentration gradient. Equilibrium is reached when the water (and solute) concentration on both sides of the membrane is the same **(Figure 3.8a)**.

If we consider the same system, but make the membrane *impermeable to solute particles*, we see quite a different result (Figure 3.8b). Water quickly diffuses from the left to the right compartment and continues to do so until its concentration is the same on the two sides of the membrane. Notice that in this case equilibrium results from the movement of water alone (the solutes are prevented from moving). Notice also that the movement of water leads to dramatic changes in the volumes of the two compartments.

The last situation mimics osmosis across plasma membranes of living cells, with one major difference. In our examples, the volumes of the compartments are infinitely expandable and the effect of pressure exerted by the added weight of the higher fluid column is not considered. In living plant cells, which have rigid cell walls external to their plasma membranes, this is not the case. As water diffuses into the cell, the point is finally reached where the **hydrostatic pressure** (the back pressure exerted by water against the membrane) within the cell is equal to its **osmotic pressure** (the tendency of water to move into the cell by osmosis). At this point, there is no further (net) water entry. As a rule, the higher the amount of nondiffusible, or *nonpenetrating*, solutes in a cell, the higher the osmotic pressure and the greater the hydrostatic pressure must be to resist further net water entry. In our plant cell, hydrostatic pressure is pushing water out, and osmotic pressure is pulling water in; therefore, you could think of the osmotic pressure as an osmotic "suck."

However, such major changes in hydrostatic (and osmotic) pressures do not occur in living animal cells, which lack rigid cell walls. Osmotic imbalances cause animal cells to swell or shrink (due to net water gain or loss) until either (1) the solute concentration is the same on both sides of the plasma membrane, or (2) the membrane stretches to its breaking point.

Tonicity Such changes in animal cells lead us to the important concept of *tonicity* (to-nis′ĭ-te). As noted, many solutes, particularly intracellular proteins and selected ions, cannot diffuse through the plasma membrane. Consequently, any change in their concentration alters the water concentration on the two sides of the membrane and results in a net loss or gain of water by the cell.

Tonicity refers to the ability of a solution to change the shape or tone of cells by altering the cells' internal water volume (*tono* = tension).

- **Isotonic** ("the same tonicity") **solutions** have the same concentrations of nonpenetrating solutes as those found in cells (0.9% saline or 5% glucose). Cells exposed to isotonic solutions retain their normal shape, and exhibit no net loss or gain of water **(Figure 3.9a)**. As you might expect, the body's extracellular fluids and most intravenous solutions (solutions infused into the body via a vein) are isotonic.
- **Hypertonic solutions** have a higher concentration of nonpenetrating solutes than seen in the cell (for example, a strong saline solution). Cells immersed in hypertonic solutions lose water and shrink, or *crenate* (kre′nat) (Figure 3.9b).

Table 3.1 Passive Membrane Transport Processes

PROCESS	ENERGY SOURCE	DESCRIPTION	EXAMPLES
Diffusion			
Simple diffusion	Kinetic energy	Net movement of molecules from an area of their higher concentration to an area of their lower concentration, that is, along their concentration gradient	Fats, oxygen, carbon dioxide move through the lipid bilayer of the membrane
Facilitated diffusion	Kinetic energy	Same as simple diffusion, but the diffusing substance is attached to a lipid-soluble membrane carrier protein (carrier-mediated facilitated diffusion) or moves through a membrane channel (channel-mediated facilitated diffusion)	Glucose and some ions move into cells
Osmosis	Kinetic energy	Diffusion of water through a selectively permeable membrane	Movement of water into and out of cells directly through the lipid bilayer of the membrane or via membrane channels (aquaporins)

- **Hypotonic solutions** are more dilute (contain a lower concentration of nonpenetrating solutes) than cells. Cells placed in a hypotonic solution plump up rapidly as water rushes into them (Figure 3.9c). Distilled water represents the most extreme example of hypotonicity. Because it contains *no* solutes, water continues to enter cells until they finally burst, or *lyse*.

Notice that osmolarity and tonicity are not the same. A solution's osmolarity is based solely on its total solute concentration. In contrast, its tonicity is based on how the solution affects cell volume, which depends on (1) solute concentration and (2) solute permeability of the plasma membrane. Osmolarity is expressed as osmoles per liter (osmol/L) where 1 osmol is equal to 1 mole of nonionizing molecules.* A 0.3 osmol/L solution of NaCl is isotonic because sodium ions are usually prevented from diffusing through the plasma membrane. But if the cell is immersed in a 0.3 osmol/L solution of a penetrating solute, the solute will enter the cell and water will follow. The cell will swell and burst, just as if it had been placed in pure water.

