32 Homeostasis and Endocrine Signaling

KEY CONCEPTS

32.1 Feedback control maintains the internal environment in many animals
32.2 Endocrine signals trigger homeostatic mechanisms in target tissues
32.3 A shared system mediates osmoregulation and excretion in many animals
32.4 Hormonal circuits link kidney function, water balance, and blood pressure

OVERVIEW

Diverse Forms, Common Challenges

The desert ant (*Cataglyphis*) in **Figure 32.1** is a scavenger, devouring insects that have succumbed to the daytime heat of the Sahara Desert. To gather corpses for feeding, the ant forages when surface temperatures on the sun-baked sand exceed 60°C (140°F), well above the thermal limit for virtually all animals. How, then, does the desert ant survive in these conditions? To answer this question, we need to look more closely at the ant's **anatomy**, or biological form.

Over the course of its life, an ant faces the same fundamental challenges as any other animal, whether hydra, hawk, or human. All animals must obtain nutrients and oxygen, fight off infection, and produce offspring. Given that they share these and other basic requirements, why do species vary so enormously in makeup, complexity, organization, and appearance? The answer is adaptation: Natural selection favors those variations in a population that increase relative fitness (see Chapter 21). The evolutionary adaptations that enable survival vary among environments and species, but they frequently result in a close match of form to function.

▼ **Figure 32.1** How do long legs help this scavenger survive in the scorching desert heat?

Because form and function are correlated, examining anatomy often provides clues to **physiology**—biological function. In the case of the desert ant, researchers noted that its stilt-like legs are disproportionately long, elevating the rest of the ant 4 mm above the sand. At this height, the ant's body is exposed to a temperature 6°C lower than that at ground level. The ant's long legs also facilitate rapid locomotion: Researchers have found that desert ants can run as fast as 1 m/sec, close to the top speed recorded for any running arthropod. Speedy sprinting minimizes the time that the ant is exposed to the sun. Thus, long legs are adaptations that allow the desert ant to be active during the heat of the day, when competition for food and the risk of predation are lowest.

In this chapter, we will begin our study of animal form and function by examining the organization of cells and tissues in the animal body, the systems for coordinating the activities of different body parts, and the general means by which animals control their internal environment. In the second half of the chapter, we'll apply these general ideas to two challenges of particular relevance for desert animals: regulating body temperature and maintaining proper balance of body salts and water.

CONCEPT 32.1

Feedback control maintains the internal environment in many animals

For animals, as for other multicellular organisms, having many cells facilitates specialization. For example, a hard outer covering can protect against predators, and large muscles can enable rapid escape. In a multicellular body, the immediate environment of most cells is the internal body fluid. Control systems that regulate the composition of this solution allow the animal to maintain a relatively stable internal environment, even if the external environment is variable. To understand how these control systems operate, we first need to explore the layers of organization that characterize animal bodies.

Hierarchical Organization of Animal Bodies

Cells form a working animal body through their emergent properties, which arise from successive levels of structural and functional organization. Cells are organized into **tissues**, groups of cells with a similar appearance and a common function. Different types of tissues are further organized into functional units called **organs**. (The simplest animals, such as sponges, lack organs or even true tissues.) Groups of organs that work together provide an additional level of organization and coordination and make up an **organ system** **(Table 32.1)**. Thus, for example, the skin is an organ of the *integumentary system*, which protects against infection and helps regulate body temperature.

Many organs contain tissues with distinct physiological roles. In some cases, the roles are different enough that we consider the organ to belong to more than one organ system. The pancreas, for instance, produces enzymes critical to the function of the digestive system and also regulates the level of sugar in the blood as a vital part of the endocrine system.

Just as viewing the body's organization from the "bottom up" (from cells to organ systems) reveals emergent properties, a "top-down" view of the hierarchy reveals the multilayered basis of specialization. Consider the human digestive system: the mouth, pharynx, esophagus, stomach, small and large intestines, accessory organs, and anus. Each organ has specific roles in digestion. One function of the stomach, for example, is to initiate the breakdown of proteins. This process requires a churning motion powered by stomach muscles, as well as digestive juices secreted by the stomach lining. Producing digestive juices, in turn, requires highly specialized cell types: One cell type secretes a protein-digesting enzyme, a second generates concentrated hydrochloric acid, and a third produces mucus, which protects the stomach lining.

The specialized and complex organ systems of animals are built from a limited set of cell and tissue types. For example, lungs and blood vessels have different functions but are lined by tissues that are of the same basic type and that therefore share many properties. Animal tissues are commonly grouped into four main types: epithelial, connective, muscle, and nervous **(Figure 32.2)**. In later chapters, we'll provide examples of how these tissue types contribute to the specific functions of the organ systems that are summarized in Table 32.1.

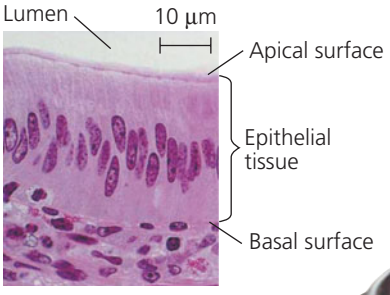
Table 32.1 Organ Systems in Mammals

Organ System	Main Components	Main Functions
Digestive	Mouth, pharynx, esophagus, stomach, intestines, liver, pancreas, anus	Food processing (ingestion, digestion, absorption, elimination)
Circulatory	Heart, blood vessels, blood	Internal distribution of materials
Respiratory	Lungs, trachea, other breathing tubes	Gas exchange (uptake of oxygen; disposal of carbon dioxide)
Immune and lymphatic	Bone marrow, lymph nodes, thymus, spleen, lymph vessels, white blood cells	Body defense (fighting infections and cancer)
Excretory	Kidneys, ureters, urinary bladder, urethra	Disposal of metabolic wastes; regulation of osmotic balance of blood
Endocrine	Pituitary, thyroid, pancreas, adrenal, and other hormone-secreting glands	Coordination of body activities (such as digestion and metabolism)
Reproductive	Ovaries or testes and associated organs	Reproduction
Nervous	Brain, spinal cord, nerves, sensory organs	Coordination of body activities; detection of stimuli and formulation of responses to them
Integumentary	Skin and its derivatives (such as hair, claws, skin glands)	Protection against mechanical injury, infection, dehydration; thermoregulation
Skeletal	Skeleton (bones, tendons, ligaments, cartilage)	Body support, protection of internal organs, movement
Muscular	Skeletal muscles	Locomotion and other movement

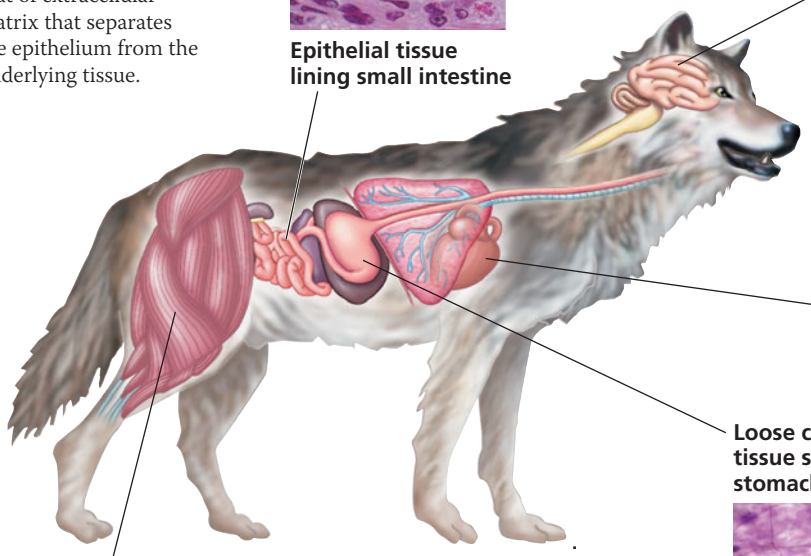
Epithelial Tissue

Occurring as sheets of closely packed cells, **epithelial tissue** covers the outside of the body and lines organs and cavities. Epithelial tissue functions as a barrier against mechanical injury, pathogens, and fluid loss. It also forms active interfaces with the environment. For example, the **epithelium** (plural, *epithelia*) that lines the intestines secretes digestive juices and absorbs nutrients.

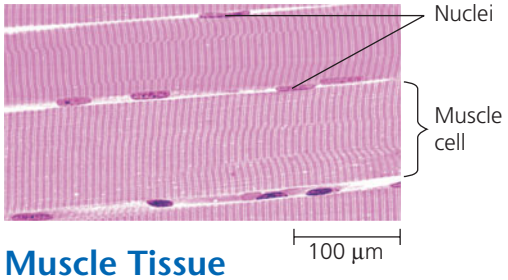
All epithelia are polarized, meaning that they have two different sides. The *apical* surface faces the lumen (cavity) or outside of the organ and is therefore exposed to fluid or air. The *basal* surface is attached to a *basal lamina*, a dense mat of extracellular matrix that separates the epithelium from the underlying tissue.



Epithelial tissue lining small intestine



Skeletal muscle tissue



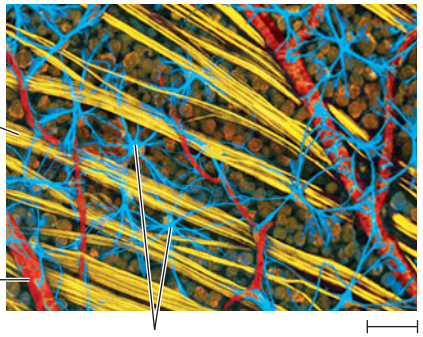
Muscle Tissue

Vertebrates have three types of **muscle tissue**: skeletal, smooth, and cardiac. All muscle cells consist of filaments containing the proteins actin and myosin, which together enable muscles to contract. Attached to bones by tendons, **skeletal muscle**, or striated muscle, is responsible for voluntary movements. The arrangement of contractile units along the cells gives them a striped (striated) appearance. **Smooth muscle**, which lacks striations and has spindle-shaped cells, is found in the walls of many internal organs. Smooth muscles are responsible for involuntary activities, such as churning of the stomach and constriction of arteries. **Cardiac muscle**, which is striated like skeletal muscle, forms the contractile wall of the heart.

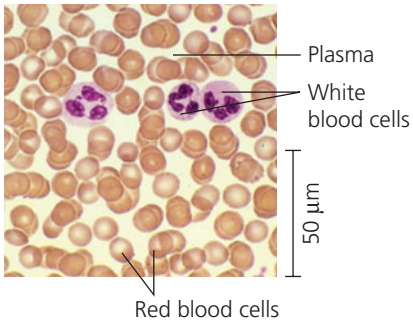
Nervous Tissue

Nervous tissue functions in the receipt, processing, and transmission of information. **Neurons** are the basic units of the nervous system. A neuron receives nerve impulses from other neurons via its cell body and multiple extensions called dendrites. Neurons transmit impulses to neurons, muscles, or other cells via extensions called axons, which are often bundled together into nerves. Nervous tissue also contains support cells called **glial cells**, or simply **glia**. The various types of glia help nourish, insulate, and replenish neurons and in some cases modulate neuron function. In many animals, a concentration of nervous tissue forms a brain, an information-processing center.

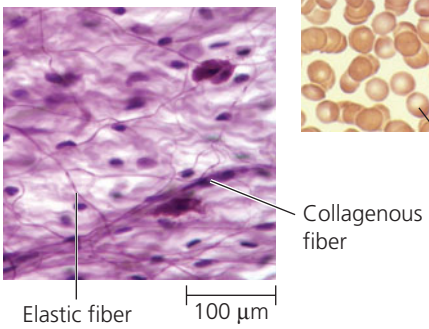
Nervous tissue in brain



Blood



Loose connective tissue surrounding stomach

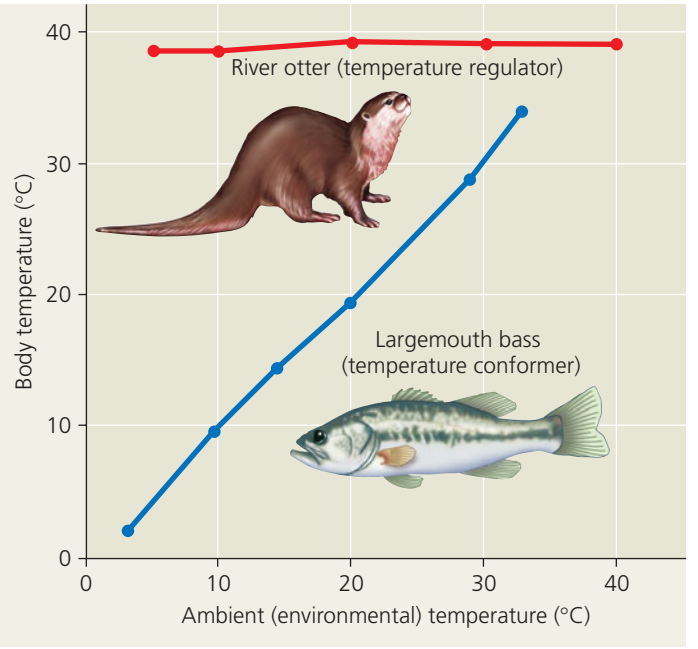


Connective Tissue

Connective tissue consists of cells scattered through an extracellular matrix, often consisting of a web of fibers embedded in a liquid, jellylike, or solid foundation. Within the matrix are numerous cells called *fibroblasts,* which secrete fiber proteins, and *macrophages,* which engulf foreign particles and cell debris.

In vertebrates, the many forms of connective tissue include loose connective tissue, which holds skin and other organs in place; fibrous connective tissue, found in tendons and ligaments; adipose tissue, which stores fat; blood, which consists of cells and cell fragments suspended in a liquid called plasma; cartilage, which provides flexible support in the spine and elsewhere; and bone, a hard mineral of calcium, magnesium, and phosphate ions in a matrix of collagen.

(All photos in figure are LMs.)



▲ **Figure 32.3 Regulating and conforming.** The river otter regulates its body temperature, keeping it stable across a wide range of environmental temperatures. The largemouth bass allows its internal environment to conform to the water temperature.

Regulating and Conforming

Many organ systems play a role in managing an animal's internal environment, a task that can present a major challenge—Imagine if your body temperature soared every time you took a hot shower or drank a freshly brewed cup of coffee. Faced with environmental fluctuations, animals manage their internal environment by either regulating or conforming **(Figure 32.3)**.

An animal is a **regulator** for an environmental variable if it uses internal mechanisms to control internal change in the face of external fluctuation. The otter in Figure 32.3 is a regulator for temperature, keeping its body at a temperature that is largely independent of that of the water in which it swims. In contrast, an animal is a **conformer** for a particular variable if it allows its internal condition to change in accordance with external changes. The bass in Figure 32.3 conforms to the temperature of the lake it inhabits. As the water warms or cools, so does the bass's body.

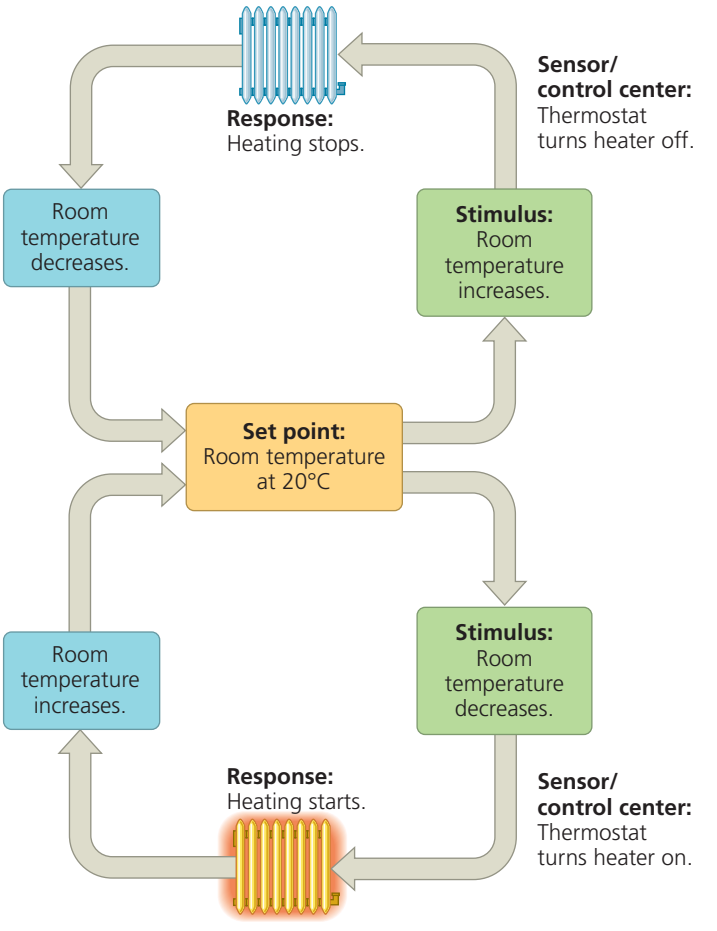
Note that an animal may regulate some internal conditions while allowing others to conform to the environment. For example, even though the bass conforms to the temperature of the surrounding water, it regulates the solute concentration in its blood and **interstitial fluid**, the fluid that surrounds body cells.

Homeostasis

The steady body temperature of a river otter and the stable concentration of solutes in a freshwater bass are examples of **homeostasis**, which means "steady state," referring to the maintenance of internal balance. In achieving homeostasis, animals maintain a relatively constant internal environment even when the external environment changes significantly.

Many animals exhibit homeostasis for a range of physical and chemical properties. For example, humans maintain a fairly constant body temperature of about 37°C (98.6°F), a blood pH within 0.1 pH unit of 7.4, and a blood glucose concentration that is predominantly in the range of 70–110 mg per 100 mL of blood.

Before exploring homeostasis in animals, let's first consider a nonliving example: the regulation of room temperature **(Figure 32.4)**. Let's assume you want to keep a room at 20°C (68°F), a comfortable temperature for normal activity. You adjust a control device—the thermostat—to 20°C and allow a thermometer in the thermostat to monitor temperature. If the room temperature falls below 20°C, the thermostat responds by turning on a radiator, furnace, or other heater. Heat is produced until the room reaches 20°C, at which point the



▲ **Figure 32.4 A nonliving example of temperature regulation: control of room temperature.** Regulating room temperature depends on a control center (a thermostat) that detects temperature change and activates mechanisms that reverse that change.

WHAT IF? *How would adding an air conditioner to the system contribute to homeostasis?*

thermostat switches off the heater. Whenever the temperature in the room again drifts below 20°C, the thermostat activates another heating cycle.

Like a home heating system, an animal achieves homeostasis by maintaining a variable, such as body temperature or solute concentration, at or near a particular value, or **set point**. Fluctuations in the variable above or below the set point serve as the **stimulus** detected by a receptor, or **sensor**. Upon receiving a signal from the sensor, a *control center* generates output that triggers a **response**, a physiological activity that helps return the variable to the set point.

Just as in the regulatory circuit shown in Figure 32.4, homeostasis in animals relies largely on **negative feedback**, a control mechanism that reduces, or "damps," the stimulus. For example, when you exercise vigorously, you produce heat, which increases your body temperature. Your nervous system detects this increase and triggers sweating. As you sweat, the evaporation of moisture from your skin cools your body, helping return your body temperature to its set point.

Homeostasis moderates but doesn't eliminate changes in the internal environment. Additional fluctuation occurs if a variable has a *normal range*—an upper and lower limit—rather than a set point. This is equivalent to a heating system that begins producing heat when the temperature drops to 19°C (66°F) and stops heating when the temperature reaches 21°C (70°F).

Although the set points and normal ranges for homeostasis are usually stable, certain regulated changes in the internal environment are essential. Some of these changes are associated with a particular stage in life, such as the radical shift in hormone balance during puberty. Others are cyclic, such as the monthly variation in hormone levels responsible for a woman's menstrual cycle (see Figure 36.13).

Thermoregulation: *A Closer Look*

As a physiological example of homeostasis, we'll examine **thermoregulation**, the process by which animals maintain an internal temperature within a normal range. Body temperatures below or above an animal's normal range can reduce the efficiency of enzymatic reactions, alter the fluidity of cellular membranes, and affect other temperature-sensitive biochemical processes, potentially with fatal results.

Endothermy and Ectothermy

Heat for thermoregulation can come from either internal metabolism or the external environment. Humans and other mammals, as well as birds, are **endothermic**, meaning that they are warmed mostly by heat generated by metabolism. In contrast, amphibians, many fishes and nonavian reptiles, and most invertebrates are **ectothermic**, meaning that they gain most of their heat from external sources.

Endotherms can maintain a stable body temperature even in the face of large fluctuations in the environmental

(a) A walrus, an endotherm

(b) A lizard, an ectotherm

▲ Figure 32.5 Endothermy and ectothermy.

temperature. In a cold environment, an endotherm generates enough heat to keep its body substantially warmer than its surroundings **(Figure 32.5a)**. In a hot environment, endothermic vertebrates have mechanisms for cooling their bodies, enabling them to withstand heat loads that are intolerable for most ectotherms.

Although ectotherms do not generate enough heat for thermoregulation, many adjust body temperature by behavioral means, such as seeking out shade or basking in the sun **(Figure 32.5b)**. Because their heat source is largely environmental, ectotherms generally need to consume much less food than endotherms of equivalent size—an advantage if food supplies are limited. Overall, ectothermy is an effective and successful strategy in most environments, as shown by the abundance and diversity of ectothermic animals.

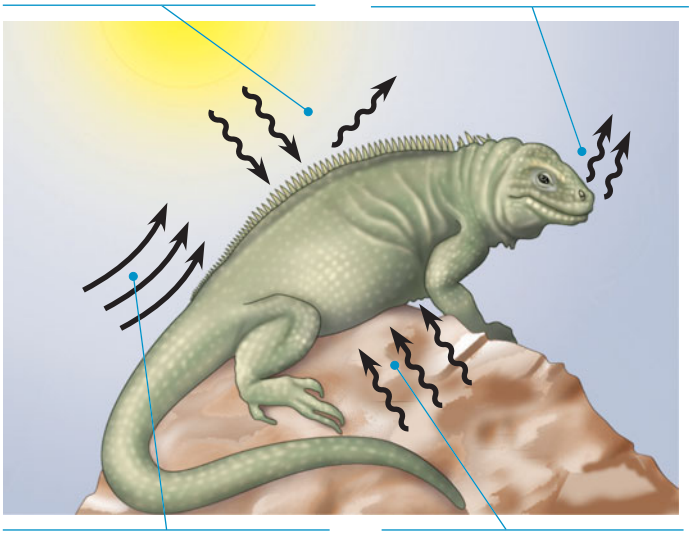
Note, however, that endothermy and ectothermy are not mutually exclusive. For example, a bird is mainly endothermic, but it may warm itself in the sun on a cold morning, much as an ectothermic lizard does.

Balancing Heat Loss and Gain

Thermoregulation depends on an animal's ability to control the exchange of heat with its environment. An organism, like any object, exchanges heat by four physical processes. These

Radiation is the emission of electromagnetic waves by all objects warmer than absolute zero. Here, a lizard absorbs heat radiating from the distant sun and radiates a smaller amount of energy to the surrounding air.

Evaporation is the removal of heat from the surface of a liquid that is losing some of its molecules as gas. Evaporation of water from a lizard's moist surfaces that are exposed to the environment has a strong cooling effect.



Convection is the transfer of heat by the movement of air or liquid past a surface, as when a breeze contributes to heat loss from a lizard's dry skin or when blood moves heat from the body core to the extremities.

Conduction is the direct transfer of thermal motion (heat) between molecules of objects in contact with each other, as when a lizard sits on a hot rock.

▲ Figure 32.6 Heat exchange between an organism and its environment.

processes—radiation, evaporation, convection, and conduction—account for the flow of heat both within an organism and between an organism and its external environment **(Figure 32.6)**. Note that heat is always transferred from an object of higher temperature to one of lower temperature.

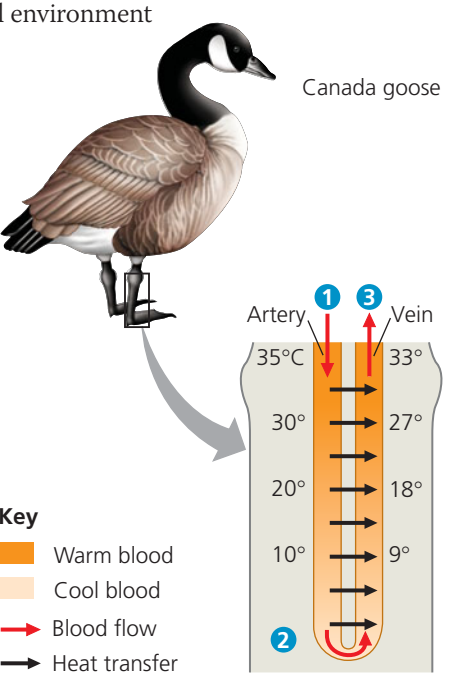
Numerous adaptations that enhance thermoregulation have evolved in animals. Mammals and birds, for instance, have insulation that reduces the flow of heat between an animal's body and its environment. Such insulation may include hair or feathers as well as layers of fat formed by adipose tissue, such as a whale's thick blubber. In response to cold, most land mammals and birds raise their fur or feathers. This action traps a thicker layer of air, thereby increasing the insulating power of the fur or feathers. Humans, lacking a fur or feather layer, must rely primarily on fat for insulation. However, we still get "goose bumps," a vestige of hair raising inherited from our furry ancestors.

Circulatory Adaptations for Thermoregulation

Circulatory systems provide a major route for heat flow between the interior and exterior of the body. Adaptations that regulate the extent of blood flow near the body surface or that trap heat within the body core play a significant role in thermoregulation.

In response to changes in the temperature of their surroundings, many animals alter the amount of blood (and hence heat) flowing between their body core and their skin. Nerve signals that relax the muscles of the vessel walls result in *vasodilation*, a widening of superficial blood vessels (those near the body surface). As a consequence of the increase in vessel diameter, blood flow in the skin increases. In endotherms, vasodilation usually warms the skin and increases the transfer of body heat to the environment by radiation, conduction, and convection (see Figure 32.6). The reverse process, *vasoconstriction*, reduces blood flow and heat transfer by decreasing the diameter of superficial vessels.

In many birds and mammals, reducing heat loss from the body relies on **countercurrent exchange**, the transfer of heat (or solutes) between fluids that are flowing in opposite directions. In a countercurrent heat exchanger, arteries and veins are located adjacent to each other **(Figure 32.7)**. As warm blood moves from the body core in the arteries, it transfers heat to the colder blood returning from the extremities in the veins. Because blood flows through the arteries and veins in opposite directions, heat is transferred along the entire length of the exchanger, maximizing the rate of heat exchange.



1. Arteries carrying warm blood to the animal's extremities are in close contact with veins conveying cool blood in the opposite direction, back toward the trunk of the body. This arrangement facilitates heat transfer from arteries to veins along the entire length of the blood vessels.

2. Near the end of the leg, where arterial blood has been cooled to far below the animal's core temperature, the artery can still transfer heat to the even colder blood in an adjacent vein. The blood in the veins continues to absorb heat as it passes warmer and warmer blood traveling in the opposite direction in the arteries.

3. As the blood in the veins approaches the center of the body, it is almost as warm as the body core, minimizing the heat loss that results from supplying blood to body parts immersed in cold water.

▲ Figure 32.7 A countercurrent heat exchanger.

Acclimatization in Thermoregulation

Acclimatization—a physiological adjustment to environmental changes—contributes to thermoregulation in many animal species. In birds and mammals, acclimatization to seasonal temperature changes often includes adjusting insulation—growing a thicker coat of fur in the winter and shedding it in the summer, for example. These changes help endotherms keep a constant body temperature year-round.

Acclimatization in ectotherms often includes adjustments at the cellular level. Cells may produce variants of enzymes that have the same function but different optimal temperatures. Also, the proportions of saturated and unsaturated lipids in membranes may change; unsaturated lipids help keep membranes fluid at lower temperatures (see Figure 5.5). Some ectotherms that experience subzero body temperatures produce antifreeze proteins that prevent ice formation in their cells. In the Arctic and Southern (Antarctic) Oceans, these compounds enable certain fishes to survive in water as cold as –2°C (28°F), below the freezing point of unprotected body fluids (about –1°C, or 30°F).

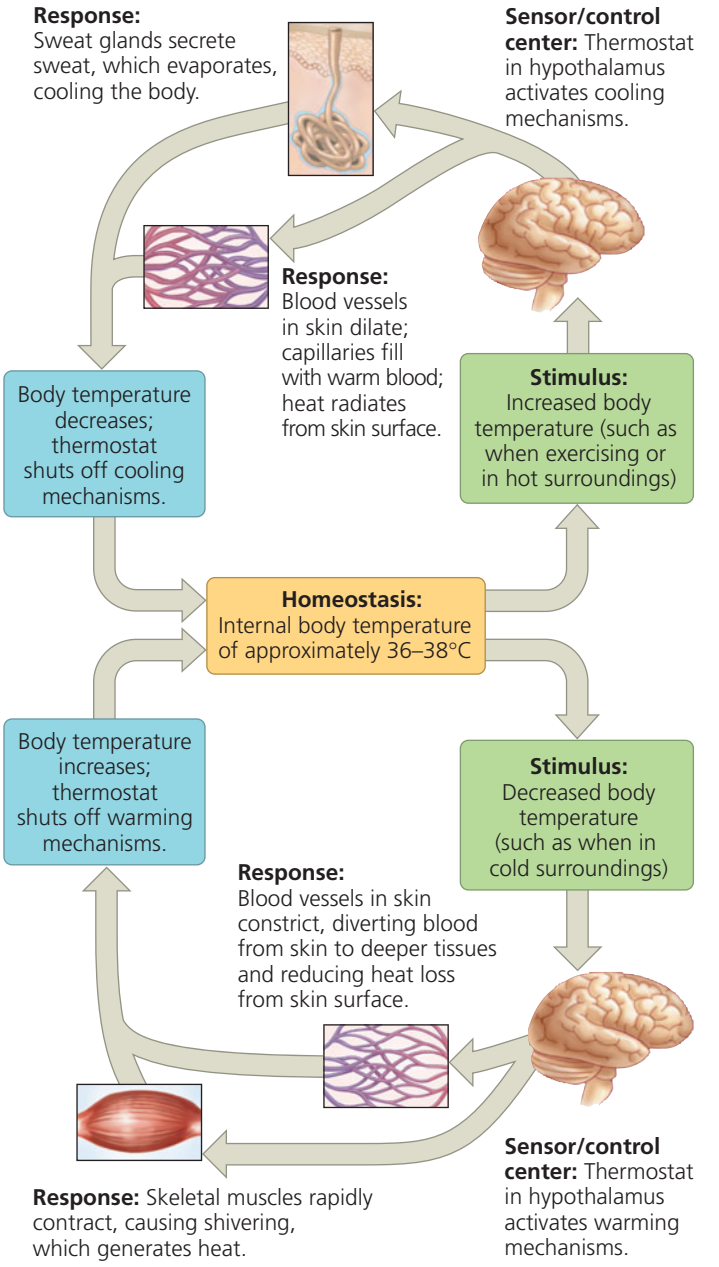
Physiological Thermostats and Fever

The regulation of body temperature in humans and other mammals is based on feedback mechanisms. The sensors for thermoregulation are concentrated in a brain region called the **hypothalamus**. Within the hypothalamus, a group of nerve cells functions as a thermostat, responding to body temperatures outside a normal range by activating mechanisms that promote heat loss or gain **(Figure 32.8)**.

Warm receptors signal the hypothalamic thermostat when body temperature increases, and cold receptors signal when it decreases. At body temperatures below the normal range, the thermostat inhibits heat loss mechanisms while activating mechanisms that either save heat, including vasoconstriction of vessels in the skin, or generate heat, such as shivering. In response to elevated body temperature, the thermostat shuts down heat retention mechanisms and promotes cooling of the body by vasodilation of vessels in the skin, sweating, or panting.

In the course of certain bacterial and viral infections, mammals and birds develop *fever*, an elevated body temperature. Many experiments have shown that fever reflects an increase in the biological thermostat's set point. For example, artificially raising the temperature of the hypothalamus in an infected animal reduces fever in the rest of the body.

Although only endotherms develop fever, lizards exhibit a related response. When infected with certain bacteria, the desert iguana (*Dipsosaurus dorsalis*) seeks a warmer environment and then maintains a body temperature that is elevated by 2–4°C (4–7°F). Similar observations in fishes, amphibians, and even cockroaches indicate that raising body temperature in this way in response to infection is a common feature of many animal species.



