UNIT One

Mechanisms of Disease

CHAPTER 1

Cell Structure and Function

The cell is the smallest functional unit that an organism can be divided into and retain the characteristics necessary for life. Cells with similar embryonic origin or function are often organized into larger functional units called *tissues*. These tissues in turn combine to form the various body structures and organs. Although the cells of different tissues

and organs vary in structure and function, certain characteristics are common to all cells. Cells are remarkably similar in their ability to exchange materials with their immediate environment, obtaining energy from organic nutrients, synthesizing complex molecules, and replicating themselves. Because most disease processes are initiated at the cellular level, an understanding of cell function is crucial to understanding the disease process. Some diseases affect the cells of a single organ, others affect the cells of a particular tissue type, and still others affect the cells of the entire organism.

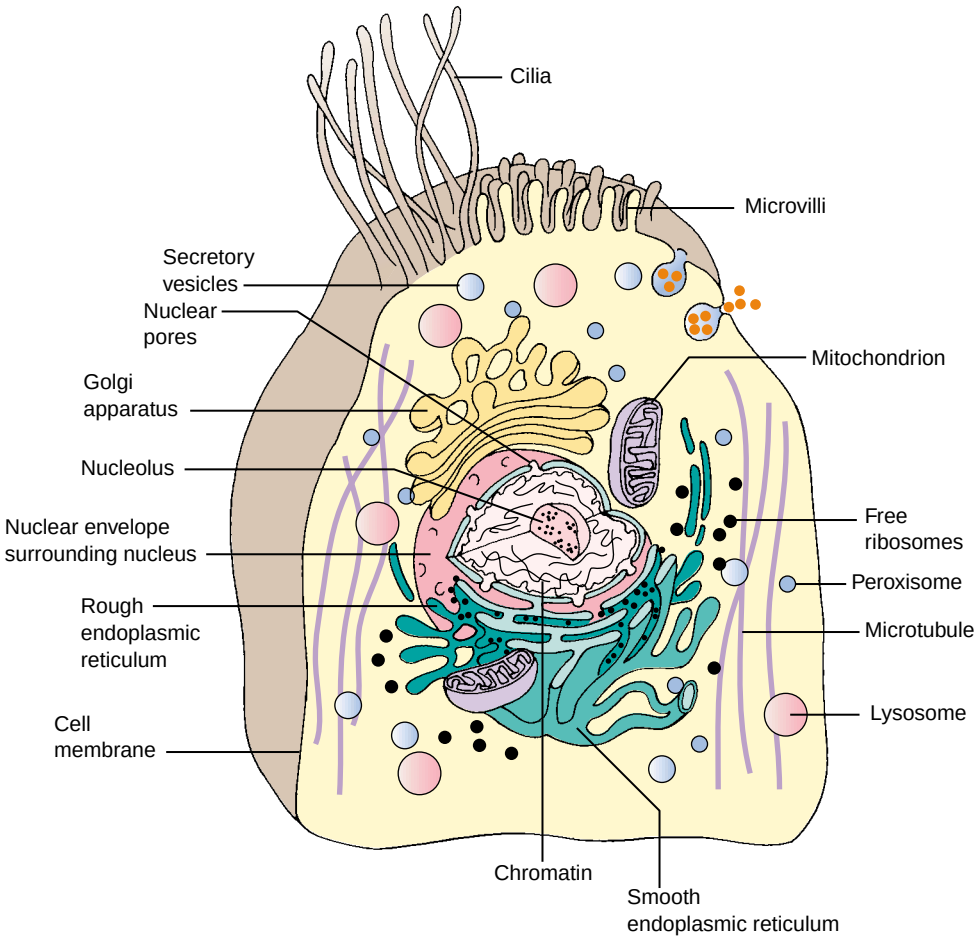
FUNCTIONAL COMPONENTS OF THE CELL

Although diverse in their organization, all eukaryotic cells (cells with a true nucleus) have in common structures that perform unique functions. When seen under a light microscope, three major components of the eukaryotic cell become evident: the nucleus, the cytoplasm, and the cell membrane (Fig. 1-1).

The internal matrix of the cell is called *protoplasm*. Protoplasm is composed of water, proteins, lipids, carbohydrates, and electrolytes. Water makes up 70% to 85% of the cell's protoplasm. The second most abundant constituents (10% to 20%) of protoplasm are the cell proteins, which form cell structures and the enzymes necessary for cellular reactions. Proteins can also be found complexed to other compounds as nucleoproteins, glycoproteins, and lipoproteins. Lipids comprise 2% to 3% of most cells. The most important lipids are the phospholipids and cholesterol, which are mainly insoluble in water; they combine with proteins to form the cell membrane and the membranous barriers that separate different cell compartments. Some cells also contain large quantities of triglycerides. In the fat cells, triglycerides can constitute up to 95% of the total cell mass. The fat stored in these cells represents stored energy, which can be mobilized and used wherever it is needed in the body. Few carbohydrates are found in the cell, and these are used primarily for fuel. Potassium, magnesium, phosphate, sulfate, and bicarbonate ions are the major intracellular electrolytes. Small quantities of sodium, chloride, and calcium ions are also present in the cell. These electrolytes facilitate the generation and transmission of electrochemical impulses in nerve and muscle cells. Intracellular electrolytes participate in reactions that are necessary for cellular metabolism.

The Nucleus

The nucleus of the cell appears as a rounded or elongated structure situated near the center of the cell (see Fig. 1-1). It is enclosed in a nuclear membrane and contains chromatin and a distinct region called the *nucleolus*. All eukaryotic cells have at least one nucleus (prokaryotic cells, such as bacteria, lack a nucleus and nuclear membrane). The nucleus is the control center for the cell. It contains deoxyribonucleic acid (DNA) that is



■ **FIGURE 1-1** ■ Composite cell designed to show in one cell all of the various components of the nucleus and cytoplasm.

KEY CONCEPTS

THE FUNCTIONAL ORGANIZATION OF THE CELL

- Cells are the smallest functional unit of the body. They contain structures that are strikingly similar to those needed to maintain total body function.
- The nucleus is the control center for the cell. It also contains most of the hereditary material.
- The organelles, which are analogous to the organs of the body, are contained in the cytoplasm. They include the mitochondria, which supply the energy needs of the cell; the ribosomes, which synthesize proteins and other materials needed for cell function; and the lysosomes, which function as the cell's digestive system.
- The cell membrane encloses the cell and provides for intracellular and intercellular communication, transport of materials into and out of the cell, and maintenance of the electrical activities that power cell function.

essential to the cell because its genes contain the information necessary for the synthesis of proteins that the cell must produce to stay alive. These proteins include structural proteins and enzymes used to synthesize other substances, including carbohydrates and lipids. The genes also represent the individual units of inheritance that transmit information from one generation to another. The nucleus is also the site of ribonucleic acid (RNA) synthesis. There are three types of RNA: messenger RNA (mRNA), which copies and carries the DNA instructions for protein synthesis to the cytoplasm; ribosomal RNA (rRNA), which moves to the cytoplasm, and becomes the site of protein synthesis; and transfer RNA (tRNA), which also moves into the cytoplasm, where it transports amino acids to the elongating protein as it is being synthesized (see Chapter 3).

The complex structure of DNA and DNA-associated proteins dispersed in the nuclear matrix is called *chromatin.* Each DNA molecule is made up of two extremely long, double-stranded helical chains containing variable sequences of four nitrogenous bases. These bases form the genetic code. In cells that are about to divide, the DNA must be replicated before *mitosis,* or cell division, occurs. During replication, complementary pairs of DNA are generated such that each daughter cell receives an identical set of genes.

The nucleus also contains the darkly stained round body called the *nucleolus.* The rRNA is transcribed exclusively in the nucleolus. Nucleoli are structures composed of regions from five different chromosomes, each with a part of the genetic code needed for the synthesis of rRNA. Cells that are actively synthesizing proteins can be recognized because their nucleoli are large and prominent and the nucleus as a whole is euchromatic.

Surrounding the nucleus is a doubled-layered membrane called the nuclear envelope or nuclear membrane. The nuclear membrane contains many structurally complex circular pores where the two membranes fuse to form a gap. Many classes of molecules, including fluids, electrolytes, RNA, some proteins, and perhaps some hormones, can move in both directions through the nuclear pores.

The Cytoplasm and Its Organelles

The cytoplasm surrounds the nucleus, and it is in the cytoplasm that the work of the cell takes place. Cytoplasm is essentially a colloidal solution that contains water, electrolytes, suspended proteins, neutral fats, and glycogen molecules. Although they do not contribute to the cell's function, pigments may also accumulate in the cytoplasm. Some pigments, such as melanin, which gives skin its color, are normal constituents of the cell.

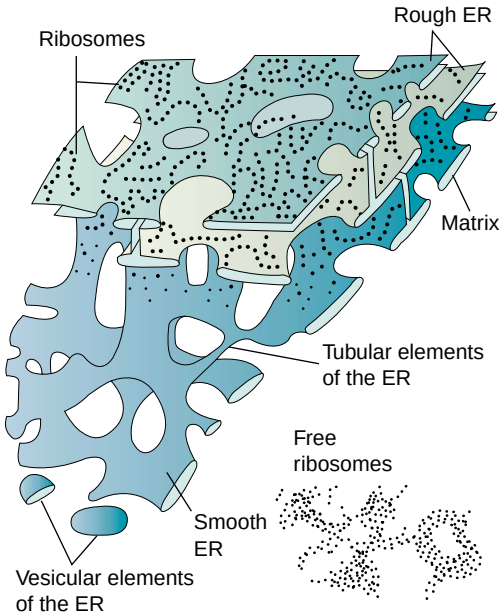
Embedded in the cytoplasm are various *organelles,* which function as the organs of the cell. These organelles include the ribosomes, endoplasmic reticulum, Golgi complex, lysosomes and peroxisomes, and mitochondria.

Ribosomes

The ribosomes serve as sites of protein synthesis in the cell. They are small particles of nucleoproteins (rRNA and proteins) that can be found attached to the wall of the endoplasmic reticulum or as free ribosomes (Fig. 1-2). Free ribosomes are scattered singly in the cytoplasm or joined by strands of mRNA to form functional units called *polyribosomes.* Free ribosomes are involved in the synthesis of proteins, mainly as intracellular enzymes.

Endoplasmic Reticulum

The endoplasmic reticulum (ER) is an extensive system of paired membranes and flat vesicles that connects various parts of the inner cell (see Fig. 1-2). The fluid-filled space, called the



■ **FIGURE 1-2** ■ Three-dimensional view of the rough endoplasmic reticulum (ER) with its attached ribosomal RNA and the smooth endoplasmic reticulum.

matrix, between the paired ER membrane layers is connected with the space between the two membranes of the double-layered nuclear membrane, the cell membrane, and various cytoplasmic organelles. It functions as a tubular communication system through which substances can be transported from one part of the cell to another. A large surface area and multiple enzyme systems attached to the ER membranes also provide the machinery for a major share of the metabolic functions of the cell.

Two forms of ER exist in cells: rough and smooth. Rough ER is studded with ribosomes attached to specific binding sites on the membrane. The ribosomes, with the accompanying strand of mRNA, synthesize proteins. Proteins produced by the rough ER are usually destined for incorporation into cell membranes and lysosomal enzymes or for exportation from the cell. The rough ER segregates these proteins from other components of the cytoplasm and modifies their structure for a specific function. For example, the production of plasma protein by liver cells take place in the rough ER. All cells require a rough ER for the synthesis of lysosomal enzymes.

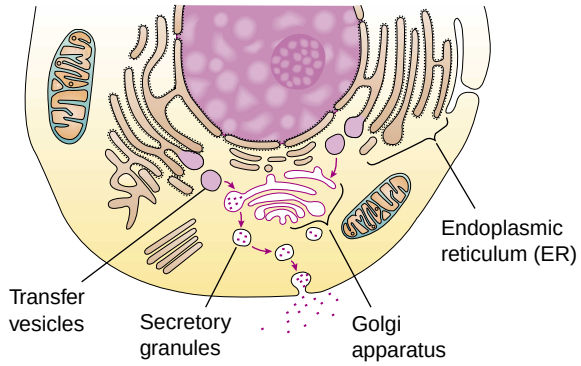
The smooth ER is free of ribosomes and is continuous with the rough ER. It does not participate in protein synthesis; instead, its enzymes are involved in the synthesis of lipid molecules, regulation of intracellular calcium, and metabolism and detoxification of certain hormones and drugs. It is the site of lipid, lipoprotein, and steroid hormone synthesis. The sarcoplasmic reticulum of skeletal and cardiac muscle cells is a form of smooth ER. Calcium ions needed for muscle contraction are stored and released from cisternae of the sarcoplasmic reticulum. Smooth ER of the liver is involved in glycogen storage and metabolism of lipid-soluble drugs.

Golgi Complex

The Golgi apparatus, sometimes called the *Golgi complex*, consists of stacks of thin, flattened vesicles or sacs. These Golgi bodies are found near the nucleus and function in association with the ER. Substances produced in the ER are carried to the Golgi complex in small, membrane-covered transfer vesicles. Many cells synthesize proteins that are larger than the active product. Insulin, for example, is synthesized as a large, inactive proinsulin molecule that is cut apart to produce a smaller, active insulin molecule within the Golgi complex of the beta cells of the pancreas. The Golgi complex modifies these substances and packages them into secretory granules or vesicles. Enzymes destined for export from the cell are packaged in secretory vesicles. After appropriate signals, the secretory vesicles move out of the Golgi complex into the cytoplasm and fuse to the inner side of the plasma membrane, where they release their contents into the extracellular fluid. Figure 1-3 is a diagram of the synthesis and movement of a hormone through the rough ER and Golgi complex. In addition to its function in producing secretory granules, the Golgi complex is thought to produce large carbohydrate molecules that combine with proteins produced by the rough ER to form glycoproteins.