Osmosis is extremely important in determining distribution of water in the various fluid-containing compartments of the body (cells, blood, and so on). In general, osmosis continues until osmotic and hydrostatic pressures acting at the membrane are equal. For example, the hydrostatic pressure of blood against the capillary wall forces water out of capillary blood, but the solutes in blood that are too large to cross the capillary membrane draw water back into the bloodstream. As a result, very little net loss of plasma fluid occurs.

Simple diffusion and osmosis occurring directly through the plasma membrane are not selective processes. In those processes, whether a molecule can pass through the membrane depends chiefly on its size or its solubility in lipid, not on its structure. Facilitated diffusion, on the other hand, is often highly selective. The carrier for glucose, for example, combines specifically with glucose, in much the same way an enzyme binds to its specific substrate and ion channels allow only selected ions to pass.

*Osmolarity (Osm) is determined by multiplying molarity (moles per liter, or *M*) by the number of particles resulting from ionization. For example, since NaCl ionizes to $Na^+ + Cl^-$, a 1 *M* solution of NaCl is a 2 Osm solution. For substances that do not ionize (e.g., glucose), molarity and osmolarity are the same. More precisely, the term *osmolality* is used, which is equal to the number of particles mixed into a kilogram of water.

Homeostatic Imbalance 3.3

Hypertonic solutions are sometimes infused intravenously into the bloodstream of patients who are edematous (swollen because their tissues retain water). This is done to draw excess water out of the extracellular space and move it into the bloodstream so the kidneys can eliminate it. Hypotonic solutions may be used (with care) to rehydrate the tissues of extremely dehydrated patients. In mild cases of dehydration, drinking hypotonic fluids (such as apple juice and sports drinks) usually does the trick. ✚

Table 3.1 summarizes passive membrane transport processes.

Check Your Understanding

7. What is the energy source for all types of diffusion?
8. What determines the direction of any diffusion process?
9. What are the two types of facilitated diffusion and how do they differ?

For answers, see Appendix H.

Active Processes

- ✓ Differentiate between primary and secondary active transport.
- ✓ Compare and contrast endocytosis and exocytosis in terms of function and direction.
- ✓ Compare and contrast pinocytosis, phagocytosis, and receptor-mediated endocytosis.

Whenever a cell uses energy to move solutes across the membrane, the process is referred to as *active*. Substances moved actively across the plasma membrane are usually unable to pass in the necessary direction by passive transport processes. The substance may be too large to pass through the channels, incapable of dissolving in the lipid bilayer, or unable to move down its concentration gradient.

There are two major means of active membrane transport: active transport and vesicular transport.

Active Transport

Like carrier-mediated facilitated diffusion, **active transport** requires carrier proteins that combine *specifically* and *reversibly* with the transported substances. However, facilitated diffusion always follows concentration gradients because its driving force is kinetic energy. In contrast, active transporters or **solute pumps** move solutes, most importantly ions, "uphill" *against* a concentration gradient. To do this work, cells must expend energy.

Active transport processes are distinguished according to their source of energy:

- In *primary active transport*, the energy to do work comes *directly from hydrolysis of ATP*.
- In *secondary active transport*, transport is driven indirectly *by energy stored in ionic gradients* created by primary active transport pumps. Secondary active transport systems are all *coupled systems*; that is, they move more than one substance at a time.

  In a **symport system,** the two transported substances move in the same direction (*sym* = same). In an **antiport system** (*anti* = opposite, against), the transported substances "wave to each other" as they cross the membrane in opposite directions.

Primary Active Transport In **primary active transport**, hydrolysis of ATP results in the phosphorylation of the transport protein. This step causes the protein to change its shape in such a manner that it "pumps" the bound solute across the membrane.

Primary active transport systems include calcium and hydrogen pumps, but the most investigated example of a primary active transport system is the **sodium-potassium pump**, for which the carrier, or "pump," is an enzyme called **Na^+-K^+ ATPase**. In the body, the concentration of K^+ inside the cell is some 10 times higher than that outside, and the reverse is true of Na^+. These ionic concentration differences are essential for excitable cells like muscle and nerve cells to function normally and for all body cells to maintain their normal fluid volume. Because Na^+ and K^+ leak slowly but continuously through leakage channels in the plasma membrane along their concentration gradient (and cross more rapidly in stimulated muscle and nerve cells), the Na^+-K^+ pump operates almost continuously as an antiporter. It simultaneously drives Na^+ out of the cell against a steep concentration gradient and pumps K^+ back in.