▲ Figure 32.8 The thermostatic function of the hypothalamus in human thermoregulation.

CONCEPT CHECK 32.1

1. Is it accurate to define homeostasis as a constant internal environment? Explain.
2. **MAKE CONNECTIONS** How does negative feedback in thermoregulation differ from feedback inhibition in an enzyme-catalyzed biosynthetic process (see Figure 6.19)?
3. **WHAT IF?** Suppose at the end of a hard run on a hot day you find that there are no drinks left in the cooler. If, out of desperation, you dunk your head into the cooler, how might the ice-cold water affect the rate at which your body temperature returns to normal?

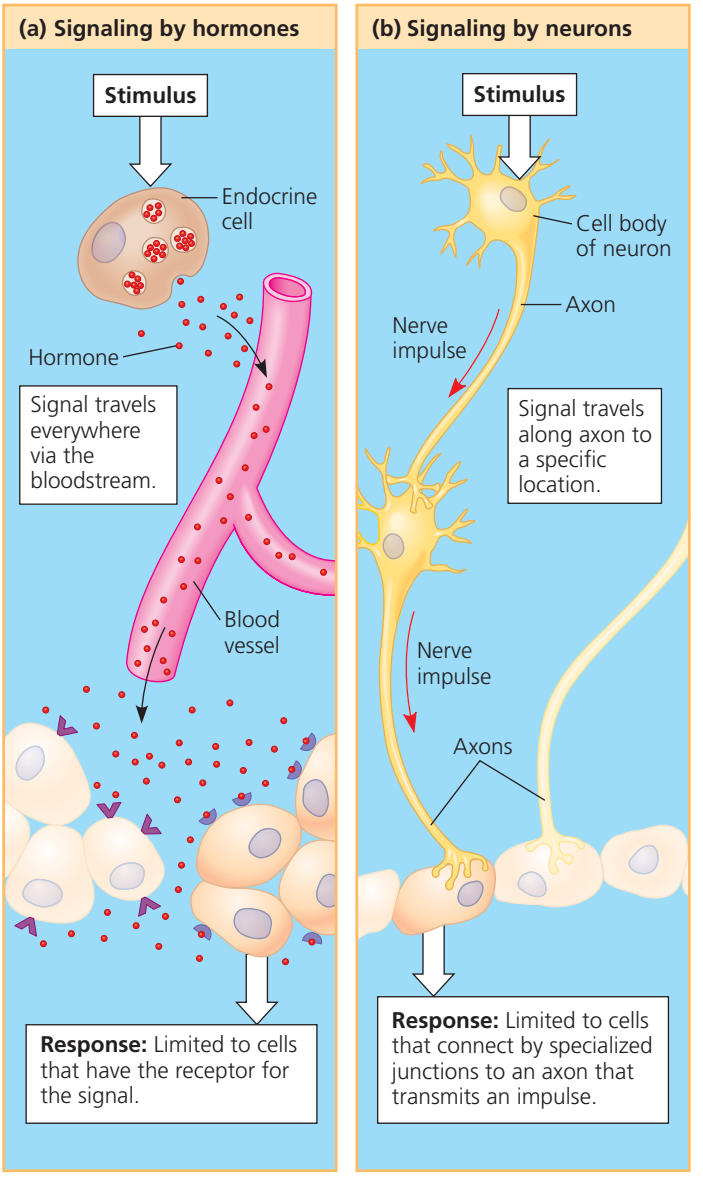
For suggested answers, see Appendix A.

CONCEPT 32.2

Endocrine signals trigger homeostatic mechanisms in target tissues

To maintain homeostasis and carry out other activities of the animal body, including behavior, the tissues, organs, and organ systems must act in concert with one another. What signals are used to coordinate activity? How do the signals move within the body? There are two sets of answers to these questions, reflecting the two major systems for coordinating and controlling an animal's responses to stimuli: the endocrine and nervous systems **(Figure 32.9)**.

▼ Figure 32.9 Signaling in the endocrine and nervous systems.



Coordination and Control Functions of the Endocrine and Nervous Systems

In the **endocrine system**, signaling molecules released into the bloodstream by endocrine cells are carried to all locations in the body. In the **nervous system**, neurons transmit signals along dedicated routes connecting specific locations in the body. In each system, the type of pathway used is the same whether the signal's ultimate target is at the other end of the body or just a few cells away.

The signaling molecules broadcast throughout the body by the endocrine system are called **hormones** (from the Greek *horman*, to excite). Different hormones cause distinct effects, and only cells that have receptors for a particular hormone respond (see Figure 32.9a). Depending on which cells have receptors for that hormone, the hormone may have an effect in just a single location or in sites throughout the body. It takes many seconds for hormones to be released into the bloodstream and carried throughout the body. The effects are often long-lasting, however, because hormones can remain in the bloodstream for minutes or even hours.

In the nervous system, signals called nerve impulses travel to specific target cells along communication lines consisting mainly of axons (see Figure 32.9b). Four types of cells can receive nerve impulses: other neurons, muscle cells, endocrine cells, and exocrine cells. Unlike the endocrine system, the nervous system conveys information by the *pathway* the signal takes. For example, a person can distinguish different musical notes because each note's frequency activates different neurons connecting the ear to the brain.

Communication in the nervous system usually involves more than one type of signal. Nerve impulses travel along axons, sometimes over long distances, as changes in voltage. In contrast, passing information from one neuron to another often involves very short-range chemical signals. Overall, transmission in the nervous system is extremely fast; nerve impulses take only a fraction of a second to reach the target and last only a fraction of a second.

Because the two major communication systems of the body differ in signal type, transmission, speed, and duration, they are adapted to different functions. The endocrine system is especially well adapted for coordinating gradual changes that affect the entire body, such as growth, development, reproduction, metabolic processes, and digestion. The nervous system is well suited for directing immediate and rapid responses to the environment, especially in controlling fast locomotion and behavior.

Although the functions of the endocrine and nervous systems are distinct, the two systems often work in close coordination. Both contribute to homeostasis. In the remainder of this chapter, we'll explore endocrine regulation in the context of homeostasis. Later chapters will discuss the role of both the endocrine and nervous systems in processes such as digestion and reproduction. At the end of the

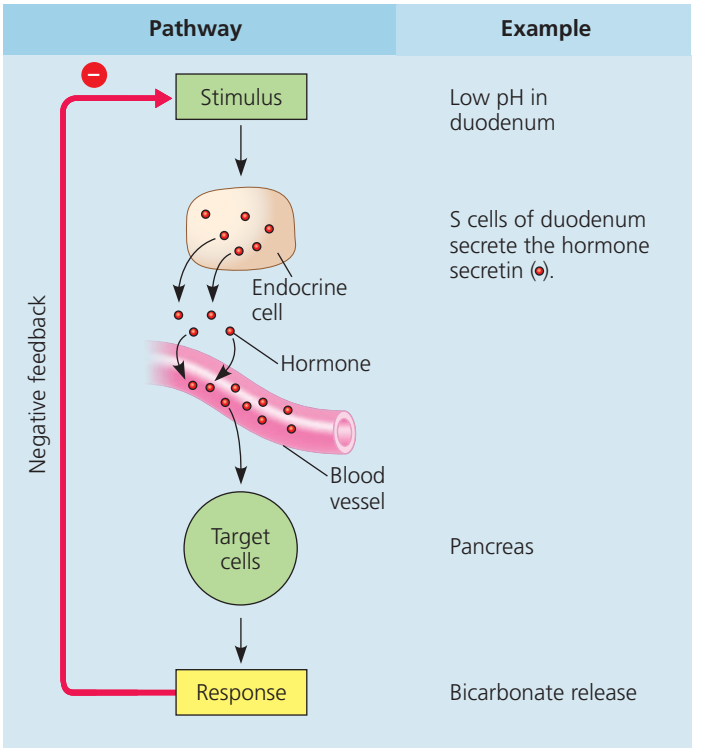
unit, in Chapters 37–39, we'll return to the nervous system for a more in-depth investigation of its organization and functions.

Simple Endocrine Pathways

In exploring how endocrine signaling contributes to homeostasis, we'll begin with a simple endocrine pathway. In such pathways, endocrine cells respond directly to an internal or environmental stimulus by secreting a particular hormone. The hormone travels in the bloodstream to target cells, where it interacts with its specific receptors. Signal transduction within target cells brings about a response.

For an example, we'll consider the control of pH in the *duodenum*, the first part of the small intestine. During digestion, partially digested food passes to the duodenum from the stomach. The digestive juices of the stomach are extremely acidic and must be neutralized before further steps of digestion can occur. Coordination of this process relies on the endocrine pathway outlined in **Figure 32.10**.

As the contents of the stomach enter the duodenum, the low pH acts as a stimulus for certain endocrine cells, called S cells, in the lining of the duodenum. The stimulated S cells secrete the hormone secretin into the bloodstream. Circulating secretin reaches target cells in the **pancreas**, a gland located behind the stomach. Target cells in the pancreas respond by releasing bicarbonate into ducts leading to the duodenum. This response—the release of bicarbonate—raises the pH in the duodenum, neutralizing the stomach acid.



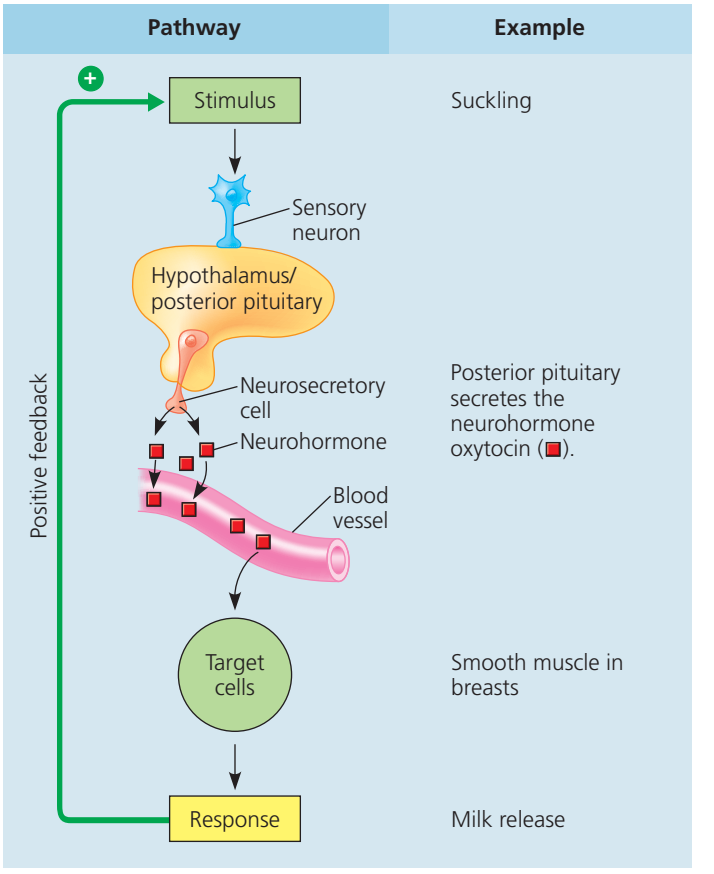
▲ **Figure 32.10** **A simple endocrine pathway.**

Neuroendocrine Pathways

Hormone pathways that respond to stimuli from the external environment typically rely on a sensor in the nervous system. In vertebrates, the hypothalamus plays a central role in integrating the endocrine and nervous systems. The hypothalamus receives information from nerves throughout the body, including the brain. Signals from the hypothalamus travel to a gland located at its base, the **pituitary gland**, which has discrete anterior and posterior parts (**Figure 32.11**, on the next page).

Hormonal signals from the hypothalamus trigger the synthesis and release of hormones from the **anterior pituitary**. These hormones in turn often regulate other endocrine glands. Figure 32.11 highlights this regulation as part of an exploration of the human endocrine system. You may want to refer back to this figure in later chapters when we return to the topic of endocrine signaling and homeostasis.

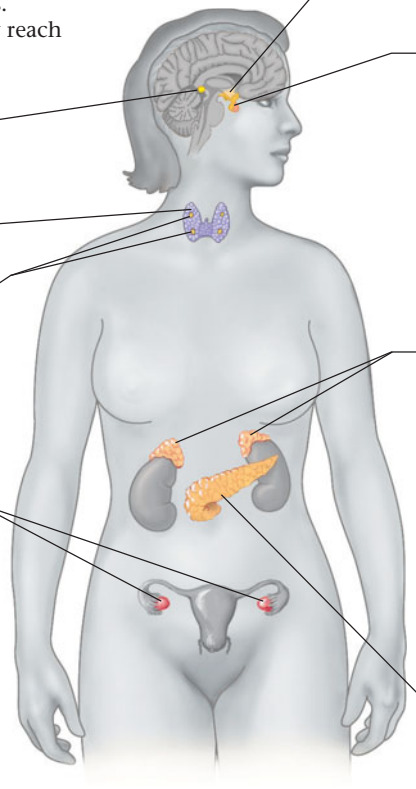
The **posterior pituitary** is an extension of the hypothalamus (see Figure 32.11). It stores and releases two hormones synthesized by neurosecretory cells of the hypothalamus. One is **oxytocin**, a hormone that regulates milk release during nursing in mammals as part of the *neuroendocrine pathway* shown in **Figure 32.12**. Suckling by an infant stimulates sensory neurons in the nipples, generating nerve impulses that reach the hypothalamus. Nerve impulses from the



▲ **Figure 32.12** **A neuroendocrine pathway.**

Major Endocrine Glands and Their Hormones

The endocrine system produces hormones that regulate growth, development, metabolism, homeostasis, and reproduction. Many hormones are secreted by ductless organs called endocrine glands, illustrated below. Others are secreted by isolated endocrine cells in other organs: the thymus, heart, liver, stomach, small intestine, and kidneys. Regardless of where hormones are produced, they reach their target cells via the circulatory system.



Hypothalamus
Hormones released from posterior pituitary (see below)
Releasing and inhibiting hormones: Regulate anterior pituitary

Pituitary gland
Anterior pituitary
See bottom of page.

Posterior pituitary
Oxytocin: Stimulates contraction of uterus and mammary gland cells
Vasopressin (also called **antidiuretic hormone**, **ADH**): Promotes retention of water by kidneys; influences social behavior and bonding

Pineal gland
Melatonin: Participates in regulation of biological rhythms

Thyroid gland
Thyroid hormone (T_3 and T_4): Stimulates and maintains metabolic processes
Calcitonin: Lowers blood calcium level

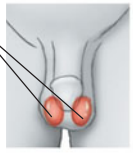
Parathyroid glands
Parathyroid hormone (PTH): Raises blood calcium level

Adrenal glands (atop kidneys)
Adrenal medulla
Epinephrine and **norepinephrine**: Raise blood glucose level; increase metabolic activities; constrict certain blood vessels

Adrenal cortex
Glucocorticoids: Raise blood glucose level
Mineralocorticoids: Promote reabsorption of Na^+ and excretion of K^+ in kidneys

Ovaries (in females)
Estrogens*: Stimulate uterine lining growth; promote development and maintenance of female secondary sex characteristics
Progesterone*: Promotes uterine lining growth

Testes (in males)
Androgens*: Support sperm formation; promote development and maintenance of male secondary sex characteristics

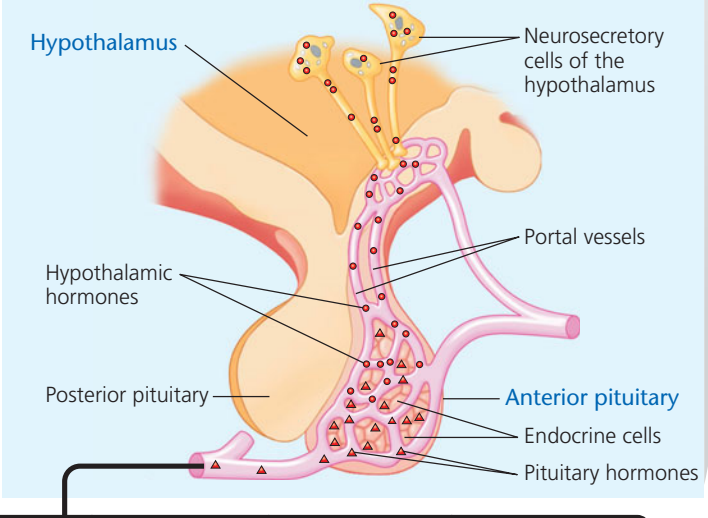


Pancreas
Insulin: Lowers blood glucose level
Glucagon: Raises blood glucose level

*Found in both males and females, but with a major role in one sex

Roles of the Hypothalamus and Anterior Pituitary

Hormones produced by the hypothalamus regulate the anterior pituitary. The hypothalamic hormones are secreted near capillaries at the base of the hypothalamus. These capillaries drain into short blood vessels, called portal vessels, which connect directly to a second capillary bed in the anterior pituitary. Hypothalamic hormones thus travel from the hypothalamus to the gland they regulate without first circulating through other body tissues. Upon reaching the anterior pituitary, each hypothalamic hormone either stimulates or inhibits the release of one or more specific hormones.

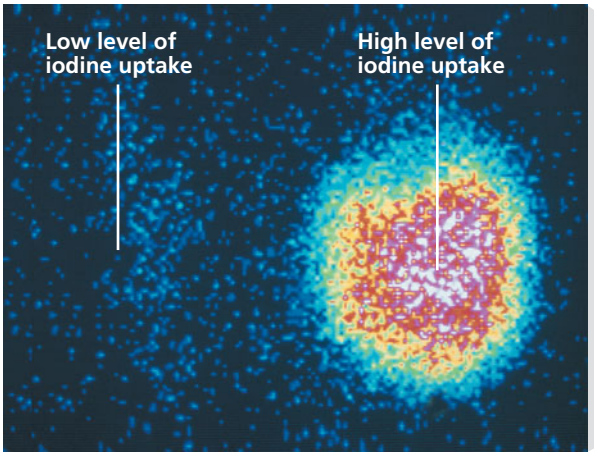


HORMONE	Follicle-stimulating hormone Luteinizing hormone	Thyroid-stimulating hormone	Adrenocorticotropic hormone	Prolactin	Melanocyte-stimulating hormone	Growth hormone
TARGET	Testes or ovaries	Thyroid gland	Adrenal cortex	Mammary glands	Melanocytes	Liver, bones, other tissues

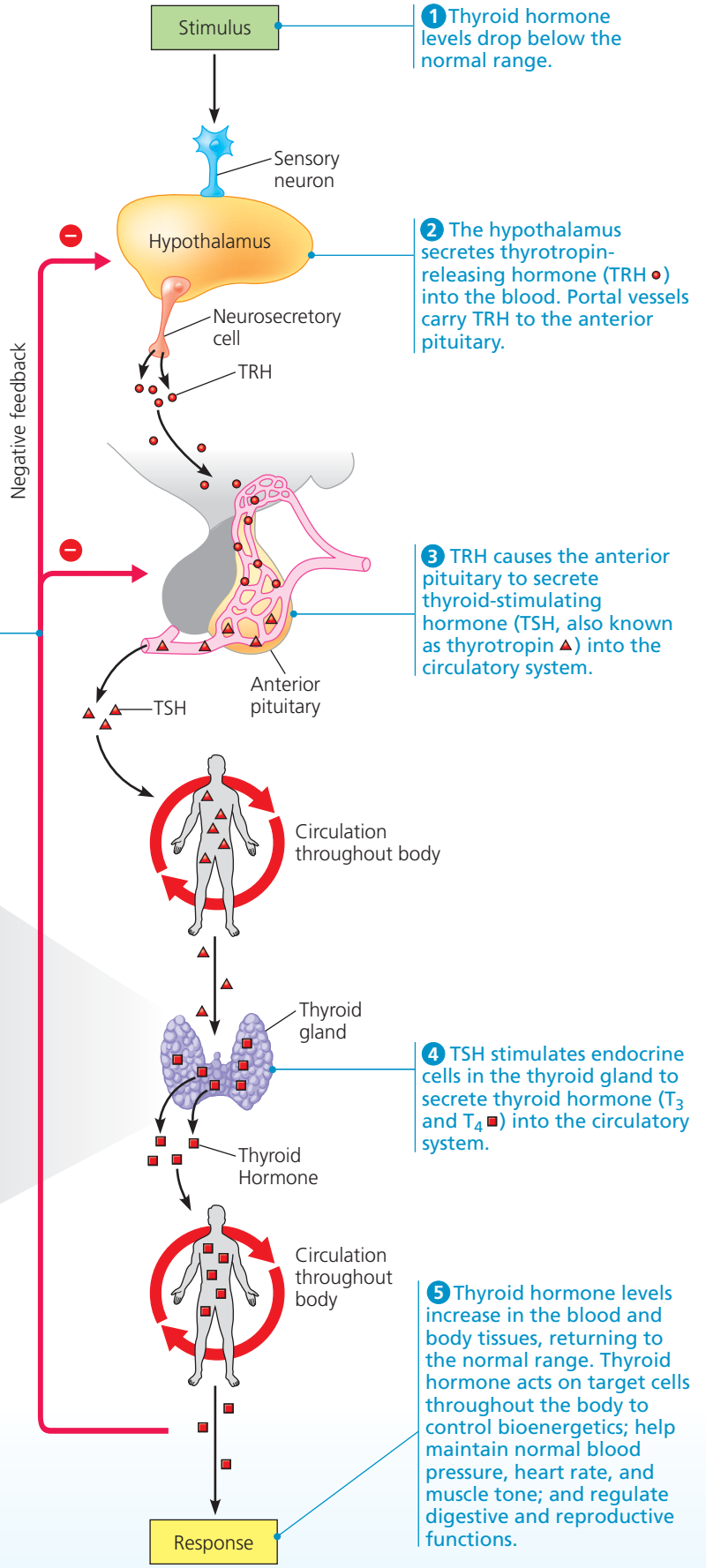
Hormone Cascade Pathways

Sets of hormones from the hypothalamus, the anterior pituitary, and a target endocrine gland are often organized into a hormone cascade pathway. Signals to the brain stimulate the hypothalamus to secrete a hormone that regulates the release of an anterior pituitary hormone. The anterior pituitary hormone in turn acts on another endocrine organ, stimulating secretion of yet another hormone, which exerts effects on specific target tissues. Because such pathways in a sense redirect signals from the hypothalamus to other endocrine glands, the anterior pituitary hormones in these pathways are called *tropic hormones* or *tropins*, from the Greek word for bending or turning.

One example of a hormone cascade pathway is the regulation of thyroid hormone levels, shown here.



Thyroid scan. Thyroid hormone contains iodine, which is readily obtained from seafood or iodized salt. Because iodine in the body is dedicated to the production of thyroid hormone, physicians can use a radioactive isotope of iodine to detect abnormal patterns of iodine uptake, which may indicate a thyroid disorder. The scan above reveals dramatically different activity in the two lobes of a thyroid gland in a patient with thyroid disease.



hypothalamus then trigger the release of oxytocin, which stimulates the mammary glands to secrete milk. We will discuss **antidiuretic hormone (ADH)**, the other posterior pituitary hormone, later in this chapter.

Feedback Regulation in Endocrine Pathways

A feedback loop linking the response back to the initial stimulus is characteristic of endocrine pathways. For many hormones, the response pathway involves negative feedback, the same type of control mechanism we saw in Figure 32.4 for a home heating system. In the case of secretin signaling (see Figure 32.10), the release of bicarbonate by the pancreas increases pH in the intestine, eliminating the stimulus and thereby shutting off the pathway. By decreasing or abolishing hormone signaling, negative-feedback regulation prevents excessive pathway activity (see also Figure 32.11).

Whereas negative feedback dampens a stimulus, **positive feedback** reinforces a stimulus, leading to an even greater response. In animals, positive-feedback loops do not play a major role in homeostasis but instead help drive processes to completion. Consider, for instance, the oxytocin pathway outlined in Figure 32.12. In response to the circulating oxytocin, the mammary glands secrete milk. Milk released in response to the oxytocin leads to more suckling and therefore more stimulation. Activation of the pathway continues until the baby stops suckling. Other functions of oxytocin, such as stimulating contractions of the uterus during birthing, also exhibit positive feedback.

Pathways of Water-Soluble and Lipid-Soluble Hormones

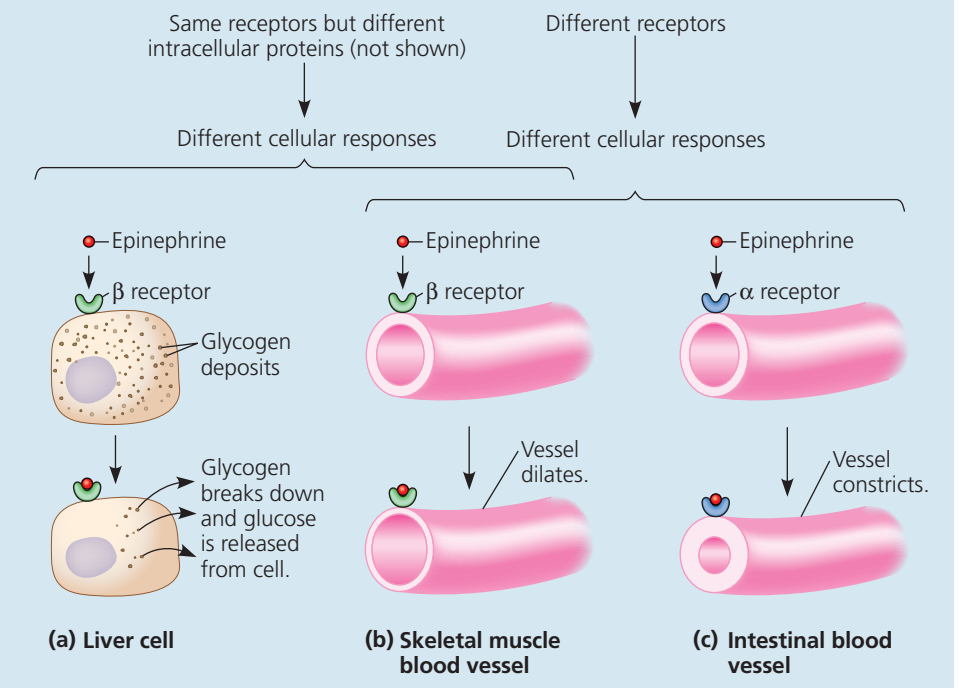
The hormones we have discussed so far are polypeptides and are soluble in water but not soluble in lipids. Unable to pass through the plasma membranes of cells, they bind to cell-surface receptors, triggering events at the plasma membrane that result in a cellular response. The series of changes in cellular proteins that converts the extracellular signal to a specific intracellular response is called *signal transduction*. A signal transduction pathway typically has multiple steps, each involving specific molecular interactions (see Chapter 5).

There are also hormones that are lipid-soluble, including the sex hormones estradiol and testosterone. The major receptors for these steroid hormones are located in the cytosol rather than on the cell surface. When a steroid hormone binds to its cytosolic receptor, a hormone-receptor complex forms, which moves into the nucleus (see Figure 5.23). There, the receptor portion of the complex alters transcription of particular genes.

Multiple Effects of Hormones

Many hormones elicit more than one type of response. Consider, for example, **epinephrine**. This hormone, also called *adrenaline*, is secreted by the *adrenal glands*, which lie atop the kidneys (see Figure 32.11). When you are in a stressful situation, perhaps running to catch a bus, the release of epinephrine rapidly triggers responses that help you chase the departing bus: raising blood glucose levels, increasing blood flow to muscles, and decreasing blood flow to the digestive system.

How can one hormone have such different effects? Target cells can vary in their response if they differ in their receptor type or in the molecules that produce the response. In the liver, epinephrine binds to a β-type epinephrine receptor in the plasma membrane of target cells. This receptor activates the enzyme protein kinase A, which regulates enzymes of glycogen metabolism, causing release of glucose into the bloodstream **(Figure 32.13a)**. In blood vessels supplying skeletal muscle, the same kinase activated by the same receptor inactivates a muscle-specific enzyme. The result is smooth muscle relaxation, vasodilation, and hence increased blood flow **(Figure 32.13b)**. In contrast, intestinal blood vessels have an α-type epinephrine receptor **(Figure 32.13c)**. Rather than activating protein kinase A, the α receptor triggers a distinct signaling pathway involving different enzymes. The result is smooth muscle contraction, vasoconstriction, and restricted blood flow to the intestines.



▲ **Figure 32.13 One hormone, different effects.** Epinephrine, the primary "fight-or-flight" hormone, produces different responses in different target cells. Target cells with the same receptor exhibit different responses if they have different signal transduction pathways and/or effector proteins; compare (a) with (b). Responses of target cells may also differ if they have different receptors for the hormone; compare (b) with (c).

▲ Tadpole

▲ Adult frog

▲ Figure 32.14 Specialized role of a hormone in frog metamorphosis. The hormone thyroxine is responsible for the resorption of the tadpole's tail as the frog develops into its adult form.

Evolution of Hormone Function

EVOLUTION Over the course of evolution, the functions of a given hormone often diverge between species. An example is thyroid hormone, which across many evolutionary lineages plays a role in regulating metabolism (see Figure 32.11). In frogs, however, the thyroid hormone thyroxine (T_4) has taken on an apparently unique function: stimulating resorption of the tadpole's tail during metamorphosis **(Figure 32.14)**.

Diverse functions have also evolved for many other vertebrate hormones. The hormone *prolactin* has an especially broad range of activities. Prolactin stimulates mammary gland growth and milk synthesis in mammals, regulates fat metabolism and reproduction in birds, delays metamorphosis in amphibians, and regulates salt and water balance in freshwater fishes. These varied roles suggest that prolactin is an ancient hormone with functions that have diversified during the evolution of vertebrate groups.

Now that we have introduced homeostasis and endocrine function, we will explore these topics in more depth by focusing on the processes of osmoregulation and excretion.

CONCEPT CHECK 32.2

1. Can cells differ in their response to a hormone if they have the same receptor for that hormone? Explain.
2. **WHAT IF?** If a hormone pathway provides a transient response to a stimulus, how would shortening the stimulus duration affect the need for negative feedback?
3. **MAKE CONNECTIONS** What parallels in properties and effects can you identify between epinephrine and the plant hormone auxin (see Concept 31.1)?

For suggested answers, see Appendix A.

CONCEPT 32.3

A shared system mediates osmoregulation and excretion in many animals

Maintaining the fluid environment of animal tissues requires that the relative concentrations of water and solutes be kept within fairly narrow limits. In addition, ions such as sodium and calcium must be maintained at concentrations that permit normal activity of muscles, neurons, and other body cells. Homeostasis thus requires **osmoregulation**, the general term for the processes by which animals control solute concentrations in the interstitial fluid and balance water gain and loss.

In safeguarding their internal fluid environment, animals must deal with a hazardous metabolite produced by the dismantling of proteins and nucleic acids. Breakdown of *nitrogenous* (nitrogen-containing) molecules releases ammonia, a very toxic compound. Several different mechanisms have evolved for **excretion**, the process that rids the body of nitrogenous metabolites and other metabolic waste products. Because systems for excretion and osmoregulation are structurally and functionally linked in many animals, we will consider both of these processes here.

Osmosis and Osmolarity

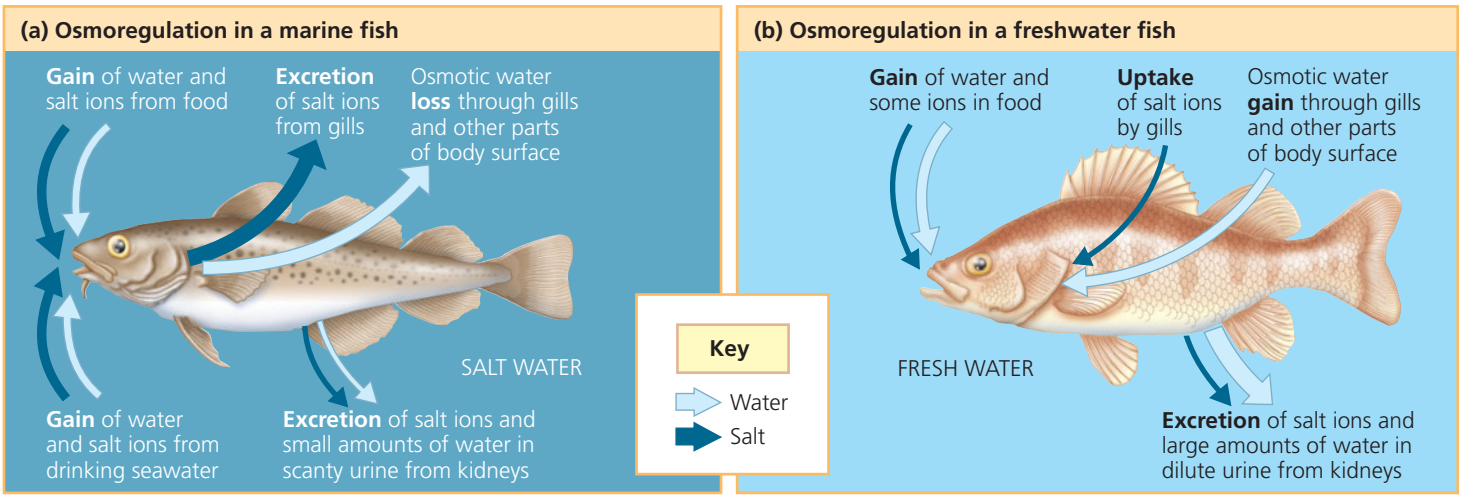
All animals—regardless of their habitat and the type of waste they produce—need to balance water uptake and loss. If animal cells take up too much water, the cells swell and burst; if the cells lose too much water, they shrivel and die (see Figure 5.11). Water enters and leaves cells by osmosis, which occurs whenever two solutions separated by a membrane differ in osmotic pressure, or **osmolarity** (total solute concentration expressed as molarity, that is, moles of solute per liter of solution). The unit of measurement for osmolarity used in this chapter is milliOsmoles per liter (mOsm/L).