Lysosomes and Peroxisomes

The lysosomes can be viewed as the digestive system of the cell. They consist of small, membrane-enclosed sacs containing hydrolytic enzymes capable of breaking down worn-out cell parts so they can be recycled. They also break down foreign substances such as bacteria taken into the cell. All of the lysosomal



■ **FIGURE 1-3** ■ Hormone synthesis and secretion. In hormone secretion, the hormone is synthesized by the ribosomes attached to the rough endoplasmic reticulum. It moves from the rough ER to the Golgi complex, where it is stored in the form of secretory granules. These leave the Golgi complex and are stored within the cytoplasm until released from the cell in response to an appropriate signal.

enzymes are acid hydrolases, which means that they require an acid environment. The lysosomes provide this environment by maintaining a pH of approximately 5 in their interior. The pH of the cytoplasm is approximately 7.2, which protects other cellular structures from this acidity.

Lysosomal enzymes are synthesized in the rough ER and then transported to the Golgi apparatus, where they are biochemically modified and packaged as lysosomes. Unlike those of other organelles, the sizes and functions of lysosomes vary considerably from one cell to another. The type of enzyme packaged in the lysosome by the Golgi complex determines this diversity. Although enzymes in the secondary lysosomes can break down most proteins, carbohydrates, and lipids to their basic constituents, some materials remain undigested. These undigested materials may remain in the cytoplasm as *residual bodies* or be extruded from the cell. In some long-lived cells, such as neurons and heart muscle cells, large quantities of residual bodies accumulate as lipofuscin granules or age pigment. Other indigestible pigments, such as inhaled carbon particles and tattoo pigments, also accumulate and may persist in residual bodies for decades.

Lysosomes play an important role in the normal metabolism of certain substances in the body. In some inherited diseases known as *lysosomal storage diseases*, a specific lysosomal enzyme is absent or inactive, in which case the digestion of certain cellular substances does not occur. As a result, these substances accumulate in the cell. In Tay-Sachs disease, an autosomal recessive disorder, the lysosomal enzyme needed for degrading the GM_2 ganglioside found in nerve cell membranes is deficient (see Chapter 4). Although GM_2 ganglioside accumulates in many tissues, such as the heart, liver, and spleen, its accumulation in the nervous system and retina of the eye causes the most damage.

Smaller than lysosomes, spherical membrane-bound organelles called *peroxisomes* contain a special enzyme that degrades peroxides (*e.g.*, hydrogen peroxide). Peroxisomes function in the control of free radicals (see Chapter 2). Unless degraded, these highly unstable chemical compounds would otherwise damage other cytoplasmic molecules. For example, catalase degrades toxic hydrogen peroxide molecules to water.

Peroxisomes also contain the enzymes needed for breaking down very–long-chain fatty acids, which are ineffectively degraded by mitochondrial enzymes. In liver cells, peroxisomal enzymes are involved in the formation of the bile acids.

Mitochondria

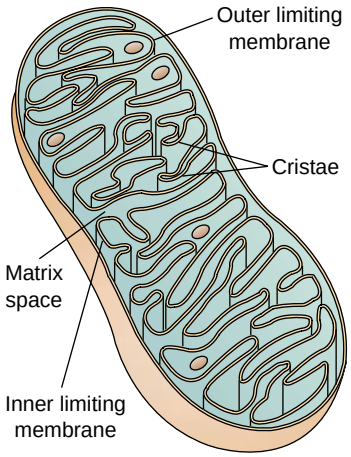
The mitochondria are literally the "power plants" of the cell because they transform organic compounds into energy that is easily accessible to the cell. Energy is not made here but is extracted from organic compounds. Mitochondria contain the enzymes needed for capturing most of the energy in foodstuffs and converting it into cellular energy. This multistep process requires oxygen and is often referred to as *aerobic metabolism*. Much of this energy is stored in the high-energy phosphate bonds of compounds such as adenosine triphosphate (ATP), which powers the various cellular activities.

Mitochondria are found close to the site of energy consumption in the cell (*e.g.*, near the myofibrils in muscle cells). The number of mitochondria in a given cell type is largely determined by the type of activity the cell performs and how much energy is needed to undertake this activity. For example, large increases in mitochondria have been observed in skeletal muscle that has been repeatedly stimulated to contract.

The mitochondria are composed of two membranes: an outer membrane that encloses the periphery of the mitochondrion and an inner membrane that forms shelflike projections, called *cristae* (Fig. 1-4). The outer and inner membranes form two spaces: an outer intramembranous space and an inner matrix that is filled with a gel-like material. The outer membrane is involved in lipid synthesis and fatty acid metabolism. The inner membrane contains the respiratory chain enzymes and transport proteins needed for the synthesis of ATP.

Mitochondria contain their own DNA and ribosomes and are self-replicating. The DNA is found in the mitochondrial matrix and is distinct from the chromosomal DNA found in the nucleus. Mitochondrial DNA, known as the "other human genome," is a double-stranded, circular molecule that encodes the rRNA and tRNA required for intramitochrondial synthesis of proteins needed for the energy-generating function of the mitochondria. Although mitochondrial DNA directs the synthesis of 13 of the proteins required for mitochondrial function, the DNA of the nucleus encodes the structural proteins of the mitochondria and other proteins needed to carry out cellular respiration.

Mitochondrial DNA is inherited matrilineally (*i.e.*, from the mother) and provides a basis for familial lineage studies. Mutations have been found in each of the mitochondrial genes, and an understanding of the role of mitochondrial DNA in certain diseases is beginning to emerge. Most tissues in the body depend to some extent on oxidative metabolism and can therefore be affected by mitochondrial DNA mutations.



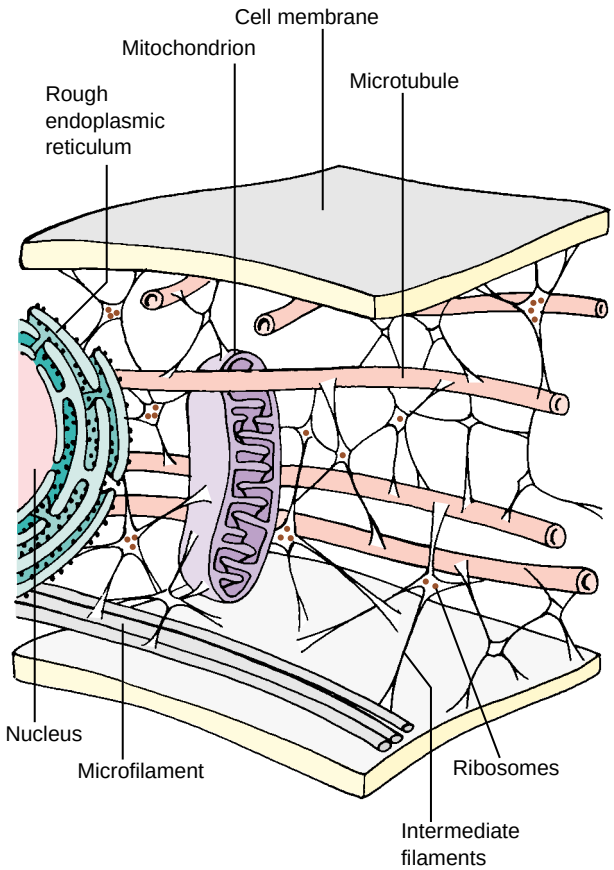
■ **FIGURE 1-4** ■ **Mitochondrion.** The inner membrane forms transverse folds called cristae, where the enzymes needed for the final step in adenosine triphosphate (ATP) production (*i.e.*, oxidative phosphorylation) are located.

The Cytoskeleton

In addition to its organelles, the cytoplasm contains a network of microtubules, microfilaments, intermediate filaments, and thick filaments (Fig. 1-5). Because they control cell shape and movement, these structures are a major component of the structural elements called the *cytoskeleton*.

Microtubules

The microtubules are slender tubular structures composed of globular proteins called *tubulin*. Microtubules function in many ways, including the development and maintenance of



■ **FIGURE 1-5** ■ Microtubes and microfilaments of the cell. The microfilaments associate with the inner surface of the cell and aid in cell motility. The microtubules form the cytoskeleton and maintain the position of the organelles.

cell form; participation in intracellular transport mechanisms, including axoplasmic transport in neurons; and formation of the basic structure for several complex cytoplasmic organelles, including the cilia, flagella, centrioles, and basal bodies. Abnormalities of the cytoskeleton may contribute to alterations in cell mobility and function. For example, proper functioning of the microtubules is essential for various stages of leukocyte migration.

Cilia and Flagella. Cilia and flagella are hairlike processes extending from the cell membrane that are capable of sweeping and flailing movements, which can move surrounding fluids or move the cell through fluid media. Cilia are found on the apical or luminal surface of epithelial linings of various body cavities or passages, such as the upper respiratory system. Removal of mucus from the respiratory passages is highly dependent on the proper functioning of the cilia. Flagella form the tail-like structures that provide motility for sperm.

Centrioles and Basal Bodies. Centrioles and basal bodies are structurally identical organelles composed of an array of highly organized microtubules. The centrioles are small, barrel-shaped bodies oriented at right angles to each other. In dividing cells, the two cylindrical centrioles form the mitotic spindle that aids in the separation and movement of the chromosomes. Basal bodies are more numerous than centrioles and are found near the cell membrane in association with cilia and flagella.

Microfilaments

Microfilaments are thin, threadlike cytoplasmic structures. Three classes of microfilaments exist: (1) thin microfilaments, which are equivalent to the thin actin filaments in muscle; (2) the thick myosin filaments, which are present in muscle cells but may also exist temporarily in other cells; and (3) the intermediate filaments, which are a heterogeneous group of filaments with diameter sizes between the thick and thin filaments. Muscle contraction depends on the interaction between the thin actin filaments and thick myosin filaments.

Microfilaments are present in the superficial zone of the cytoplasm in most cells. Contractile activities involving the microfilaments and associated thick myosin filaments contribute to associated movement of the cytoplasm and cell membrane during endocytosis and exocytosis. Microfilaments are also present in the microvilli of the intestine. The intermediate filaments function in supporting and maintaining the asymmetric shape of cells. Examples of intermediate filaments are the keratin filaments that are found anchored to the cell membrane of epidermal keratinocytes of the skin and the glial filaments that are found in astrocytes and other glial cells of the nervous system. The *neurofibrillary tangle* found in the brain in Alzheimer's disease contains microtubule-associated proteins and neurofilaments, evidence of a disrupted neuronal cytoskeleton.

The Cell Membrane

The cell is enclosed in a thin membrane that separates the intracellular contents from the extracellular environment. To differentiate it from the other cell membranes, such as the mitochondrial or nuclear membranes, the cell membrane is often called the *plasma membrane*. In many respects, the plasma membrane is one of the most important parts of the cell. It acts as a semipermeable structure that separates the intracellular and extracellular environments. It provides receptors for hormones and other biologically active substances, participates in the electrical events that occur in nerve and muscle cells, and aids in the regulation of cell growth and proliferation.

The cell membrane consists of an organized arrangement of lipids (phospholipids, glycolipids, and cholesterol), carbohydrates, and proteins (Fig. 1-6). The lipids form a bilayer structure that is essentially impermeable to all but lipid-soluble substances. About 75% of the lipids are phospholipids, each with a hydrophilic (water-soluble) head and hydrophobic (water-insoluble) tails. The phospholipid molecules along with the glycolipids are aligned such that their hydrophobic heads face outward on each side of the membrane and their hydrophobic tails project toward the center of the membrane. The hydrophilic heads retain water and help cells adhere to each other. At

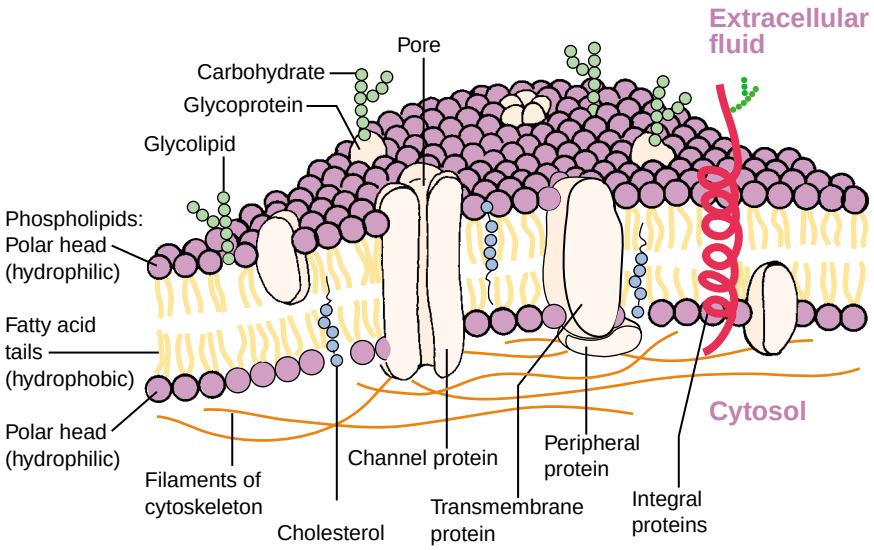


FIGURE 1-6 The structure of the cell membrane showing the hydrophilic (polar) heads and the hydrophobic (fatty acid) tails and the position of the integral and peripheral proteins in relation to the interior and exterior of the cell.

normal body temperature, the viscosity of the lipid component of the membrane is equivalent to that of olive oil. The presence of cholesterol stiffens the membrane.