Earlier we said that solutes diffuse down their concentration gradients. This is true for uncharged solutes, but only partially true for ions. The negatively and positively charged faces of the plasma membrane can help or hinder diffusion of ions driven by a concentration gradient. It is more correct to say that ions diffuse according to **electrochemical gradients**, thereby recognizing the effect of both electrical and concentration (chemical) forces. Hence, the electrochemical gradients maintained by the Na^+-K^+ pump underlie most secondary active transport of nutrients and ions, and are crucial for cardiac, skeletal muscle, and neuron function.

Figure 3.10 on p. 74, *Focus on Primary Active Transport: The Na^+-K^+ Pump*, describes the operation of the Na^+-K^+pump. Make sure you understand this process thoroughly before moving on to the topic of secondary active transport.

Secondary Active Transport A single ATP-powered pump, such as the Na^+-K^+ pump, can indirectly drive the **secondary active transport** of several other solutes. By moving sodium across the plasma membrane against its concentration gradient, the pump stores energy (in the ion gradient). Then, just as water pumped uphill can do work as it flows back down (to turn a water wheel, for instance), a substance pumped across a membrane can do work as it leaks back, propelled "downhill" along its concentration gradient. In this way, as sodium moves back into the cell with the help of a carrier protein, other substances are "dragged along," or cotransported, by the same carrier protein **(Figure 3.11)**. This is a symport system.

For example, some sugars, amino acids, and many ions are cotransported via secondary active transport into cells lining the small intestine. Because the energy for this type of transport is the concentration gradient of the ion (in this case Na^+), Na^+ has to be pumped back out of the cell to maintain its diffusion gradient. Ion gradients can also drive antiport systems such as those that help regulate intracellular pH by using the sodium gradient to expel hydrogen ions.

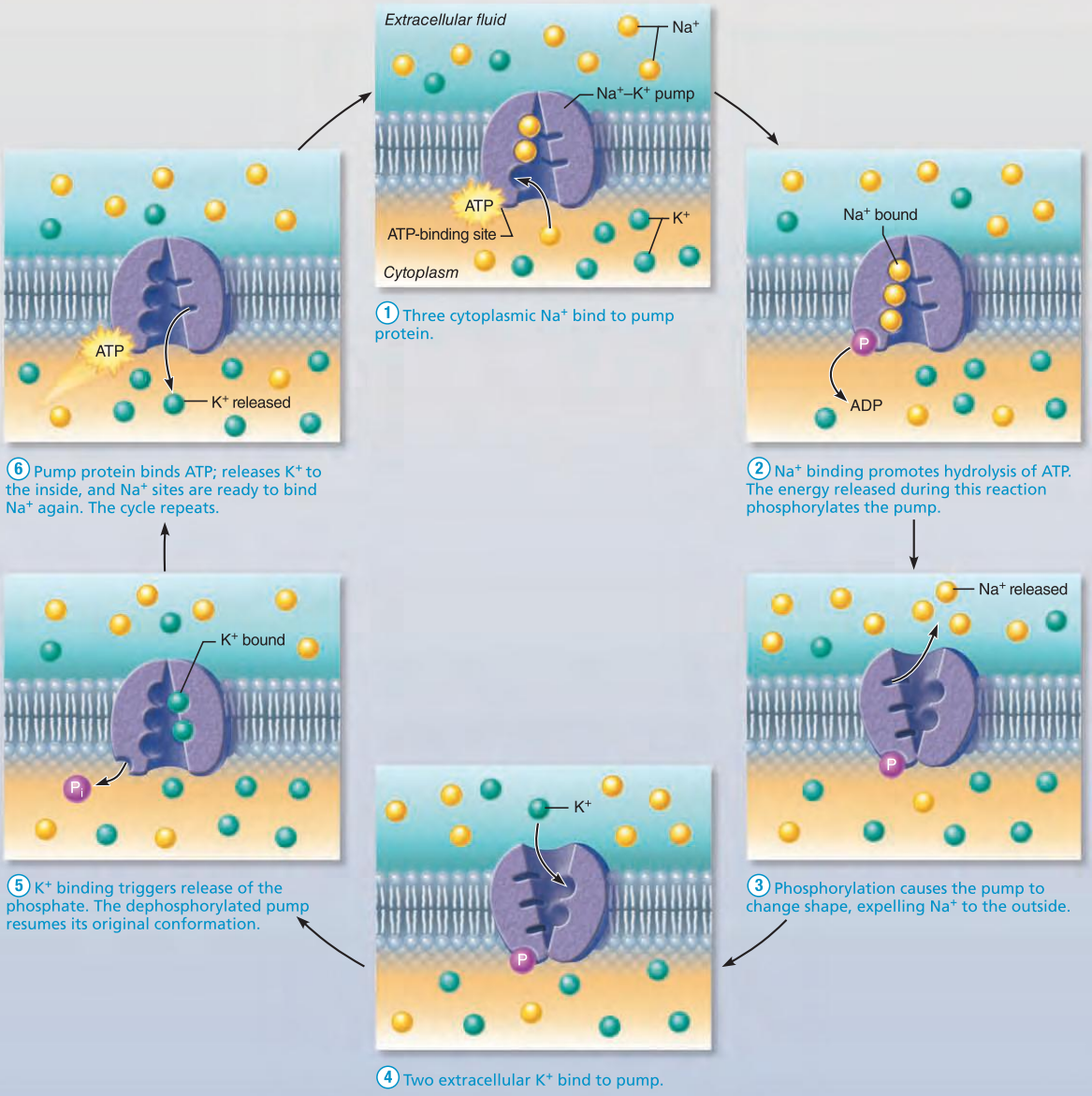
Regardless of whether the energy is provided directly (primary active transport) or indirectly (secondary active transport), each membrane pump or cotransporter transports only specific substances. Active transport systems provide a way for the cell to be very selective in cases where substances cannot pass by diffusion. No pump—no transport.