If two solutions separated by a selectively permeable membrane have the same osmolarity, they are said to be *isoosmotic*. When two solutions differ in osmolarity, the one with the greater concentration of solutes is said to be *hyperosmotic*, and the more dilute solution is said to be *hypoosmotic*. Water flows by osmosis from a hypoosmotic solution to a hyperosmotic one.

Osmoregulatory Challenges and Mechanisms

An animal can maintain water balance in two ways. One is to be an **osmoconformer**: to be isoosmotic with its surroundings. All osmoconformers are marine animals. The second way to maintain water balance is to be an **osmoregulator**: to control internal osmolarity independent of the environment. Osmoregulation enables animals to live in environments that are uninhabitable for osmoconformers, such as fresh water and terrestrial habitats.

▼ **Figure 32.15** **Osmoregulation in marine and freshwater bony fishes: a comparison.**



The opposite challenges of marine and freshwater environments are illustrated in **Figure 32.15** for a marine cod and a freshwater perch. For the cod (see Figure 32.15a), the ocean is a strongly dehydrating environment. Constantly losing water by osmosis, such fishes balance the water loss by drinking large amounts of seawater. In ridding themselves of salts, they make use of both their gills and kidneys. In the gills, specialized *chloride cells* actively transport chloride ions (Cl^-) out and allow sodium ions (Na^+) to follow passively. In the kidneys, excess calcium, magnesium, and sulfate ions are excreted with the loss of only small amounts of water.

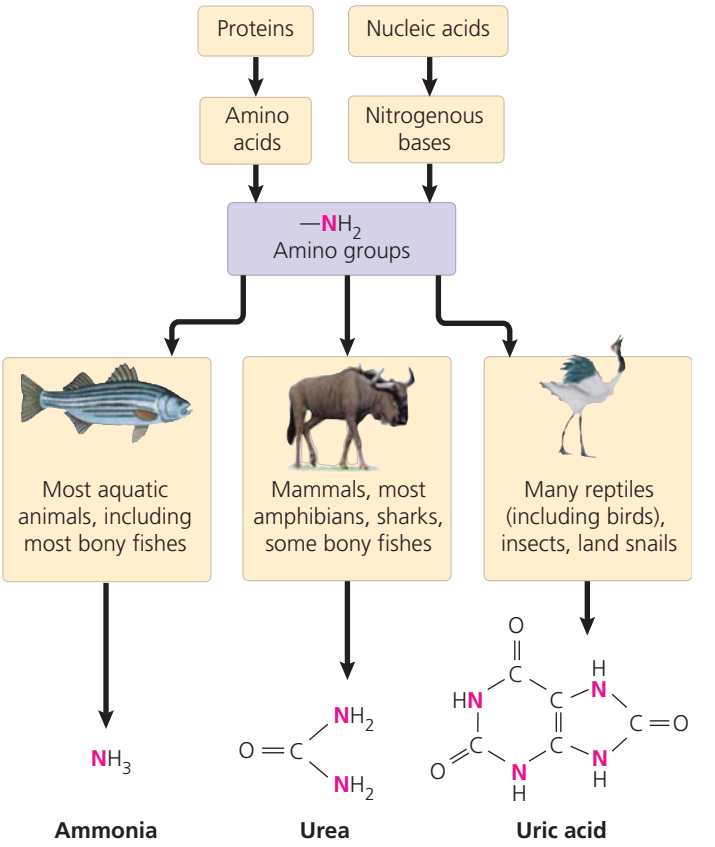
The freshwater perch (see Figure 32.15b) lives in an environment with a very low osmolarity, so it faces the problem of gaining water by osmosis and losing salts by diffusion. Like many freshwater animals, the perch solves this problem by drinking almost no water and excreting large amounts of very dilute urine. At the same time, salts lost by diffusion and in the urine are replenished by eating. Freshwater fishes such as the perch also replenish salts by uptake across the gills.

For land animals, the threat of dehydration is a major regulatory problem. Although most terrestrial animals have body coverings that help prevent dehydration, they lose water through many routes: in urine and feces, across their skin, and from the surfaces of gas exchange organs. Land animals maintain water balance by drinking and eating moist foods and by producing water metabolically through cellular respiration. In the **Scientific Skills Exercise**, you can examine water balance in one species of desert-dwelling mammal.

Nitrogenous Wastes

Because most metabolic wastes must be dissolved in water to be excreted from the body, the type and quantity of an animal's waste products may have a large impact on its water balance. In this regard, some of the most significant waste products are the nitrogenous breakdown products of proteins and nucleic acids **(Figure 32.16)**. When proteins and nucleic acids are broken apart for energy or converted to carbohydrates or fats, enzymes remove nitrogen in the form of **ammonia** (NH_3). Ammonia is very toxic, in part because its ion, ammonium (NH_4^+), interferes with oxidative phosphorylation. Although some animals excrete ammonia directly, many species expend energy to convert it to a less toxic compound, either urea or uric acid, prior to excretion.

Animals that excrete nitrogenous wastes as ammonia need access to lots of water because ammonia can be



▲ **Figure 32.16** **Forms of nitrogenous waste.**

Scientific Skills Exercise

Describing and Interpreting Quantitative Data

How Do Desert Mice Maintain Osmotic Homeostasis? The sandy inland mouse (*Leggadina hermannsburgensis*) is an Australian desert mammal that can survive indefinitely on a diet of dried seeds without drinking water. To study this species' adaptations to its arid environment, researchers conducted a laboratory experiment in which they controlled access to water. In this exercise, you will analyze some of the data from the experiment.

How the Experiment Was Done Nine captured mice were housed in individual cages in an environmentally controlled room. The mice were given birdseed (10% water by weight) to eat. In Part A of the study, the mice also had unlimited access to tap water; in Part B of the study, they were not given any additional water for 35 days, similar to conditions in their natural habitat. For each mouse at the end of each part of the study, the researchers measured the osmolarity and urea concentration of the urine and blood. The researchers also weighed the mice three times a week.

Data from the Experiment

Condition	Mean Osmolarity (mOsm/L)		Mean Urea Concentration (m*M*)	
	Urine	Blood	Urine	Blood
Part A: Unlimited access to water	490	350	330	7.6
Part B: No water	4,700	320	2,700	11
When the mice were given unlimited access to water, they drank about 33% of their body weight each day. The change in body weight during the study was negligible for all mice.				

Interpret the Data

1. In words, describe how the data differ between the unlimited-water and no-water conditions for the following: (a) osmolarity of urine; (b) osmolarity of blood; (c) urea concentration in urine; (d) urea concentration in blood. (e) Does this data set provide evidence of homeostatic regulation? Explain.
2. (a) Calculate the ratio of urine osmolarity to blood osmolarity for mice with unlimited access to water. (b) Calculate this ratio for mice with no access to water. (c) What conclusion would you draw from these ratios?
3. If the amount of urine produced were different in the two conditions, how would that affect your calculation? Explain.

Data from R. E. MacMillen et al., Water economy and energy metabolism of the sandy inland mouse, *Leggadina hermannsburgensis*, *Journal of Mammalogy* 53:529–539 (1972).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.

tolerated only at very low concentrations. Therefore, ammonia excretion is most common in aquatic species. The highly soluble ammonia molecules easily pass through membranes and are readily lost by diffusion to the surrounding water.

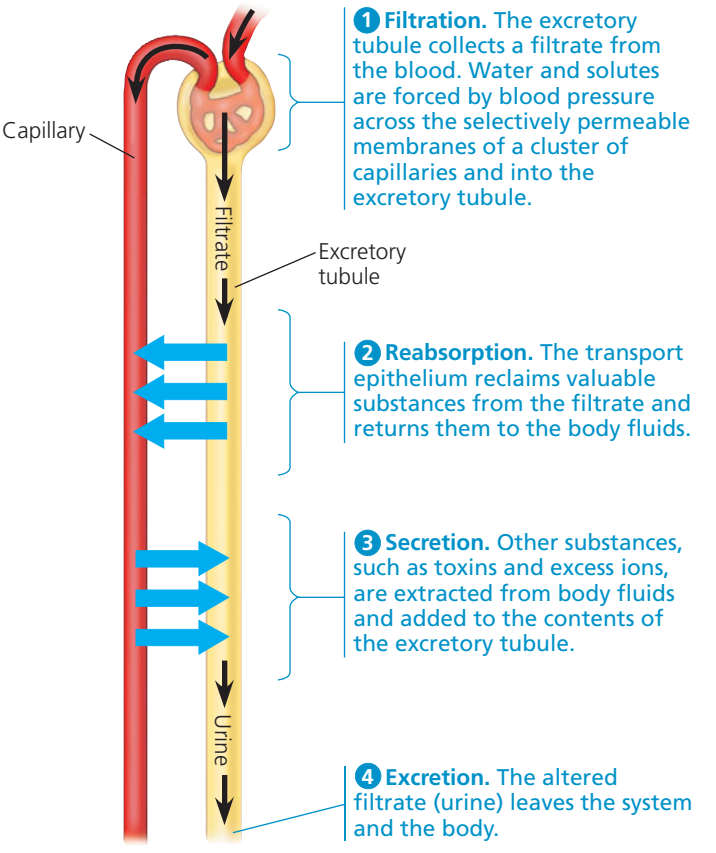
Most terrestrial animals and many marine species cannot afford to lose the amount of water necessary to routinely excrete ammonia. Instead, they mainly excrete a different nitrogenous waste, **urea**. In vertebrates, urea is the product of a metabolic cycle that combines ammonia with carbon dioxide in the liver. The main advantage of urea for nitrogenous waste excretion is its very low toxicity.

Insects, land snails, and many reptiles, including birds, excrete **uric acid** as their primary nitrogenous waste. Uric acid is relatively nontoxic and does not readily dissolve in water. It therefore can be excreted as a semisolid paste with very little water loss. However, uric acid is even more energetically expensive to produce than urea.

Excretory Processes

In most animals, both osmoregulation and metabolic waste disposal rely on **transport epithelia**, one or more layers of epithelial cells specialized for moving particular solutes in controlled amounts in specific directions. Transport epithelia are typically arranged in complex tubular networks with extensive surface areas. Some transport epithelia face the outside environment directly, while others line channels connected to the outside by an opening on the body surface.

Animals across a wide range of species produce a fluid waste called urine through the basic steps shown in **Figure 32.17**. In



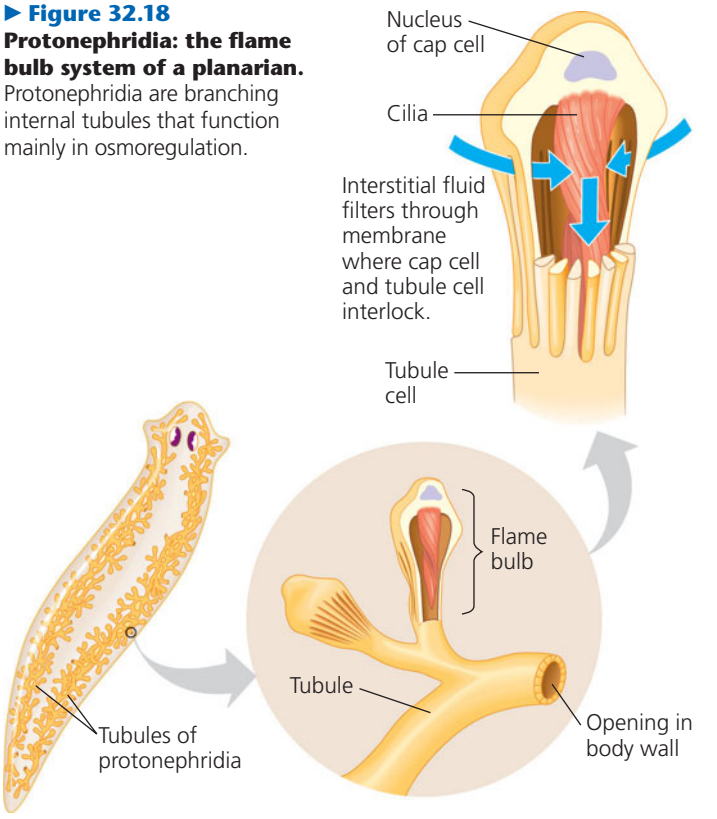
▲ Figure 32.17 Key steps of excretory system function: an overview. Most excretory systems produce a filtrate by pressure-filtering body fluids and then modify the filtrate's contents. This diagram is modeled after the vertebrate excretory system.

the first step, body fluid (blood, coelomic fluid, or hemolymph) is brought in contact with the selectively permeable membrane of a transport epithelium. In most cases, hydrostatic pressure (blood pressure in many animals) drives a process of **filtration**. Cells, as well as proteins and other large molecules, cannot cross the epithelial membrane and remain in the body fluid. In contrast, water and small solutes, such as salts, sugars, amino acids, and nitrogenous wastes, cross the membrane, forming a solution called the **filtrate**.

The filtrate is converted to a waste fluid by the specific transport of materials into or out of the filtrate. The process of selective **reabsorption** recovers useful molecules and water from the filtrate and returns them to the body fluids. Valuable solutes—including glucose, certain salts, vitamins, hormones, and amino acids—are reabsorbed by active transport. Nonessential solutes and wastes are left in the filtrate or are added to it by selective **secretion**, which also occurs by active transport. The pumping of various solutes adjusts the osmotic movement of water into or out of the filtrate. In the last step—excretion—the processed filtrate containing nitrogenous wastes is released from the body as urine.

The systems that perform the basic excretory functions vary widely among animal groups. We'll examine examples from invertebrates and vertebrates.

▶ Figure 32.18
Protonephridia: the flame bulb system of a planarian.
Protonephridia are branching internal tubules that function mainly in osmoregulation.



Invertebrates

Flatworms (phylum Platyhelminthes) have excretory systems called *protonephridia* (singular, *protonephridium*), which form a network of dead-end tubules **(Figure 32.18)**. The tubules, which are connected to external openings, branch throughout the flatworm body, which lacks a coelom or body cavity. Cellular units called *flame bulbs* cap the branches of each protonephridium. Consisting of a tubule cell and a cap cell, each flame bulb has a tuft of cilia projecting into the tubule. During filtration, the beating of the cilia draws water and solutes from the interstitial fluid through the flame bulb, releasing filtrate into the tubule network. (The moving cilia resemble a flickering flame, hence the name *flame bulb*.) The processed filtrate then moves outward through the tubules and empties as urine into the external environment. The urine excreted by freshwater flatworms has a low solute concentration, helping to balance the osmotic uptake of water from the environment.

In the freshwater flatworms, protonephridia serve chiefly in osmoregulation. However, in some parasitic flatworms, which are isoosmotic to the surrounding fluids of their host organisms, the main function of protonephridia is the disposal of nitrogenous wastes. Natural selection has thus adapted protonephridia to different tasks in different environments.

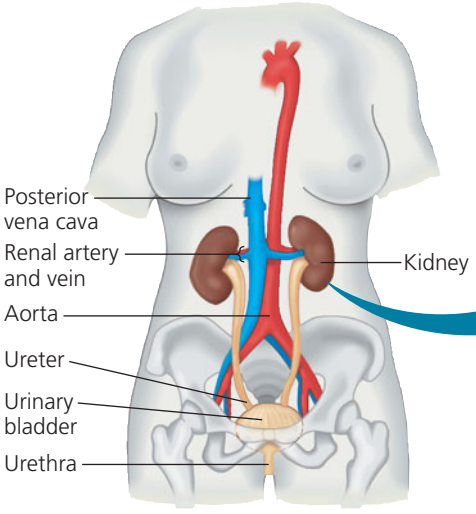
In insects and other terrestrial arthropods, the filtration step common to other excretory systems is absent. Instead, the transport epithelium of organs called *Malpighian tubules* secretes certain solutes and wastes into the lumen of the tubule. The filtrate passes to the digestive tract, where most solutes are pumped back into the hemolymph, and water reabsorption by osmosis follows. The nitrogenous wastes are eliminated as nearly dry matter along with the feces. Capable of conserving water very effectively, the insect excretory system is a key adaptation contributing to these animals' success on land.

Vertebrates

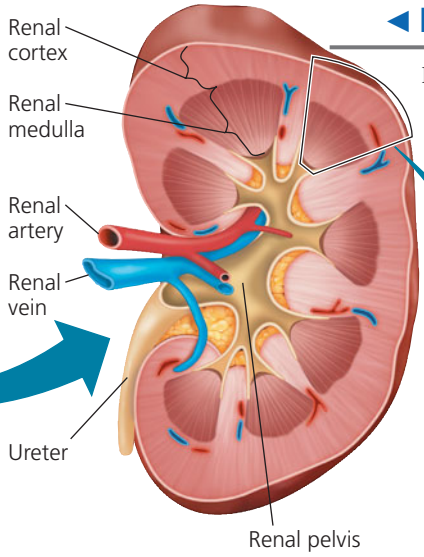
In vertebrates and some other chordates, a specialized organ called the **kidney** functions in both osmoregulation and excretion. Like the excretory organs of most animal phyla, kidneys consist of tubules. The numerous tubules of these compact organs are arranged in a highly organized manner and are closely associated with a network of capillaries. The vertebrate excretory system also includes ducts and other structures that carry urine from the tubules out of the kidney and, eventually, the body.

Because kidney organization is integral to kidney function, we begin with **Figure 32.19**, an exploration of the anatomy of the mammalian kidney and associated structures. Familiarizing yourself with the terms and diagrams in this figure will provide you with a solid foundation for learning about filtrate processing in the kidney, the focus of the next section of the chapter.

▼ Excretory Organs

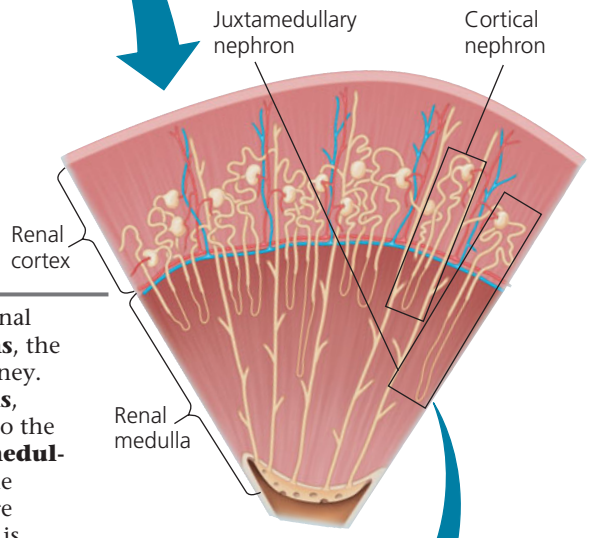


In humans, the excretory system consists of a pair of **kidneys**, bean-shaped organs about 10 cm in length, as well as organs for transporting and storing urine. Urine produced by each kidney exits through a duct called the **ureter**; the two ureters drain into a common sac called the **urinary bladder**. During urination, urine is expelled from the bladder through a tube called the **urethra**, which empties to the outside near the vagina in females and through the penis in males. Sphincter muscles near the junction of the urethra and bladder regulate urination.



◀ Kidney Structure

Each kidney has an outer **renal cortex** and an inner **renal medulla**. Both regions are supplied with blood by a renal artery and drained by a renal vein. Within the cortex and medulla lie tightly packed excretory tubules and associated blood vessels. The inner **renal pelvis** collects urine from the excretory tubules and passes it to the urinary bladder.

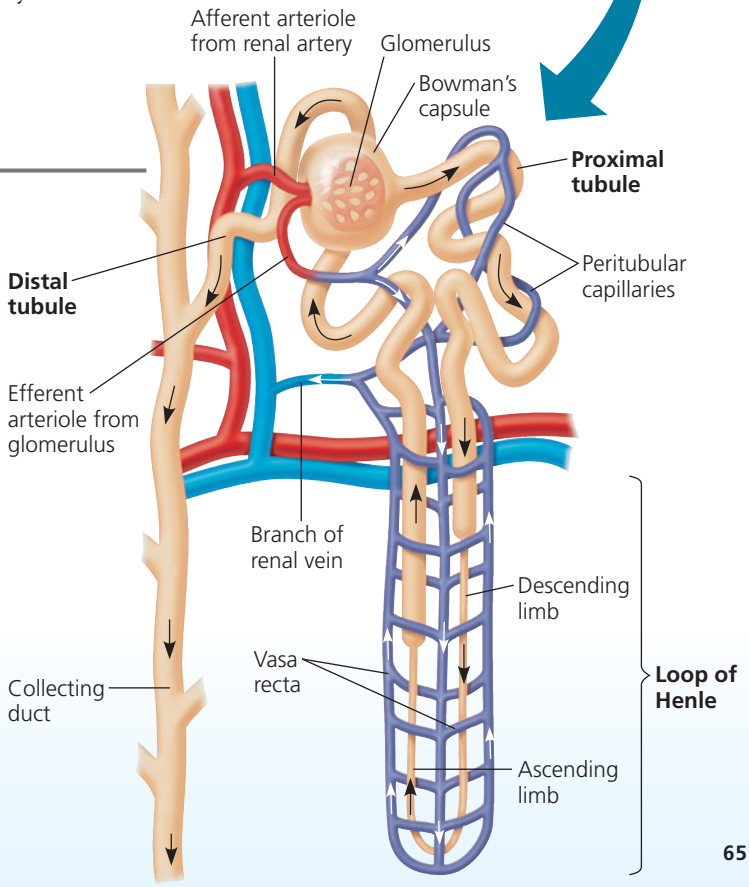


▶ Nephron Types

Weaving back and forth across the renal cortex and medulla are the **nephrons**, the functional units of the vertebrate kidney. Most of these are **cortical nephrons**, which reach only a short distance into the medulla. The remainder, the **juxtamedullary nephrons**, extend deep into the medulla. Juxtamedullary nephrons are essential for production of urine that is hyperosmotic to body fluids.

▶ Nephron Organization

Each nephron consists of a single long tubule and a ball of capillaries called the **glomerulus**. The blind end of the tubule forms a cup-shaped swelling, called **Bowman's capsule**, which surrounds the glomerulus. Filtrate is formed when blood pressure forces fluid from the blood in the glomerulus into the lumen of Bowman's capsule. Processing occurs as the filtrate passes through three major regions of the nephron: the **proximal tubule**, the **loop of Henle** (a hair-pin turn with a descending limb and an ascending limb), and the **distal tubule**. A **collecting duct** receives processed filtrate from many nephrons and transports it to the renal pelvis. Each nephron is supplied with blood by an *afferent arteriole*, an offshoot of the renal artery that branches and forms the capillaries of the glomerulus. The capillaries converge as they leave the glomerulus, forming an *efferent arteriole*. Branches of this vessel form the **peritubular capillaries**, which surround the proximal and distal tubules. Other branches extend downward and form the **vasa recta**, hairpin-shaped capillaries that serve the renal medulla and surround the loop of Henle.



CONCEPT CHECK 32.3

1. What is the function of the filtration step in excretory systems?
2. What advantage does uric acid offer as a nitrogenous waste in arid environments?
3. **WHAT IF?** A camel standing in the sun requires much more water when its fur is shaved off, although its body temperature remains the same. What can you conclude about the relationship between osmoregulation and the insulation provided by fur?

For suggested answers, see Appendix A.

CONCEPT 32.4

Hormonal circuits link kidney function, water balance, and blood pressure

The nephrons of the mammalian kidney are highly specialized for processing filtrate. As you read how tubules, capillaries, and surrounding tissue work together, note the close relationship between structure and function. Hormones and feedback circuits are the key to managing the complex osmoregulatory activities of the kidney.

The porous capillaries and specialized cells of Bowman's capsule are permeable to water and small solutes, but not to blood cells or large molecules such as plasma proteins. Consequently, the filtrate produced in the capsule contains salts, glucose, amino acids, vitamins, nitrogenous wastes, and other small molecules. Because such molecules pass freely between glomerular capillaries and Bowman's capsule, the concentrations of these substances in the initial filtrate are the same as those in blood plasma.

From Blood Filtrate to Urine: *A Closer Look*

In this section, we will follow the filtrate along its path in the nephron and collecting duct, examining how each region contributes to the stepwise processing of filtrate into urine. Each circled number refers to the processing in a particular region, as illustrated in **Figure 32.20.**

1 **Proximal tubule.** Reabsorption in the proximal tubule is critical for the recapture of ions, water, and valuable nutrients from the huge volume of initial filtrate. NaCl (salt) in the filtrate enters the cells of the transport epithelium by facilitated diffusion and cotransport mechanisms (see Figures 5.13 and 5.17). There Na^+ is actively transported into the interstitial fluid. This transfer of positive charge out of the tubule drives the passive transport of Cl^-.

As salt moves from the filtrate to the interstitial fluid, water follows by osmosis. The salt and water then diffuse from the interstitial fluid into the peritubular capillaries. Glucose, amino acids, potassium ions (K^+), and other essential substances are also actively or passively transported from the filtrate to the interstitial fluid and then into the peritubular capillaries. In contrast, some toxic materials, such as drugs and toxins that have been processed in the liver, are actively secreted into filtrate by the transport epithelium.

2 **Descending limb of the loop of Henle.** Reabsorption of water continues as the filtrate moves into the descending limb of the loop of Henle. Here numerous water channels formed by **aquaporin** proteins make the transport epithelium freely permeable to water. In contrast, there are almost no channels for salt and other small solutes, resulting in very low permeability for these substances.

For water to move out of the tubule by osmosis, the interstitial fluid bathing the tubule must be hyperosmotic to the filtrate. This condition is met along the entire length of the descending limb because the osmolarity of the interstitial fluid increases progressively from the outer cortex to the inner medulla of the kidney. Consequently, the filtrate loses water and increases in solute concentration all along its journey down the descending limb.

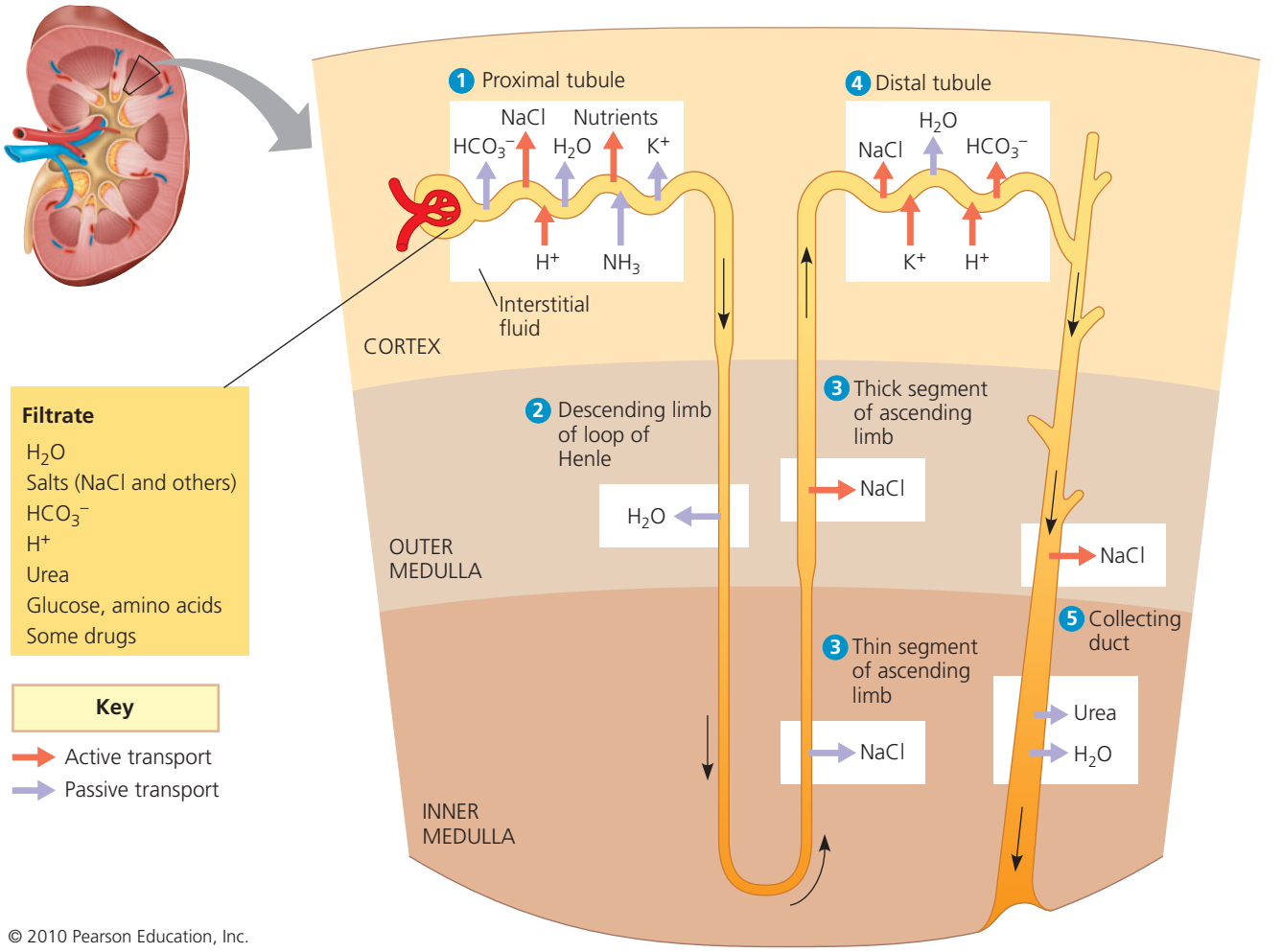
3 **Ascending limb of the loop of Henle.** The filtrate reaches the tip of the loop and then returns to the cortex within the ascending limb. Unlike the descending limb, the ascending limb has a transport epithelium that lacks water channels. As a result, in this region the epithelial membrane that faces the filtrate is impermeable to water.

The ascending limb has two specialized regions: a thin segment near the loop tip and a thick segment adjacent to the distal tubule. As filtrate ascends in the thin segment, NaCl, which became concentrated in the descending limb, diffuses out of the permeable tubule into the interstitial fluid. This movement of NaCl out of the tubule helps maintain the osmolarity of the interstitial fluid in the medulla. In the thick segment of the ascending limb, the movement of NaCl out of the filtrate continues. Here, however, the epithelium actively transports NaCl into the interstitial fluid. As a result of losing salt but not water, the filtrate becomes progressively more dilute as it moves up to the cortex in the ascending limb of the loop.

4 **Distal tubule.** The distal tubule plays a key role in regulating the K^+ and NaCl concentrations of body fluids. This regulation involves variation in the amount of K^+ secreted into the filtrate as well as the amount of NaCl reabsorbed from the filtrate. Like the proximal tubule, the distal tubule contributes to pH regulation by the controlled secretion of H^+ and reabsorption of HCO_3^-.

5 **Collecting duct.** The collecting duct carries the filtrate through the medulla to the renal pelvis (see Figure 32.19). Final processing of the filtrate by the transport epithelium of the collecting duct forms the urine.

Under normal conditions, approximately 1,600 L of blood flows through a pair of human kidneys each day. Processing of this enormous traffic of blood by the nephrons and collecting ducts yields about 180 L of initial filtrate. Of this, about 99% of



▲ Figure 32.20 The nephron and collecting duct: regional functions of the transport epithelium.
The numbered regions in this diagram are keyed to the circled numbers in the text discussion of kidney function.