Although the basic structure of the cell membrane is provided by the lipid bilayer, most of the specific functions are carried out by proteins. Some proteins, called *transmembrane proteins,* pass directly through the membrane and communicate with the intracellular and extracellular environments. Many of the transmembrane proteins are tightly bound to lipids in the bilayer and are essentially part of the membrane. These transmembrane proteins are called *integral proteins.* The *peripheral proteins,* a second type of protein, are bound to one or the other side of the membrane and do not pass into the lipid bilayer. Thus, the peripheral proteins are associated with functions involving the inner and outer side of the membrane where they are located. In contrast, the transmembrane proteins can function on both sides of the membrane or transport molecules across it. Many of the integral transmembrane proteins form the ion channels found on the cell surface. These channel proteins have complex structures and are selective with respect to the ions that pass through their channels.

The membrane carbohydrates are incorporated in a fuzzy-looking layer, called the *cell coat* or *glycocalyx,* which surrounds the cell surface. The glycocalyx, which is part of the cell membrane, consists of long, complex carbohydrate chains that are attached to proteins and lipids in the form of glycoproteins and glycolipids. The cell coat participates in cell-to-cell recognition and adhesion. It contains tissue transplant antigens that label cells as self or nonself. ABO blood group antigens are contained in the cell coat of red blood cells.

In summary, the cell is a remarkably autonomous structure that functions in a manner strikingly similar to that of the total organism. The nucleus controls cell function and is the mastermind of the cell. It contains DNA, which provides the information necessary for the synthesis of the various proteins that the cell must produce to stay alive and to transmit information from one generation to another.

The cytoplasm contains the cell's organelles. Ribosomes serve as sites for protein synthesis in the cell. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and lipid (smooth ER) synthesis. Golgi bodies modify materials synthesized in the ER and package them into secretory granules for transport within the cell or for export from the cell. Lysosomes, which can be viewed as the digestive system of the cell, contain hydrolytic enzymes that digest worn-out cell parts and foreign materials. The mitochondria serve as power plants for the cell because they transform food energy into ATP, which is used to power cell activities. Mitochondria contain their own extrachromosomal DNA, which is used in the synthesis of mitochondrial RNAs and proteins used in oxidative metabolism. Microtubules are slender, stiff tubular structures that influence cell shape, provide a means of moving organelles through the cytoplasm, and effect movement of the cilia and of chromosomes during cell division. Several types of threadlike filaments, including actin and myosin filaments, participate in muscle contraction.

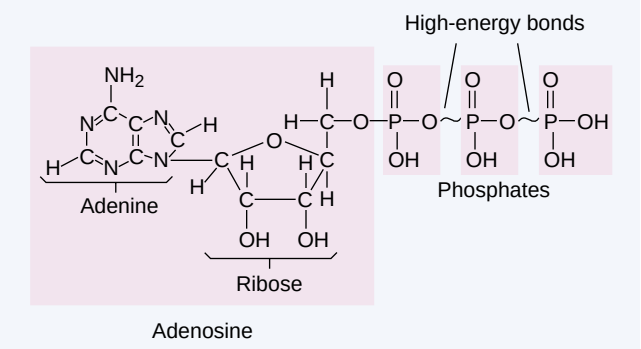
The plasma membrane is a lipid bilayer that surrounds the cell and separates it from its surrounding external environment. It contains receptors for hormones and other biologically active substances, participates in the electrical events that occur in nerve and muscle cells, and aids in the regulation of cell growth and proliferation. The cell surface is surrounded by a fuzzy-looking layer called the cell coat or glycocalyx. The cell coat participates in cell-to-cell recognition and adhesion, and it contains tissue transplant antigens.

CELL METABOLISM AND ENERGY SOURCES

Energy metabolism refers to the processes by which fats, proteins, and carbohydrates from the foods we eat are converted into energy or complex energy sources in the cell. Catabolism and anabolism are the two phases of metabolism. *Catabolism* consists of breaking down stored nutrients and body tissues to produce energy. *Anabolism* is a constructive process in which more complex molecules are formed from simpler ones.

The special carrier for cellular energy is ATP. ATP molecules consist of adenosine, a nitrogenous base; ribose, a five-carbon sugar; and three phosphate groups (see Fig. 1-7). The last two phosphate groups are attached to the remainder of the molecule by two high-energy bonds, which are indicated by the symbol ~. Each bond releases a large amount of energy when hydrolyzed. ATP is hydrolyzed to form adenosine diphosphate (ADP) with the loss of one high-energy bond and to adenosine monophosphate (AMP) with the loss of two such bonds. The energy liberated from the hydrolysis of ATP is used to drive reactions that require free energy, such as muscle contraction and active transport mechanisms. Energy from foodstuffs is used to convert ADP back to ATP. ATP is often called the *energy currency* of the cell; energy can be "saved" or "spent" using ATP as an exchange currency.

Two types of energy production are present in the cell: the anaerobic (*i.e.,* without oxygen) glycolytic pathway, occurring in the cytoplasm, and the aerobic (*i.e.,* with oxygen) pathways occurring in the mitochondria. The glycolytic pathway serves as the prelude to the aerobic pathways.

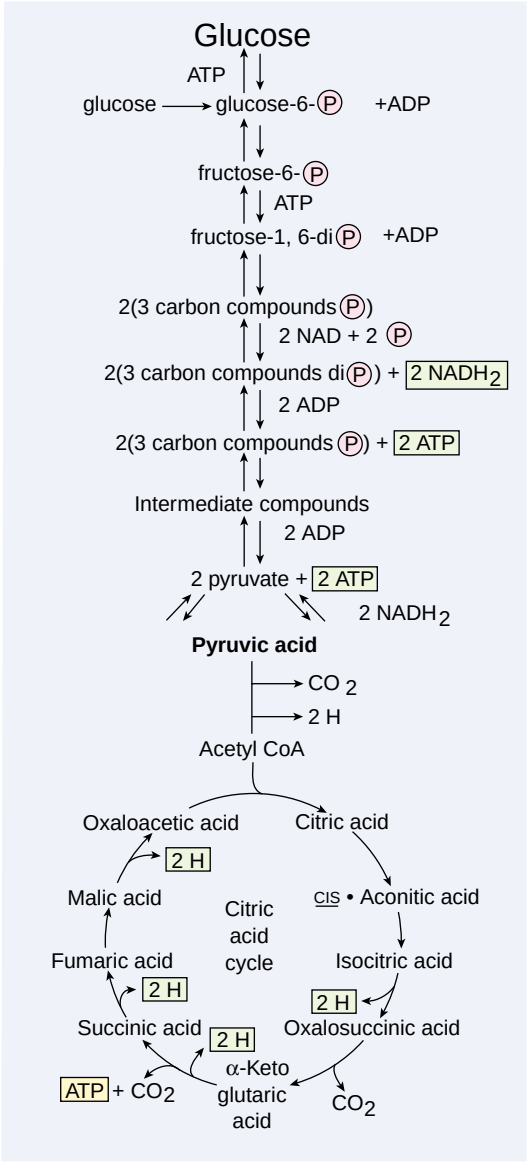


■ **FIGURE 1-7** ■ Structure of the adenosine triphosphate (ATP) molecule.

Anaerobic Metabolism

Glycolysis is anaerobic process by which energy is liberated from glucose (Fig. 1-8). It is an important source of energy for cells that lack mitochondria. This process provides energy in situations when delivery of oxygen to the cell is delayed or impaired. Glycolysis involves a sequence of reactions that converts glucose to pyruvate, with the concomitant production of ATP from ADP. The net gain of energy from the glycolysis of one molecule of glucose is two ATP molecules. Although relatively inefficient as to energy yield, the glycolytic pathway is important during periods of decreased oxygen delivery, such as occurs in skeletal muscle during the first few minutes of exercise.

Glycolysis requires the presence of nicotinamide-adenine dinucleotide (NAD^+), a hydrogen carrier. The end-products of glycolysis are pyruvate and NADH. When oxygen is present, pyruvate moves into the aerobic mitochondrial pathway, and NADH subsequently enters into oxidative chemical reactions that remove the hydrogen atoms. The transfer of hydrogen from NADH during the oxidative reactions allows the glycolytic process to continue by facilitating the regeneration of NAD^+. Under anaerobic conditions, such as cardiac arrest or circulatory shock, pyruvate is converted to lactic acid, which diffuses out of the cells into the extracellular fluid. Conversion of pyruvate to lactic acid is reversible, and after the oxygen supply has been restored, lactic acid is reconverted back to pyruvate and used directly for energy or to synthesize glucose.



■ **FIGURE 1-8** ■ Glycolytic pathway and citric acid cycle.

Aerobic Metabolism

Aerobic metabolism, which supplies 90% of the body's energy needs, occurs in the cell's mitochondria and requires oxygen. It is here that hydrogen and carbon molecules from dietary fats, proteins, and carbohydrates are broken down and combined with molecular oxygen to form carbon dioxide, and water as energy is released. Unlike lactic acid, which is an end-product of anaerobic metabolism, carbon dioxide and water are relatively harmless and easily eliminated from the body. In a 24-hour period, oxidative metabolism produces 300 to 500 mL of water.

Aerobic metabolism uses the *citric acid cycle*, sometimes called the *tricarboxylic acid* or *Krebs cycle*, as the final common pathway for the metabolism of nutrients (see Fig. 1-8). In the citric acid cycle, each of the two pyruvate molecules formed in the cytoplasm from the glycolysis of one molecule of glucose yields another molecule of ATP along with two molecules of carbon dioxide and eight hydrogen ions. In addition to pyruvate from the glycolysis of glucose, products from amino acid and fatty acid breakdown enter the citric acid cycle.

In the initial stage of the citric acid cycle, acetyl coenzyme A (acetyl-CoA) combines with oxaloacetic acid to form citric acid. The coenzyme A portion of acetyl-CoA can be used again and again to generate more acetyl-CoA from pyruvate, while the acetyl portion becomes part of the citric acid cycle and moves through a series of enzyme-mediated steps that produce carbon dioxide and hydrogen atoms. The carbon dioxide is carried to the lungs and exhaled. The hydrogen atoms are transferred to the electron transport system on the inner mitochondrial membrane for oxidation. Oxidation of hydrogen is accomplished through a series of enzyme-mediated steps that change the hydrogen atoms to hydrogen ions and electrons. The electrons are used to reduce elemental oxygen, which combines with the hydrogen ions to form water. During this sequence of oxidative reactions, large amounts of energy are released and used to convert ADP to ATP. Because the formation of ATP involves the addition of a high-energy phosphate bond to ADP, the process is called *oxidative phosphorylation*. Cyanide poisoning kills by binding to the enzymes needed for a final step in the oxidative phosphorylation sequence.

In summary, metabolism is the process whereby the carbohydrates, fats, and proteins we eat are broken down and subsequently converted into the energy needed for cell function. Energy is stored in the high-energy phosphate bonds of ATP, which serves as the energy currency for the cell. Two sites of energy conversion are present in cells: the glycolytic or anaerobic pathway in the cell's cytoplasmic matrix and the

aerobic or citric acid cycle in the mitochondria. The most efficient of these pathways is the citric acid pathway. This pathway, which requires oxygen, produces carbon dioxide and water as end-products and results in the release of large amounts of energy that is used to convert ADP to ATP. The glycolytic pathway, which is located in the cytoplasm, involves the breakdown of glucose to form ATP. This pathway can function without oxygen by producing lactic acid.

CELL MEMBRANE TRANSPORT, SIGNAL TRANSDUCTION, AND GENERATION OF MEMBRANE POTENTIALS

Movement Across the Cell Membrane

The unique properties of the cell's membrane are responsible for differences in the composition of the intracellular and extracellular fluids. However, a constant movement of molecules and ions across the cell membrane is required to maintain the functions of the cell. Movement through the cell membrane occurs in essentially two ways: passively, without an expenditure of energy, or actively, using energy-consuming processes. The cell membrane can also engulf substances, forming a membrane-coated vesicle; this membrane-coated vesicle is moved into the cell by *endocytosis* or out of the cell by *exocytosis*.