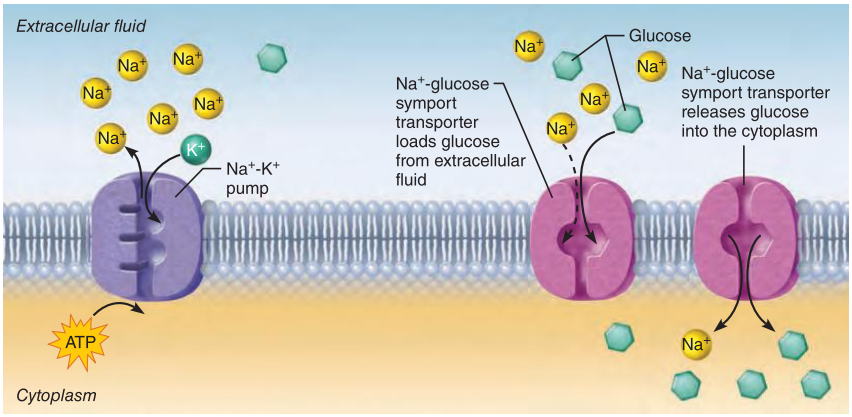
Vesicular Transport

In **vesicular transport**, fluids containing large particles and macromolecules are transported across cellular membranes inside membranous sacs called *vesicles*. Like active transport, vesicular transport moves substances into the cell (endocytosis) and out of the cell (exocytosis). It is also used for combination processes such as *transcytosis*, moving substances into, across, and then out of the cell, and *vesicular trafficking*, moving substances from one area (or membranous organelle) in the cell to another. Vesicular transport processes are energized by ATP (or in some cases another energy-rich compound, *GTP*—guanosine triphosphate).

Endocytosis, Transcytosis, and Vesicular Trafficking Virtually all forms of vesicular transport involve an assortment of protein-coated vesicles of three types and, with some exceptions, all are mediated by membrane receptors. Before we get specific about each type of coated vesicular transport, let's look at the general scheme of endocytosis.

Figure 3.10 Primary active transport is the process in which solutes are moved across cell membranes against electrochemical gradients using energy supplied directly by ATP. The action of the Na^+–K^+ pump is an important example of primary active transport. A&PFlix Available at www.masteringaandp.com





① **Primary active transport**
The ATP-driven Na^+-K^+ pump stores energy by creating a steep concentration gradient for Na^+ entry into the cell.

② **Secondary active transport**
As Na^+ diffuses back across the membrane through a membrane cotransporter protein, it drives glucose against its concentration gradient into the cell.

Figure 3.11 **Secondary active transport is driven by the concentration gradient created by primary active transport.**

Protein-coated vesicles provide the main route for endocytosis and transcytosis of bulk solids, most macromolecules, and fluids. On occasion, these vesicles are also hijacked by pathogens seeking entry into a cell.

Figure 3.12 shows the basic steps in endocytosis and transcytosis. ① An infolding portion of the plasma membrane, called a *coated pit*, progressively encloses the substance to be taken into the cell. The coating found on the cytoplasmic face of the pit is most often the bristlelike protein **clathrin** (klă′thrin; "lattice clad"). The clathrin coat (clathrin and some accessory proteins) acts in both selecting the cargo and deforming the membrane to produce the vesicle. ② The vesicle detaches, and ③ the coat proteins are recycled back to the plasma membrane. ④ The uncoated vesicle then typically fuses with a sorting vesicle called an *endosome*. ⑤ Some membrane components and receptors of the fused vesicle may be recycled back to the plasma membrane in a transport vesicle. ⑥ The remaining contents of the vesicle may (a) combine with a *lysosome* (li′so-sōm), a specialized cell structure containing digestive enzymes, where the ingested substance is degraded or released (if iron or cholesterol), or (b) be transported completely across the cell and released by exocytosis on the opposite side (*transcytosis*). Transcytosis is common in the endothelial cells lining blood vessels because it provides a quick means to get substances from the blood to the interstitial fluid.