? *Some cells lining tubules in the kidney synthesize organic solutes to maintain normal cell volume. Where in the kidney would you find these cells? Explain.*

the water and nearly all of the sugars, amino acids, vitamins, and other organic nutrients are reabsorbed into the blood, leaving only about 1.5 L of urine to be transported to the bladder.

As filtrate passes along the transport epithelium of the collecting duct, regulation of permeability and transport across the epithelium determines the extent to which the urine becomes concentrated.

When the kidneys are conserving water, aquaporin channels in the collecting duct allow water molecules to cross the epithelium. The filtrate becomes increasingly concentrated, losing more and more water by osmosis to the hyperosmotic interstitial fluid. In the inner medulla, the duct becomes permeable to urea. Because of the high urea concentration in the filtrate at this point, some urea diffuses out of the duct and into the interstitial fluid. The net result is urine that is hyperosmotic to the general body fluids.

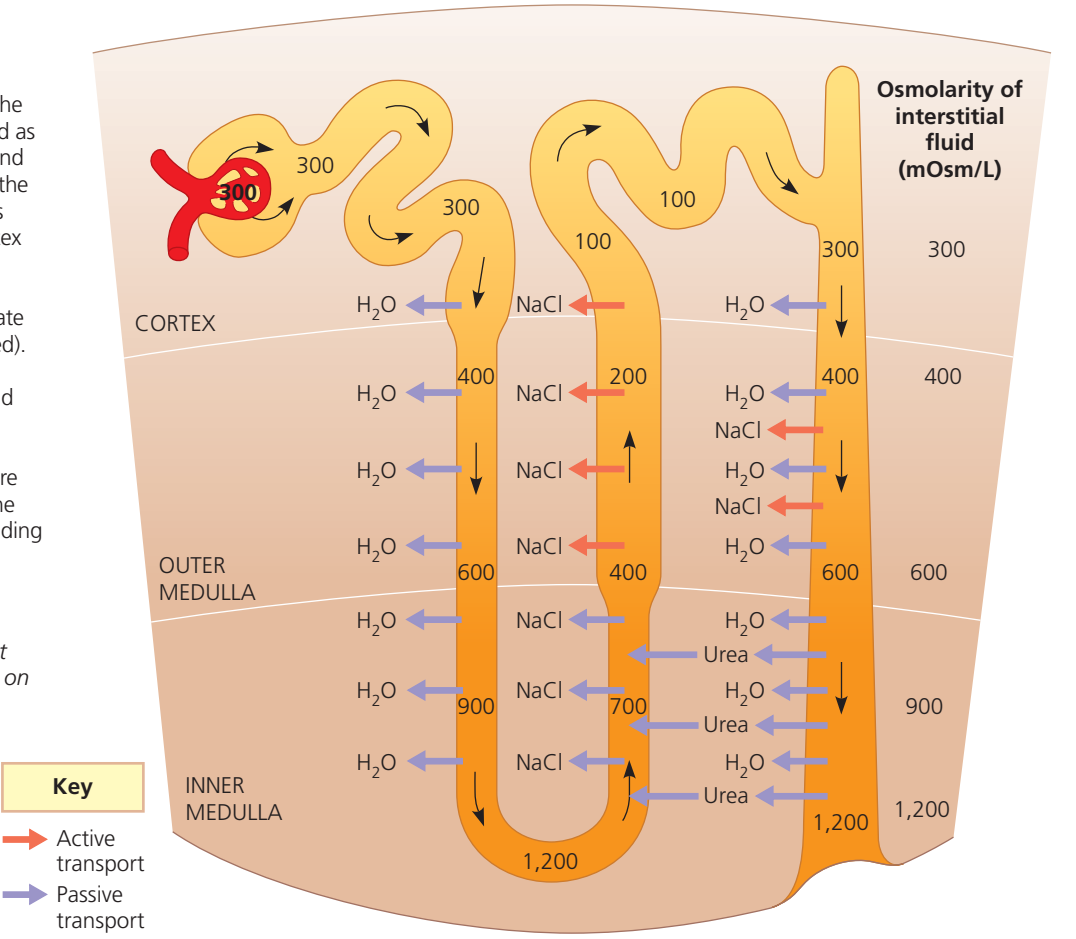
When maintaining salt and water balance requires the production of dilute rather than concentrated urine, the kidney actively absorbs salts without allowing water to follow by osmosis. At these times, the epithelium lacks water channels, and NaCl is actively transported out of filtrate.

As we will see, the state of the collecting duct epithelium is controlled by hormones that together maintain homeostasis for osmolarity, blood pressure, and blood volume.

Concentrating Urine in the Mammalian Kidney

The mammalian kidney's ability to conserve water is a key terrestrial adaptation. In humans, the osmolarity of blood is about 300 mOsm/L, but the kidney can excrete urine up to four times as concentrated.

To better understand the physiology of the mammalian kidney as a water-conserving organ, let's retrace the flow of filtrate through the excretory tubule. This time, let's focus on how the juxtamedullary nephrons maintain an osmolarity gradient in the tissues that surround the loop of Henle and how they use that



▶ Figure 32.21 How the human kidney concentrates urine: the two-solute model. Two solutes contribute to the osmolarity of the interstitial fluid: NaCl (used as shorthand here to refer collectively to Na^+ and Cl^-) and urea. The loop of Henle maintains the interstitial gradient of NaCl, which increases continuously in concentration from the cortex to the inner medulla. Urea diffuses into the interstitial fluid of the medulla from the collecting duct (most of the urea in the filtrate remains in the collecting duct and is excreted). The filtrate makes three trips between the cortex and medulla: first down, then up, and then down again in the collecting duct. As the filtrate flows in the collecting duct past interstitial fluid of increasing osmolarity, more water moves out of the duct by osmosis. The loss of water concentrates the solutes, including urea, that will be excreted in the urine.

WHAT IF? *The drug furosemide blocks the cotransporters for Na^+ and Cl^- in the ascending limb of the loop of Henle. What effect would you expect this drug to have on urine volume?*

gradient to excrete a hyperosmotic urine **(Figure 32.21)**. Filtrate passing from Bowman's capsule to the proximal tubule has about the same osmolarity as blood. A large amount of water *and* salt is reabsorbed from the filtrate as it flows through the proximal tubule in the renal cortex. As a result, the filtrate's volume decreases substantially, but its osmolarity remains about the same.

As the filtrate flows from cortex to medulla in the descending limb of the loop of Henle, water leaves the tubule by osmosis. Solutes, including NaCl, become more concentrated, increasing the osmolarity of the filtrate. The highest osmolarity (about 1,200 mOsm/L) occurs at the elbow of the loop of Henle. This maximizes the diffusion of salt out of the tubule as the filtrate rounds the curve and enters the ascending limb, which is permeable to salt but not to water. NaCl diffusing from the ascending limb helps maintain a high osmolarity in the interstitial fluid of the renal medulla.

The loop of Henle and surrounding capillaries act as a type of countercurrent system to generate the steep osmotic gradient between the medulla and cortex. Recall that some endotherms have a countercurrent heat exchanger that reduces heat loss (see Figure 32.7). In that system there is passive movement along a heat gradient. In contrast, the countercurrent system of the loop of Henle involves active transport and thus an expenditure of energy. The active transport of NaCl from the filtrate in the upper part of the ascending limb of the loop maintains a high salt concentration in the interior of the kidney, enabling the kidney to form concentrated urine. Such a system, which expends energy to create a concentration gradient, is called a **countercurrent multiplier system**.

As a result of active transport of NaCl out of the thick segment of the ascending limb, the filtrate is actually hypoosmotic to body fluids by the time it reaches the distal tubule. Next the filtrate descends again toward the medulla, this time in the collecting duct, which is permeable to water but not to salt. Therefore, osmosis extracts water from the filtrate as it passes from cortex to medulla, concentrating salt, urea, and other solutes in the filtrate.

When the human kidney concentrates urine maximally, the urine reaches an osmolarity of 1,200 mOsm/L. Some mammals can do even better: Australian hopping mice, small marsupials that live in dry desert regions, can produce urine with an osmolarity of 9,300 mOsm/L, 25 times as concentrated as the animal's blood.

Adaptations of the Vertebrate Kidney to Diverse Environments

EVOLUTION Vertebrates occupy habitats ranging from rain forests to deserts and from some of the saltiest bodies of water to the nearly pure waters of high mountain lakes. Variations in nephron structure and function equip the kidneys of different vertebrates for osmoregulation in their various habitats. These adaptations are made apparent by comparing species

that inhabit a range of environments or by comparing the responses of different vertebrates to similar conditions.

Mammals that excrete the most hyperosmotic urine, such as hopping mice, kangaroo rats, and other desert mammals, have loops of Henle that extend deep into the medulla. Long loops maintain steep osmotic gradients in the kidney, resulting in urine becoming very concentrated as it passes from cortex to medulla in the collecting ducts.

Birds have loops of Henle that extend less far into the medulla than those of mammals. Thus, bird kidneys cannot concentrate urine to the high osmolarities achieved by mammalian kidneys. Although birds can produce hyperosmotic urine, their main water conservation adaptation is excreting their nitrogenous waste in the form of uric acid.

In mammals, both the volume and osmolarity of urine are adjusted according to an animal's water and salt balance. In situations of high salt intake and low water availability, a mammal can excrete small volumes of hyperosmotic urine with minimal water loss. If salt is scarce and fluid intake is high, the kidney can instead produce large volumes of hypoosmotic urine, getting rid of the excess water with little salt loss. At such times, the urine can be as dilute as 70 mOsm/L.

The vampire bat shown in **Figure 32.22** illustrates the versatility of the mammalian kidney. This species feeds at night on the blood of large birds and mammals. The bat uses its sharp teeth to make a small incision in the prey's skin and then laps up blood from the wound (the prey animal is typically not seriously harmed). Anticoagulants in the bat's saliva prevent the blood from clotting. Because a vampire bat may fly long distances to locate a suitable victim, when it does find prey it benefits from consuming as much blood as possible—often more than half its body mass. By itself, this blood intake would make the bat too heavy to fly. As the bat feeds, however, its kidneys enable it to excrete large volumes of dilute urine, up to 24% of body mass per hour. Having lost enough weight to take off, the bat can fly back to its roost in a cave or hollow tree, where it spends the day.

▲ Figure 32.22 A vampire bat (*Desmodus rotundas*), a mammal with a unique excretory challenge.

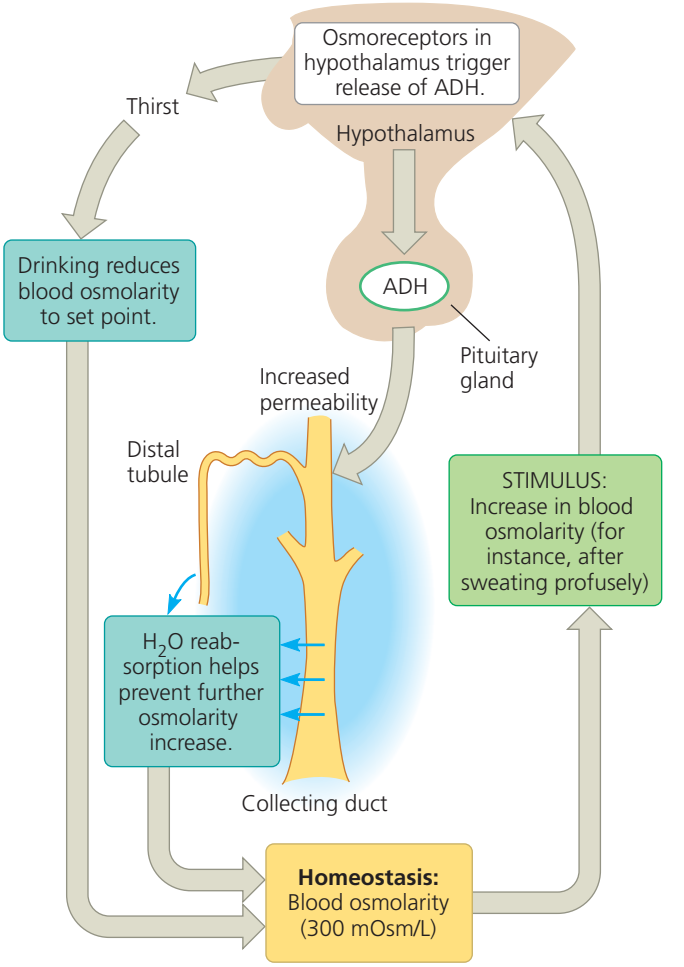
In the roost, the vampire bat faces a different regulatory problem. Most of the nutrition it derives from blood comes in the form of protein. Digesting proteins generates large quantities of urea, but roosting bats lack access to the drinking water necessary to dilute it. Instead, their kidneys shift to producing small quantities of highly concentrated urine (up to 4,600 mOsm/L), an adjustment that disposes of the urea load while conserving as much water as possible. The bat's ability to alternate rapidly between large amounts of dilute urine and small amounts of very hyperosmotic urine is an essential part of its adaptation to an unusual food source.

Homeostatic Regulation of the Kidney

A combination of nervous and hormonal inputs regulates the osmoregulatory function of the mammalian kidney. Through their effect on the amount and osmolarity of urine, these inputs contribute to homeostasis for both blood pressure and blood volume.

Antidiuretic Hormone

One key hormone in the regulatory circuitry of the kidney is antidiuretic hormone (ADH), also called *vasopressin* **(Figure 32.23)**. Osmoreceptor cells in the hypothalamus monitor the



▲ Figure 32.23 Regulation of fluid retention in the kidney by antidiuretic hormone (ADH).

osmolarity of blood and regulate release of ADH from the posterior pituitary. ADH binds to receptor molecules on epithelial cells in the collecting duct, leading to a temporary increase in the number of aquaporin proteins in the plasma membrane. Because aquaporin proteins form water channels, the net effect is an increased permeability of the epithelium to water.

To see how the response to ADH in the kidney contributes to osmoregulation, let's consider first what occurs when blood osmolarity rises, such as after eating salty food or losing water through sweating. When osmolarity rises above the set point (300 mOsm/L), ADH release into the bloodstream is increased. The collecting duct's permeability to water rises, resulting in water reabsorption, which concentrates urine, reduces urine volume, and lowers blood osmolarity back toward the set point. (Only the gain of additional water in food or drink can fully restore osmolarity to 300 mOsm/L.) As the osmolarity of the blood falls, a negative-feedback mechanism reduces the activity of osmoreceptor cells in the hypothalamus, and ADH secretion is reduced.

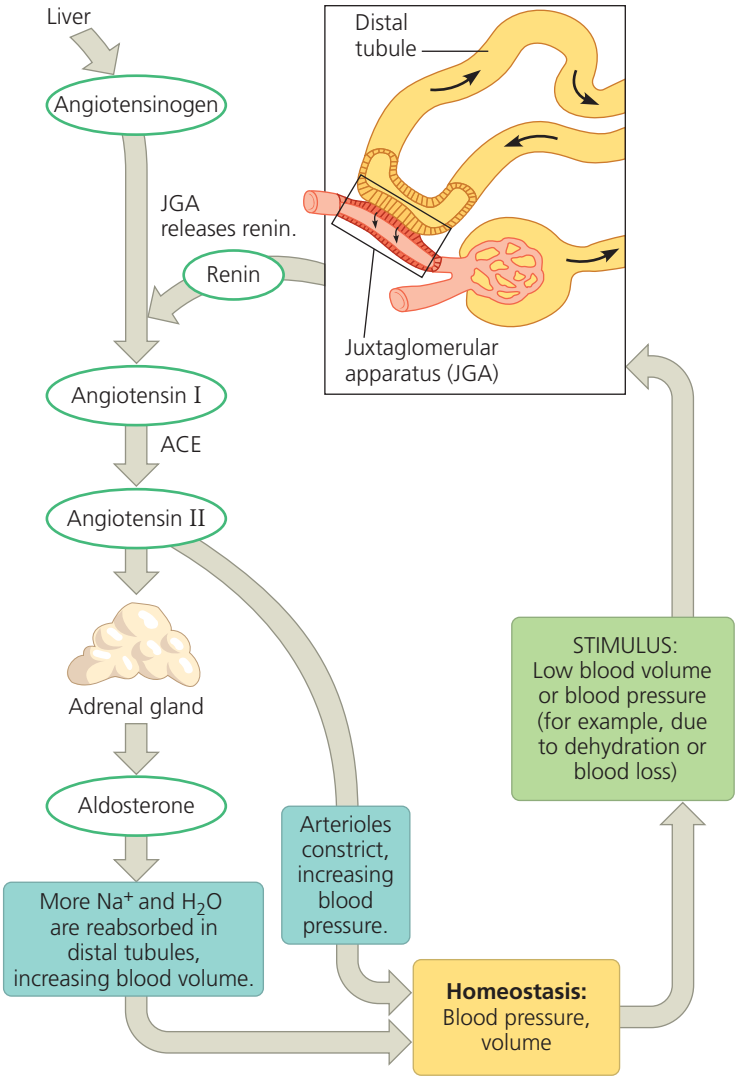
What happens if, instead of ingesting salt or sweating profusely, you drink a large amount of water? The resulting reduction in blood osmolarity below the set point causes a drop in ADH secretion to a very low level. The number of aquaporin channels decreases, lowering permeability of the collecting ducts. Water reabsorption is reduced, resulting in discharge of large volumes of dilute urine. (A high level of urine production is called diuresis; ADH opposes this state and is therefore called *anti*diuretic hormone.)

The Renin-Angiotensin-Aldosterone System

A second regulatory mechanism acting on the kidney is the **renin-angiotensin-aldosterone system (RAAS)**. The RAAS involves the **juxtaglomerular apparatus (JGA)**, a specialized tissue consisting of cells of and around the afferent arteriole, which supplies blood to the glomerulus **(Figure 32.24)**. When blood pressure or blood volume in the afferent arteriole drops (for instance, as a result of dehydration), the JGA releases the enzyme renin. Renin initiates a sequence of chemical reactions that cleave a plasma protein called angiotensinogen, ultimately yielding a peptide called **angiotensin II**.

Functioning as a hormone, angiotensin II triggers vasoconstriction, increasing blood pressure and decreasing blood flow to capillaries in the kidney (and elsewhere). Angiotensin II also stimulates the adrenal glands to release a hormone called **aldosterone**. This hormone acts on the nephrons' distal tubules and collecting ducts, making them reabsorb more Na^+ and water, thus increasing blood volume and pressure.

Because angiotensin II acts in several ways that increase blood pressure, drugs that block angiotensin II production are widely used to treat hypertension (chronic high blood pressure). Many of these drugs are specific inhibitors of angiotensin converting enzyme (ACE), which catalyzes one of the steps in the production of angiotensin II.



▲ Figure 32.24 Regulation of blood volume and blood pressure by the renin-angiotensin-aldosterone system (RAAS).

The renin-angiotensin-aldosterone system operates as a feedback circuit. A drop in blood pressure and blood volume triggers renin release. The resulting production of angiotensin II and release of aldosterone cause a rise in blood pressure and volume, reducing the release of renin from the JGA.

Coordination of ADH and RAAS Activity

The functions of ADH and the RAAS may seem to be redundant, but this is not the case. Both increase water reabsorption in the kidney, but they counter different osmoregulatory problems. The release of ADH is a response to an increase in blood osmolarity, as when the body is dehydrated from excessive water loss or inadequate water intake. However, an excessive loss of both salt and body fluids—caused, for example, by a major wound or severe diarrhea—will reduce blood volume *without* increasing osmolarity. This will not affect ADH release, but the RAAS will respond to the drop in blood volume and pressure by increasing water and Na^+

reabsorption. Thus, ADH and the RAAS are partners in homeostasis. ADH alone would lower blood Na^+ concentration by stimulating water reabsorption in the kidney, but the RAAS helps maintain the osmolarity of body fluids at the set point by stimulating Na^+ reabsorption.

In all animals, certain of the intricate physiological machines we call organs work continuously in maintaining solute and water balance and excreting nitrogenous wastes. The details that we have reviewed in this chapter only hint at the great complexity of the neural and hormonal mechanisms involved in regulating these homeostatic processes.

CONCEPT CHECK 32.4

1. Why could it be dangerous to drink a very large amount of water in a short period of time?
2. Many medications make the epithelium of the collecting duct less permeable to water. How would taking such a drug affect kidney output?
3. **WHAT IF?** If blood pressure in the afferent arteriole leading to a glomerulus decreased, how would the rate of blood filtration within Bowman's capsule be affected? Explain.

For suggested answers, see Appendix A.

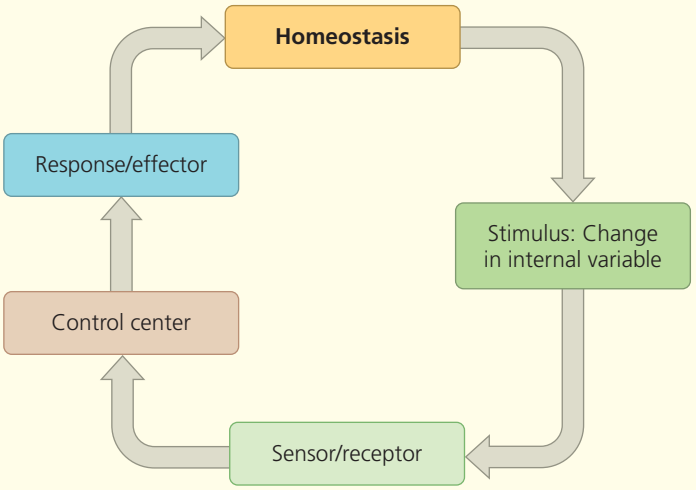
32 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 32.1

Feedback control maintains the internal environment in many animals (pp. 642–647)

- Animal bodies are based on a hierarchy of cells, **tissues**, **organs**, and **organ systems**. **Epithelial tissue** forms active interfaces on external and internal surfaces; **connective tissue** binds and supports other tissues; **muscle tissue** contracts, moving body parts; and **nervous tissue** transmits nerve impulses throughout the body.
- Animals *regulate* certain internal variables while allowing other internal variables to *conform* to external changes. **Homeostasis** is the maintenance of a steady state despite internal and external changes.



- An animal maintains its internal temperature within a tolerable range by **thermoregulation**. **Endotherms** are warmed mostly by heat generated by metabolism. **Ectotherms** get most of their heat from external sources. The **hypothalamus** acts as the thermostat in mammalian regulation of body temperature.

? *Given that humans thermoregulate, explain why your skin is cooler than your body core.*

CONCEPT 32.2

Endocrine signals trigger homeostatic mechanisms in target tissues (pp. 648–653)

- In communicating between different locations in the body, the **endocrine system** broadcasts signaling molecules called **hormones** everywhere via the bloodstream. Only certain cells are responsive to each hormone. The **nervous system** uses dedicated cellular circuits involving electrical and chemical signals to send information to specific locations. Hormone pathways may be regulated by **negative feedback**, which damps the stimulus, or **positive feedback**, which amplifies the stimulus and drives the response to completion.

? *Why would a water-soluble hormone likely have no effect if injected directly into the cytosol of a target cell?*

CONCEPT 32.3

A shared system mediates osmoregulation and excretion in many animals (pp. 653–658)

- Cells balance water gain and loss through **osmoregulation**, a process based on the controlled movement of solutes between internal fluids and the external environment and on the movement of water, which follows by osmosis.
- Protein and nucleic acid metabolism generates **ammonia**, which in many animals is converted to **urea** or **uric acid** for **excretion**. Most excretory systems carry out **filtration**, **reabsorption**, **secretion**, and excretion. Excretory tubules (consisting of **nephrons** and **collecting ducts**) and blood vessels pack the mammalian **kidney**.

DRAW IT *Construct a table summarizing the three major types of nitrogenous wastes and their relative toxicity, energy content, and associated water loss during excretion.*

CONCEPT 32.4

Hormonal circuits link kidney function, water balance, and blood pressure (pp. 658–663)

- Within the nephron, selective secretion and reabsorption in the **proximal tubule** alter **filtrate** volume and composition. The *descending limb* of the **loop of Henle** is permeable to water but not salt, whereas the *ascending limb* is permeable to salt but not water. The **distal tubule** and collecting duct regulate K^+ and NaCl levels in body fluids.
- In a mammalian kidney, **a countercurrent multiplier system** involving the loop of Henle maintains the gradient of salt concentration in the kidney interior. In response to hormonal signals, urine can be concentrated in the collecting duct.
- Natural selection has shaped the form and function of nephrons in vertebrates to the challenges of the animals' habitats. For example, desert mammals, which excrete the most hyperosmotic urine, have loops of Henle that extend deep into the **renal medulla**.

- When blood **osmolarity** rises, the posterior pituitary releases **antidiuretic hormone (ADH)**, which increases permeability to water in collecting ducts by increasing the number of water channels. When blood pressure or blood volume in the afferent arteriole drops, the **juxtaglomerular apparatus (JGA)** releases renin. **Angiotensin II**, formed in response to renin, constricts arterioles and triggers release of the hormone **aldosterone**, raising blood pressure. This **renin-angiotensin-aldosterone system (RAAS)** has functions that overlap with those of ADH.

? *How do cortical nephrons and juxtamedullary nephrons differ in reabsorbing nutrients and concentrating urine?*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. The body tissue that consists largely of material located outside of cells is
   a. epithelial tissue.
   b. connective tissue.
   c. skeletal muscle.
   d. smooth muscle.
   e. nervous tissue.
2. Which of the following would increase the rate of heat exchange between an animal and its environment?
   a. feathers or fur
   b. vasoconstriction
   c. wind blowing across the body surface
   d. countercurrent heat exchanger
   e. blubber or fat layer
3. Which process in the nephron is *least* selective?
   a. filtration
   b. reabsorption
   c. active transport
   d. secretion
   e. salt pumping by the loop of Henle

Level 2: Application/Analysis

4. Homeostasis typically relies on negative feedback because positive feedback
   a. requires a response but not a stimulus.
   b. drives processes to completion rather than to a balance point.
   c. acts within, but not beyond, a normal range.
   d. can decrease but not increase a variable.
   e. involves one location rather than several across the body.
5. Which of the following is an accurate statement about thermoregulation?
   a. Endotherms are regulators and ectotherms are conformers.
   b. Endotherms maintain a constant body temperature and ectotherms do not.
   c. Endotherms are warm-blooded and ectotherms are cold-blooded.
   d. Endotherms and ectotherms differ in their primary source of heat for thermoregulation.
   e. Endothermy has a lower energy cost than ectothermy.
6. Natural selection should favor the highest proportion of juxtamedullary nephrons in which of the following species?
   a. a river otter
   b. a mouse species living in a tropical rain forest
   c. a mouse species living in a temperate broadleaf forest
   d. a mouse species living in a desert
   e. a beaver
7. African lungfish, which are often found in small stagnant pools of fresh water, produce urea as a nitrogenous waste. What is the advantage of this adaptation?
   a. Urea takes less energy to synthesize than ammonia.
   b. Small stagnant pools do not provide enough water to dilute the toxic ammonia.
   c. The highly toxic urea makes the pool uninhabitable to potential competitors.
   d. Urea forms an insoluble precipitate.
   e. Urea makes lungfish tissue hypoosmotic to the pool.

Level 3: Synthesis/Evaluation

8. **DRAW IT** Draw a model of the control circuit(s) required for driving an automobile at a fairly constant speed over a hilly road. Indicate each feature that represents a sensor, stimulus, or response.
9. **SCIENTIFIC INQUIRY**
   You are exploring kidney function in kangaroo rats. You measure urine volume and osmolarity, as well as the amount of chloride ions (Cl^-) and urea in the urine. If the water source provided to the animals were switched from tap water to a 2% NaCl solution, what change in urine osmolarity would you expect? How would you determine if this change was more likely due to a change in the excretion of Cl^- or urea?
10. **FOCUS ON EVOLUTION**
    Merriam's kangaroo rats (*Dipodomys merriami*) live in North American habitats ranging from moist, cool woodlands to hot deserts. Assuming that natural selection has resulted in differences in water conservation between *D. merriami* populations, propose a hypothesis concerning the relative rates of evaporative water loss by populations that live in moist versus dry environments. Using a humidity sensor to detect evaporative water loss by kangaroo rats, how could you test your hypothesis?
11. **FOCUS ON ORGANIZATION**
    In a short essay (100–150 words), compare how membrane structures in the loop of Henle and collecting duct of the mammalian kidney enable water to be recovered from filtrate in the process of osmoregulation.

For selected answers, see Appendix A.

33 Animal Nutrition

KEY CONCEPTS

33.1 An animal's diet must supply chemical energy, organic molecules, and essential nutrients

33.2 The main stages of food processing are ingestion, digestion, absorption, and elimination

33.3 Organs specialized for sequential stages of food processing form the mammalian digestive system

33.4 Evolutionary adaptations of vertebrate digestive systems correlate with diet

33.5 Feedback circuits regulate digestion, energy allocation, and appetite

OVERVIEW

The Need to Feed

Dinnertime has arrived for the Kodiak bear in **Figure 33.1** (and for the salmon, though in quite a different sense). The skin, muscles, and other parts of the fish will be chewed into pieces, broken down by acid and enzymes in the bear's digestive system, and finally absorbed as small molecules into the body of the bear. Such a process is what is meant by animal **nutrition**: food being taken in, taken apart, and taken up.

Although a diet of fish plucked from a waterfall is not common, all animals eat other organisms—dead or alive, piecemeal or whole. Unlike plants, animals must consume food for both energy and the organic molecules used to assemble new molecules, cells, and tissues. Despite this shared need, animals have diverse diets. **Herbivores**, such as cattle, sea slugs, and termites, dine mainly on plants or algae. **Carnivores**, such as sharks, hawks, and spiders, mostly eat other animals. Bears and other **omnivores** (from the Latin *omni*, all) don't in fact eat everything, but they do regularly consume animals as well as plants or algae. We humans are typically omnivores, as are cockroaches and crows.

The terms *herbivore*, *carnivore*, and *omnivore* represent the kinds of food an animal usually eats. Keep in mind, however, that most animals are opportunistic feeders, eating foods outside their standard diet when their usual foods aren't available. For example, deer are herbivores, but in addition to feeding on grass and other plants, they occasionally eat insects, worms, or bird eggs. Note as well that microorganisms are an unavoidable "supplement" in every animal's diet.

Animals must eat. But to survive and reproduce, they must also balance their consumption, storage, and use of food. Bears, for example, store energy, largely in the form of body fat, in preparation for their winter sleep. Eating too little food, too much food, or the wrong mixture of foods can endanger an animal's health. In this chapter, we'll survey the nutritional requirements of animals, explore some of the diverse evolutionary adaptations for obtaining and processing food, and investigate the regulation of energy intake and expenditure.

▼ **Figure 33.1** How does a fish help a bear make fat?

CONCEPT 33.1

An animal's diet must supply chemical energy, organic molecules, and essential nutrients

Overall, an adequate diet must satisfy three nutritional needs: chemical energy for cellular processes, organic building blocks for macromolecules, and essential nutrients.

The activities of cells, tissues, organs, and whole animals depend on sources of chemical energy in the diet. This energy is used to produce ATP, which powers processes ranging from DNA replication and cell division to vision and flight. To meet the continuous requirement for ATP, animals ingest and digest nutrients, including carbohydrates, proteins, and lipids, for use in cellular respiration and energy storage.

In addition to providing fuel for ATP production, an animal's diet must supply the raw materials needed for biosynthesis. To build complex molecules, animals need a source of organic carbon (such as sugar) and a source of organic nitrogen (such as protein). Starting with these materials, animals can construct a great variety of organic molecules.

Essential Nutrients

Some cellular processes require materials that an animal cannot assemble from simpler organic precursors. These materials—preassembled organic molecules and minerals—are called **essential nutrients**. Obtained from an animal's diet, essential nutrients include essential fatty acids and amino acids, vitamins, and minerals. Essential nutrients have key functions in cells, including serving as substrates, coenzymes, and cofactors in biosynthetic reactions **(Figure 33.2)**. Needs for particular nutrients vary among species. For instance, ascorbic acid (vitamin C) is an essential nutrient for humans and guinea pigs, but not for many other animals.