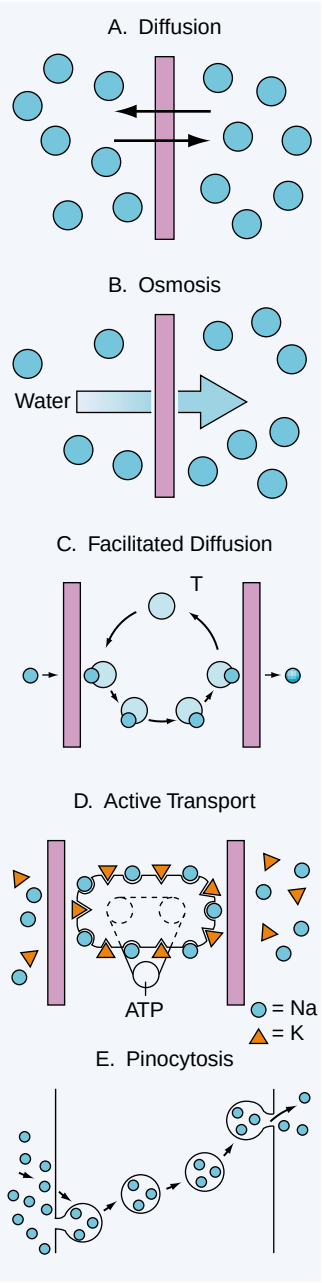
Passive Movement

The passive movement of particles or ions across the cell membrane is directly influenced by chemical or electrical gradients and does not require an expenditure of energy. A difference in the number of particles on either side of the membrane creates a chemical gradient, and a difference in charged particle or ions creates an electrical gradient. Chemical and electrical gradients are often linked and are called *electrochemical gradients*.

Diffusion. *Diffusion* refers to the process by which molecules and other particles in a solution become widely dispersed and reach a uniform concentration because of energy created by their spontaneous kinetic movements (Fig. 1-9). In the process of reaching a uniform concentration, these molecules and particles move from an area of higher to an area of lower concentration. With ions, diffusion is affected by energy supplied by their electrical charge. Lipid-soluble molecules, such as oxygen, carbon dioxide, alcohol, and fatty acids, become dissolved in the lipid matrix of the cell membrane and diffuse through the membrane in the same manner that diffusion occurs in water. Other substances diffuse through minute pores of the cell membrane. The rate of movement depends on how many particles are available for diffusion and the velocity of the kinetic movement of the particles. Temperature changes the motion of the particles; the greater the temperature, the greater is the thermal motion of the molecules.

Osmosis. Most cell membranes are semipermeable in that they are permeable to water but not all solute particles. Water moves through a semipermeable membrane along a concentration gradient, moving from an area of higher to one of lower concentration (see Fig. 1-9). This process is called *osmosis*, and the pressure that water generates as it moves through the membrane is called *osmotic pressure*.

Osmosis is regulated by the concentration of nondiffusible particles on either side of a semipermeable membrane. When there is a difference in the concentration of particles, water



■ **FIGURE 1-9** ■ Mechanisms of membrane transport. (**A**) Diffusion, in which particles move to become equally distributed across the membrane. (**B**) The osmotically active particles regulate the flow of water. (**C**) Facilitated diffusion uses a carrier system. (**D**) In active transport, selected molecules are transported across the membrane using the energy-driven (ATP) pump. (**E**) The membrane forms a vesicle that engulfs the particle and transports it across the membrane, where it is released. This is called pinocytosis.

moves from the side with the lower concentration of particles and higher concentration of water to the side with the higher concentration of particles and lower concentration of water. The movement of water continues until the concentration of particles on both sides of the membrane is equally diluted or until the hydrostatic (osmotic) pressure created by the movement of water opposes its flow.

Facilitated Diffusion. Facilitated diffusion occurs through a transport protein that is not linked to metabolic energy (see Fig. 1-9). Some substances, such as glucose, cannot pass unassisted through the cell membrane because they are not lipid soluble or are too large to pass through the membrane's pores. These substances combine with special transport proteins at the membrane's outer surface, are carried across the membrane attached to the transporter, and then released. In facilitated diffusion, a substance can move only from an area of higher concentration to one of lower concentration. The rate at which a substance moves across the membrane because of facilitated diffusion depends on the difference in concentration between the two sides of the membrane. Also important are the availability of transport proteins and the rapidity with which they can bind and release the substance being transported. It is thought that insulin, which facilitates the movement of glucose into cells, acts by increasing the availability of glucose transporters in the cell membrane.

Active Transport and Cotransport

The process of diffusion describes particle movement from an area of higher concentration to one of lower concentration, resulting in an equal distribution across the cell membrane. However, sometimes different concentrations of a substance are needed in the intracellular and extracellular fluids. For example, the intracellular functioning of the cell requires a much higher concentration of potassium than is present in the extracellular fluid while maintaining a much lower concentration of sodium than in the extracellular fluid. In these situations, energy is required to pump the ions "uphill" or against their concentration gradient. When cells use energy to move ions against an electrical or chemical gradient, the process is called *active transport.*

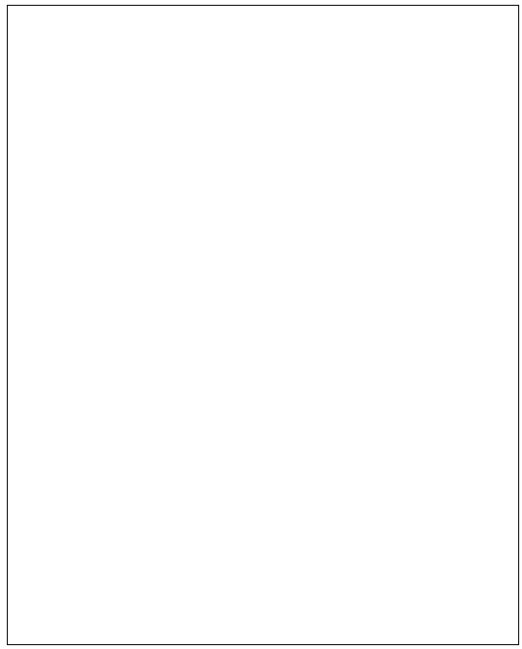
The active transport system studied in the greatest detail is the sodium–potassium pump, or Na^+/K^+ ATPase pump (see Fig. 1-9). The Na^+/K^+ ATPase pump moves sodium from inside the cell to the extracellular region, where its concentration is approximately 14 times greater than inside; the pump also returns potassium to the inside, where its concentration is approximately 35 times greater than it is outside the cell. If it were not for the activity of the sodium–potassium pump, the osmotically active sodium particles would accumulate in the cell, causing cellular swelling because of an accompanying influx of water (see Chapter 2).

There are two types of active transport: primary active transport and secondary active transport. In *primary active transport,* the source of energy (*e.g.,* ATP) is used directly in the transport of a substance. *Secondary active transport* mechanisms harness the energy derived from the primary active transport of one substance, usually sodium ions, for the cotransport of a second substance. For example, when sodium ions are actively transported out of a cell by primary active transport, a large concentration gradient develops (*i.e.,* high concentration on the outside and low on the inside). This concentration gradient represents a large storehouse of energy because sodium ions are always attempting to diffuse into the cell. Similar to facilitated diffusion, secondary transport mechanisms use membrane transport proteins. These proteins have two binding sites: one for sodium ions and the other for the substance undergoing secondary transport. Secondary transport systems are classified into two groups: *cotransport,* in which the sodium ion and solute are transported in the same direction, and *countertransport,* in which sodium ions and the solute are transported in the opposite direction (Fig. 1-10). An example of cotransport occurs in the intestine, where the absorption of glucose and amino acids is coupled with sodium transport.

Endocytosis and Exocytosis

Endocytosis is the process by which cells engulf materials from their surroundings. It includes pinocytosis and phagocytosis. *Pinocytosis* involves the ingestion of small solid or fluid particles. The particles are engulfed into small, membrane-surrounded vesicles for movement into the cytoplasm. The process of pinocytosis is important in the transport of proteins and strong solutions of electrolytes (see Fig. 1-9).

Phagocytosis literally means *cell eating* and can be compared with pinocytosis, which means *cell drinking.* Phagocytosis involves the engulfment and subsequent killing or degradation of microorganisms and other particulate matter. During phagocytosis, a particle contacts the cell surface and is surrounded on all sides by the cell membrane, forming a phagocytic vesicle or phagosome. Once formed, the phagosome breaks away from the cell membrane and moves into the cytoplasm, where it eventually fuses with a lysosome, allowing the ingested material to be degraded by lysosomal enzymes. Certain cells, such



■ **FIGURE 1-10** ■ Secondary active transport systems. (**A**) carries the transported solute (**S**) in the same direction as the Na^+ ion. (**B**) Counter-transport carries the solute and Na^+ in the opposite direction.

as macrophages and polymorphonuclear leukocytes (neutrophils), are adept at engulfing and disposing of invading organisms, damaged cells, and unneeded extracellular constituents (see Chapter 9).

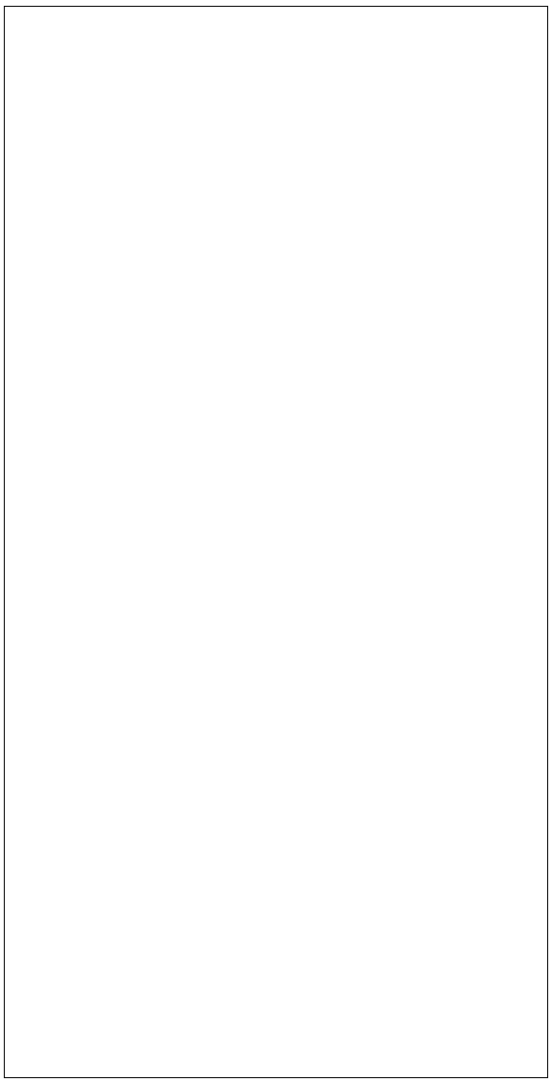
Exocytosis is the mechanism for the secretion of intracellular substances into the extracellular spaces. It is the reverse of endocytosis in that a secretory granule fuses to the inner side of the cell membrane, and an opening occurs in the cell membrane. This opening allows the contents of the granule to be released into the extracellular fluid. Exocytosis is important in removing cellular debris and releasing substances, such as hormones, synthesized in the cell.

During endocytosis, portions of the cell membrane become an endocytotic vesicle. During exocytosis, the vesicular membrane is incorporated into the plasma membrane. In this way, cell membranes can be conserved and reused.

Ion Channels

The electrical charge on small ions such as Na^+ and K^+ makes it difficult for these ions to move across the lipid layer of the cell membrane. However, rapid movement of these ions is required for many types of cell functions, such as nerve activity. This is accomplished by facilitated diffusion through selective ion channels. Ion channels are made up of integral proteins that span the width of the cell membrane and are normally composed of several polypeptides or protein subunits that form a gating system. Specific stimuli cause the protein subunits to undergo conformational changes to form an open channel or gate through which the ions can move. In this way, ions do not need to cross the lipid-soluble portion of the membrane but can remain in the aqueous solution that fills the ion channel. Ion channels are highly selective; some channels allow only for passage of sodium ions, and others are selective for potassium, calcium, or chloride ions.

The plasma membrane contains two basic groups of ion channels: nongated and gated channels (Fig. 1-11). Nongated or leakage channels are open even in the unstimulated state, whereas gated channels open and close in response to specific stimuli. There are two types of gated channels: voltage-gated and ligand-gated channels. Voltage-gated channels have electrically operated gates that open when the membrane potential changes beyond a certain point. Ligand-gated channels have chemically operated gates that respond to specific receptor-bound ligands, such as the neurotransmitter acetylcholine.



■ **FIGURE 1-11** ■ **Ion channels.** (**A**) Nongated ion channel remains open, permitting free movement of ions across the membrane. (**B**) Ligand-gated channel is controlled by ligand binding to the receptor. (**C**) Voltage-gated channel is controlled by a change in membrane potential. (Rhoades R.A., Tanner G.A. [1996]. *Medical physiology.* Boston: Little, Brown)

Signal Transduction and Cell Communication

Cells in multicellular organisms need to communicate with one another to coordinate their function and control their growth. Cells communicate with each other by means of chemical messenger systems. In some tissues, messengers move from cell to cell through gap junctions without entering the extracellular fluid. In other tissues, cells communicate by chemical messengers secreted into the extracellular fluid. Many types of chemical messengers that cannot cross the cell membrane bind to receptors on or near the cell surface. These chemical messengers are sometimes called *first messengers* because, by one means or another, their external signal is converted into internal signals carried by a second chemical called a *second messenger*. It is the second messenger that triggers the intracellular changes that produce the desired physiologic effect. Some lipid-soluble chemical messengers move through the membrane and bind to cytoplasmic or nuclear receptors to exert their physiologic effects.