Based on the nature and quantity of material taken up and the means of uptake, three types of endocytosis that use clathrin-coated vesicles are recognized: phagocytosis, pinocytosis, and receptor-mediated endocytosis.

- **Phagocytosis.** In **phagocytosis** (fag″o-si-to′sis; "cell eating"), the cell engulfs some relatively large or solid material, such as a clump of bacteria, cell debris, or inanimate particles (asbestos fibers or glass, for example) **(Figure 3.13a)**. When a particle binds to receptors on the cell's surface, cytoplasmic extensions called pseudopods (soo′do-pahdz; *pseudo* = false, *pod* = foot) form and flow around the particle. This forms an endocytotic vesicle called a **phagosome** (fag′o-sōm; "eaten body"). In most cases, the phagosome then fuses with a lysosome and its contents are digested. Any indigestible contents are ejected from the cell by exocytosis.

  In the human body, only macrophages and certain white blood cells are "experts" at phagocytosis. Commonly referred to as *phagocytes*, these cells help protect the body by ingesting and disposing of bacteria, other foreign substances, and dead tissue cells. The disposal of dying cells is crucial, because dead cell remnants trigger inflammation in the surrounding area or may stimulate an undesirable immune response. Most phagocytes move about by **amoeboid motion** (ah-me′boyd; "changing shape"); that is, the flowing of their cytoplasm into temporary extensions allows them to creep along.

- **Pinocytosis.** In **pinocytosis** ("cell drinking"), also called **fluid-phase endocytosis**, a bit of infolding plasma membrane (which begins as a protein-coated pit) surrounds a very small volume of extracellular fluid containing dissolved molecules (Figure 3.13b). This droplet enters the cell and fuses with an endosome. Unlike phagocytosis, pinocytosis is a routine activity of most cells, affording them a nonselective way of sampling the extracellular fluid. It is particularly important in cells that absorb nutrients, such as cells that line the intestines.

  As mentioned, bits of the plasma membrane are removed when the membranous sacs are internalized. However, these membranes are recycled back to the plasma membrane by exocytosis as described shortly, so the surface area of the plasma membrane remains remarkably constant.

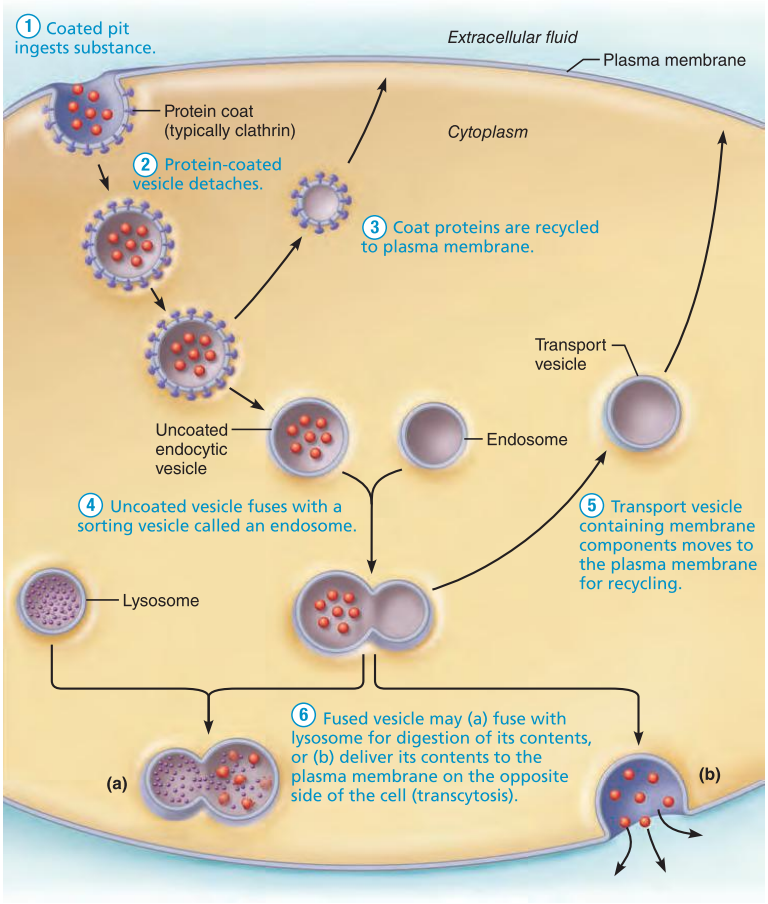


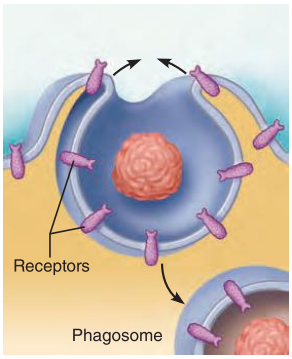
Figure 3.12 Events of endocytosis mediated by protein-coated pits. Note the three possible fates for a vesicle and its contents, shown in (5) and (6).