Essential Fatty Acids and Amino Acids

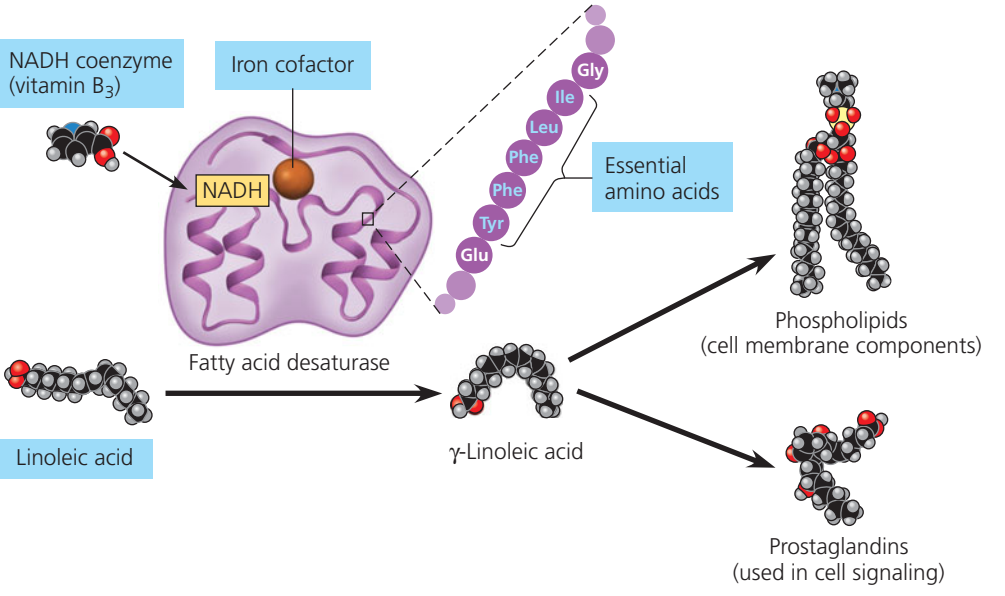
Animals convert fatty acids to a variety of cellular components, including membrane phospholipids, signaling molecules, and storage fats. The **essential fatty acids**, which animals cannot synthesize (but plants can), contain one or more double bonds; an example is linoleic acid (see Figure 33.2). Because seeds, grains, and other plant matter in animal diets generally furnish ample quantities of essential fatty acids, deficiencies in this class of nutrients are rare.

Like fatty acids, amino acids serve as building blocks for biosynthesis. Animals use a set of 20 amino acids to synthesize proteins. Most animals can produce about half of these amino acids, as long as their diet includes sulfur and organic nitrogen. The remaining **essential amino acids** must be obtained from food in prefabricated form. Many animals, including adult humans, require eight amino acids in their diet (infants also need a ninth, histidine).

The proteins in animal products such as meat, eggs, and cheese are "complete," which means that they provide all the essential amino acids in their proper proportions. In contrast, most plant proteins are "incomplete," being deficient in one or more essential amino acids. Corn (maize), for example, is deficient in tryptophan and lysine, whereas beans are lacking in methionine. However, vegetarians can easily obtain all of the essential amino acids by eating a varied diet of plant proteins.

Vitamins

As Albert Szent-Györgyi, the physiologist who discovered vitamin C, once quipped, "A vitamin is a substance that makes you ill if you *don't* eat it." **Vitamins** are organic molecules that are required in the diet in very small amounts (0.01–100 mg per day, depending on the vitamin). For humans, 13 vitamins have been identified. Some are water-soluble, including the B vitamins, which generally function as coenzymes (see Figure 33.2). Vitamin C, which is required for the production of connective



▶ Figure 33.2 Roles of essential nutrients. This biosynthetic reaction illustrates typical functions for the four classes of essential nutrients (an example of each class is highlighted in blue). Linoleic acid, the substrate, is an essential fatty acid. The enzyme fatty acid desaturase converts it to γ-linoleic acid, a precursor for phospholipids and prostaglandins. Some of the amino acids making up the polypeptide portion of the enzyme are essential, including the five following glutamine (Glu) in the partial sequence shown. In addition, the desaturase requires a mineral (iron) as a cofactor and a vitamin (B_3) as a coenzyme.

tissue, is also water-soluble. The remaining vitamins are fat-soluble. These include vitamin A, which is incorporated into visual pigments of the eye, and vitamin D, which aids in calcium absorption and bone formation. The dietary requirement for vitamin D varies because we can actually synthesize this vitamin from other molecules when our skin is exposed to sunlight.

For people with poorly balanced diets, taking vitamin supplements that provide recommended daily levels is reasonable. It is far less clear whether massive doses of vitamins confer any benefits or are in fact even safe. Moderate overdoses of water-soluble vitamins are probably harmless because excess amounts are excreted in urine. However, excesses of fat-soluble vitamins are deposited in body fat, so overconsumption may result in toxic levels of these compounds.

Minerals

Dietary **minerals** are inorganic nutrients, such as iron and sulfur, that are usually required in small amounts—from less than 1 mg to about 2,500 mg per day. Minerals have diverse functions in animals. Some are assembled into the structure of proteins; iron, for example, is incorporated into the oxygen carrier protein hemoglobin as well as some enzymes (see Figure 33.2). In contrast, sodium, potassium, and chloride are important in the functioning of nerves and muscles and in maintaining osmotic balance between cells and the surrounding body fluid. In vertebrates, the mineral iodine is incorporated into thyroid hormones, which regulate metabolic rate. Vertebrates also require relatively large quantities of calcium and phosphorus for building and maintaining bone.

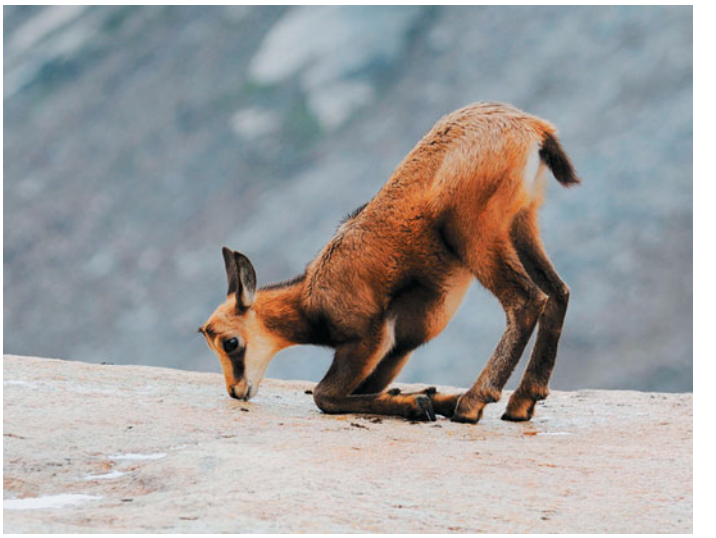
Ingesting large amounts of some minerals can upset homeostatic balance and impair health. For example, excess salt (sodium chloride) can contribute to high blood pressure. This is a particular problem in the United States, where the typical person consumes about 20 times the required amount of sodium.

Dietary Deficiencies

A diet that lacks one or more essential nutrients or consistently supplies less chemical energy than the body requires results in *malnutrition*, a failure to obtain adequate nutrition. Malnutrition resulting from either type of dietary deficiency can have negative impacts on health and survival.

Deficiencies in Essential Nutrients

Insufficient intake of essential nutrients can cause deformities, disease, and even death. For example, cattle, deer, and other herbivores may develop dangerously fragile bones if they graze on plants growing in soil that lacks phosphorus. In such environments, some grazing animals obtain missing nutrients by consuming concentrated sources of salt or other minerals **(Figure 33.3)**. Similarly, some birds supplement their diet with snail shells, and certain tortoises ingest stones.



▲ **Figure 33.3 Dietary supplements in nature.** A juvenile chamois (*Rupicapra rupicapra*), an herbivore, licks exposed salts and minerals in its rocky alpine habitat. This behavior is common among herbivores living where soils and plants provide insufficient amounts of essential nutrients, such as sodium, calcium, phosphorus, and iron.

Like other animals, humans sometimes suffer from diets lacking in essential nutrients. A diet that provides insufficient amounts of one or more essential amino acids causes protein deficiency, the most common type of malnutrition among humans. For example, protein deficiency may arise if a child's diet shifts from breast milk to foods that provide almost all of the child's calories in the form of a starch, such as rice. Such children, if they survive infancy, often have impaired physical and mental development.

In populations subsisting on simple rice diets, individuals are often deficient in vitamin A, which can result in blindness or death. To overcome this problem, scientists have engineered a strain of rice that synthesizes beta-carotene, a pigment that is converted to vitamin A in the body (see Chapter 30).

Undernutrition

A diet that fails to provide adequate sources of chemical energy results in *undernutrition*. When an animal is undernourished, a series of events unfold: The body uses up stored carbohydrates and fat and then begins breaking down its own proteins for fuel; muscles begin to decrease in size; and the brain may become protein-deficient. If energy intake remains less than energy expenditures, the animal will eventually die. Even if a seriously undernourished animal survives, some of the damage may be irreversible.

Human undernutrition is most common when drought, war, or another crisis severely disrupts the food supply. However, undernutrition sometimes occurs within well-fed human populations as a result of eating disorders. For example, anorexia nervosa leads individuals, usually female, to starve themselves compulsively.

Assessing Nutritional Needs

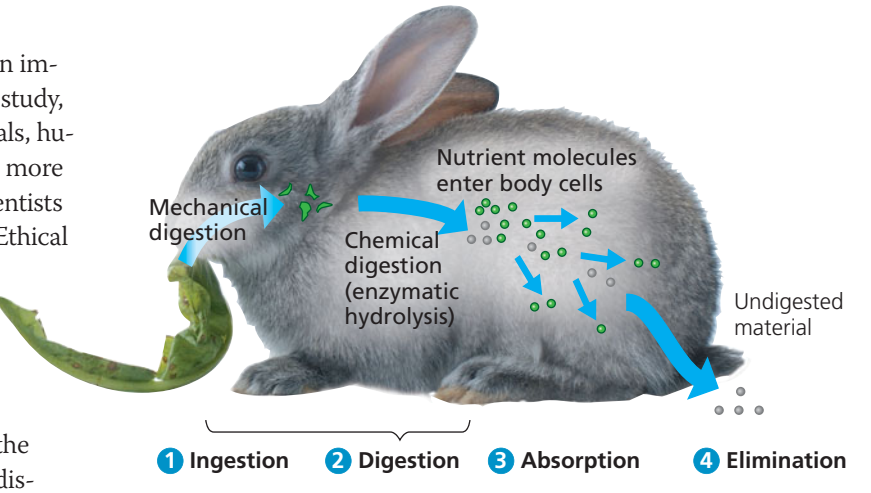
Determining the ideal diet for the human population is an important but difficult problem for scientists. As objects of study, people present many challenges. Unlike laboratory animals, humans are genetically diverse. They also live in settings far more varied than the stable and uniform environment that scientists use to facilitate comparisons in laboratory experiments. Ethical concerns present an additional barrier. For example, it is not acceptable to investigate the nutritional needs of children in a way that might harm a child's growth or development.

Many insights into human nutrition have come from *epidemiology*, the study of human health and disease at the population level. In the 1970s, for instance, researchers discovered that children born to women of low socioeconomic status were more likely to have neural tube defects, which occur when tissue fails to enclose the developing brain and spinal cord. Hypothesizing that malnutrition among these women was responsible, researchers used dietary studies to show that supplementary folic acid (vitamin B_9) greatly reduced the risk of neural tube defects. The United States now requires that folic acid be added to enriched grain products used to make bread, cereals, and other foods.

CONCEPT CHECK 33.1

1. All 20 amino acids are needed to make animal proteins. Why aren't they all essential to animal diets?
2. **MAKE CONNECTIONS** Review the role of enzymes in metabolic reactions (see Concept 6.4). Then explain why vitamins are required in very small amounts in the diet.
3. **WHAT IF?** If a zoo animal eating ample food shows signs of malnutrition, how might a researcher determine which nutrient is lacking in its diet?

For suggested answers, see Appendix A.



▲ **Figure 33.4 The four stages of food processing.**

CONCEPT 33.2

The main stages of food processing are ingestion, digestion, absorption, and elimination

In this section, we turn from nutritional requirements to the mechanisms by which animals process food. Food processing can be divided into four distinct stages: ingestion, digestion, absorption, and elimination **(Figure 33.4)**. The first stage, **ingestion**, is the act of eating or feeding. **Figure 33.5** surveys and classifies the principal feeding mechanisms that have evolved in animals. Given the variation in food sources among animal species, it is not surprising that strategies for extracting resources from food also differ widely. We will focus, however, on the shared processes, pausing periodically to consider some adaptations to particular diets or environments.

In **digestion**, the second stage of food processing, food is broken down into molecules small enough for the body to absorb. Mechanical digestion, such as chewing, typically precedes chemical digestion. Mechanical digestion breaks food into smaller pieces, increasing the surface area available for chemical processes. Chemical digestion is necessary because animals cannot directly use the proteins, carbohydrates, nucleic acids, fats, and phospholipids in food. One problem is that these molecules are too large to pass through membranes and enter the cells of the animal. In addition, the large molecules in food are not all identical to those the animal needs for its particular tissues and functions. When large molecules in food are broken down into their components, however, the animal can use these smaller molecules to assemble the large molecules it needs. For example, although fruit flies and humans have very different diets, both convert proteins in their food to the same 20 amino acids from which they assemble all of the proteins in their bodies.

Recall that a cell makes a macromolecule or fat by linking together smaller components; it does so by removing a molecule of water for each new covalent bond formed. Chemical digestion by enzymes reverses this process by breaking bonds through the addition of water (see Figure 3.6). This splitting process is called *enzymatic hydrolysis*. Polysaccharides and disaccharides are split into simple sugars; proteins are broken down into amino acids; and nucleic acids are cleaved into nucleotides and their components. Enzymatic hydrolysis also releases fatty acids and other components from fats and phospholipids.

The last two stages of food processing occur after the food is digested. In the third stage, **absorption**, the animal's cells take up (absorb) small molecules such as amino acids and simple sugars. **Elimination** completes the process as undigested material passes out of the digestive system.

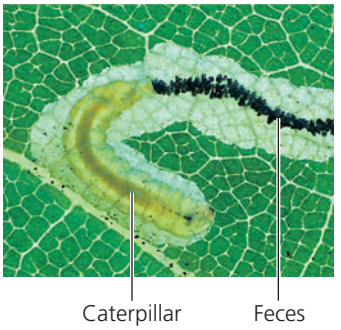
▼ Figure 33.5 Exploring Four Main Feeding Mechanisms of Animals

Filter Feeders

Many aquatic animals are *filter feeders*, which use a filtration mechanism to strain small organisms or food particles from their surroundings. The humpback whale shown above is one example. The comblike plates attached to the whale's upper jaw, called baleen, strain small invertebrates and fish from enormous volumes of water and sometimes mud. Many other filter feeders are invertebrates, including most sponges, which draw water in through their pores. Filter feeding in water is a type of *suspension feeding*, removing suspended food particles from an animal's surrounding medium. Other types of suspension feeding include capture or trapping mechanisms.

Substrate Feeders

Substrate feeders are animals that live in or on their food source. This leaf miner caterpillar, the larva of a moth, is eating through the soft tissue of an oak leaf, leaving a dark trail of feces in its wake. Some other substrate feeders include maggots (fly larvae), which burrow into animal carcasses.



Fluid Feeders

Fluid feeders suck nutrient-rich fluid from a living host. This mosquito has pierced the skin of its human host with hollow, needlelike mouthparts and is consuming a blood meal (colorized SEM). Similarly, aphids are fluid feeders that tap the phloem sap of plants. In contrast to such parasites, some fluid feeders actually benefit their hosts. For example, hummingbirds and bees move pollen between flowers as they fluid-feed on nectar.

Bulk Feeders

Most animals, including humans, are *bulk feeders*, which eat relatively large pieces of food. Their adaptations include tentacles, pincers, claws, poisonous fangs, jaws, and teeth that kill their prey or tear off pieces of meat or vegetation. In this amazing scene, a rock python is beginning to ingest a gazelle it has captured and killed. Snakes cannot chew their food into pieces and must swallow it whole—even if the prey is much bigger than the diameter of the snake. They can do so because the lower jaw is loosely hinged to the skull by an elastic ligament that permits the mouth and throat to open very wide. After swallowing its prey, which may take more than an hour, the python will spend two weeks or longer digesting its meal.

Digestive Compartments

In our overview of food processing, we have seen that digestive enzymes hydrolyze the same biological materials (such as proteins, fats, and carbohydrates) that make up the bodies of the animals themselves. How, then, are animals able to digest food without digesting their own cells and tissues? The evolutionary adaptation found across a wide range of animal species is the processing of food within specialized compartments. Such compartments can be intracellular, in the form of food vacuoles, or extracellular, as in digestive organs and systems.

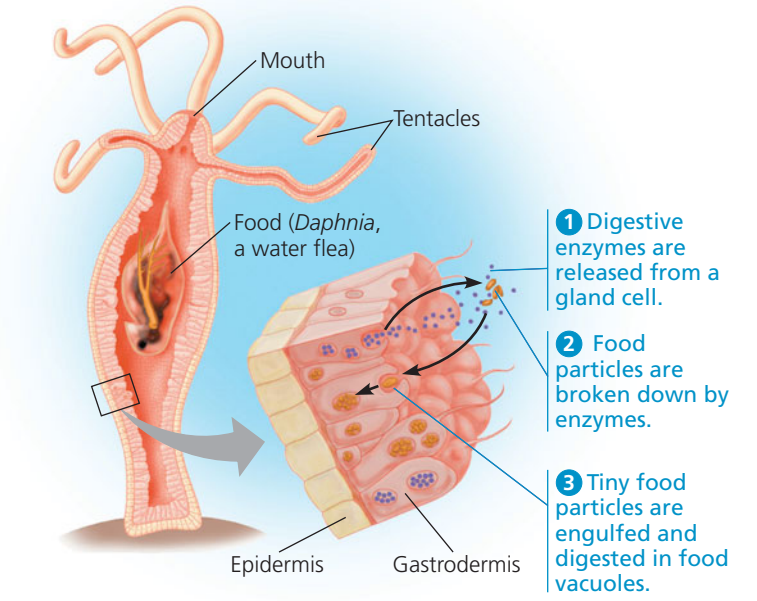
Intracellular Digestion

Food vacuoles—cellular organelles in which hydrolytic enzymes break down food—are the simplest digestive compartments. The hydrolysis of food inside vacuoles, called intracellular digestion, begins after a cell engulfs solid food by phagocytosis or liquid food by pinocytosis (see Figure 5.18). Newly formed food vacuoles fuse with lysosomes, bringing food in contact with hydrolytic enzymes within a compartment enclosed by a protective membrane. A few animals, such as sponges, digest their food entirely by this intracellular mechanism (see Figure 27.3).

Extracellular Digestion

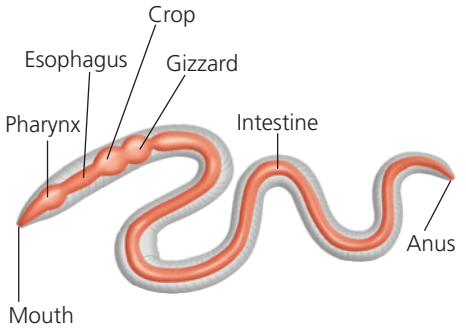
In most animal species, hydrolysis occurs largely by extracellular digestion, the breakdown of food in compartments that are continuous with the outside of the animal's body. Having one or more extracellular compartments for digestion enables an animal to devour much larger pieces of food than can be ingested by phagocytosis.

Many animals with relatively simple body plans have a digestive compartment with a single opening. This pouch, called a **gastrovascular cavity**, functions in digestion as well as in the distribution of nutrients throughout the body (hence the *vascular* part of the term). In a hydra, for example, digestion begins when the animal uses its tentacles to stuff captured prey through its mouth into its gastrovascular cavity **(Figure 33.6)**. After the hydra has digested its meal, undigested materials that remain in its gastrovascular cavity, such as exoskeletons of small crustaceans, are eliminated through its mouth. Many flatworms also have a gastrovascular cavity.

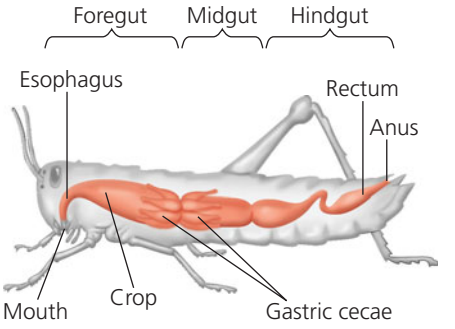


▲ Figure 33.6 Digestion in a hydra. Digestion begins in the gastrovascular cavity and is completed intracellularly after small food particles are engulfed by specialized cells of the gastrodermis.

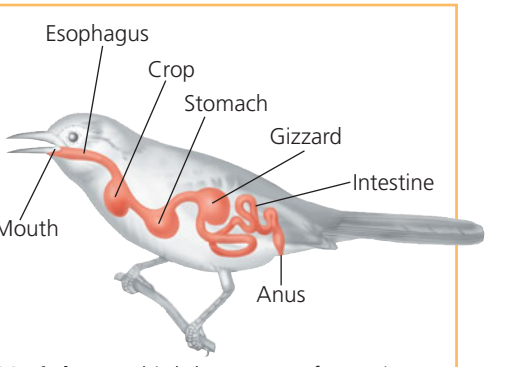
In contrast with cnidarians and flatworms, most animals have a digestive tube extending between two openings, a mouth and an anus. Such a tube is called a *complete digestive tract* or, more commonly, an **alimentary canal (Figure 33.7)**. Because



(a) Earthworm. The earthworm's muscular pharynx sucks food in through the mouth. Food is stored and moistened in the crop. Mechanical digestion occurs in the muscular gizzard, which pulverizes food with sand and gravel. Further digestion and absorption occur in the intestine.



(b) Grasshopper. A grasshopper has a foregut, with an esophagus and crop; a midgut; and a hindgut. Food is moistened and stored in the crop, but most digestion occurs in the midgut. Pouches called gastric cecae extend from the midgut and function in digestion and absorption.



(c) Bird. Many birds have a crop for storing food and a stomach and gizzard for mechanically digesting it. Chemical digestion and absorption of nutrients occur in the intestine.

▲ Figure 33.7 Variation in alimentary canals. These examples illustrate variation in the organization and structure of compartments that carry out stepwise digestion, storage, and absorption in different species.

food moves along the alimentary canal in a single direction, the tube can be organized into specialized compartments that carry out digestion and nutrient absorption in a stepwise fashion. An animal with an alimentary canal can ingest food while earlier meals are still being digested, a feat that is likely to be difficult or inefficient for an animal with a gastrovascular cavity. In the next section, we'll explore the organization of a mammalian alimentary canal.

CONCEPT CHECK 33.2

1. Distinguish the overall structure of a gastrovascular cavity from that of an alimentary canal.
2. In what sense are nutrients from a recently ingested meal not really "inside" your body prior to the absorption stage of food processing?
3. **WHAT IF?** Thinking in broad terms, what similarities can you identify between digestion in an animal body and the breakdown of gasoline in an automobile? (You don't have to know about auto mechanics.)

For suggested answers, see Appendix A.

CONCEPT 33.3

Organs specialized for sequential stages of food processing form the mammalian digestive system

Because most animals, including mammals, have an alimentary canal, we can use the mammalian digestive system to illustrate the general principles of food processing. In mammals, the digestive system consists of the alimentary canal and various accessory glands that secrete digestive juices through ducts into the canal **(Figure 33.8)**. The accessory glands of the mammalian digestive system are three pairs of salivary glands, the pancreas, the liver, and the gallbladder.

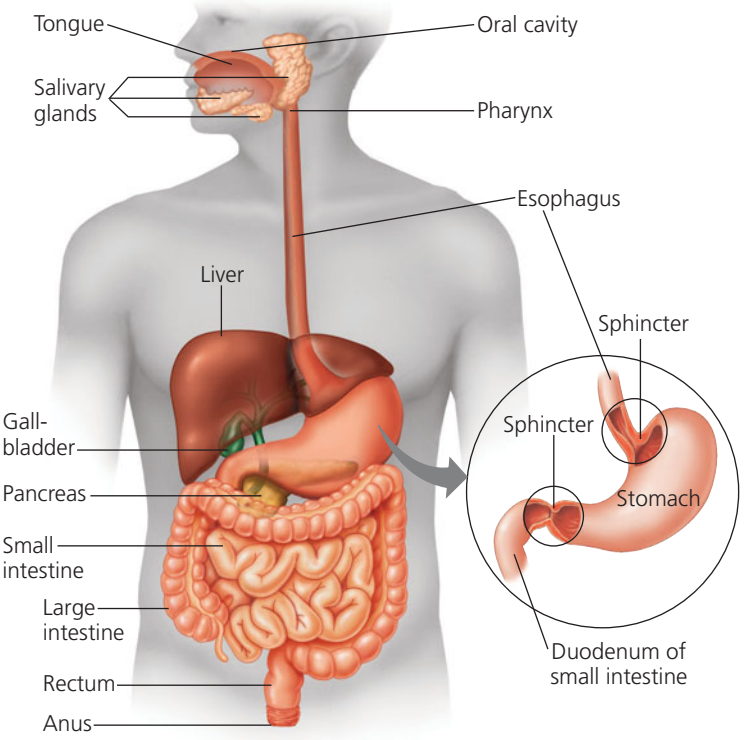
Food is pushed along the alimentary canal by **peristalsis**, alternating waves of contraction and relaxation in the smooth muscles lining the canal. At some of the junctions between specialized compartments, the muscular layer forms ringlike valves called **sphincters**. Acting like drawstrings to close off the alimentary canal, sphincters regulate the passage of material between compartments.

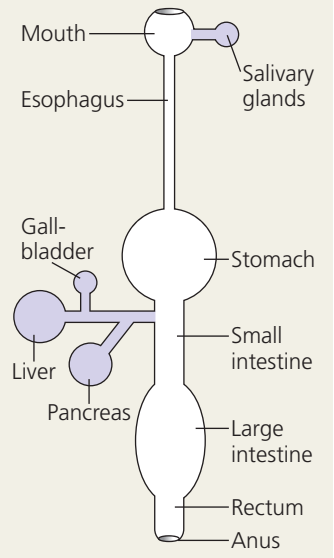
Using the human digestive system as a model, let's now follow a meal through the alimentary canal.

The Oral Cavity, Pharynx, and Esophagus

Ingestion and the initial steps of digestion occur in the mouth, or **oral cavity**. Mechanical digestion begins as teeth of various shapes cut, mash, and grind food, making the food easier to swallow and increasing its surface area. Meanwhile, the presence of food stimulates a nervous reflex that causes the **salivary glands** to deliver saliva through ducts to the oral cavity. Saliva may also be released before food enters the mouth, triggered by a learned association between eating and the time of day, a cooking odor, or another stimulus.

Saliva initiates chemical digestion while also protecting the oral cavity. The enzyme **amylase**, found in saliva, hydrolyzes starch (a glucose polymer from plants) and glycogen (a glucose polymer from animals) into smaller polysaccharides and the disaccharide maltose. Much of the protective effect of saliva is provided by **mucus**, which is a viscous mixture of water, salts, cells, and slippery glycoproteins (carbohydrate-protein





A schematic diagram of the human digestive system (accessory glands in purple)

◀ Figure 33.8 The human digestive system. After food is chewed and swallowed, it takes 5–10 seconds for it to pass down the esophagus and into the stomach, where it spends 2–6 hours being partially digested. Final digestion and nutrient absorption occur in the small intestine over a period of 5–6 hours. In 12–24 hours, any undigested material passes through the large intestine, and feces are expelled through the anus.

complexes). Mucus in saliva protects the lining of the mouth from abrasion and lubricates food for easier swallowing. Additional components of saliva include buffers, which help prevent tooth decay by neutralizing acid, and antimicrobial agents (such as lysozyme; see Figure 3.19), which protect against bacteria that enter the mouth with food.

Much as a doorman screens and assists people entering a fancy hotel, the tongue aids digestive processes by evaluating ingested material and then enabling its further passage. When food arrives at the oral cavity, the tongue plays a critical role in distinguishing which foods should be processed further. (See Chapter 38 for a discussion of the sense of taste.) After food is deemed acceptable and chewing commences, tongue movements manipulate the food, helping shape it into a ball called a **bolus**. During swallowing, the tongue provides further help, pushing the bolus to the back of the oral cavity and into the pharynx.

The **pharynx**, or throat region, opens to two passageways: the esophagus and the trachea (windpipe). The **esophagus** connects to the stomach, whereas the trachea leads to the lungs. Swallowing must therefore be carefully choreographed to keep food from entering and blocking the airway. When you swallow, a flap of cartilage covers your vocal cords and the opening between them. Guided by movements of the *larynx*, the upper part of the respiratory tract, this swallowing reflex directs each bolus into the entrance of the esophagus. If the swallowing reflex fails, food or liquids can reach the trachea and cause choking, a blockage of the trachea. The resulting lack of airflow into the lungs can be fatal if the material is not dislodged by vigorous coughing, back slaps, or a forced upward thrust of the diaphragm (the Heimlich maneuver).

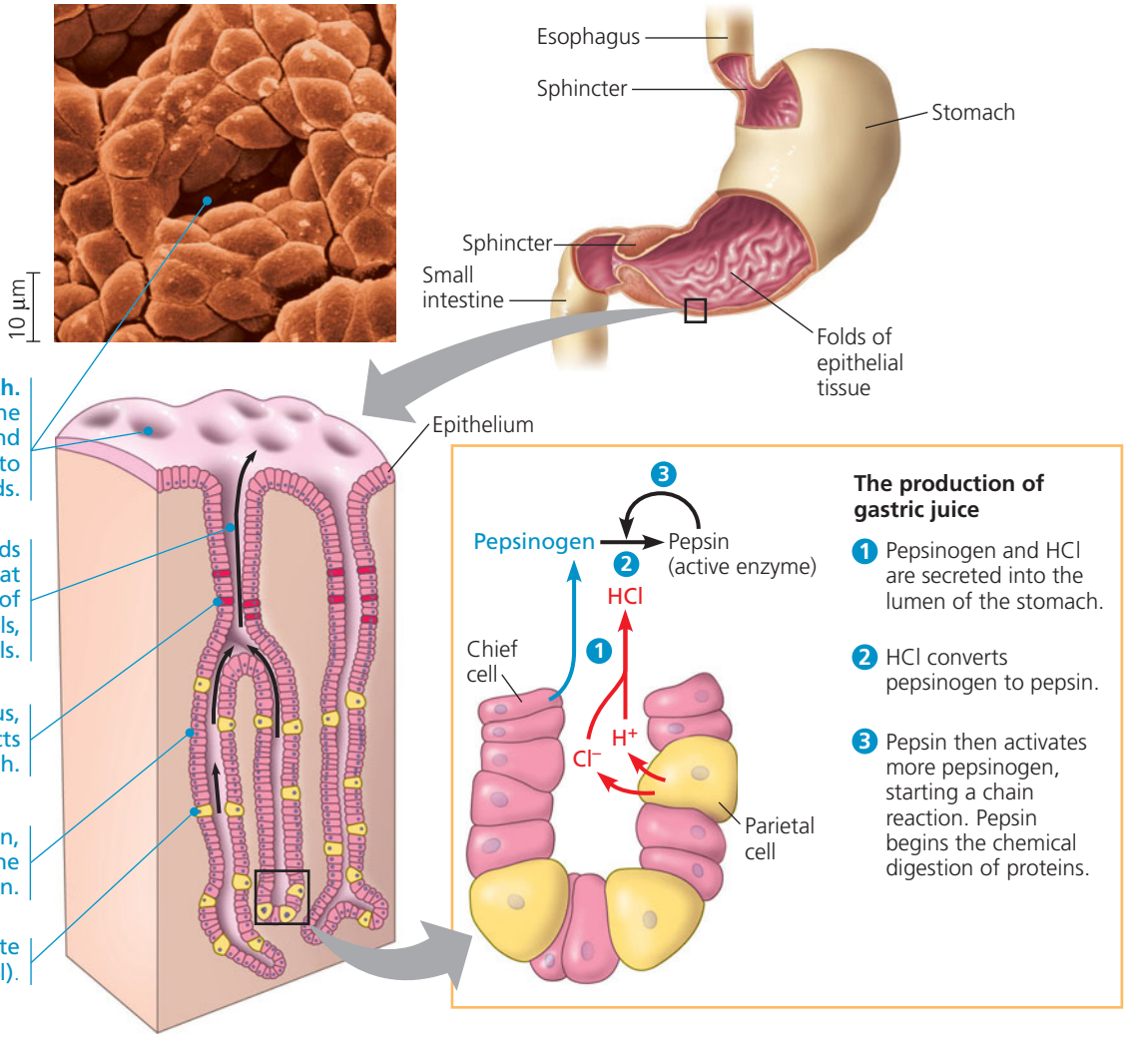
Digestion in the Stomach

The **stomach**, which is located just below the diaphragm, stores food and begins digestion of proteins. With accordion-like folds and a very elastic wall, this organ can stretch to accommodate about 2 L of food and fluid. As shown in **Figure 33.9**, the stomach secretes the components of a digestive fluid called **gastric juice**. It then mixes these secretions with the food through a churning action, forming a mixture of ingested food and digestive juice called **chyme**.