Cell Membrane Receptors

Neurotransmitters, protein and peptide hormones, and other chemical messengers do not exert their effects by entering cells. Instead, they attach to receptors on the cell surface, and their messages are conveyed across the membrane and converted by cell membrane proteins into signals within the cell, a process often called *signal transduction.* Many molecules involved in signal transduction are proteins. A unique property of proteins that allows them to function in this way is their ability to change their shape or conformation, thereby changing their function and consequently the functions of the cell. These conformational changes are often accomplished through

KEY CONCEPTS

CELL COMMUNICATION

- Cells communicate with each other and with the internal and external environments by a number of mechanisms, including electrical and chemical signaling systems that control electrical potentials, the overall function of a cell, and gene activity needed for cell division and cell replication.
- Chemical messengers exert their effects by binding to cell membrane proteins or receptors that convert the chemical signal into signals within the cell, in a process called *signal transduction.*
- Cells regulate their responses to chemical messengers by increasing or decreasing the number of active receptors on their surface.

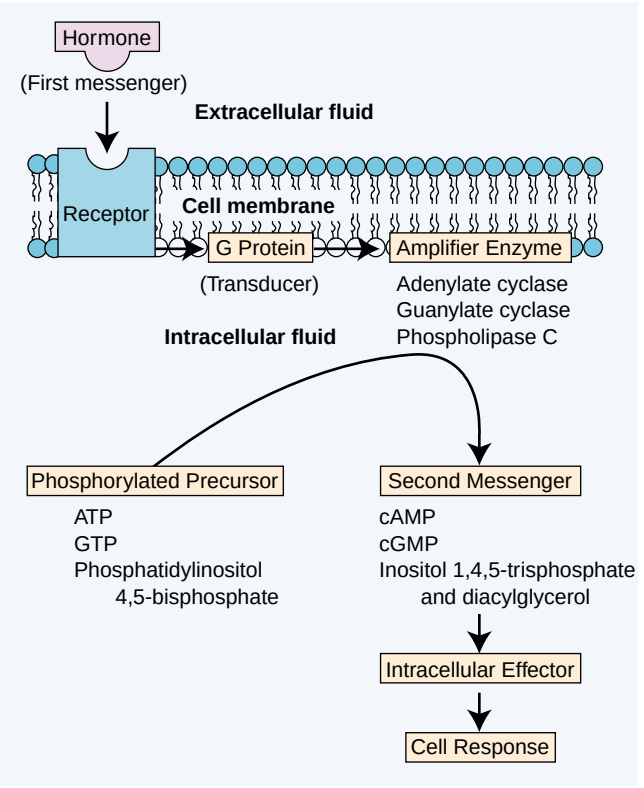


FIGURE 1-12 Signal transduction pattern common to several second messenger systems. A protein or peptide hormone is the first messenger to a membrane receptor, stimulating or inhibiting a membrane-bound enzyme by means of a G protein. The amplifier enzyme catalyzes the production of a second messenger from a phosphorylated precursor. The second messenger then activates an internal effector, which leads to the cell response. (Redrawn from Rhoades R.A., Tanner G.A. [1996]. *Medical physiology.* Boston: Little, Brown)

enzymes called *protein kinases* that catalyze the phosphorylation of amino acids in the protein structure.

Each cell type in the body contains a distinctive set of receptor proteins that enable it to respond to a complementary set of signaling molecules in a specific, preprogrammed way. These receptors, which span the cell membrane, relay information to a series of intracellular intermediates that eventually pass the signal to its final destination. Many receptors for chemical messengers have been isolated and characterized. These proteins are not static components of the cell membrane; they increase or decrease in number, according to the needs of the cell. When excess chemical messengers are present, the number of active receptors decreases in a process called *down-regulation;* when there is a deficiency of the messenger, the number of active receptors increases through *up-regulation.* There are three known classes of cell surface receptor proteins: ion channel linked, G protein linked, and enzyme linked.

Ion-Channel–Linked Receptors. Ion-channel–linked receptors are involved in the rapid synaptic signaling between electrically excitable cells. This type of signaling is mediated by a small number of neurotransmitters that transiently open or close ion channels formed by integral proteins in the cell membrane. This type of signaling is involved in the transmission of impulses in nerve and muscle cells.

G-Protein–Linked Receptors and Signal Transduction. G proteins constitute the on–off switch for signal transduction. Although there are numerous intercellular messengers, many of them rely on a class of molecules called G *proteins* to convert external signals (first messengers) into internal signals (second messengers). These internal signals induce biochemical changes in the cell that lead to the desired physiologic effects. G proteins are so named because they bind to guanine nucleotides, such as guanine diphosphate (GDP) and guanine triphosphate (GTP).

G-protein–mediated signal transduction relies on a series of orchestrated biochemical events (Fig. 1-12). All signal transduction systems have a receptor component that functions as a signal discriminator by recognizing a specific first messenger. After a first messenger binds to a receptor, conformational changes occur in the receptor, which activates the G protein. The activated G protein, in turn, acts on other membrane-bound intermediates called *effectors.* Often, the effector is an enzyme that converts an inactive precursor molecule into a second messenger, which diffuses into the cytoplasm and carries the signal beyond the cell membrane.

Although there are differences between the G proteins, all share a number of features. All are found on the cytoplasmic side of the cell membrane, and all incorporate the GTPase cycle, which functions as the on–off switch for G-protein activity. Certain bacterial toxins can bind to the G proteins, causing inhibition or stimulation of its signal function. One such toxin, the toxin of *Vibrio cholerae,* binds and activates the stimulatory G protein linked to the cAMP system that controls the secretion of fluid into the intestine. In response to the cholera toxin, these cells overproduce fluid, leading to severe diarrhea and life-threatening depletion of extracellular fluid volume. There is also interest in the role that G-protein signaling may play in the pathogenesis of cancer.

Enzyme-Linked Receptors. The receptors for certain protein hormones, such as insulin, and peptide growth factors activate an intracellular domain with enzyme (protein-tyrosine kinase) activity. The enzyme catalyzes the phosphorylation of tyrosine residues of intracellular proteins, thereby transferring an external message to the cell interior. Enzyme-linked receptors mediate cellular responses such as calcium influx, increased sodium/potassium exchange, and stimulation of the uptake of sugars and amino acids.

Growth factors are signal molecules that are similar to hormones in function but act closer to their sites of synthesis. As their name implies, many of the growth factors are important messengers in signaling cell replacement and cell growth. Most of the growth factors belong to one of three groups: factors that foster the multiplication and development of various cell types (*e.g.*, growth factor and epidermal growth factor); lymphokines and cytokines, which are important in the regulation of the immune system; and colony-stimulating factors, which regulate the proliferation and maturation of white and red blood cells.

Messenger-Mediated Control of Nuclear Function

Some messengers, such as thyroid hormone and steroid hormones, do not bind to membrane receptors but move directly across the lipid layer of the cell membrane and are carried to the cell nucleus, where they influence DNA activity. Many of these hormones bind to a cytoplasmic receptor, and together they are carried to the nucleus. In the nucleus, the receptor–hormone complex binds to DNA, thereby increasing transcription of mRNA. The mRNAs are translated in the ribosomes, with the production of increased amounts of proteins that alter cell function.

Membrane Potentials

The human body runs on a system of self-generated electricity. Electrical potentials exist across the membranes of most cells in the body. Because these potentials occur at the level of the cell membrane, they are called *membrane potentials*. In excitable tissues, such as nerve or muscle cells, changes in the membrane potential are necessary for generation and conduction of nerve impulses and muscle contraction. In other types of cells, such as glandular cells, changes in the membrane potential contribute to hormone secretion and other functions.

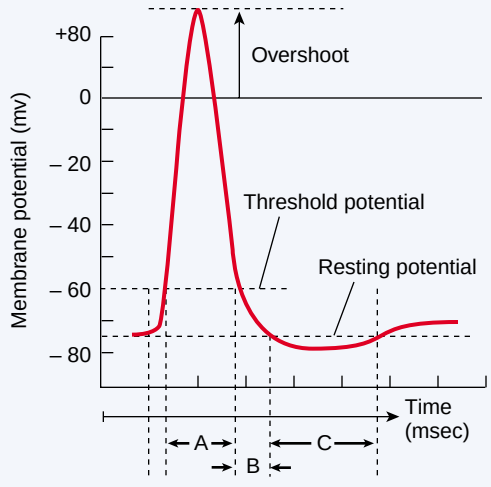
Electrical Potential

Electrical potential, measured in volts (V), describes the ability of separated electrical charges of opposite polarity (+ and –) to do work. The potential difference is the difference between the separated charges. The terms *potential difference* and *voltage* are synonymous. Voltage is always measured with respect to two points in a system. For example, the voltage in a car battery (6 or 12 V) is the potential difference between the two battery terminals. Because the total amount of charge that can be separated by a biologic membrane is small, the potential differences are small and are measured in *millivolts* (1/1000 of a volt). Potential differences across the cell membrane can be measured by inserting a very fine electrode into the cell and another into the extracellular fluid surrounding the cell and connecting the two electrodes to a voltmeter. The movement of charge between two points is called *current*. It occurs when a potential difference has been established and a connection is made such that the charged particles can move between the two points.

Extracellular and intracellular fluids are electrolyte solutions containing approximately 150 to 160 mmol/L of positively charged ions and an equal concentration of negatively charged ions. These are the current-carrying ions responsible for generating and conducting membrane potentials. Usually, a small excess of positively charged ions exists at the outer surface of the cell membrane. This is represented as positive charges on the outside of the membrane and is balanced by an equal number of negative charges on the inside of the membrane. Because of the extreme thinness of the cell membrane, the accumulation of these ions at the surfaces of the membrane contributes to the establishment of a membrane potential.

Action Potentials

Action potentials are abrupt, pulselike changes in the membrane potential that last a few ten thousandths to a few thousandths of a second (Fig 1-13). In a nerve fiber, an action potential can be elicited by any factor that suddenly increases the membrane potential, usually by opening a voltage-gated sodium channel. The *threshold potential* represents the membrane potential at which the ion channels open and neurons and other excitable tissues are stimulated to "fire." In large nerve



A = Absolute refractory period (active potential and partial recovery)
B = Relative refractory period
C = Positive relative refractory period

■ **FIGURE 1-13** ■ Time course of the action potential recorded at one point of an axon with one electrode inside and one on the outside of the plasma membrane. The rising part of the action potential is called the spike. The rising phase plus approximately the first half of the repolarization phase is equal to the absolute refractory period (**A**). The portion of the repolarization phase that extends from the threshold to the resting membrane potential represents the relative refractory period (**B**). The remaining portion of the repolarization phase to the resting membrane potential is equal to the negative after potential (**C**). Hyperpolarization is equal to the positive relative refractory period.

fibers the sodium channels open at approximately −60 mV. Under normal circumstances, the threshold potential is sufficient to open large numbers of ion channels, triggering massive depolarization of the membrane.

Action potentials can be divided into three phases: (1) resting, (2) depolarization, and (3) repolarization phases. The resting phase is the undisturbed period of the action potential, during which neurons and other excitable tissues are not transmitting impulses. During this phase, the membrane is highly permeable to potassium and there is approximately 70 to 90 mV less charge (−70 mV to −90 mV) on the inside than on the outside of the membrane. This difference in charge is necessary for establishment of current flow once the membrane becomes permeable to the flow of charged ions. During this period, the membrane is said to be polarized because charges of opposite polarity (+ and −) are aligned across the membrane. *Depolarization* is characterized by the flow of positively charged sodium ions to the interior of the membrane. During the depolarization phase of the action potential, the interior side of the membrane becomes positive (approximately +30 mV to +45 mV). Repolarization is the phase in which the polarity of the resting membrane is re-established. This is accomplished by closure of the sodium channels and opening of the potassium channels. The outflow of positively charged potassium ions returns the membrane potential to negativity. The activity of the Na+/K+ ATPase pump helps to reestablish the resting membrane potential. During repolarization, the membrane remains refractory (*i.e.*, does not fire) until the repolarization is approximately one-third complete. This period, which lasts approximately one half of a millisecond, is called the *absolute refractory period* (Fig. 1-13). During the *relative refractory period,* which follows the absolute refractory period, the membrane can be excited, although only by a stronger-than-normal stimuli.

Two main factors alter membrane excitability: (1) the difference in the concentration of ions on the inside and outside of the membrane and (2) changes in membrane permeability. The resting membrane potential is strongly influenced by serum potassium levels and the resulting difference in concentration on the inside and outside of the membrane. When serum levels of potassium are decreased, the resting membrane potential becomes more negative, and nerve and muscle cells become less excitable, sometimes to the extent that they cannot be re-excited (see Chapter 6). An increase in serum potassium has the opposite effect, causing the resting membrane to become more positive, moving closer to threshold. When this happens, the amplitude of the action potential is decreased because the membrane has not been fully repolarized. Should the resting membrane potential reach the level of the threshold potential during the absolute refractory period, the nerve or muscle cell will remain depolarized and unexcitable.

Neural excitability is markedly altered by changes in membrane permeability to current-carrying ions such as sodium. Calcium ions decrease membrane permeability to sodium ions and increase the threshold for initiation of action potentials. If insufficient calcium ions are available, the permeability of the membrane to sodium increases, and as a result, membrane excitability increases, sometimes causing spontaneous muscle movements (tetany) to occur. Local anesthetic agents (*e.g.*, procaine, cocaine) act directly on neural membranes to decrease their permeability to sodium.