- **Receptor-mediated endocytosis.** The main mechanism for the *specific* endocytosis and transcytosis of most macromolecules by body cells is **receptor-mediated endocytosis** (Figure 3.13c). This exquisitely selective mechanism allows cells to concentrate material that is present only in small amounts in the extracellular fluid. The receptors for this process are plasma membrane proteins that bind only certain substances. Both the receptors and attached molecules are internalized in a clathrin-coated pit and then dealt with in one of the ways discussed above. Substances taken up by receptor-mediated endocytosis include enzymes, insulin (and some other hormones), low-density lipoproteins (such as cholesterol attached to a transport protein), and iron. Unfortunately, flu viruses, diphtheria, and cholera toxins also use this route to enter our cells.

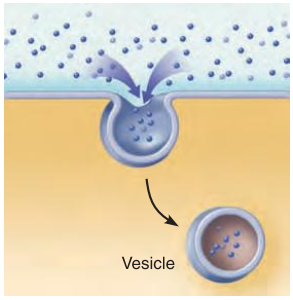
Different coat proteins are used for certain other types of vesicular transport. For example, **caveolae** (ka″ve-o′le; "little caves"), tubular or flask-shaped inpocketings of the plasma membrane seen in many cell types, are involved in a unique kind of receptor-mediated endocytosis. Like clathrin-coated pits, caveolae capture specific molecules (folic acid, tetanus toxin) from the extracellular fluid in coated vesicles and participate in some forms of transcytosis. However, caveolae are smaller than clathrin-coated vesicles. Additionally, their cage-like protein coat is thinner.

Caveolae are closely associated with lipid rafts that are platforms for G proteins, receptors for hormones (for example, insulin), and enzymes involved in cell regulation. These vesicles appear to provide sites for cell signaling and cross talk between signaling pathways. Their precise role in the cell is still being worked out.

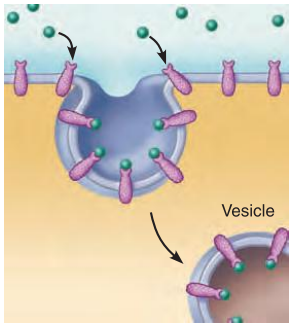
Vesicles coated with still another coat protein (coatomer) function in most types of intracellular vesicular trafficking. Perhaps the most important thing to remember about the coat



(a) Phagocytosis
The cell engulfs a large particle by forming projecting pseudopods ("false feet") around it and enclosing it within a membrane sac called a phagosome. The phagosome is combined with a lysosome. Undigested contents remain in the vesicle (now called a residual body) or are ejected by exocytosis. Vesicle may or may not be protein-coated but has receptors capable of binding to microorganisms or solid particles.



(b) Pinocytosis
The cell "gulps" a drop of extracellular fluid containing solutes into tiny vesicles. No receptors are used, so the process is nonspecific. Most vesicles are protein-coated.

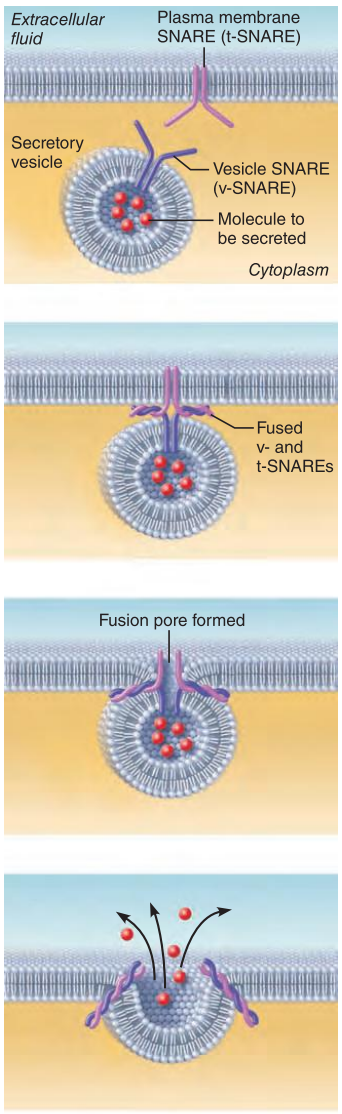


(c) Receptor-mediated endocytosis
Extracellular substances bind to specific receptor proteins, enabling the cell to ingest and concentrate specific substances (ligands) in protein-coated vesicles. Ligands may simply be released inside the cell, or combined with a lysosome to digest contents. Receptors are recycled to the plasma membrane in vesicles.