Chemical Digestion in the Stomach

Two components of gastric juice carry out chemical digestion. One is hydrochloric acid (HCl), which disrupts the extracellular matrix that binds cells together in meat and plant material.

▶ Figure 33.9 The stomach and its secretions. The micrograph (colorized SEM) shows a gastric pit on the interior surface of the stomach, through which digestive juices are secreted.



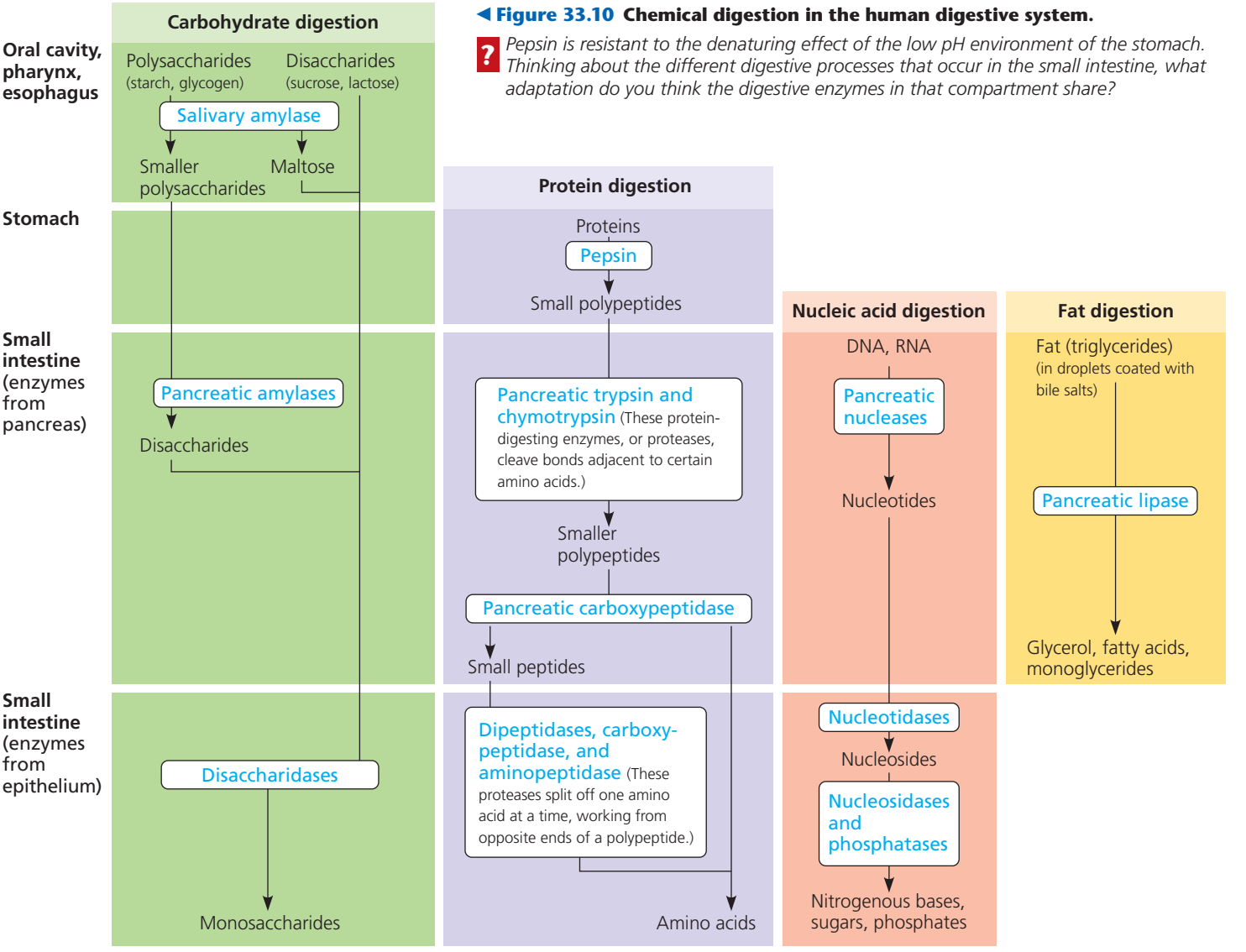
The concentration of HCl is so high that the pH of gastric juice is about 2, acidic enough to dissolve iron nails (and to kill most bacteria). This low pH denatures (unfolds) proteins in food, increasing exposure of their peptide bonds. The exposed bonds are attacked by the second component of gastric juice—a **protease**, or protein-digesting enzyme, called **pepsin**. Unlike most enzymes, pepsin works best in a strongly acidic environment. By breaking peptide bonds, it cleaves proteins into smaller polypeptides. Further digestion to individual amino acids occurs in the small intestine **(Figure 33.10)**.

Why doesn't gastric juice destroy the stomach cells that make it? The answer is that the ingredients of gastric juice are kept inactive until they are released into the lumen (cavity) of the stomach. The components of gastric juice are produced by cells in the gastric glands of the stomach. As detailed in Figure 33.9, *parietal cells* and *chief cells* function together to produce HCl and pepsin in the lumen of the stomach, not within the cells themselves.

Why don't HCl and pepsin damage the cells that line the stomach? Actually, these cells are vulnerable to gastric juice as well as to acid-tolerant pathogens in food or water. However, the stomach lining protects against self-digestion by secreting mucus. In addition, cell division adds a new epithelial layer every three days, replacing cells eroded by digestive juices. Despite these defenses, damaged areas of the stomach lining called gastric ulcers do sometimes appear. For decades, scientists thought that psychological stress and resulting excess acid secretion caused ulcers. In 1982, however, Australian researchers Barry Marshall and Robin Warren reported that infection by the acid-tolerant bacterium *Helicobacter pylori* causes ulcers. They also demonstrated that an antibiotic treatment could cure most gastric ulcers. For these findings, they were awarded the Nobel Prize in 2005.

Stomach Dynamics

Chemical digestion by gastric juice is facilitated by the churning action of the stomach. This coordinated series of muscle contractions and relaxations mixes the stomach contents about every 20 seconds. As a result of mixing and enzyme action, what begins as a recently swallowed meal becomes the



◀ Figure 33.10 Chemical digestion in the human digestive system.

? *Pepsin is resistant to the denaturing effect of the low pH environment of the stomach. Thinking about the different digestive processes that occur in the small intestine, what adaptation do you think the digestive enzymes in that compartment share?*

acidic, nutrient-rich broth known as chyme. Most of the time, sphincters close off the stomach at both ends (see Figure 33.8). The sphincter between the esophagus and the stomach normally opens only when a bolus arrives. Occasionally, however, a person experiences acid reflux, a backflow of chyme from the stomach into the lower end of the esophagus. The resulting irritation of the esophagus is commonly called "heartburn."

Peristaltic contractions typically move the contents of the stomach into the small intestine within 2–6 hours after a meal. The sphincter located where the stomach opens to the small intestine helps regulate passage into the small intestine, allowing only one squirt of chyme at a time.

Digestion in the Small Intestine

Although chemical digestion of some nutrients begins in the oral cavity or stomach, most enzymatic hydrolysis of macromolecules from food occurs in the **small intestine**. The small intestine is the alimentary canal's longest compartment—over 6 m (20 feet) long in humans! Its name refers to its small diameter, compared with that of the large intestine. The first 25 cm or so of the small intestine forms the **duodenum**. It is here that chyme from the stomach mixes with digestive juices from the pancreas, liver, and gallbladder, as well as from gland cells of the intestinal wall itself.

Pancreatic Secretions

The **pancreas** aids chemical digestion by producing an alkaline solution rich in bicarbonate as well as several enzymes (see Figure 33.10). The bicarbonate neutralizes the acidity of chyme and acts as a buffer. Among the pancreatic enzymes are trypsin and chymotrypsin, proteases secreted into the duodenum in inactive forms. In a chain reaction similar to activation of pepsin (see Figure 33.9), they are activated when safely located in the lumen within the duodenum.

Bile Production by the Liver

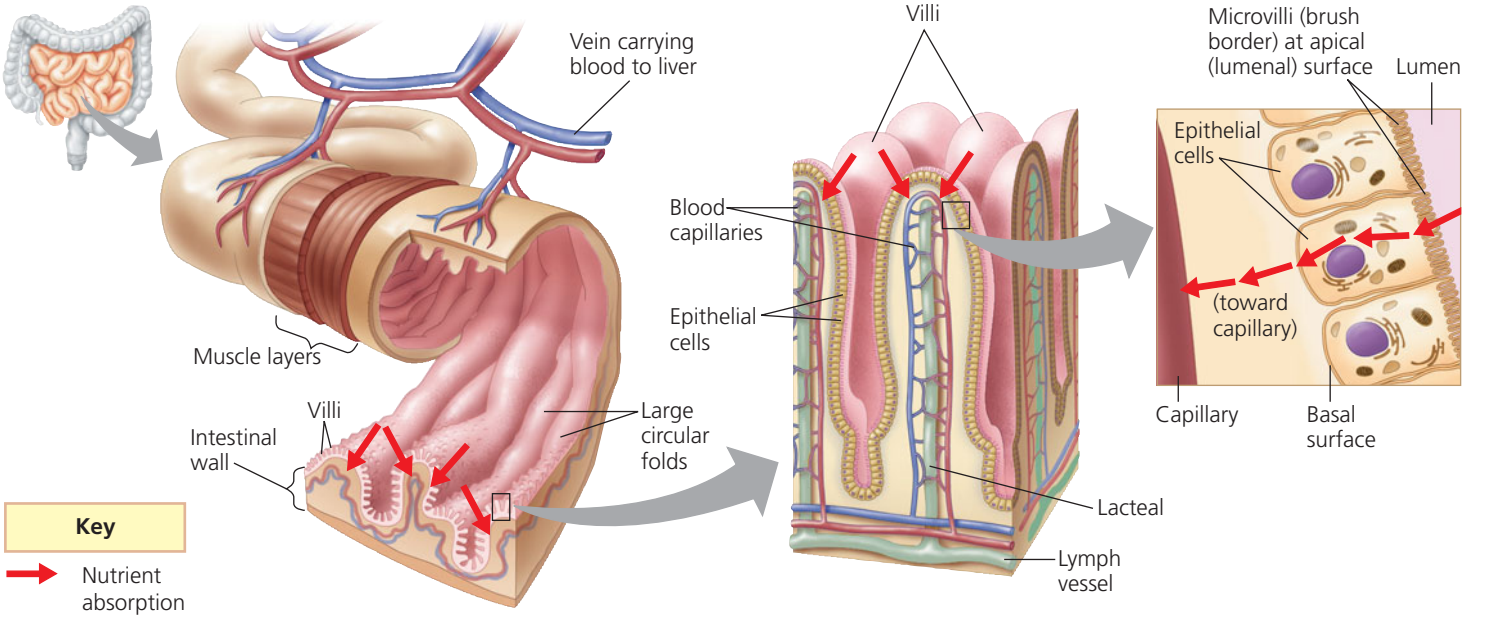
Digestion of fats and other lipids begins in the small intestine and relies on the production of **bile**, a mixture of substances that is made in the **liver**. Bile contains bile salts, which act as emulsifiers (detergents) that aid in digestion and absorption of lipids. Bile is stored and concentrated in the **gallbladder**.

Bile production is integral to one of the other vital functions of the liver: the destruction of red blood cells that are no longer fully functional. In producing bile, the liver incorporates some pigments that are by-products of red blood cell disassembly. These bile pigments are then eliminated from the body with the feces. In some liver or blood disorders, bile pigments accumulate in the skin, resulting in a characteristic yellowing condition called jaundice.

Secretions of the Small Intestine

The epithelial lining of the duodenum is the source of several digestive enzymes (see Figure 33.10). Some are secreted into the lumen of the duodenum, whereas others are bound to the surface of epithelial cells.

While enzymatic hydrolysis proceeds, peristalsis moves the mixture of chyme and digestive juices along the small intestine. Most digestion is completed in the duodenum. The remaining regions of the small intestine, the *jejunum* and *ileum*, are the major site for absorption of nutrients, as illustrated in **Figure 33.11** and discussed next.



▲ Figure 33.11 Nutrient absorption in the small intestine.

? *Tapeworms sometimes infect humans, anchoring themselves to the wall of the small intestine. Based on the way digestion is compartmentalized along the mammalian alimentary canal, what digestive functions would you expect these parasites to have?*

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Absorption in the Small Intestine

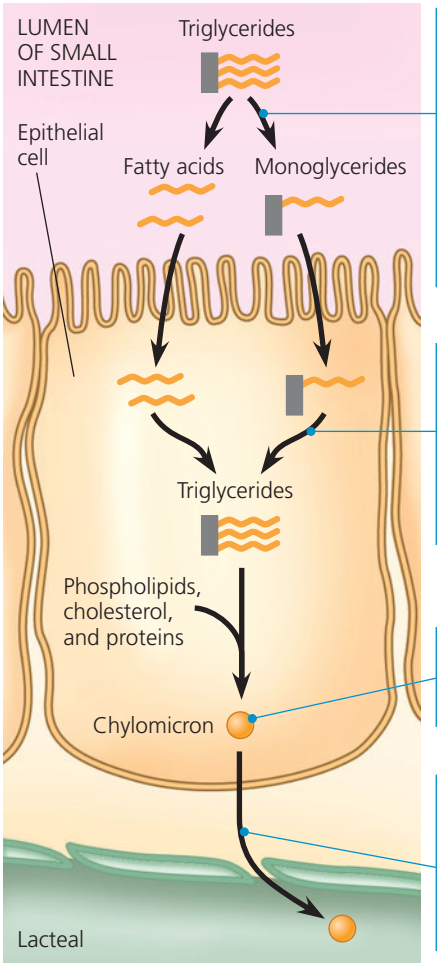
To reach body tissues, nutrients in the lumen must first cross the lining of the alimentary canal. Most of this absorption occurs across the highly folded surface of the small intestine, as illustrated in Figure 33.11. Large folds in the lining are studded with finger-like projections called **villi**. In turn, each epithelial cell of a villus has many microscopic projections, or **microvilli**, that are exposed to the intestinal lumen. The microvilli give cells of the intestinal epithelium a brush-like appearance that is reflected in the name *brush border*. Together, the folds, villi, and microvilli of the small intestine have a surface area of 200–300 m^2, roughly the size of a tennis court. This enormous surface area is an evolutionary adaptation that greatly increases the rate of nutrient absorption.

Depending on the nutrient, transport across the epithelial cells can be passive or active (see Chapter 5). The sugar fructose, for example, moves by facilitated diffusion down its concentration gradient from the lumen of the small intestine into the epithelial cells. From there, fructose exits the basal surface and is absorbed into microscopic blood vessels, or capillaries, at the core of each villus. Other nutrients, including amino acids, small peptides, vitamins, and most glucose molecules, are pumped against concentration gradients by the epithelial cells of the villus.

The capillaries and veins that carry nutrient-rich blood away from the villi converge into the **hepatic portal vein**, a blood vessel that leads directly to the liver. From the liver, blood travels to the heart and then to other tissues and organs. This arrangement serves two major functions. First, it allows the liver to regulate the distribution of nutrients to the rest of the body. Because the liver can interconvert many organic molecules, blood that leaves the liver may have a very different nutrient balance than the blood that entered. Second, the arrangement allows the liver to remove toxic substances before the blood circulates broadly. The liver is the primary site for the detoxification of many organic molecules, including drugs, that are foreign to the body.

Although many nutrients leave the small intestine through the bloodstream, some products of fat (triglyceride) digestion take a different path **(Figure 33.12)**. Hydrolysis of a fat by lipase generates fatty acids and a monoglyceride (glycerol joined to a fatty acid). These products are absorbed by epithelial cells and recombined into triglycerides. They are then coated with phospholipids, cholesterol, and proteins, forming water-soluble globules called **chylomicrons**.

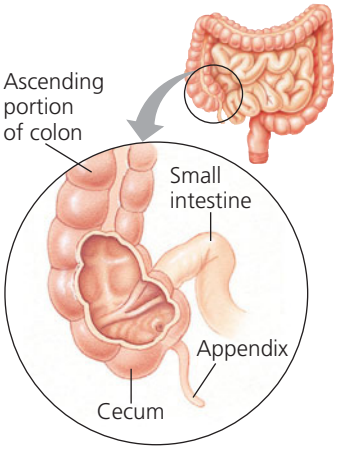
In exiting the intestine, chylomicrons first enter a **lacteal**, a vessel at the core of each villus (see Figures 33.11 and 33.12). Lacteals are part of the lymphatic system, which is a network of vessels filled with a clear fluid called lymph. Starting at the lacteals, lymph containing the chylomicrons passes into the larger vessels of the lymphatic system and eventually into large veins that return the blood to the heart.



▲ Figure 33.12 Absorption of fats. Because fats are insoluble in water, adaptations are needed to digest and absorb them. Bile salts (not shown) break up large fat droplets and maintain a small droplet size in the intestinal lumen, increasing surface area for enzymatic hydrolysis. The fatty acids and monoglycerides released by hydrolysis can diffuse into epithelial cells, where fats are reassembled and incorporated into water-soluble chylomicrons that enter the lymphatic system.

Absorption in the Large Intestine

The alimentary canal ends with the **large intestine**, which includes the colon, cecum, and rectum. The small intestine connects to the large intestine at a T-shaped junction **(Figure 33.13)**. One arm of the T is the 1.5-m-long **colon**, which leads to the rectum and anus. The other arm is a pouch called the **cecum**. The cecum is important for fermenting ingested material, especially in animals that eat large amounts of plant material. Compared with many other



▲ Figure 33.13 Junction of the small and large intestines.

mammals, humans have a small cecum. The **appendix**, a finger-like extension of the human cecum, has a minor and dispensable role in immunity.

A major function of the colon is to recover water that has entered the alimentary canal as the solvent of digestive juices. About 7 L of fluid is secreted into the lumen of the alimentary canal each day, and about 90% of that is reabsorbed in the small intestine and colon. There is no mechanism for active transport of water. Instead, water is reabsorbed by osmosis when sodium and other ions are pumped out of the lumen of the colon.

The **feces**, the wastes of the digestive system, become increasingly solid as they are moved along the colon by peristalsis. It takes approximately 12–24 hours for material to travel the length of the colon. If the lining of the colon is irritated—by a viral or bacterial infection, for instance—less water than normal may be reabsorbed, resulting in diarrhea. The opposite problem, constipation, occurs when the feces move along the colon too slowly. Too much water is reabsorbed and the feces become compacted.

A rich community of mostly harmless bacteria lives on unabsorbed organic material in the human colon, contributing approximately one-third of the dry weight of feces. Some bacteria produce vitamins that are absorbed into the blood, supplementing our dietary intake. One bacterial inhabitant, *Escherichia coli*, is so common in the human digestive system that its presence in lakes and streams is a useful indicator of contamination by untreated sewage. As by-products of their metabolism, many colon bacteria generate gases, including methane and hydrogen sulfide, the latter of which has an offensive odor. These gases and ingested air are expelled through the anus.

Besides bacteria, feces contain undigested material, including cellulose fiber. Although it provides no caloric value (energy) to humans, fiber helps move food along the alimentary canal.

The terminal portion of the large intestine is the **rectum**, where feces are stored until they can be eliminated. Between the rectum and the anus are two sphincters, the inner one being involuntary and the outer one being voluntary. Periodically, strong contractions of the colon create an urge to defecate. Because filling of the stomach triggers a reflex that increases the rate of contractions in the colon, the urge to defecate often follows a meal.

We have followed a meal from one opening (the mouth) of the alimentary canal to the other (the anus). Next we'll look at some adaptations of this general digestive plan in different animals.

CONCEPT CHECK 33.3

1. How does swallowed food reach the stomach of a weightless astronaut in orbit?
2. Explain why a proton pump inhibitor, such as the drug Prilosec, relieves the symptoms of acid reflux.
3. **WHAT IF?** If you mixed gastric juice with crushed food in a test tube, what would happen?

For suggested answers, see Appendix A.

CONCEPT 33.4

Evolutionary adaptations of vertebrate digestive systems correlate with diet

EVOLUTION The digestive systems of mammals and other vertebrates are variations on a common plan, but there are many intriguing adaptations, often associated with the animal's diet. To highlight how form fits function, we'll examine a few of them.

Dental Adaptations

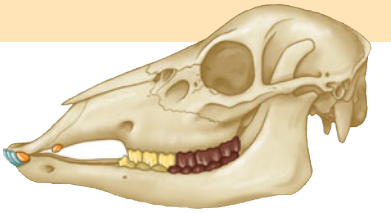
Dentition, an animal's assortment of teeth, is one example of structural variation reflecting diet **(Figure 33.14)**. The

▼ Figure 33.14 Dentition and diet.

Carnivore

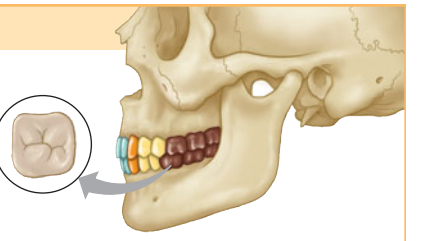
Carnivores, such as members of the dog and cat families, generally have large, pointed incisors and canines that can be used to kill prey and rip or cut away pieces of flesh. The jagged premolars and molars crush and shred food.

Herbivore



Herbivores, such as horses and deer, usually have premolars and molars with broad, ridged surfaces that grind tough plant material. The incisors and canines are generally modified for biting off pieces of vegetation. In some herbivores, canines are absent.

Omnivore



As omnivores, humans are adapted to eating both plants and meat. Adults have 32 teeth. From front to back along either side of the mouth are four bladelike incisors for biting, a pair of pointed canines for tearing, four premolars for grinding, and six molars for crushing (see inset, top view).

Key Incisors Canines Premolars Molars

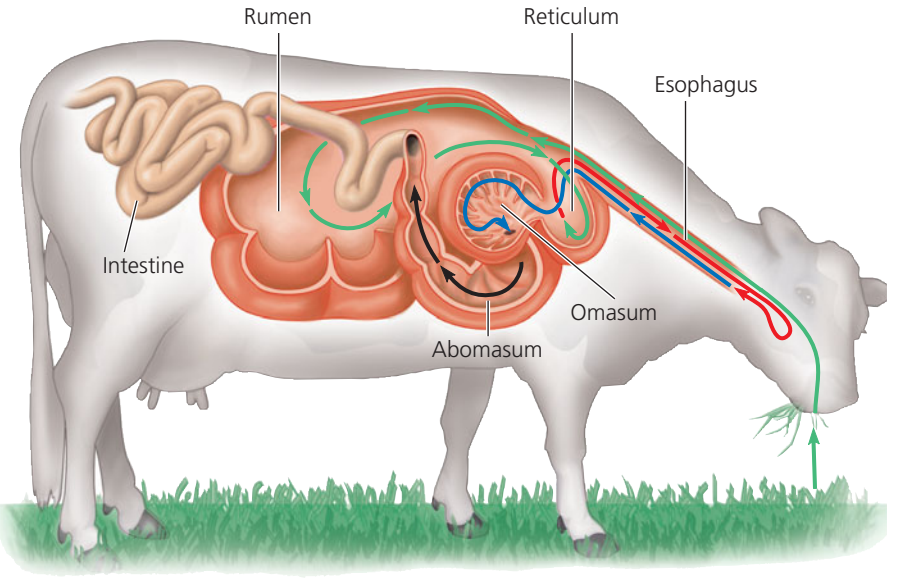
evolutionary adaptation of teeth for processing different kinds of food is one of the major reasons mammals have been so successful. Nonmammalian vertebrates generally have less specialized dentition, but there are interesting exceptions. For example, venomous snakes, such as rattlesnakes, have fangs, modified teeth that inject venom into prey. Some fangs are hollow, like syringes, whereas others drip the toxin along grooves on the surfaces of the teeth.

Mutualistic Adaptations

Some digestive adaptations involve mutualistic symbiosis, a mutually beneficial interaction between two species (see Chapter 41). For example, microorganisms help herbivores digest plants. Much of the chemical energy in herbivore diets comes from the cellulose of plant cell walls, but animals do not produce enzymes that hydrolyze cellulose. Instead, many vertebrates (as well as termites, whose wooden diets consist largely of cellulose) host mutualistic bacteria and protists in fermentation chambers in their alimentary canals. These microorganisms have enzymes that can digest cellulose to simple sugars and other compounds that the animal can absorb. In many cases, the microorganisms also use the sugars from digested cellulose in the production of a variety of nutrients essential to the animal, such as vitamins and amino acids.

In horses and koalas, symbiotic microorganisms are housed in a large cecum; in rabbits and some rodents, mutualistic bacteria live in the large intestine and cecum. Since most nutrients are absorbed in the small intestine, nourishing by-products of fermentation by bacteria in the large intestine are initially lost with the feces. Rabbits and rodents recover these nutrients by *coprophagy* (from the Greek, meaning "dung eating"), feeding on some of their feces and then passing the food through the alimentary canal a second time. The familiar rabbit "pellets," which are not reingested, are the feces eliminated after food has passed through the digestive tract twice.

The most elaborate adaptations for an herbivorous diet have evolved in the animals called **ruminants**, which include deer, sheep, and cattle **(Figure 33.15)**.

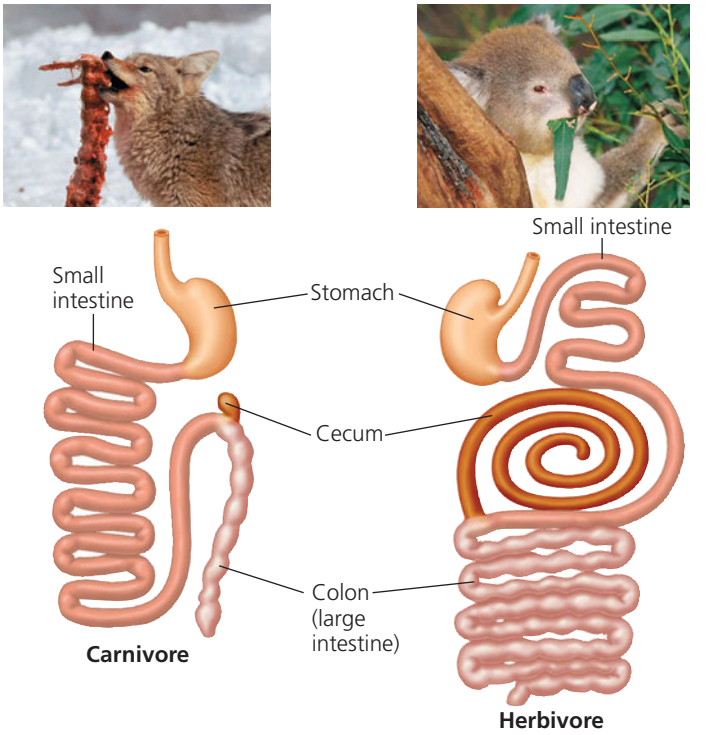


▲ **Figure 33.15 Ruminant digestion.** The stomach of a ruminant has four chambers. Chewed food first enters the rumen and reticulum, where mutualistic microorganisms digest cellulose in the plant material. Periodically, the cow regurgitates and rechews "cud" from the reticulum, further breaking down fibers and thereby enhancing microbial action. The reswallowed cud passes to the omasum, where some water is removed, and then to the abomasum, for digestion by the cow's enzymes. In this way, the cow obtains significant nutrients from both the grass and the mutualistic microorganisms, which maintain a stable population in the rumen.

Stomach and Intestinal Adaptations

Variation in the dimensions of digestive organs also reflects evolutionary adaptation to differences in diet. For example, large, expandable stomachs are common in carnivorous vertebrates, which may wait a long time between meals and must eat as much as they can when they do catch prey. A 200-kg African lion can consume 40 kg of meat in one meal!

Adaptation is likewise apparent in the length of the digestive system in different vertebrates. In general, herbivores and omnivores have longer alimentary canals relative to their body size than do carnivores **(Figure 33.16)**. As we have seen, plant



▲ **Figure 33.16 The alimentary canals of a carnivore (coyote) and herbivore (koala).** The relatively short digestive tract of the coyote is sufficient for digesting meat and absorbing its nutrients. In contrast, the koala's long alimentary canal is specialized for digesting eucalyptus leaves. Extensive chewing chops the leaves into tiny pieces, increasing exposure to digestive juices. In the long cecum and the upper portion of the colon, symbiotic bacteria convert the shredded leaves to a more nutritious diet.

matter is more difficult to digest than meat because it contains cell walls. A longer digestive tract furnishes more time for digestion and more surface area for the absorption of nutrients. As an example, consider the koala and coyote in Figure 33.16. Although these two mammals are about the same size, the koala's intestines are much longer, enhancing the processing of fibrous, protein-poor eucalyptus leaves from which the koala obtains nearly all of its food and water.

Having examined how animals optimize their extraction of nutrients from food, we will next turn to the challenge of balancing the use of these nutrients.

CONCEPT CHECK 33.4

1. What are two advantages of a longer alimentary canal for processing plant material that is difficult to digest?
2. What features of a mammal's digestive system make it an attractive habitat for mutualistic microorganisms?
3. **WHAT IF?** "Lactose-intolerant" people have a shortage of lactase, the enzyme that breaks down lactose in milk. As a result, they sometimes develop cramps, bloating, or diarrhea after consuming dairy products. Suppose such a person ate yogurt containing bacteria that produce lactase. Why would eating yogurt likely provide at best only temporary relief of the symptoms?

For suggested answers, see Appendix A.

CONCEPT 33.5

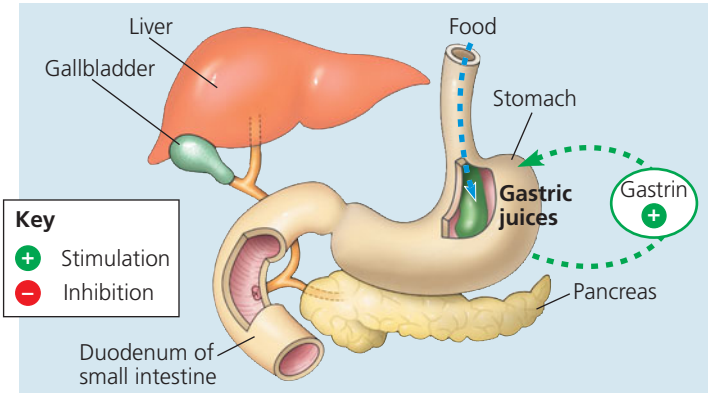
Feedback circuits regulate digestion, energy allocation, and appetite

The processes that enable an animal to obtain nutrients are matched to the organism's circumstances and need for energy.

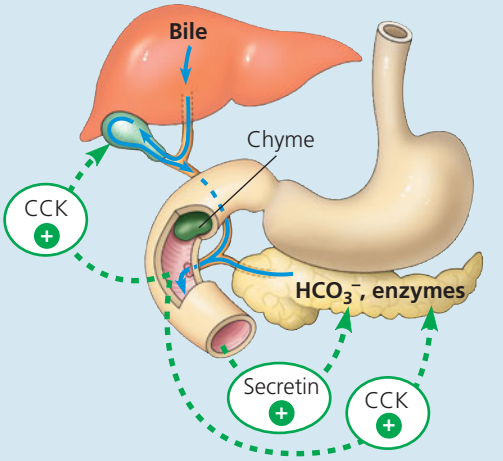
Regulation of Digestion

Many animals have long intervals between meals and do not need their digestive systems to be active continuously. Instead, each step in processing is activated as food reaches a new compartment in the alimentary canal. The arrival of food triggers the secretion of substances that promote the next stage of chemical digestion, as well as muscular contractions that propel food farther along the canal. For example, you learned earlier that nervous reflexes stimulate the release of saliva when food enters the oral cavity and orchestrate swallowing when a bolus of food reaches the pharynx. Similarly, the arrival of food in the stomach triggers churning and the release of gastric juices. A branch of the nervous system called the *enteric division*, which is dedicated to the digestive organs, regulates these events as well as peristalsis in the small and large intestines.