In summary, the movement of materials across the cell's membrane is essential for survival of the cell. Diffusion is a process by which substances such as ions move from areas of greater concentration to areas of lesser concentration in an attempt to reach a uniform distribution. Osmosis refers to the diffusion of water molecules through a semipermeable membrane along a concentration gradient. Facilitated diffusion is a passive process, in which molecules that cannot normally pass through the cell's membranes, do so with the assistance of a carrier molecule. Another type of transport, called active transport, requires the cell to expend energy in moving ions against a concentration gradient. The Na^+/K^+ ATPase pump is the best-known type of active transport. Endocytosis is a process by which cells engulf materials from the surrounding medium. Small particles are ingested by a process called pinocytosis; larger particles are engulfed by a process called phagocytosis. Exocytosis involves the removal of large particles from the cell and is essentially the reverse of endocytosis. Ion channels are integral transmembrane proteins that span the width of the cell membrane to form a gating system that controls the movement of ions across the cell membrane.

Cells communicate with each other by means of chemical messenger systems. In some tissues, chemical messengers move from cell to cell through gap junctions without entering the extracellular fluid. Other types of chemical messengers bind to receptors on or near the cell surface. There are three known classes of cell surface receptor proteins: ion channel linked, G protein linked, and enzyme linked. Ion-channel–linked signaling is mediated by neurotransmitters that transiently open or close ion channels formed by integral proteins in the cell membrane. G-protein–linked receptors rely on a class of molecules called G proteins that function as an on–off switch to convert external signals (first messengers) into internal signals (second messengers). Enzyme-linked receptors interact with certain peptide hormones (*e.g.*, insulin and growth factors) to directly initiate the activity of an intracellular enzyme, which in turn, triggers multiple cellular responses, such as stimulation of glucose and amino acid uptake or transcription of certain genes that control cell proliferation.

Electrical potentials (negative on the inside and positive on the outside) exist across the membranes of most cells in the body. Membrane excitability depends on a separation of charge across the membrane and the permeability of the membrane to the current-carrying ion. Action potentials are abrupt pulselike changes in the membrane potential that last a few ten thousandths to a few thousandths of a second. Action potentials can be divided into three phases: the resting phase, during which neurons and excitable tissues are not generating or transmitting impulses; the depolarization phase, which is characterized by flow of current across the membrane; and the repolarization phase, during which the resting membrane potential is restored.

BODY TISSUES

In the preceding sections, we discussed the individual cell, its metabolic processes, and mechanisms of communication. Although cells are similar, their structure and function vary ac-

cording to the special needs of the body. For example, muscle cells perform functions different from those of skin cells or nerve cells. Groups of cells that are closely associated in structure and have common or similar functions are called *tissues*. Four categories of tissue exist: epithelium, connective (supportive) tissue, muscle, and nerve. These tissues do not exist in isolated units, but in association with each other and in variable proportions, forming different structures and organs. This section provides a brief overview of the cells in epithelial, connective, and muscle tissue. Nervous tissue is described in Chapter 36.

Cell Differentiation

After conception, the fertilized ovum undergoes a series of divisions, ultimately forming approximately 200 different cell types. The formation of different types of cells and the disposition of these cells into tissue types is called *cell differentiation*, a process controlled by a system that switches genes on and off. Embryonic cells must become different to develop into all of the various organ systems, and they must remain different after the signal that initiated cell diversification has disappeared. The process of cell differentiation is controlled by cell memory, which is maintained through regulatory proteins contained in the individual members of a particular cell type. Cell differentiation also involves the sequential activation of multiple genes and their protein products. This means that after differentiation has occurred, the tissue type does not revert to an earlier stage of differentiation. The process of cell differentiation normally moves forward, producing cells that are more specialized than their predecessors. Usually, highly differentiated cell types, such as skeletal muscle and nervous tissue, lose their ability to undergo cell division. Cancer is a disorder of cell differentiation in which cells of a single cell line fail to differentiate properly (see Chapter 5).

KEY CONCEPTS

ORGANIZATION OF CELLS INTO TISSUES

- Cells with a similar embryonic origin or function are often organized into larger functional units called *tissues,* and these tissues in turn associate with other, dissimilar tissues to form the various organs of the body.
- Epithelial tissue forms sheets that cover the body's outer surface, lines internal surfaces, and forms glandular tissue. It is supported by a basement membrane, is avascular, and must receive nourishment from capillaries in supporting connective tissues.
- Connective tissue is the most abundant tissue of the body. It is found in a variety of forms, ranging from solid bone to blood cells that circulate in the vascular system.
- Muscle tissue contains actin and myosin filaments that allow it to contract and provide locomotion and movement of skeletal structures (skeletal muscle), pumping of blood through the heart (cardiac muscle), and contraction of blood vessels and visceral organs (smooth muscle).

Embryonic Origin of Tissue Types

All of the approximately 200 different types of body cells can be classified into four basic or primary tissue types: epithelial, connective, muscle, and nervous (Table 1-1). These basic tissue types are often described by their embryonic origin. The embryo is essentially a three-layered tubular structure. The outer layer of the tube is called the *ectoderm;* the middle layer, the *mesoderm;* and the inner layer, the *endoderm*. All of the adult body tissues originate from these three cellular layers. Epithelium has its origin in all three embryonic layers; connective tissue and muscle develop mainly from the mesoderm; and nervous tissue develops from the ectoderm.

Epithelial Tissue

Epithelial tissue forms sheets that cover the body's outer surface, line the internal surfaces, and form the glandular tissue. Underneath all types of epithelial tissue is an extracellular matrix, called the *basement membrane,* which serves to attach the epithelial cells to adjacent connective tissue and provides them with flexible support.

Epithelial cells have strong intracellular protein filaments (*i.e.*, cytoskeleton) that are important in transmitting mechanical stresses from one cell to another. The cells of epithelial tissue are tightly bound together by specialized junctions. These specialized junctions enable these cells to form barriers to the movement of water, solutes, and cells from one body compartment to the next. Epithelial tissue is avascular (*i.e.*, without blood vessels) and must therefore receive oxygen and nutrients from the capillaries of the connective tissue on which the epithelial tissue rests (Fig. 1-14). To survive, the epithelial cells must be kept moist. Even the seemingly dry skin epithelium is kept moist by a nonvitalized, waterproof layer of superficial skin cells called *keratin,* which prevents evaporation of moisture from the deeper living cells. Epithelium is able to regenerate quickly when injured

Epithelial tissues are classified according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudostratified. Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. The terms *squamous* (thin and flat), *cuboidal* (cube shaped), and *columnar* (resembling a column) refer to the cells' shape (Fig. 1-15).

Simple Epithelium

Simple epithelium contains a single layer of cells, all of which rest on the basement membrane. Simple squamous epithelium is adapted for filtration; it is found lining the blood vessels, lymph nodes, and alveoli of the lungs. The single layer of squamous epithelium lining the heart and blood vessels is known as the *endothelium.* A similar type of layer, called the *mesothelium,* forms the serous membranes that line the pleural, pericardial, and peritoneal cavities and cover the organs of these cavities. A *simple cuboidal epithelium* is found on the surface of the ovary and in the thyroid. *Simple columnar epithelium* lines the intestine. One form of a simple columnar epithelium

TABLE 1-1 Classification of Tissue Types

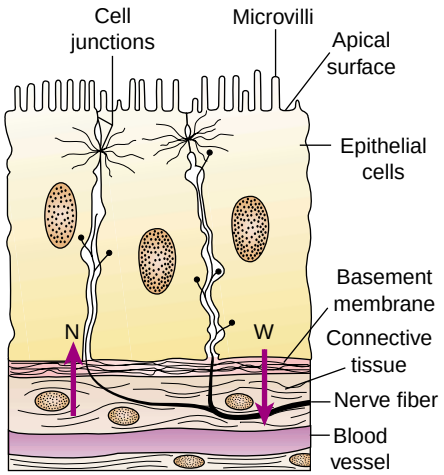
Tissue Type	Location
Epithelial Tissue	
Covering and lining of body surfaces	
Simple epithelium	
Squamous	Lining of blood vessels, body cavities, alveoli of lungs
Cuboidal	Collecting tubules of kidney; covering of ovaries
Columnar	Lining of intestine and gallbladder
Stratified epithelium	
Squamous keratinized	Skin
Squamous nonkeratinized	Mucous membranes of mouth, esophagus, and vagina
Cuboidal	Ducts of sweat glands
Columnar	Large ducts of salivary and mammary glands; also found in conjunctiva
Transitional	Bladder, ureters, renal pelvis
Pseudostratified	Tracheal and respiratory passages
Glandular	
Endocrine	Pituitary gland, thyroid gland, adrenal, and other glands
Exocrine	Sweat glands and glands in gastrointestinal tract
Neuroepithelium	Olfactory mucosa, retina, tongue
Reproductive epithelium	Seminiferous tubules of testis; cortical portion of ovary
Connective Tissue	
Embryonic connective tissue	
Mesenchymal	Embryonic mesoderm
Mucous	Umbilical cord (Wharton's jelly)
Adult connective tissue	
Loose or areolar	Subcutaneous areas
Dense regular	Tendons and ligaments
Dense irregular	Dermis of skin
Adipose	Fat pads, subcutaneous layers
Reticular	Framework of lymphoid organs, bone marrow, liver
Specialized connective tissue	
Bone	Long bones, flat bones
Cartilage	Tracheal rings, external ear, articular surfaces
Hematopoietic	Blood cells, myeloid tissue (bone marrow)
Muscle Tissue	
Skeletal	Skeletal muscles
Cardiac	Heart muscles
Smooth	Gastrointestinal tract, blood vessels, bronchi, bladder, and others
Nervous Tissue	
Neurons	Central and peripheral neurons and nerve fibers
Supporting cells	Glial and ependymal cells in central nervous system; Schwann and satellite cells in peripheral nervous system

has hairlike projections called *cilia*, often with specialized mucus-secreting cells called *goblet cells*. This form of simple columnar epithelium lines the airways of the respiratory tract.

Stratified and Pseudostratified Epithelium

Stratified epithelium contains more than one layer of cells, with only the deepest layer resting on the basement membrane. It is designed to protect the body surface. *Stratified squamous keratinized* epithelium makes up the epidermis of the skin. Keratin is a tough, fibrous protein existing as filaments in the outer cells of skin. A stratified squamous keratinized epithelium is made up of many layers. The layers closest to the underlying tissues are cuboidal or columnar. The cells become more irregular and thinner as they move closer to the surface. Surface cells become totally filled with keratin and die, are sloughed off, and then replaced by the deeper cells. A stratified squamous nonkeratinized epithelium is found on moist surfaces, such as the mouth and tongue. Stratified cuboidal and columnar epithelia are found in the ducts of salivary glands and the larger ducts of the mammary glands. In smokers, the normal columnar ciliated epithelial cells of the trachea and bronchi are often replaced with stratified squamous epithelium cells that are better able to withstand the irritating effects of cigarette smoke.

Pseudostratified epithelium is a type of epithelium in which all of the cells are in contact with the underlying intercellular matrix, but some do not extend to the surface. A pseudostratified ciliated columnar epithelium with goblet cells forms the lining of most of the upper respiratory tract. All of the tall cells reaching the surface of this type of epithelium are either ciliated cells or mucus-producing goblet cells. The basal cells that do not



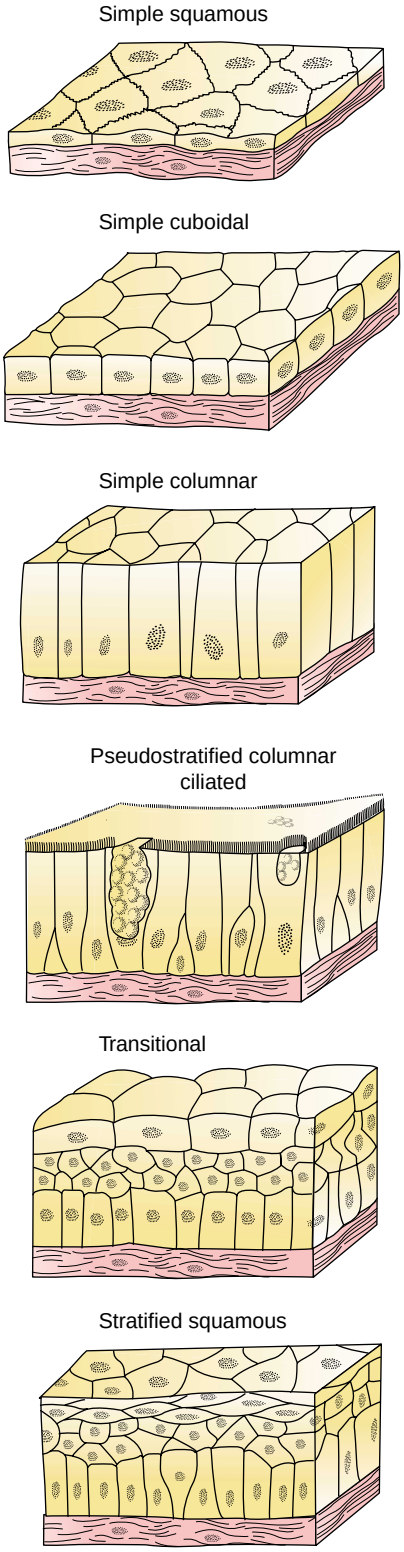
■ **FIGURE 1-14** ■ Typical arrangement of epithelial cells in relation to underlying tissues and blood supply. Epithelial tissue has no blood supply of its own but relies on the blood vessels in the underlying connective tissue for nutrition (**N**) and elimination of wastes (**W**).

reach the surface serve as stem cells for ciliated and goblet cells. *Transitional epithelium* is a stratified epithelium characterized by cells that can change shape and become thinner when the tissue is stretched. Such tissue can be stretched without pulling the superficial cells apart. Transitional epithelium is well adapted for the lining of organs that are constantly changing their volume, such as the urinary bladder.