Figure 3.13 **Comparison of three types of endocytosis.**

proteins in general is that they play a significant role in all forms of endocytosis.

Exocytosis Vesicular transport processes that eject substances from the cell interior into the extracellular fluid are called **exocytosis** (ek″so-si-to′sis; "out of the cell"). Typically stimulated by a cell-surface signal such as binding of a hormone to a membrane receptor or a change in membrane voltage, exocytosis accounts for hormone secretion, neurotransmitter release, mucus secretion, and in some cases, ejection of wastes. The substance to be removed from the cell is first enclosed in a protein-coated membranous sac called a *secretory vesicle*. In most cases, the vesicle migrates to the plasma membrane, fuses with it, and then ruptures, spilling the sac contents out of the cell **(Figure 3.14)**.



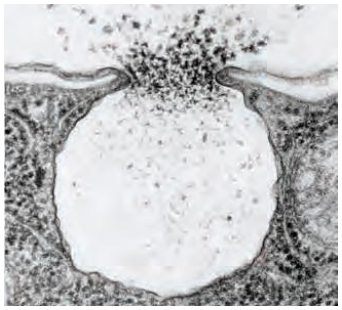
(a) The process of exocytosis

1 The membrane-bound vesicle migrates to the plasma membrane.

2 There, proteins at the vesicle surface (v-SNAREs) bind with t-SNAREs (plasma membrane proteins).

3 The vesicle and plasma membrane fuse and a pore opens up.

4 Vesicle contents are released to the cell exterior.



(b) Photomicrograph of a secretory vesicle releasing its contents by exocytosis (100,000×)

Figure 3.14 **Exocytosis.**

Table 3.2 Active Membrane Transport Processes

PROCESS	ENERGY SOURCE	DESCRIPTION	EXAMPLES
Active Transport			
Primary active transport	ATP	Transport of substances against a concentration (or electrochemical) gradient. Performed across the plasma membrane by a solute pump, directly using energy of ATP hydrolysis.	Ions (Na^+, K^+, H^+, Ca^{2+}, and others)
Secondary active transport	Ion concentration gradient maintained with ATP	Cotransport (coupled transport) of two solutes across the membrane. Energy is supplied indirectly by the ion gradient created by primary active transport. Symporters move the transported substances in the same direction; antiporters move transported substances in opposite directions across the membrane.	Movement of polar or charged solutes, e.g., amino acids (into cell by symporters); Ca^{2+}, H^+ (out of cells via antiporters)
Vesicular Transport			
Endocytosis			
▪ Via clathrin-coated vesicles			
Phagocytosis	ATP	"Cell eating": A large external particle (proteins, bacteria, dead cell debris) is surrounded by a "seizing foot" and becomes enclosed in a vesicle (phagosome).	In the human body, occurs primarily in protective phagocytes (some white blood cells and macrophages)
Pinocytosis (fluid-phase endocytosis)	ATP	Plasma membrane sinks beneath an external fluid droplet containing small solutes. Membrane edges fuse, forming a fluid-filled vesicle.	Occurs in most cells; important for taking in dissolved solutes by absorptive cells of the kidney and intestine
Receptor-mediated endocytosis	ATP	Selective endocytosis and transcytosis. External substance binds to membrane receptors.	Means of intake of some hormones, cholesterol, iron, and most macromolecules
▪ Via caveolin-coated vesicles (caveolae)	ATP	Selective endocytosis (and transcytosis). External substance binds to membrane receptors (often associated with lipid rafts).	Roles not fully known; proposed roles include cholesterol regulation and trafficking, and platforms for signal transduction
Vesicular trafficking			
▪ Via coatomer-coated vesicles	ATP	Vesicles pinch off from organelles and travel to other organelles to deliver their cargo.	Accounts for nearly all intracellular trafficking between certain organelles (endoplasmic reticulum and Golgi apparatus). Exceptions include vesicles budding from the trans face of the Golgi apparatus, which are clathrin-coated.
Exocytosis	ATP	Secretion or ejection of substances from a cell. The substance is enclosed in a membranous vesicle, which fuses with the plasma membrane and ruptures, releasing the substance to the exterior.	Secretion of neurotransmitters, hormones, mucus, etc.; ejection of cell wastes

Exocytosis, like other mechanisms in which vesicles are targeted to their destinations, involves a "docking" process in which transmembrane proteins on the vesicles, fancifully called v-SNAREs (*v* for vesicle), recognize certain plasma membrane proteins, called t-SNAREs (*t* for target), and bind with them. This binding causes the membranes to "corkscrew" together and fuse, rearranging the lipid monolayers without mixing them (Figure 3.14a). As described, membrane material added by exocytosis is removed by endocytosis—the reverse process.