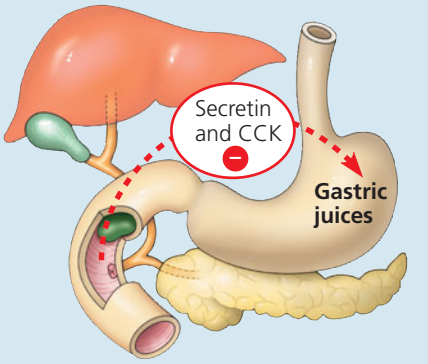
The endocrine system also plays a critical role in controlling digestion. As described in **Figure 33.17**, a series of hormones released by the stomach and duodenum help ensure that



1 As food arrives at the stomach, it stretches the stomach walls, triggering release of the hormone *gastrin*. Gastrin circulates via the bloodstream back to the stomach, where it stimulates production of gastric juices.



2 Chyme—an acidic mixture of partially digested food—eventually passes from the stomach to the duodenum. The duodenum responds to amino acids or fatty acids in the chyme by releasing the digestive hormones cholecystokinin and secretin. *Cholecystokinin (CCK)* stimulates the release of digestive enzymes from the pancreas and of bile from the gallbladder. *Secretin* stimulates the pancreas to release bicarbonate (HCO_3^-), which neutralizes chyme.



3 If the chyme is rich in fats, the high levels of secretin and CCK released act on the stomach to inhibit peristalsis and secretion of gastric juices, thereby slowing digestion.

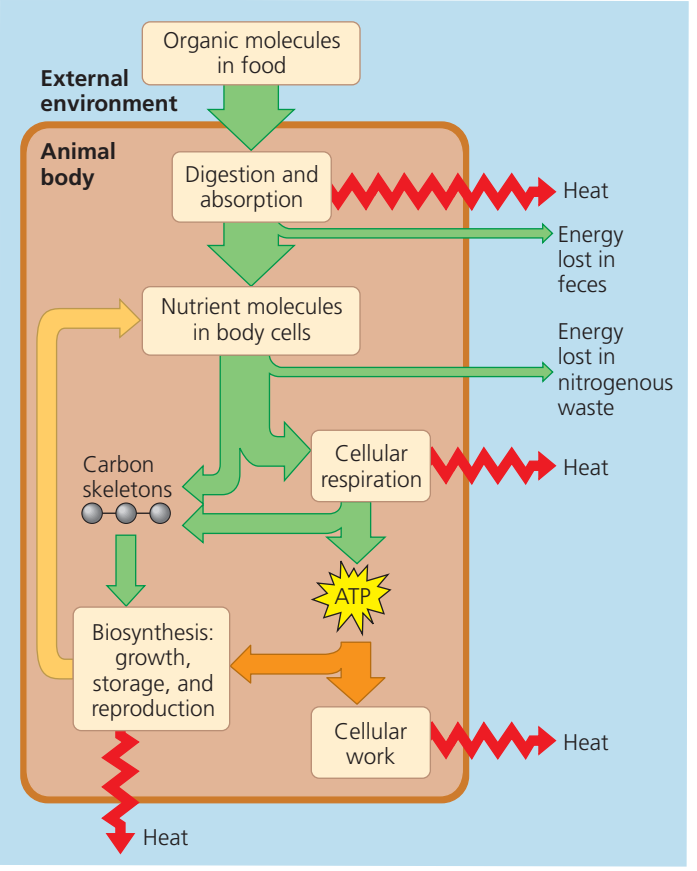
▲ **Figure 33.17 Hormonal control of digestion.**

digestive secretions are present only when needed. Like all hormones, they are transported through the bloodstream. This is true even for the hormone gastrin, whose target (the stomach) is the same organ that secretes it.

Energy Allocation

Digested food provides animals with chemical energy to fuel metabolism and activity. In turn, the flow and transformation of energy in an animal—its **bioenergetics**—determine nutritional needs **(Figure 33.18)**. Energy extracted from nutrients is converted to ATP by cellular respiration and fermentation. Stores of ATP enable cells, organs, and organ systems to perform the functions that keep an animal alive. ATP is also used in biosynthesis, which is needed for body growth and repair, for energy storage, and for reproduction. The production and use of ATP generate heat, which the animal eventually gives off to its surroundings.

How much of the total energy obtained from food does an animal need just to stay alive? How much energy must be expended to walk, run, swim, or fly from one place to another? What fraction of the energy intake is used for reproduction? Physiologists answer such questions by measuring the rate at which an animal uses chemical energy and how this rate changes in different circumstances.



▲ **Figure 33.18 Bioenergetics of an animal: an overview.**

MAKE CONNECTIONS *Review the idea of energy coupling (see Concept 6.3). Then use that idea to explain why heat is produced in the absorption of nutrients, in cellular respiration, and in the synthesis of large biological molecules.*

An animal's energy use per unit of time is called its **metabolic rate**. Energy is measured in joules or in calories and kilocalories; 1 kcal = 1,000 cal = 4,184 J. (The unit Calorie, with a capital C, as used by many nutritionists, is actually a kilocalorie.) Because nearly all chemical energy used eventually appears as heat, metabolic rate can be measured by monitoring an animal's rate of heat loss. For this approach, researchers use a calorimeter, which is a recording device in a closed, insulated chamber. Metabolic rate can also be determined from the amount of oxygen consumed or carbon dioxide produced. To calculate metabolic rate over longer periods, researchers record the rate of food consumption, the energy content of the food, and the chemical energy lost in waste products (see Figure 33.18).

Minimum Metabolic Rate

Animals must maintain a minimum metabolic rate for basic functions such as cell maintenance, breathing, and heartbeat. Researchers measure this minimum metabolic rate differently for endotherms and ectotherms. The minimum metabolic rate of a nongrowing endotherm that is at rest, has an empty stomach, and is not experiencing stress is called the *basal metabolic rate* (*BMR*). BMR is measured under a "comfortable" temperature range—a range that requires no generation or shedding of heat above the minimum. For ectotherms, the minimum metabolic rate must instead be determined at a specific temperature because changes in the environmental temperature alter body temperature and therefore metabolic rate. The metabolic rate of a fasting, nonstressed ectotherm at rest at a particular temperature is called its *standard metabolic rate* (*SMR*).

Comparisons of minimum metabolic rates confirm that endothermy and ectothermy have different energy costs. The BMR per day for adult humans averages 1,600–1,800 kcal for males and 1,300–1,500 kcal for females. These BMRs are about equivalent to the rate of energy use by a ceiling fan or an electric blanket. In contrast, the SMR of an American alligator is about 60 kcal per day at 20°C (68°F), less than $\frac{1}{20}$ the energy used by a comparably sized adult human.

For both ectotherms and endotherms, activity greatly affects metabolic rate. Even a person reading quietly at a desk or an insect twitching its wings consumes energy beyond the BMR or SMR. Maximum metabolic rates (the highest rates of ATP use) occur during peak activity, such as lifting heavy weights, sprinting, or high-speed swimming. In general, the maximum metabolic rate an animal can sustain is inversely related to the duration of activity.

For most terrestrial animals, the average daily rate of energy consumption is 2 to 4 times BMR (for endotherms) or SMR (for ectotherms). People in most developed countries have an unusually low average daily metabolic rate of about 1.5 times BMR—an indication of their relatively sedentary lifestyles.

Regulation of Energy Storage

When an animal takes in more energy-rich molecules than it needs for metabolism and activity, it stores the excess energy. In humans, the first sites used for energy storage are liver and muscle cells. In these cells, excess energy from the diet is stored in glycogen, a polymer made up of many glucose units. Once glycogen depots are full, any additional excess energy is usually stored in fat in adipose cells.

When fewer calories are taken in than are expended—perhaps because of sustained heavy exercise or lack of food—the human body generally expends liver glycogen first and then draws on muscle glycogen and fat. Fats are especially rich in energy; oxidizing a gram of fat liberates about twice the energy liberated from a gram of carbohydrate or protein. For this reason, adipose tissue provides the most space-efficient way for the body to store large amounts of energy. Most healthy people have enough stored fat to sustain them through several weeks without food.

Glucose Homeostasis

The synthesis and breakdown of glycogen are central not only to energy storage, but also to maintaining metabolic balance through glucose homeostasis. Tissues throughout the body rely on the generation of ATP by glucose oxidation to fuel cellular processes (see Chapter 7). The pancreatic hormones insulin and glucagon maintain glucose homeostasis by tightly regulating the synthesis and breakdown of glycogen.

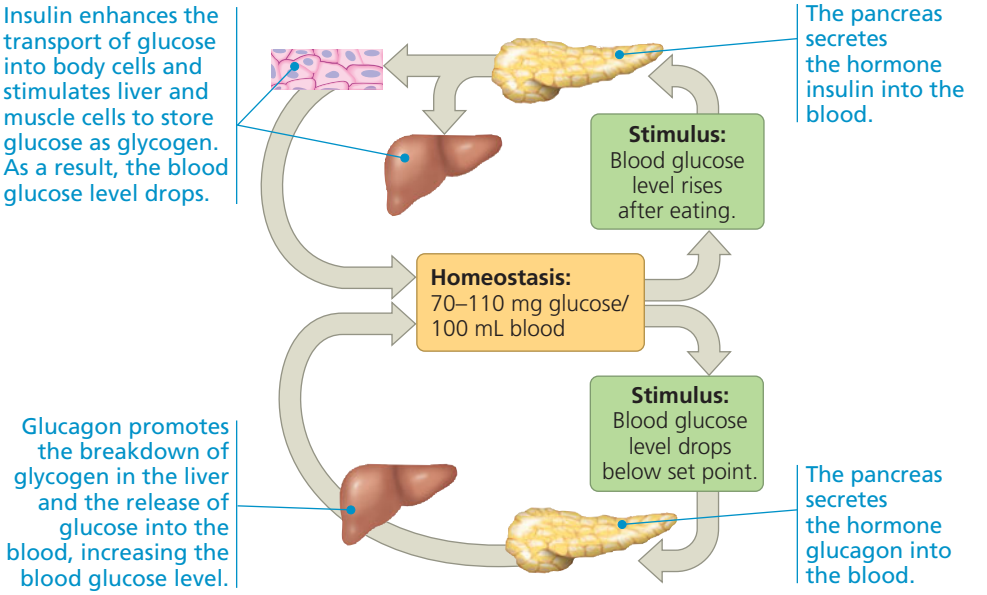
The liver is a key site for glucose regulation **(Figure 33.19)**. When insulin levels rise after a carbohydrate-rich meal, glucose entering the liver in the hepatic portal vein is used to synthesize glycogen. Between meals, when blood in the hepatic portal vein has a much lower glucose concentration, glucagon stimulates the liver to break down glycogen, releasing glucose into the blood. Because insulin and glucagon have opposing effects, the combined activity of these two hormones maintains a glucose concentration of 70–110 mg per 100 mL of blood exiting the liver at nearly all times.

Glucagon and insulin are produced in the pancreas. Scattered throughout this organ are clusters of endocrine cells called pancreatic islets. Each pancreatic islet has *alpha cells*, which make glucagon, and *beta cells*, which make insulin. Like all hormones, insulin and glucagon are secreted into the interstitial fluid and from there enter the circulatory system.

Diabetes Mellitus

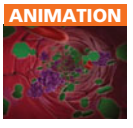
A number of disorders can disrupt glucose homeostasis with potentially serious consequences, especially for the heart, blood vessels, eyes, and kidneys. The best known and most prevalent is **diabetes mellitus**, a disease caused by a deficiency of insulin or a decreased response to insulin in target cells. Blood glucose levels rise, but cells are unable to take up enough glucose to meet metabolic needs. Instead, fat becomes the main substrate for cellular respiration. In severe cases, acidic metabolites formed during fat breakdown accumulate in the blood, threatening life by lowering blood pH and depleting sodium and potassium ions from the body.

In people with diabetes mellitus, the level of glucose in the blood may exceed the capacity of the kidneys to reabsorb this nutrient. Glucose that remains in the kidney filtrate is excreted. For this reason, the presence of sugar in urine is one test for this disorder. As glucose is concentrated in the urine, more water is excreted along with it, resulting in excessive volumes of urine. *Diabetes* (from the Greek *diabainein*, to pass through) refers to this copious urination; and *mellitus* (from the Greek *meli*, honey) refers to the presence of sugar in urine.



▶ Figure 33.19 Homeostatic regulation of cellular fuel. After a meal is digested, glucose and other monomers are absorbed into the blood from the digestive tract. The human body regulates the use and storage of glucose, a major cellular fuel.

MAKE CONNECTIONS *What form of feedback control does each of these regulatory circuits reflect (see Concept 32.1)?*



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There are two main types of diabetes mellitus. *Type 1 diabetes*, or insulin-dependent diabetes, is an autoimmune disorder in which the immune system destroys the insulin-producing beta cells of the pancreas. Treatment consists of insulin, typically injected several times daily. *Type 2 diabetes*, or non-insulin-dependent diabetes, is characterized by a failure of target cells to respond normally to insulin. Insulin is produced, but target cells fail to take up glucose from the blood, and blood glucose levels remain elevated. Although heredity can play a role in type 2 diabetes, excess body weight and lack of exercise significantly increase the risk. Type 2 diabetes is the seventh most common cause of death in the United States.

Regulation of Appetite and Consumption

Consuming more calories than the body needs for normal metabolism, or *overnourishment*, can lead to obesity, the excessive accumulation of fat. Obesity, in turn, contributes to a number of health problems, including type 2 diabetes, cancer of the colon and breast, and cardiovascular disease that can lead to heart attacks and strokes. Obesity is a factor in an estimated 300,000 deaths per year in the United States.

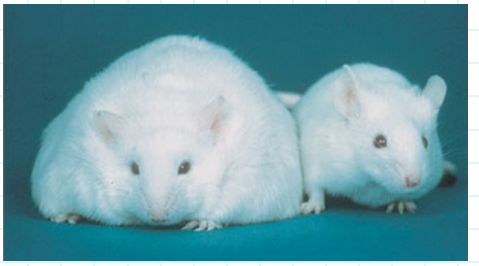
Researchers have discovered several homeostatic mechanisms that help regulate body weight. Operating as feedback circuits, these mechanisms control the storage and metabolism of fat. Several hormones regulate long-term and short-term appetite by affecting a "satiety center" in the brain. For example, *ghrelin*, a hormone secreted by the stomach wall, triggers feelings of hunger before meals. In contrast, both insulin and *PYY*, a hormone secreted by the small intestine after meals, suppress appetite. *Leptin*, a hormone produced by adipose (fat) tissue, also suppresses appetite and appears to play a major role in regulating body fat levels. In the **Scientific Skills Exercise**, you'll interpret data from an experiment studying genes that affect leptin production and function in mice.

Scientific Skills Exercise

Interpreting Data from an Experiment with Genetic Mutants

What Are the Roles of the *ob* and *db* Genes in Appetite Regulation? A mutation that disrupts a physiological process is often used to study the normal function of the mutated gene. Ideally, researchers use a standard set of conditions and compare animals that differ genetically only in whether a particular gene is mutant (nonfunctional) or wild-type (normal). In this way, a difference in phenotype, the physiological property being measured, can be attributed to a difference in genotype, the presence or absence of the mutation. To study the role of specific genes in regulating appetite, researchers used laboratory animals with known mutations in those genes.

Mice in which recessive mutations inactivate both copies of either the *ob* gene or the *db* gene eat voraciously and grow much more massive than wild-type mice. In the photograph below, the mouse on the right is wild-type, whereas the obese mouse on the left has an inactivating mutation in both copies of the *ob* gene.



One hypothesis for the normal role of the *ob* and *db* genes is that they participate in a hormone pathway that suppresses appetite when caloric intake is sufficient. Before setting out to isolate the potential hormone, researchers explored this hypothesis genetically.

How the Experiment Was Done The researchers measured the mass of young subject mice of various genotypes and surgically linked the circulatory system of each one to that of another mouse. This procedure ensured that any factor circulating in the bloodstream of either mouse would be transferred to the other in the pair. After eight weeks, they again measured the mass of each subject mouse.

Data from the Experiment

	Genotype Pairing (red type indicates mutant genes) Subject	Paired with	Average Change in Body Mass of Subject (g)
(a)	ob^+/ob^+, db^+/db^+	ob^+/ob^+, db^+/db^+	8.3
(b)	*ob/ob*, db^+/db^+	*ob/ob*, db^+/db^+	38.7
(c)	*ob/ob*, db^+/db^+	ob^+/ob^+, db^+/db^+	8.2
(d)	*ob/ob*, db^+/db^+	ob^+/ob^+, *db/db*	−14.9*

* Due to pronounced weight loss and weakening, subjects in this pairing were remeasured after less than eight weeks.

Interpret the Data

1. First, practice reading the genotype information given in the data table. For example, pairing (a) joined two mice that each had the wild-type version of both genes. Describe the two mice in pairing (b), in pairing (c), and pairing (d). Explain how each pairing contributed to the experimental design.
2. Compare the results observed for pairing (a) and for pairing (b) in terms of phenotype. If the results had been identical for these two pairings, what would that outcome have implied about the experimental design?
3. Compare the results observed for pairing (c) to those observed for pairing (b). Based on these results, does the ob^+ gene product appear to promote or suppress appetite? Explain your answer.
4. Describe the results observed for pairing (d). Note how this result contrasts with the experiment in pairing (b). Suggest a hypothesis to explain this result. How could you test your hypothesis using the kinds of mice in this study?

Data from D. L. Coleman, Effects of parabiosis of obese mice with diabetes and normal mice. *Diabetologia* 9:294–298 (1973).

MB A version of this Scientific Skills Exercise, as well as a related Experimental Inquiry Tutorial, can be assigned in MasteringBiology.

Our understanding of leptin may lead to treatments for obesity, but questions remain. For one thing, most obese people have a high leptin level that somehow fails to elicit a response from the brain's satiety center. Clearly, there is still much to learn in this important area of human physiology.

The processes of obtaining, digesting, absorbing, and storing nutrients are part of the larger story of how animals fuel their activities. Provisioning the body also involves distributing nutrients (circulation), and using nutrients for metabolism requires exchanging respiratory gases with the environment. The closely related circulatory and respiratory systems are explored in our next chapter.

CONCEPT CHECK 33.5

1. Explain how people can become obese even if their intake of dietary fat is relatively low compared with carbohydrate intake.
2. The energy required to maintain each gram of body mass is much greater for a mouse than for an elephant. What can you conclude about metabolic rates for the mouse and the elephant?
3. **WHAT IF?** Consider a diabetes patient who has a family history of type 2 diabetes but is active and not obese. To identify genes that might be defective in the patient, which genes would you examine first?

For suggested answers, see Appendix A.

33 Chapter Review

SUMMARY OF KEY CONCEPTS

- Animals have diverse diets. **Herbivores** mainly eat plants; **carnivores** mainly eat other animals; and **omnivores** eat both. Animals must balance consumption, storage, and use of food.

CONCEPT 33.1

An animal's diet must supply chemical energy, organic molecules, and essential nutrients (pp. 666–668)

- Food provides animals with energy for ATP production, carbon skeletons for biosynthesis, and **essential nutrients**—nutrients that must be supplied in preassembled form. Essential nutrients include certain amino acids and fatty acids that animals cannot synthesize; **vitamins**, which are organic molecules; and **minerals**, which are inorganic substances.
- Animals can suffer from two types of malnutrition: an inadequate intake of essential nutrients and a deficiency in sources of chemical energy. Studies of genetic defects and of disease at the population level help researchers determine human dietary requirements.

? *How can an enzyme cofactor needed for a process essential to all animals be an essential nutrient (vitamin) for only some?*

CONCEPT 33.2

The main stages of food processing are ingestion, digestion, absorption, and elimination (pp. 668–671)

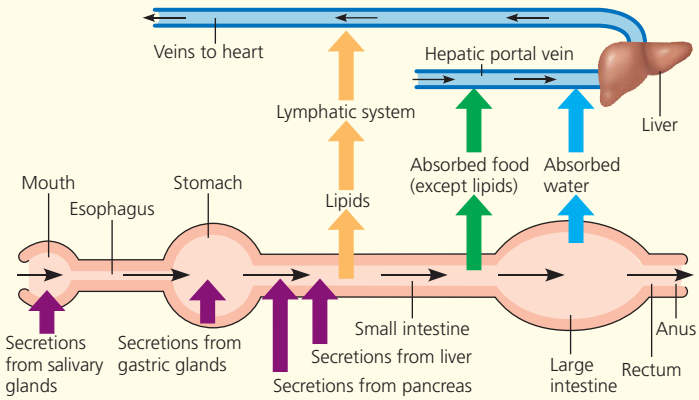
- Food processing in animals involves **ingestion** (eating), **digestion** (enzymatic breakdown of large molecules), **absorption** (uptake of nutrients by cells), and **elimination** (passage of undigested materials out of the body in feces).
- Animals differ in the ways they obtain and ingest food. Many animals are **bulk feeders**, eating large pieces of food.
- Compartmentalization is necessary to avoid self-digestion. In intracellular digestion, food particles are engulfed by endocytosis and digested within food vacuoles that have fused with lysosomes. In extracellular digestion, which is used by most animals, enzymatic hydrolysis occurs outside cells in a **gastrovascular cavity** or **alimentary canal**.

? *Propose an artificial diet that would eliminate the need for one of the first three steps in food processing.*

CONCEPT 33.3

Organs specialized for sequential stages of food processing form the mammalian digestive system (pp. 671–676)

- The mammalian digestive system is composed of a tubular alimentary canal and accessory glands that secrete digestive juices into the canal. Food is pushed along the alimentary canal by **peristalsis**. Digestion and absorption occur in specialized portions of the canal.



? *What structural feature of the small intestine makes it better suited for absorption of nutrients than the stomach?*

CONCEPT 33.4

Evolutionary adaptations of vertebrate digestive systems correlate with diet (pp. 676–678)

- Vertebrate digestive systems display many evolutionary adaptations associated with diet. For example, dentition, which is the assortment of teeth, generally correlates with diet. Many herbivores, including cows, also have fermentation chambers where microorganisms digest cellulose, a form of mutualism. In addition, herbivores usually have longer alimentary canals than carnivores, reflecting the longer time needed to digest vegetation.

? *How does human anatomy indicate that our ancestors were not strict vegetarians?*

CONCEPT 33.5

Feedback circuits regulate digestion, energy allocation, and appetite (pp. 678–682)

- Nutrition is regulated at multiple levels. Food in the alimentary canal triggers nervous and hormonal responses that control the secretion of digestive juices and that promote the movement of ingested material through the canal. The availability of glucose for energy production is regulated by the hormones insulin and glucagon, which control the synthesis and breakdown of glycogen.
- Animals obtain chemical energy from food. The total amount used in a unit of time defines an animal's metabolic rate. Animals allocate energy for basal (or standard) metabolism, activity, growth, and reproduction.
- Vertebrates store excess calories in glycogen (in liver and muscle cells) and in fat (in adipose cells). These energy stores can be tapped when an animal expends more calories than it consumes. If, however, an animal consumes more calories than it needs for normal metabolism, the resulting overnourishment can lead to the serious health problem of obesity.
- Several hormones, including leptin and insulin, regulate appetite by affecting the brain's satiety center.

? *Explain why your stomach might make growling noises when you skip a meal.*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. The mammalian trachea and esophagus both connect to the
   a. large intestine.
   b. stomach.
   c. pharynx.
   d. rectum.
   e. gastrovascular cavity.
2. Which of the following organs is *incorrectly* paired with its function?
   a. stomach—protein digestion
   b. oral cavity—starch digestion
   c. large intestine—bile production
   d. small intestine—nutrient absorption
   e. pancreas—enzyme production
3. Which of the following is *not* a major activity of the stomach?
   a. mechanical digestion
   b. HCl secretion
   c. mucus secretion
   d. nutrient absorption
   e. enzyme secretion
4. Fat digestion yields fatty acids and glycerol, whereas protein digestion yields amino acids; both digestive processes
   a. are catalyzed by the same enzyme.
   b. occur inside cells in most animals.
   c. add a water molecule to break bonds.
   d. require a low pH resulting from HCl production.
   e. consume ATP.

Level 2: Application/Analysis

5. After surgical removal of an infected gallbladder, a person must be especially careful to restrict dietary intake of
   a. starch.
   b. protein.
   c. sugar.
   d. fat.
   e. water.
6. If you were to jog 1 km a few hours after lunch, which stored fuel would you probably tap?
   a. muscle proteins
   b. muscle and liver glycogen
   c. fat stored in the liver
   d. fat stored in adipose tissue
   e. blood proteins

Level 3: Synthesis/Evaluation

7. **DRAW IT** Make a flowchart of the events that occur after partially digested food leaves the stomach. Use the following terms: bicarbonate secretion, circulation, decrease in acidity, secretin secretion, increase in acidity, signal detection. Next to each term, indicate the compartment(s) involved. You may use terms more than once.
8. **SCIENTIFIC INQUIRY**
   In human populations of northern European origin, the disorder called hemochromatosis causes excess iron uptake from food and affects one in 200 adults. Among adults, men are ten times as likely as women to suffer from iron overload. Taking into account the existence of a menstrual cycle in humans, devise a hypothesis for this difference.
9. **FOCUS ON EVOLUTION**
   The human esophagus and trachea share a passage leading from the mouth and nasal passages, which can cause problems. How does the evolutionary concept of descent with modification explain this "imperfect" anatomy? (See Concept 21.4.)
10. **FOCUS ON ORGANIZATION**
    Hair is largely made up of the protein keratin. In a short essay (100–150 words), explain why a shampoo containing protein is not effective in replacing the protein in damaged hair.

For selected answers, see Appendix A.

34 Circulation and Gas Exchange

KEY CONCEPTS

OVERVIEW

Trading Places

The animal in **Figure 34.1** may look like a creature from a science fiction film, but it's actually an axolotl, an amphibian native to shallow ponds in central Mexico. Unlike other amphibians, an axolotl doesn't develop into an air-breathing adult. Instead, it remains in a larval form indefinitely, using feathery gills behind its head to extract oxygen (O_2) from water.

▼ **Figure 34.1** How does a feathery fringe help this animal survive?

Although external gills are uncommon among adult animals, they help the axolotl carry out a process common to all organisms—the exchange of substances between body cells and the environment. The resources that an animal cell requires, such as nutrients and O_2, enter the cytoplasm by crossing the plasma membrane. Metabolic by-products, such as carbon dioxide (CO_2), exit the cell by crossing the same membrane.

In unicellular organisms, exchange occurs directly with the external environment. For most multicellular organisms, however, direct transfer of materials between every cell and the environment is not possible. Instead, these organisms rely on specialized systems that carry out exchange with the environment and that transport materials between sites of exchange and the rest of the body.

The filamentous structure of the axolotl's gills reflects the intimate association between exchange and transport. Oxygen passes from the water into tiny blood vessels near the surface of each gill filament, turning the pigment in the blood cells a bright red. Pumping of the axolotl's heart propels the oxygen-rich blood from the gill filaments to all other tissues of the body. There, more short-range exchange occurs, involving nutrients and O_2 as well as CO_2 and other wastes.

Because internal transport and gas exchange are functionally related in most animals, not just axolotls, circulatory and respiratory systems are discussed together in this chapter. By considering examples of these systems from a range of species, we'll explore the common elements as well as the remarkable variation in form and organization. We'll also highlight the roles of circulatory and respiratory systems in maintaining homeostasis.

CONCEPT 34.1

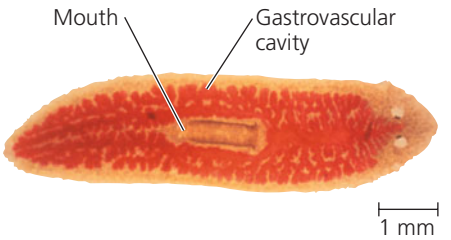
Circulatory systems link exchange surfaces with cells throughout the body

The molecular trade that an animal carries out with its environment—gaining O_2 and nutrients while shedding CO_2 and other waste products—must ultimately involve every cell in the body. Small molecules, including O_2 and CO_2, can move between cells and their immediate surroundings by **diffusion** (see Chapter 5). When there is a difference in concentration, diffusion can result in net movement. But such movement is very slow for distances of more than a few millimeters. That's because the time it takes for a substance to diffuse from one place to another is proportional to the *square* of the distance. For example, a quantity of glucose that takes 1 second to diffuse 100 µm will take 100 seconds to diffuse 1 mm and almost 3 hours to diffuse 1 cm! This relationship between diffusion time and distance places a substantial constraint on the body plan of any animal.

Given that net movement by diffusion is rapid only over very small distances, how does each cell of an animal participate in exchange? Natural selection has resulted in two basic adaptations that allow for effective exchange for all of an animal's cells. One adaptation is a body size and shape that places many or all cells in direct contact with the environment. Each cell can thus exchange materials directly with the surrounding medium. This type of body plan is found only in certain invertebrates, including cnidarians and flatworms. The other adaptation, found in all other animals, is a circulatory system. Such systems move fluid between each cell's immediate surroundings and the body tissues where exchange with the environment occurs.

Gastrovascular Cavities

Let's begin by looking at some animals whose body shapes put many of their cells into contact with their environment; these animals lack a distinct circulatory system. In hydras and other cnidarians, a central **gastrovascular cavity** functions in the distribution of substances throughout the body and in digestion (see Figure 33.6). Planarians and most other flatworms also survive without a circulatory system. Their combination of a gastrovascular cavity and a flat body is well suited for exchange with the environment **(Figure 34.2)**.



▶ Figure 34.2 Internal transport in the planarian *Dugesia* (LM). The mouth, on the ventral (bottom) side, leads to a gastrovascular cavity (here stained red) that branches throughout the body.

Open and Closed Circulatory Systems

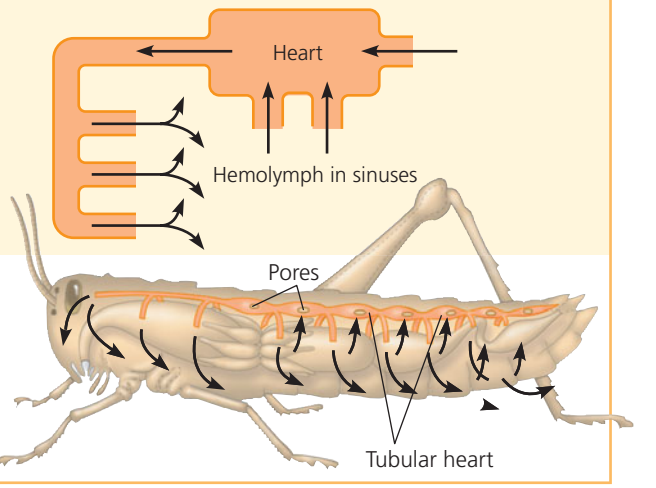
A circulatory system has three basic components: a circulatory fluid, a set of interconnecting vessels, and a muscular pump, the **heart**. The heart powers circulation by using metabolic energy to elevate the hydrostatic pressure of the circulatory fluid, which then flows through the vessels and back to the heart.

Circulatory systems are either open or closed. In an **open circulatory system**, the circulatory fluid, called **hemolymph**, is also the *interstitial fluid* that bathes body cells; arthropods and some molluscs, such as clams, have open systems. Heart contraction pumps the hemolymph through circulatory vessels into sinuses, spaces surrounding the organs **(Figure 34.3a)**. There, exchange with body cells occurs. Heart relaxation draws hemolymph back in through pores, which have valves that close when the heart contracts. Body movements periodically squeeze the sinuses, helping circulate the hemolymph.

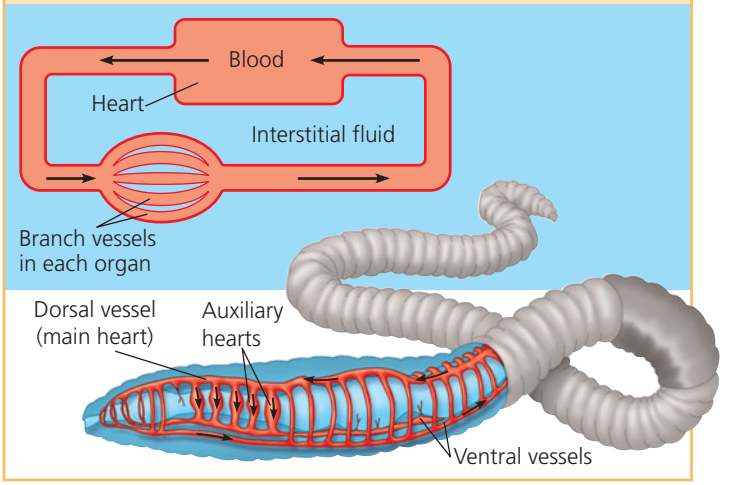
In a **closed circulatory system**, a circulatory fluid called **blood** is confined to vessels and is distinct from the interstitial fluid **(Figure 34.3b)**. This type of circulatory system is

▼ Figure 34.3 Open and closed circulatory systems.