Glandular Epithelium

Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. This process is usually accompanied by the intracellular synthesis of macromolecules. The chemical nature of these macromolecules is variable. The macromolecules typically are stored in the cells in small, membrane-bound vesicles called *secretory granules*. For example, glandular epithelia can synthesize, store, and secrete proteins (*e.g.*, insulin), lipids (*e.g.*, adrenocortical hormones, secretions of the sebaceous glands), and complexes of carbohydrates and proteins (*e.g.*, saliva). Less common are secretions such as those produced by the sweat glands, which require minimal synthetic activity.

All glandular cells arise from surface epithelia by means of cell proliferation and invasion of the underlying connective tissue. Epithelial glands can be divided into two groups: exocrine and endocrine glands. *Exocrine glands*, such as the sweat glands and lactating mammary glands, retain their connection with the surface epithelium from which they originated. This connection takes the form of epithelium-lined tubular ducts through which the secretions pass to reach the surface. Exocrine glands are often classified according to the way secretory products are released by their cells. In *holocrine* type cells (*e.g.*, sebaceous glands), the glandular cell ruptures, releasing its entire contents into the duct system. New generations of cells are replaced by mitosis of basal cells. *Merocrine* or *eccrine* type glands (*e.g.*, salivary glands, exocrine glands of the pancreas) release their glandular products by exocytosis. In apocrine secretions (*e.g.*, mammary glands, certain sweat glands), the apical por-



■ **FIGURE 1-15** ■ Representation of the various epithelial tissue types.

tion of the cell, along with small portions of the cytoplasm, is pinched off the glandular cells. *Endocrine glands* are epithelial structures that have had their connection with the surface obliterated during development. These glands are ductless and produce secretions (*i.e.*, hormones) that move directly into the bloodstream.

Connective or Supportive Tissue

Connective tissue (or supportive tissue) is the most abundant tissue in the body. As its name suggests, it connects and binds or supports the various tissues. The capsules that surround organs of the body are composed of connective tissue. Bone, adipose tissue, and cartilage are specialized types of connective tissue that function to support the soft tissues of the body and store fat. Connective tissue is unique in that its cells produce the extracellular matrix that supports and holds tissues together. Connective tissue has a role in tissue nutrition. The close proximity of the extracellular matrix to blood vessels allows it to function as an exchange medium through which nutrients and metabolic wastes pass.

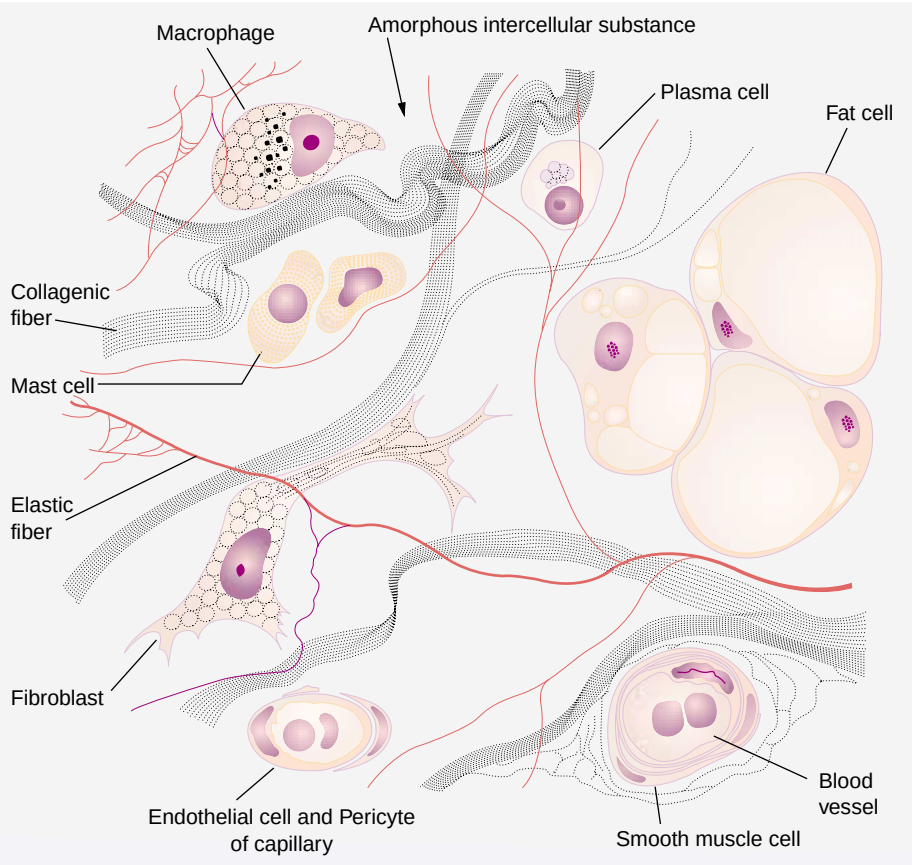
Adult connective tissue proper can be divided into two main types: loose or areolar and dense connective tissue.

Loose Connective Tissue

Loose connective tissue, also known as areolar tissue, is soft and pliable. Although it is more cellular than dense connective tissue, it contains large amounts of intercellular substance. It fills spaces between muscle sheaths and forms a layer that encases blood and lymphatic vessels. Areolar connective tissue supports the epithelial tissues and provides the means by which these tissues are nourished. In an organ containing functioning epithelial tissue and supporting connective tissue, the term *parenchymal tissue* is used to describe the functioning epithelium as opposed to the connective tissue framework or stroma.

Cells of loose connective tissue include fibroblasts, mast cells, adipose or fat cells, macrophages, plasma cells, and leukocytes (Fig. 1-16). Loose connective tissue cells secrete substances that form the extracellular matrix that supports and connects body cells. Fibroblasts are the most abundant of these cells. They are responsible for the synthesis of the fibrous and gel-like substance that fills the intercellular spaces of the body and for the production of collagen, elastic, and reticular fibers.

Adipose tissue is a special form of connective tissue in which adipocytes predominate. Adipocytes do not generate an extracellular matrix but maintain a large intracellular space. These cells store large quantities of triglycerides and are the largest repository of energy in the body. Adipose tissue helps fill spaces between tissues and helps to keep organs in place. Subcutaneous layers of fat help to shape the body. Because fat is a poor conductor of heat, adipose tissue serves as thermal insulation for the body. Adipose tissue exists in two forms. Unilocular (white) adipose tissue is composed of cells in which the fat is contained in a single, large droplet in the cytoplasm. Multilocular (brown) adipose tissue is composed of cells that contain multiple droplets of fat and numerous mitochondria.



■ **FIGURE 1-16** ■ Diagrammatic representation of cells that may be seen in loose connective tissue. The cells lie in an intercellular matrix that is bathed in tissue fluid that originates in capillaries. (From Cormack D.H. [1987]. *Ham's histology* [9th ed.]. Philadelphia: J.B. Lippincott)

Reticular tissue is characterized by a network of reticular fibers associated with reticular cells. Reticular fibers provide the framework for capillaries, nerves, and muscle cells. They also constitute the main supporting elements for the blood forming tissues and the liver.

Dense Connective Tissue

Dense connective tissue exists in two forms: dense irregular and dense regular. Dense irregular connective tissue consists of the same components found in loose connective tissue, but there is a predominance of collagen fibers and fewer cells. This type of tissue can be found in the dermis of the skin (*i.e.*, reticular layer), the fibrous capsules of many organs, and the fibrous sheaths of cartilage (*i.e.*, perichondrium) and bone (*i.e.*, periosteum). It also forms the fascia that covers muscles and organs. Dense regular connective tissues are rich in collagen fibers and form the tendons and aponeuroses that join muscles to bone or other muscles and the ligaments that join bone to bone. Tendons and ligaments are white fibers because of an abundance of collagen. Ligaments such as the ligamenta flava of the vertebral column and the true vocal folds are called *yellow fibers* because of the abundance of elastic fibers.

Muscle Tissue

Three types of muscle tissues exist: *skeletal*, *cardiac*, and *smooth*. Skeletal and cardiac muscles are striated muscles. The actin and myosin filaments are arranged in large parallel arrays in bundles, giving the muscle fibers a striped or striated appearance when they are viewed through a microscope.

Skeletal muscle is the most abundant tissue in the body, accounting for 40% to 45% of the total body weight. Most skeletal muscles are attached to bones, and their contractions are responsible for movements of the skeleton. Cardiac muscle, which is found in the heart, is designed to pump blood continuously. Smooth muscle is found in the iris of the eye, the walls of blood vessels, hollow organs such as the stomach and urinary bladder, and hollow tubes, such as the ureters, that connect internal organs.

Neither skeletal nor cardiac muscle can undergo the mitotic activity needed to replace injured cells. However, smooth muscle may proliferate and undergo mitotic activity. Some increases in smooth muscle are physiologic, as occurs in the uterus during pregnancy. Other increases, such as the increase in smooth muscle that occurs in the arteries of persons with chronic hypertension, are pathologic.

Although the three types of muscle tissue differ significantly in structure, contractile properties, and control mechanisms, they have many similarities. In the following section, the structural properties of skeletal muscle are presented as the prototype of striated muscle tissue. Smooth muscle and the ways in which it differs from skeletal muscle are also discussed. Cardiac muscle is described in Chapter 14.

Skeletal Muscle

Skeletal muscle tissue is packaged into skeletal muscles that attach to and cover the body skeleton. Each skeletal muscle is a discrete organ made up of hundreds and thousands of muscle fibers. Even though muscle fibers predominate, substantial amounts of connective tissue, blood vessels, and nerve fibers are present. In an intact muscle, several different layers of connective tissue hold the individual muscle fibers together. A dense connective tissue covering called the *epimysium* forms the outermost layer surrounding the whole muscle (Fig. 1-17). Each muscle is subdivided into smaller bundles called *fascicles*, which are surrounded by a connective tissue covering called the *perimysium*. The number of fascicles and their size vary among muscles. Fascicles consist of many elongated structures called *muscle fibers*, each of which is surrounded by connective tissue called the *endomysium*.

Skeletal muscles are syncytial or multinucleated structures, meaning there are no true cell boundaries within a skeletal muscle fiber. The cytoplasm or sarcoplasm of the muscle fiber is contained within the sarcolemma, which represents the cell membrane. Embedded throughout the sarcoplasm are the contractile elements actin and myosin, which are arranged in parallel bundles (*i.e.*, *myofibrils*). The thin, lighter-staining myofilaments are composed of actin, and the thicker, darker-staining myofilaments are composed of myosin. Each myofibril consists of regularly repeating units along the length of the myofibril; each of these units is called a *sarcomere* (see Fig. 1-17). Sarcomeres are the structural and functional units of cardiac and skeletal muscle. A sarcomere extends from one Z line to another Z line. Within the sarcomere are alternating light and dark bands. The central dark band (A band) contains mainly myosin filaments, with some overlap with actin filaments. The lighter I band contains only actin filaments and straddles the Z band; therefore, it takes two sarcomeres to complete an I band. An H zone is found in the middle of the A band and represents the region where only myosin filaments are found. In the center of the H zone is a thin, dark band, the M band or line, that is produced by linkages between the myosin filaments. Z bands consist of short elements that interconnect and provide the thin actin filaments from two adjoining sarcomeres with an anchoring point.

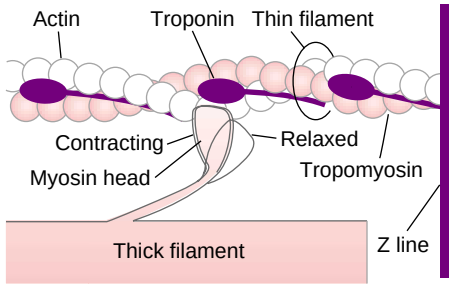
The *sarcoplasmic reticulum*, which is comparable to the smooth ER, is composed of longitudinal tubules that run parallel to the muscle fiber and surround each myofibril. This network ends in enlarged, saclike regions called the *lateral sacs* or *terminal cisternae*. These sacs store calcium to be released during muscle contraction. A second system of tubules consists of the *transverse* or *T tubules*, which are extensions of the plasma membrane and run perpendicular to the muscle fiber. The hollow portion or lumen of the transverse tubule is continuous with the extracellular fluid compartment. Action potentials, which are rapidly conducted over the surface of the muscle fiber, are in turn propagated by the T tubules and into the sarcoplasmic reticulum. As the action potential moves through the lateral sacs, the sacs release calcium, initiating muscle contraction. The membrane of the sarcoplasmic reticulum also has an active transport mechanism for pumping calcium ions back into the reticulum. This prevents interactions between calcium ions and the actin and myosin myofilaments after cessation of a muscle contraction.

Skeletal Muscle Contraction. Muscle contraction involves the sliding of the thick myosin and thin actin filaments over each other to produce shortening of the muscle fiber, while the actual length of the individual thick and thin filaments remains unchanged. The thick myosin filaments consist of a thin tail, which provides the structural backbone for the filament, and a globular head that forms cross-bridges with the thin actin

■ **FIGURE 1-17** ■ (**A**) Connective tissue components of a skeletal muscle. (**B**) Structure of the myofibril and the relationship between actin and myosin myofilaments. (**C**) Sarcoplasmic reticulum and system of transverse tubules.

filaments (Fig. 1-18). Myosin molecules are bundled together side by side in the thick filaments such that one half have their heads toward one end of the filament and their tails toward the other end; the other half are arranged in the opposite manner. Each globular myosin head contains a binding site able to bind to a complementary site on the actin molecule. In addition to the binding site for actin, each myosin head has a separate active site that catalyzes the breakdown of ATP to provide the energy needed to activate the myosin head so it can form a cross-bridge with actin. After contraction, myosin also binds ATP, thus breaking the linkage between actin and myosin.