Table 3.2 summarizes active membrane transport processes.

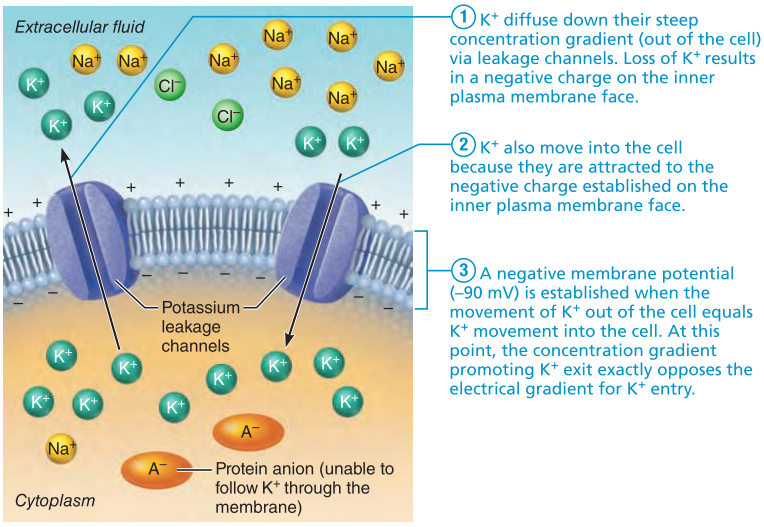


Figure 3.15 The key role of K^+ in generating the resting membrane potential. The resting membrane potential is largely determined by K^+ because at rest, the membrane is much more permeable to K^+ than Na^+. The active transport of sodium and potassium ions (in a ratio of 3:2) by the Na^+-K^+ pump maintains these conditions.

Check Your Understanding

10. What happens when the Na^+-K^+ pump is phosphorylated? When K^+ binds to the pump protein?
11. As a cell grows, its plasma membrane expands. Does this membrane expansion involve endocytosis or exocytosis?
12. Phagocytic cells gather in the lungs, particularly in the lungs of smokers. What is the connection?
13. Which vesicular transport process allows a cell to take in cholesterol from the extracellular fluid?

For answers, see Appendix H.

The Plasma Membrane: Generation of a Resting Membrane Potential

✓ Define membrane potential and explain how the resting membrane potential is established and maintained.

As you're now aware, the selective permeability of the plasma membrane can lead to dramatic osmotic flows, but that is not its only consequence. An equally important result is the generation of a **membrane potential**, or voltage, across the membrane. A *voltage* is electrical potential energy resulting from the separation of oppositely charged particles. In cells, the oppositely charged particles are ions, and the barrier that keeps them apart is the plasma membrane.

In their resting state, all body plasma membranes exhibit a **resting membrane potential** that typically ranges from −50 to −100 millivolts (mV), depending on cell type. For this reason, all cells are said to be **polarized**. The minus sign before the voltage indicates that the *inside* of the cell is negative compared to its outside. This voltage (or charge separation) exists *only at the membrane*. If we added up all the negative and positive charges in the cytoplasm, we would find that the cell interior is electrically neutral. Likewise, the positive and negative charges in the extracellular fluid balance each other exactly.

So how does the resting membrane potential come about, and how is it maintained? The short answer is that diffusion causes ionic imbalances that polarize the membrane, and active transport processes *maintain* that membrane potential. First, let's look at how diffusion polarizes the membrane.

Selective Diffusion Establishes Membrane Potential

Many kinds of ions are found both inside cells and in the extracellular fluid, but the resting membrane potential is determined mainly by the concentration gradient of potassium (K^+) and by the differential permeability of the plasma membrane to K^+ and other ions **(Figure 3.15)**. Recall that K^+ and protein anions predominate inside body cells, and the extracellular fluid contains relatively more Na^+, which is largely balanced by Cl^-. The unstimulated plasma membrane is somewhat permeable to K^+ because of leakage channels, but impermeable to the protein anions. Consequently, K^+ diffuses out of the cell along its concentration gradient but the protein anions are unable to follow, and this loss of positive charges makes the membrane interior more negative (Figure 3.15 (1)).