The thin filaments are composed mainly of actin, a globular protein lined up in two rows that coil around each other to form a long helical strand. Associated with each actin filament are two regulatory proteins, tropomyosin and troponin. *Tropomyosin,* which lies in grooves of the actin strand, provides the site for attachment of the globular heads of the myosin filament. In the noncontracted state, *troponin* covers the tropomyosin binding sites and prevents formation of cross-bridges between the actin and myosin. During an action potential, calcium ions



■ **FIGURE 1-18** ■ Molecular structure of the thin actin filament and the thicker myosin filament of striated muscle. The thin filament is a double-stranded helix of actin molecules with tropomyosin and troponin molecules lying along the grooves of the actin strands. During muscle contraction, the ATP-activated heads of the thick myosin filament swivel into position, much like the oars on a boat, form a cross-bridge with a reactive site on tropomyosin, and then pull the actin filament forward. During muscle relaxation, the troponin molecules cover the reactive sites on tropomyosin.

released from the sarcoplasmic reticulum diffuse to the adjacent myofibrils, where they bind to troponin. The binding of calcium to troponin uncovers the tropomyosin binding sites such that the myosin heads can attach and form cross-bridges.

Muscle contraction begins with activation of the cross-bridges from the myosin filaments and uncovering of the tropomyosin binding sites on the actin filament. When activated by ATP, the heads of the myosin heads swivel in a fixed arc, much like the oars of a boat, as they become attached to the actin filament. During contraction, each myosin head undergoes its own cycle of movement, forming a bridge attachment and releasing it, and moving to another site where the same sequence of movement occurs. This pulls the thin and thick filaments past each other. Energy from ATP is used to break the actin and myosin cross-bridges, stopping the muscle contraction. With the breaking of the linkage between actin and myosin, the concentration of calcium around the myofibrils decreases as calcium is actively transported into the sarcoplasmic reticulum by a membrane pump that uses energy derived from ATP.

Smooth Muscle

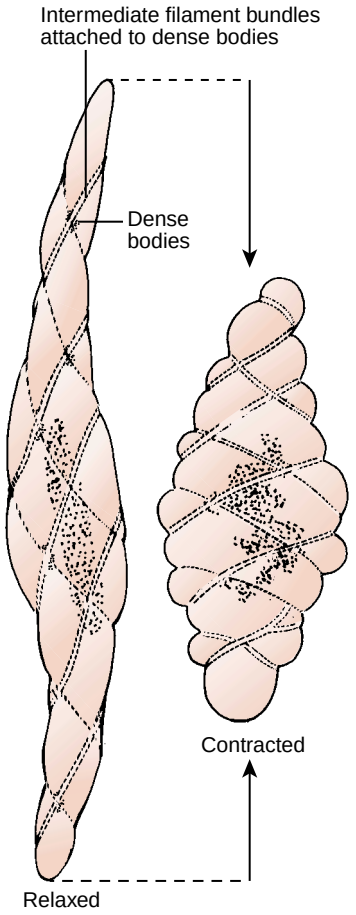
Smooth muscle is often called *involuntary muscle* because its activity arises spontaneously or through activity of the autonomic nervous system. Smooth muscle contractions are slower and more sustained than skeletal or cardiac muscle contractions.

Organization and Structure. Smooth muscle cells are spindle shaped and smaller than skeletal muscle fibers. Each smooth muscle cell has one centrally positioned nucleus. Z bands or M lines are not present in smooth muscle fibers, and the cross-striations are absent because the bundles of filaments are not parallel but crisscross obliquely through the cell. Instead, the actin filaments are attached to structures called *dense bodies*. Some of the dense bodies are attached to the cell membrane, and others are dispersed in the cell and linked together by structural proteins (Fig. 1-19).

The lack of Z lines and regular overlapping of the contractile elements provides a greater range of tension development. This is important in hollow organs that undergo changes in volume, with consequent changes in the length of the smooth muscle fibers in their walls. Even with the distention of a hollow organ, the smooth muscle fiber retains some ability to develop tension, whereas such distention would stretch skeletal muscle beyond the area where the thick and thin filaments overlap.

Smooth muscle usually is arranged in sheets or bundles. In hollow organs, such as the intestines, the bundles are organized into the two-layered muscularis externa, consisting of an outer, longitudinal layer and an inner, circular layer. A thinner muscularis mucosae often lies between the muscularis externa and the endothelium. In blood vessels, the bundles are arranged circularly or helically around the vessel wall.

Smooth Muscle Contraction. As with cardiac and skeletal muscle, smooth muscle contraction is initiated by an increase in intracellular calcium. However, smooth muscle differs from skeletal muscle in the way its cross-bridges are formed. The sarcoplasmic reticulum of smooth muscle is less developed than in skeletal muscle, and no transverse tubules are present. Thus, smooth muscle relies heavily on the entrance



■ **FIGURE 1-19** ■ Structure of smooth muscle showing the dense bodies. In smooth muscle, the force of contraction is transmitted to the cell membrane by bundles of intermediate fibers. (Cormack D.H. [1993]. *Essential histology* [p. 229]. Philadelphia: J.B. Lippincott)

of extracellular calcium for muscle contraction. This dependence on movement of extracellular calcium across the cell membrane during muscle contraction is the basis for the action of calcium-blocking drugs used in the treatment of cardiovascular disease.

Smooth muscle also lacks the calcium-binding regulatory protein troponin, which is found in skeletal and cardiac muscle. Instead, it relies on another cytoplasmic protein called *calmodulin*. The calcium–calmodulin complex binds to and activates the myosin-containing thick filaments, which interact with actin.

Types of Smooth Muscle. Smooth muscle may be divided into two broad categories according to the mode of activation: multiunit and single-unit smooth muscle. In *multiunit* smooth muscle, each unit operates almost independently of the others and is often enervated by a single nerve, such as occurs in skeletal muscle. It has little or no inherent activity and depends on the autonomic nervous system for its activation. Smooth muscle of this type is found in the iris, in the walls of the vas deferens, and attached to hairs in the skin. The fibers in *single-unit* smooth muscle are in close contact with each

other and can contract spontaneously without nerve or hormonal stimulation. Normally, most muscle fibers contract synchronously, thus the term *single-unit* smooth muscle. Some single-unit smooth muscle, such as that found in the gastrointestinal tract, is self-excitable. This is usually associated with a basic slow-wave rhythm transmitted from cell to cell by nexuses (*i.e.*, gap junctions) formed by the fusion of adjacent cell membranes. The cause of this slow wave is unknown. The intensity of contraction increases with the frequency of the action potential. Certain hormones, other agents, and local factors can modify smooth muscle activity by depolarizing or hyperpolarizing the membrane. The smooth muscle of the uterus and small-diameter blood vessels is also single-unit smooth muscle.

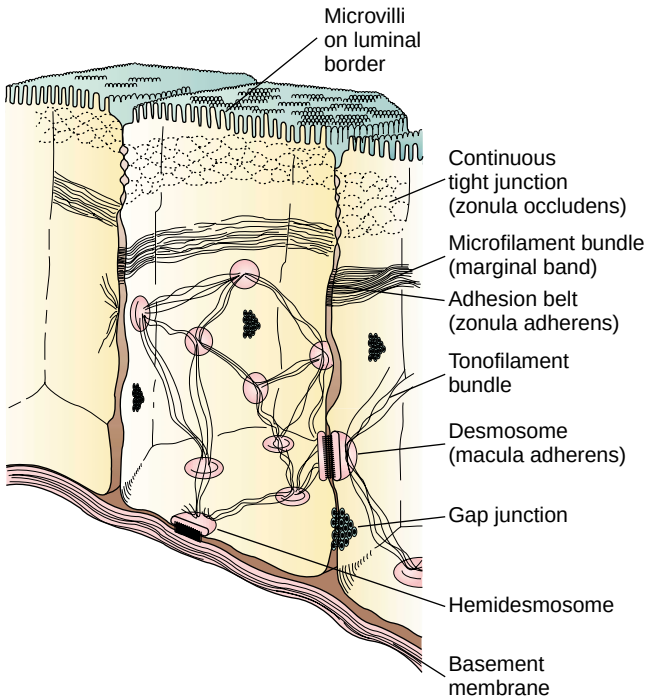
Cell Junctions and Cell-to-Cell Adhesion

Cell junctions occur at many points in cell-to-cell contact, but they are particularly plentiful and important in epithelial tissue. Three basic types of intercellular junctions are observed: tight junctions, adhering junctions, and gap junctions (Fig. 1-20). Often, the cells in epithelial tissue are joined by all three types of junctions. *Continuous tight* or occluding junctions (*i.e.*, zona occludens), which are found only in epithelial tissue, seal the surface membranes of adjacent cells together. This type of intercellular junction prevents materials such as macromolecules present in the intestinal contents from entering the intercellular space.

Adhering junctions represent a site of strong adhesion between cells. The primary role of adhering junctions may be that of preventing cell separation. Adhering junctions are not restricted to epithelial tissue; they provide adherence between adjacent cardiac muscle cells as well. Adhering junctions are found as continuous, beltlike adhesive junctions (*i.e.*, zonula adherens), or scattered, spotlike adhesive junctions called *desmosomes* (*i.e.*, macula adherens). A special feature of the adhesion belt junction is that it provides a site for anchorage of microfilaments to the cell membrane. In epithelial desmosomes, bundles of keratin-containing intermediate filaments (*i.e.*, tonofilaments) are anchored to the junction on the cytoplasmic area of the cell membrane.

Gap junctions, or *nexus junctions*, involve the close adherence of adjoining cell membranes with the formation of channels that link the cytoplasm of the two cells. Gap junctions are not unique to epithelial tissue; they play an essential role in many types of cell-to-cell communication. Because they are low-resistance channels, gap junctions are important in cell-to-cell conduction of electrical signals (*e.g.*, between cells in sheets of smooth muscle or between adjacent cardiac muscle cells, where they function as electrical synapses). These multiple communication channels also enable ions and small molecules to pass directly from one cell to another.

Hemidesmosomes are another type of junction. They are found at the base of epithelial cells and help attach the epithelial cell to the underlying connective tissue. They resemble half a desmosome, thus their name.



■ **FIGURE 1-20** ■ The chief types of intercellular junctions found in epithelial tissue. (From Cormack D.H. [1993]. *Essential histology*. Philadelphia: J.B. Lippincott)

In summary, body cells are organized into four basic tissue types: epithelial, connective, muscle, and nervous. The epithelium covers and lines the body surfaces and forms the functional components of glandular structures. Epithelial tissue is classified into three types according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudo-stratified. The cells in epithelial tissue are held together by three types of intercellular junctions: tight, adhering, and gap. They are attached to the underlying tissue by hemidesmosomes.

Connective tissue supports and connects body structures; it forms the bones and skeletal system, the joint structures, the blood cells, and the intercellular substances. Adult connective tissue can be divided into four types: loose or areolar, reticular, adipose, and dense (regular and irregular).

Muscle tissue is a specialized tissue designed for contractility. Three types of muscle tissue exist: skeletal, cardiac, and smooth. Actin and myosin filaments interact to produce muscle shortening, a process activated by the presence of calcium. In skeletal muscle, calcium is released from the sarcoplasmic reticulum in response to an action potential. Smooth muscle is often called involuntary muscle because it contracts spontaneously or through activity of the autonomic nervous system. It differs from skeletal muscle in that its sarcoplasmic reticulum is less defined and it depends on the entry of extracellular calcium ions for muscle contraction.

The cells of tissues are joined by cell junctions. There are three basic types of cell junctions: tight junctions, which prevent materials from entering the intercellular space and are found only in epithelial tissue; adhering junctions, which hold cells together and are found in epithelial as well as cardiac tissue; and gap junctions, which contain channels that link the cytoplasm of two cells and are important in cell-to-cell conduction of electrical impulses.

REVIEW QUESTIONS

- State why the nucleus is called the "control center" of the cell, and explain the relationships among DNA, genes, and chromosomes.
- List the cellular organelles and state their functions.
- Explain how the composition of the lipid bilayer structure of the cell membrane controls access to the interior of the cell, and describe how ions, nutrients, water, and other substances cross the cell membrane.
- Relate the function of ATP to cell metabolism and compare the processes involved in the aerobic and anaerobic metabolic pathways that generate ATP.
- Trace the pathway for cell communication, beginning at the receptor and ending with effector response, and explain why the process is often referred to as "signal transduction."
- Two conditions are necessary for a membrane potential to occur by diffusion: the membrane must be selectively permeable to a single type of ion, and the concentration of the diffusible ion must be greater on one side of the membrane than the other. Relate this concept to the role that potassium and sodium ions play in the generation of an action potential.
- Describe the characteristics of the simple epithelium, stratified epithelium, and glandular epithelium; loose and dense connective tissue; skeletal and smooth muscle; and the neurons and supporting cells of the nervous system.
- Characterize the function of the intracellular adhesions and junctions.

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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