(a) An open circulatory system



(b) A closed circulatory system



found in annelids (including earthworms), most cephalopod molluscs (including squids and octopuses), and all vertebrates. In closed circulatory systems, one or more hearts pump blood into large vessels that branch into smaller ones that infiltrate the organs. Chemical exchange occurs between the blood and the interstitial fluid, as well as between the interstitial fluid and body cells.

The fact that both open and closed circulatory systems are widespread suggests that each system offers evolutionary advantages. The lower hydrostatic pressures typically associated with open circulatory systems make them less costly than closed systems in terms of energy expenditure. In some invertebrates, open circulatory systems serve additional functions. For example, spiders use the hydrostatic pressure generated by their open circulatory system to extend their legs.

The benefits of closed circulatory systems include relatively high blood pressure, which enables the effective delivery of O_2 and nutrients to the cells of larger and more active animals. Among the molluscs, for instance, closed circulatory systems are found in the largest and most active species, the squids and octopuses. Closed systems are also particularly well suited to regulating the distribution of blood to different organs, as you'll learn later in this chapter. In examining closed circulatory systems in more detail, we'll focus on the vertebrates.

Organization of Vertebrate Circulatory Systems

The closed circulatory system of humans and other vertebrates is often called the **cardiovascular system**. Blood circulates to and from the heart through an amazingly extensive network of vessels: The total length of blood vessels in an average human adult is twice Earth's circumference at the equator!

Arteries, veins, and capillaries are the three main types of blood vessels. Within each type, blood flows in only one direction. **Arteries** carry blood from the heart to organs throughout the body. Within organs, arteries branch into *arterioles*. These small vessels convey blood to **capillaries**, microscopic vessels with very thin, porous walls. Networks of these vessels, called **capillary beds**, infiltrate tissues, passing within a few cell diameters of every cell in the body. Across the thin walls of capillaries, chemicals, including dissolved gases, are exchanged by net diffusion between the blood and the interstitial fluid around the tissue cells. At their "downstream" end, capillaries converge into *venules*, and venules converge into **veins**, the vessels that carry blood back to the heart.

Note that arteries and veins are distinguished by the *direction* in which they carry blood, not by the O_2 content or other characteristics of the blood they contain. Arteries carry blood *away* from the heart toward capillaries, and veins carry blood *toward* the heart from capillaries.

The hearts of all vertebrates contain two or more muscular chambers. The chambers that receive blood entering the heart are called **atria** (singular, *atrium*). The chambers responsible for pumping blood out of the heart are called **ventricles**. The number of chambers and the extent to which they are separated from one another differ substantially among vertebrate groups, as we'll discuss next. These differences reflect the close fit of form to function that arises from natural selection.

Single Circulation

In bony fishes, rays, and sharks, the heart consists of two chambers: an atrium and a ventricle **(Figure 34.4a)**. The blood passes through the heart once in each complete circuit, an arrangement called **single circulation**. Blood entering the heart collects in the atrium before transfer to the ventricle. Contraction of the ventricle pumps blood to the gills, where there is a net diffusion of O_2 into the blood and of CO_2 out of the blood. As blood leaves the gills, the capillaries converge into a vessel that carries oxygen-rich blood to capillary beds throughout the body. Blood then returns to the heart.

In single circulation, blood that leaves the heart passes through two sets of capillary beds before returning to the heart. When blood flows through a capillary bed, blood pressure drops substantially, for reasons we will explain shortly. The drop in blood pressure in the gills limits the velocity of blood flow in the rest of the animal's body. As the animal swims, however, the contraction and relaxation of its muscles help accelerate the relatively sluggish pace of circulation.

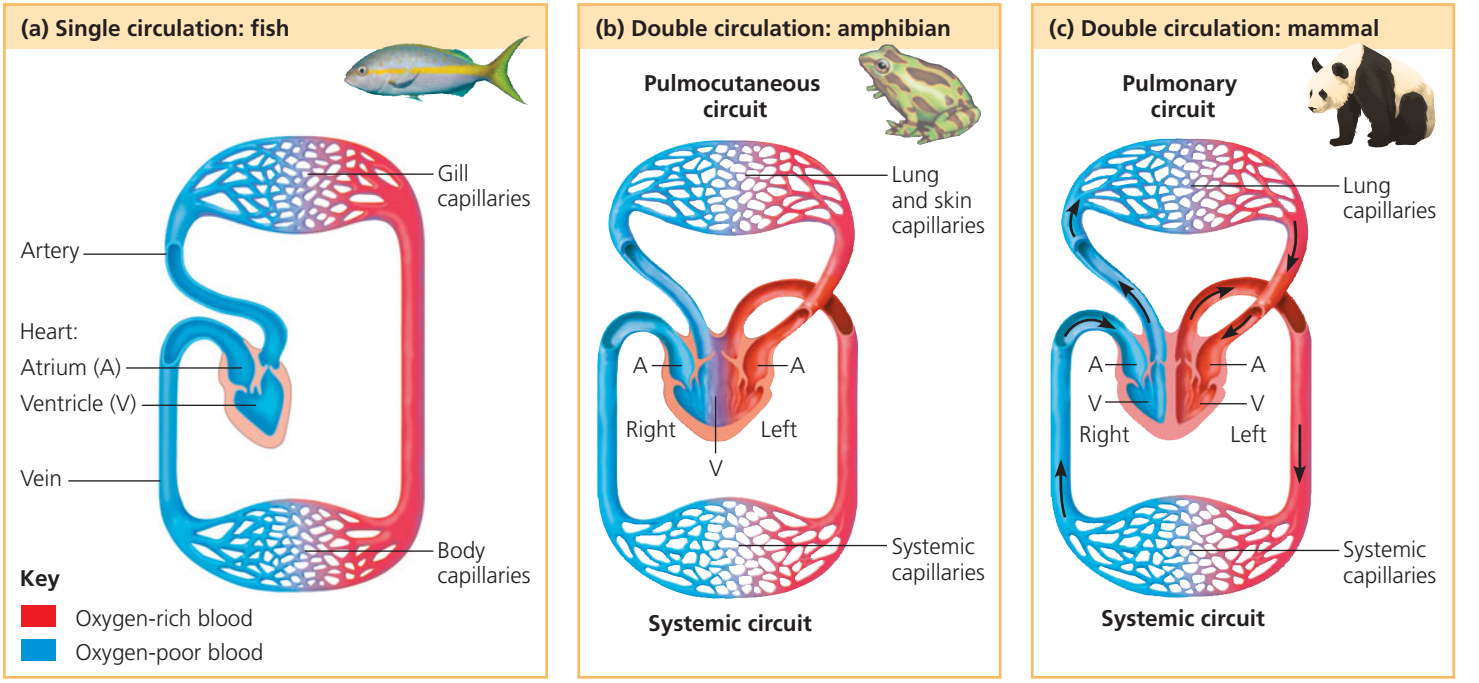
Double Circulation

The circulatory systems of amphibians, reptiles, and mammals have two circuits, an arrangement called **double circulation** **(Figure 34.4b** and **c)**. In animals with double circulation, the pumps for the two circuits are combined into a single organ, the heart. Having both pumps within a single heart simplifies coordination of the pumping cycles. One pump, the right side of the heart, delivers oxygen-poor blood to the capillary beds of the gas exchange tissues, where there is a net movement of O_2 into the blood and of CO_2 out of the blood. This **gas exchange circuit** is called a *pulmonary circuit* if the capillary beds involved are all in the lungs, as in reptiles and mammals. It is called a *pulmocutaneous circuit* if it includes capillaries in both the lungs and the skin, as in many amphibians.

After the oxygen-enriched blood leaves the gas exchange tissues, it enters the other pump, the left side of the heart. Contraction of the heart propels this blood to capillary beds in organs and tissues throughout the body. Following the exchange of O_2 and CO_2, as well as nutrients and waste products, the now oxygen-poor blood returns to the heart, completing the **systemic circuit**.

Double circulation provides a vigorous flow of blood to the brain, muscles, and other organs because the heart

▼ Figure 34.4 Generalized circulatory schemes of vertebrates. (a) Fishes provide an example of single circulation, in which blood passes through the heart once per complete circuit. In contrast, **(b)** amphibians and **(c)** mammals offer examples of double circulation, with separate gas exchange and systemic circuits. Comparing (b) and (c) indicates some variations of heart structure and gas exchange tissue types that have evolved in different groups of vertebrates with double circulation. (Note that circulatory systems are shown as if the body were facing you: The right side of the heart is shown on the left, and vice versa.)



repressurizes the blood destined for these tissues after it passes through the capillary beds of the lungs or skin. Indeed, blood pressure is often much higher in the systemic circuit than in the gas exchange circuit. This contrasts sharply with single circulation, in which blood flows under reduced pressure directly from the gas exchange organs to other organs.

Evolutionary Variation in Double Circulation

EVOLUTION Some vertebrates with double circulation are intermittent breathers. For example, amphibians and many reptiles fill their lungs with air periodically, passing long periods of time without gas exchange or relying on another gas exchange tissue, typically the skin. These animals have adaptations that enable the circulatory system to temporarily bypass the lungs in part or in whole:

- Frogs and other amphibians have a heart with three chambers—two atria and one ventricle (see Figure 34.4b). A ridge within the ventricle diverts most (about 90%) of the oxygen-rich blood from the left atrium into the systemic circuit and most of the oxygen-poor blood from the right atrium into the gas exchange (pulmocutaneous) circuit. When a frog is underwater, the incomplete division of the ventricle allows the frog to adjust its circulation, shutting off most blood flow to its temporarily ineffective lungs. Blood flow continues to the skin, which acts as the sole site of gas exchange while the frog is submerged.
- In the three-chambered heart of turtles, snakes, and lizards, an incomplete septum partially divides the single ventricle into separate right and left chambers. Two major arteries, called aortas, lead to the systemic circulation. As with amphibians, the circulatory system enables control of the relative amount of blood flowing to the lungs and the body.
- In alligators, caimans, and other crocodilians, the ventricles are divided by a complete septum, but the pulmonary and systemic circuits connect where the arteries exit the heart. This connection allows arterial valves to shunt blood flow away from the lungs temporarily, such as when the animal is underwater.

Double circulation in birds and mammals is quite different. As shown for a panda in Figure 34.4c, the heart has two atria and two completely divided ventricles. The left side of the heart receives and pumps only oxygen-rich blood, while the right side receives and pumps only oxygen-poor blood. Unlike amphibians and many reptiles, birds and mammals cannot vary blood flow to the lungs without altering blood flow throughout the body.

How has natural selection shaped the double circulation of birds and mammals? As endotherms, birds and mammals use

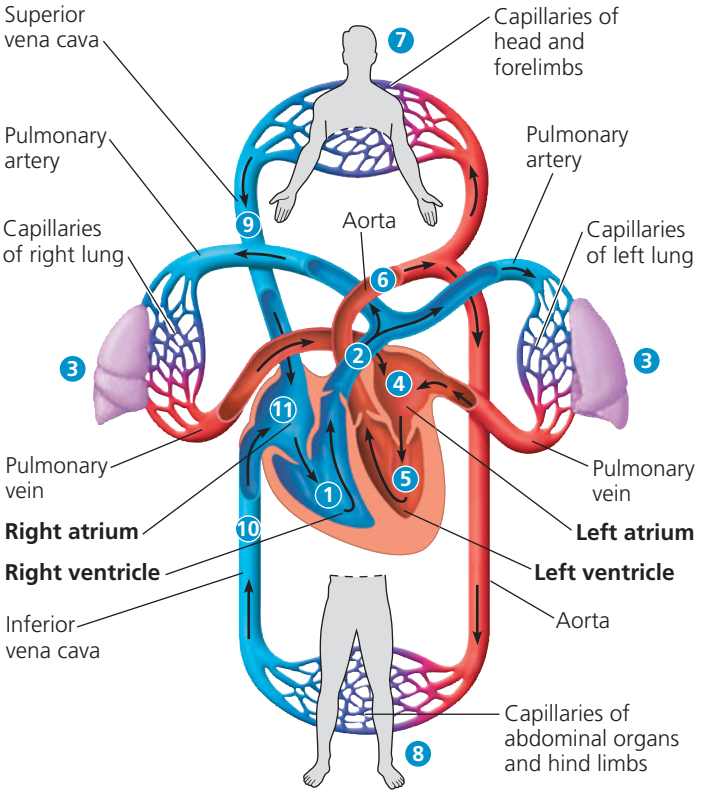
about ten times as much energy as equal-sized ectotherms. Their circulatory systems therefore need to deliver about ten times as much fuel and O_2 to their tissues (and remove ten times as much CO_2 and other wastes). This large traffic of substances is made possible by the separate and independently powered systemic and pulmonary circuits and by large hearts that pump the necessary volume of blood. A powerful four-chambered heart arose independently in the different ancestors of birds and mammals and thus reflects convergent evolution (see Chapter 27).

In the next section, we'll restrict our focus to circulation in mammals and to the anatomy and physiology of the key circulatory organ—the heart.

CONCEPT CHECK 34.1

1. How is the flow of hemolymph through an open circulatory system similar to the flow of water through an outdoor fountain?
2. Three-chambered hearts with incomplete septa were once viewed as being less adapted to circulatory function than mammalian hearts. What advantage of such hearts did this viewpoint overlook?
3. **WHAT IF?** The heart of a normally developing human fetus has a hole between the left and right atria. In some cases, this hole does not close completely before birth. If the hole weren't surgically corrected, how would it affect the O_2 content of the blood entering the systemic circuit?

For suggested answers, see Appendix A.



▲ Figure 34.5 The mammalian cardiovascular system: an overview. Note that the dual circuits operate simultaneously, not in the serial fashion that the numbering in the diagram suggests. The two ventricles pump almost in unison; while some blood is traveling in the pulmonary circuit, the rest of the blood is flowing in the systemic circuit.

CONCEPT 34.2

Coordinated cycles of heart contraction drive double circulation in mammals

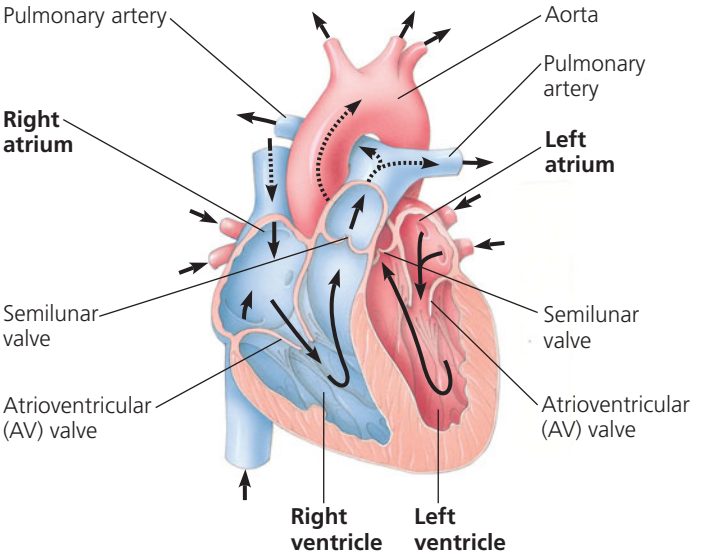
Timely delivery of O_2 to body organs is critical: Some brain cells, for example, die if their O_2 supply is interrupted for even a few minutes. How does the mammalian cardiovascular system meet the body's continuous (although variable) demand for O_2? To answer this question, we need to consider how the parts of the system are arranged and how each part functions.

Mammalian Circulation

Let's first examine the overall organization of the mammalian cardiovascular system, beginning with the pulmonary circuit. (The circled numbers refer to corresponding locations in **Figure 34.5**.) Contraction of 1 the right ventricle pumps blood to the lungs via 2 the pulmonary arteries. As the blood flows through 3 capillary beds in the left and right lungs, it loads O_2 and unloads CO_2. Oxygen-rich blood returns from the lungs via the pulmonary veins to 4 the left atrium of the heart. Next, the oxygen-rich blood flows into 5 the heart's left ventricle, which pumps the oxygen-rich blood out to body tissues through the systemic circuit. Blood leaves the left ventricle via 6 the aorta, which conveys blood to arteries leading throughout the body. The first branches leading from the aorta are the coronary arteries (not shown), which supply blood to the heart muscle itself. Then branches lead to 7 capillary beds in the head and arms (forelimbs). The aorta then descends into the abdomen, supplying oxygen-rich blood to arteries leading to 8 capillary beds in the abdominal organs and legs (hind limbs). Within the capillaries, there is a net diffusion of O_2 from the blood to the tissues and of CO_2 (produced by cellular respiration) into the blood. Capillaries rejoin, forming venules, which convey blood to veins. Oxygen-poor blood from the head, neck, and forelimbs is channeled into a large vein, 9 the superior vena cava. Another large vein, 10 the inferior vena cava, drains blood from the trunk and hind limbs. The two venae cavae empty their blood into 11 the right atrium, from which the oxygen-poor blood flows into the right ventricle.

The Mammalian Heart: *A Closer Look*

Located behind the sternum (breastbone), the human heart is about the size of a clenched fist and consists mostly of cardiac muscle. The two atria have relatively thin walls and serve as collection chambers for blood returning to the heart from the lungs or other body tissues **(Figure 34.6)**. Much of the blood that enters the atria flows into the ventricles while all



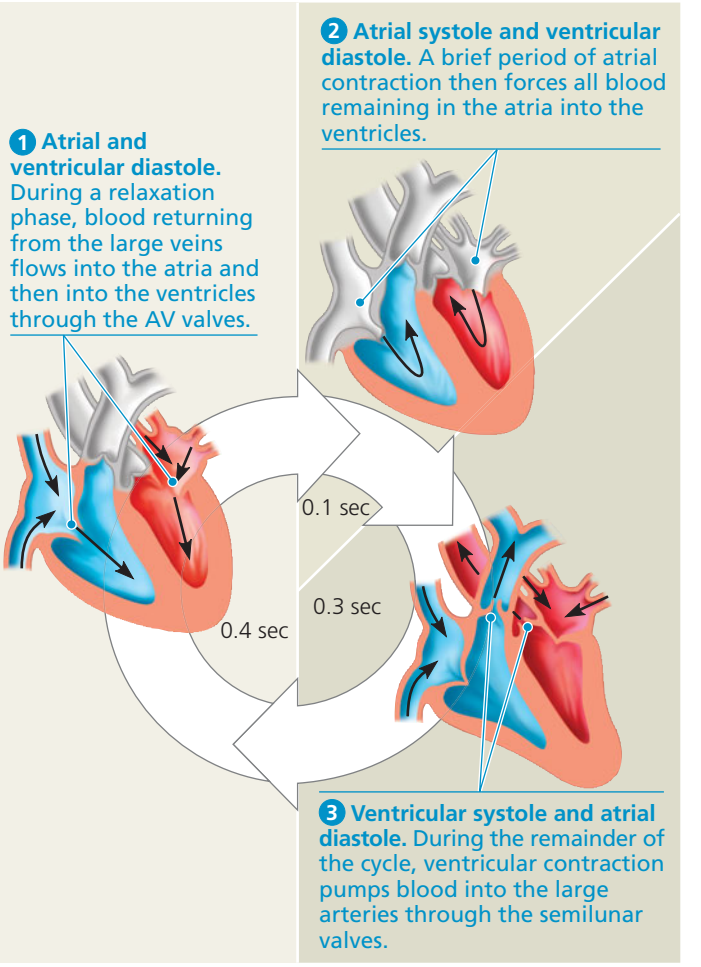
▲ Figure 34.6 The mammalian heart: a closer look. Notice the locations of the valves, which prevent backflow of blood within the heart. Also notice how the atria and left and right ventricles differ in the thickness of their muscular walls.

heart chambers are relaxed. The remainder is transferred by contraction of the atria before the ventricles begin to contract. Compared to the atria, the ventricles have thicker walls and contract much more forcefully—especially the left ventricle, which pumps blood to all body organs through the systemic circuit. Although the left ventricle contracts with greater force than the right ventricle, it pumps the same volume of blood as the right ventricle during each contraction.

The heart contracts and relaxes in a rhythmic cycle. When it contracts, it pumps blood; when it relaxes, its chambers fill with blood. One complete sequence of pumping and filling is referred to as the **cardiac cycle (Figure 34.7)**. The contraction phase of the cycle is called **systole**, and the relaxation phase is called **diastole**.

The volume of blood each ventricle pumps per minute is the cardiac output. Two factors determine cardiac output: the rate of contraction, or heart rate (number of beats per minute), and the *stroke volume*, the amount of blood pumped by a ventricle in a single contraction. The average stroke volume in humans is about 70 mL. Multiplying this stroke volume by a resting heart rate of 72 beats per minute yields a cardiac output of 5 L/min—about equal to the total volume of blood in the human body. During heavy exercise, cardiac output increases as much as fivefold.

Four valves in the heart prevent backflow and keep blood moving in the correct direction (see Figures 34.6 and 34.7). Made of flaps of connective tissue, the valves open when pushed from one side and close when pushed from the other. An **atrioventricular (AV) valve** lies between each atrium and ventricle. The AV valves are anchored by strong fibers that prevent them from turning inside out. Pressure generated by the powerful contraction of the ventricles closes the AV valves, keeping blood from flowing back into the atria. **Semilunar valves** are located at

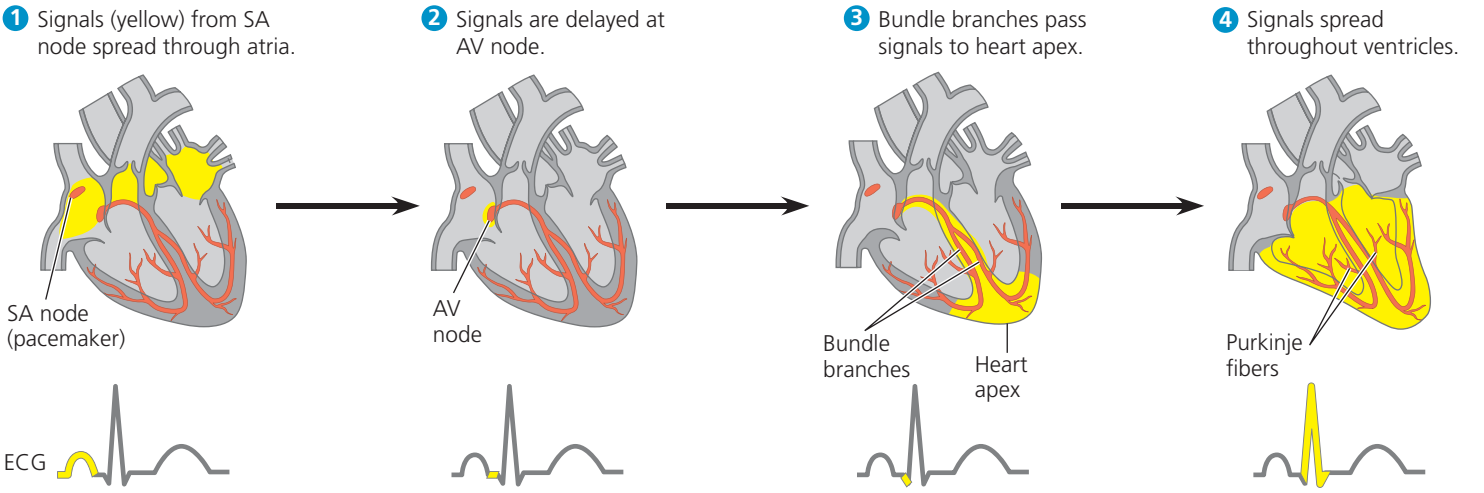


▲ Figure 34.7 The cardiac cycle. Note that during all but 0.1 second of the cardiac cycle, the atria are relaxed and are filling with blood returning via the veins.

the two exits of the heart: where the aorta leaves the left ventricle and where the pulmonary artery leaves the right ventricle. These valves are pushed open by the pressure generated during contraction of the ventricles. When the ventricles relax, blood pressure built up in the aorta and pulmonary artery closes the semilunar valves and prevents significant backflow.

You can follow the closing of the two sets of heart valves either with a stethoscope or by pressing your ear tightly against the chest of a friend (or a friendly dog). The sound pattern is "lub-dup, lub-dup, lub-dup." The first heart sound ("lub") is created by the recoil of blood against the closed AV valves. The second sound ("dup") is due to the vibrations caused by closing of the semilunar valves.

If blood squirts backward through a defective valve, it may produce an abnormal sound called a heart murmur. Some people are born with heart murmurs; in others, the valves may be damaged by infection (from rheumatic fever, for instance). When a valve defect is severe enough to endanger health, surgeons may implant a mechanical replacement valve. However, not all heart murmurs are caused by a defect, and most valve defects do not reduce the efficiency of blood flow enough to warrant surgery.



▲ Figure 34.8 The control of heart rhythm. Electrical signals follow a set path through the heart in establishing the heart rhythm. The diagrams at the top trace the movement of electrical signals (yellow) during the cardiac cycle; specialized cells involved in electrical control of the rhythm are indicated in orange. Under each step, the corresponding portion of an electrocardiogram (ECG) is highlighted in yellow. In step 4, the portion of the ECG to the right of the "spike" represents electrical activity that reprimes the ventricles for the next round of contraction.

WHAT IF? *If your doctor gave you a copy of your ECG recording, how could you determine what your heart rate had been during the test?*

Maintaining the Heart's Rhythmic Beat

In vertebrates, the heartbeat originates in the heart itself. Some cardiac muscle cells are autorhythmic, meaning they contract and relax repeatedly without any signal from the nervous system. A group of such cells forms the **sinoatrial (SA) node**, or *pacemaker*, which sets the rate and timing at which all other cardiac muscle cells contract. (In contrast, some arthropods have pacemakers located in the nervous system, outside the heart.)

The SA node produces electrical impulses that spread rapidly within heart tissue. Because body fluids can conduct electricity, currents generated by those impulses can be detected at the surface of the body in an **electrocardiogram** (**ECG** or, often, **EKG**, from the German spelling). The resulting graph of current against time has a characteristic shape that represents the stages in the cardiac cycle **(Figure 34.8)**.

Impulses from the SA node first spread rapidly through the walls of the atria, causing both atria to contract in unison. During atrial contraction, the impulses originating at the SA node reach other autorhythmic cells located in the wall between the left and right atria. These cells form a relay point called the **atrioventricular (AV) node**. Here the impulses are delayed for about 0.1 second before spreading to the heart apex. This delay allows the atria to empty completely before the ventricles contract. Then the signals from the AV node are conducted to the heart apex and throughout the ventricular walls.

Physiological cues alter heart tempo by regulating the pacemaker function of the SA node. For example, when you stand up and start walking, the nervous system speeds up your pacemaker. The resulting increase in heart rate provides the additional O_2 needed by the muscles that are powering your activity. If you then sit down and relax, the nervous system slows down your pacemaker, decreasing your heart rate and thus conserving energy. Hormones and temperature also influence the pacemaker. For instance, epinephrine, the "fight-or-flight" hormone secreted by the adrenal glands, causes the heart rate to increase, as does an increase in body temperature.

Having examined the operation of the circulatory pump, we turn in the next section to the forces and structures that influence blood flow in the vessels of each circuit.

CONCEPT CHECK 34.2

1. Explain why blood in the pulmonary veins has a higher O_2 concentration than in the venae cavae, which are also veins.
2. Why is it important that the AV node delay the electrical impulse moving from the SA node and the atria to the ventricles?
3. **WHAT IF?** After you exercise regularly for several months, your resting heart rate decreases, but your cardiac output at rest is unchanged. What change in the function of your heart at rest could explain these findings?

For suggested answers, see Appendix A.

CONCEPT 34.3

Patterns of blood pressure and flow reflect the structure and arrangement of blood vessels

The vertebrate circulatory system enables blood to deliver oxygen and nutrients and remove wastes throughout the body. In doing so, the circulatory system relies on a branching network

of vessels much like the plumbing system that delivers fresh water to a city and removes its wastes. In fact, the same physical principles that govern the operation of plumbing systems apply to the functioning of blood vessels.

Blood Vessel Structure and Function

Blood vessels contain a central lumen (cavity) lined with an **endothelium**, a single layer of flattened epithelial cells. The smooth surface of the endothelium minimizes resistance to the flow of blood. Surrounding the endothelium are layers of tissue that differ in capillaries, arteries, and veins, reflecting the specialized functions of these vessels.

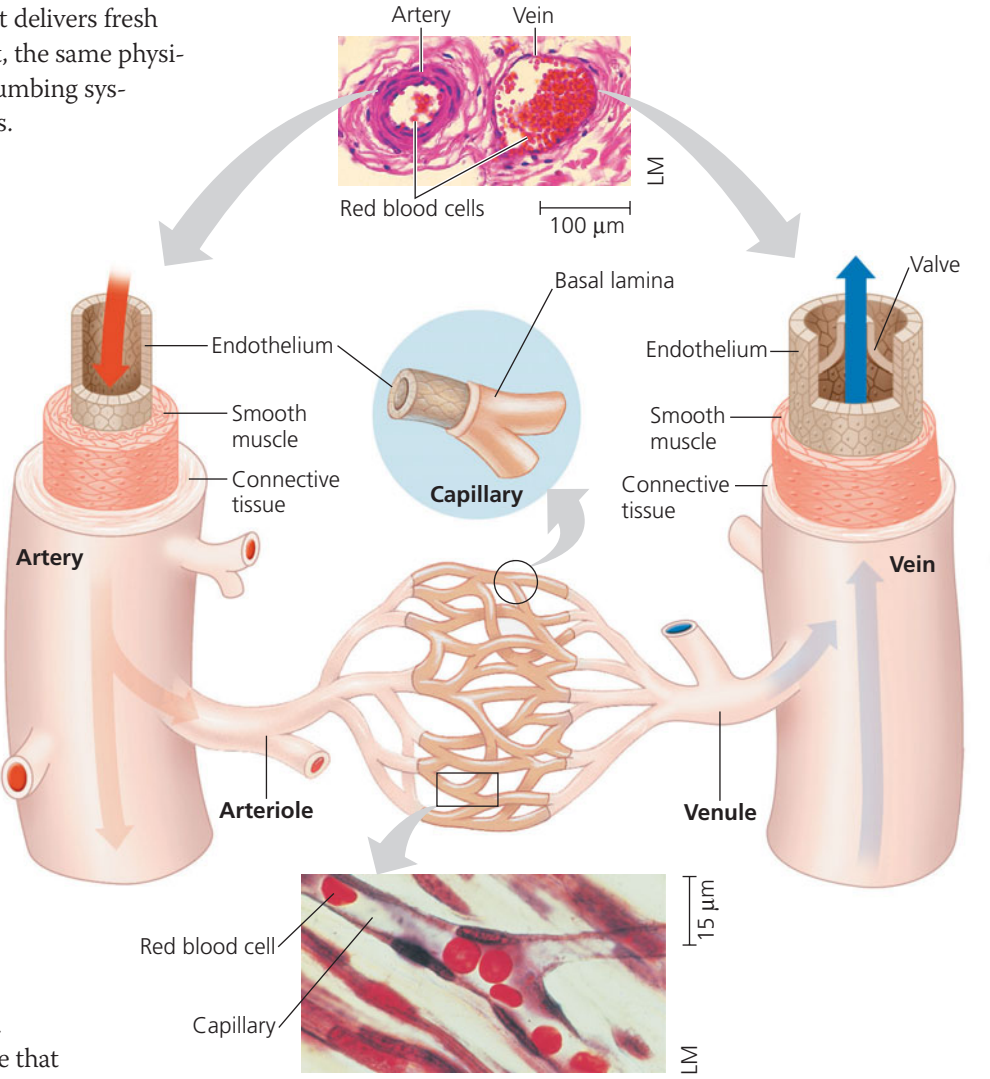
Capillaries are the smallest blood vessels, having a diameter only slightly greater than that of a red blood cell **(Figure 34.9)**. Capillaries also have very thin walls, which consist of just the endothelium and its basal lamina. The exchange of substances between the blood and interstitial fluid occurs in capillaries because only there are blood vessel walls thin enough to permit this transfer.

The walls of other blood vessels have a more complex organization than those of capillaries. Both arteries and veins have two layers of tissue surrounding the endothelium. The outer layer is formed by connective tissue that contains elastic fibers, which allow the vessel to stretch and recoil, and collagen, which provides strength. The layer next to the endothelium contains smooth muscle and more elastic fibers.

While similar in organization, the walls of arteries and veins differ, reflecting adaptations to distinct functions. The walls of arteries are thick and strong, accommodating blood pumped at high pressure by the heart. Arterial walls also have an elastic recoil that helps maintain blood pressure and flow to capillaries when the heart relaxes between contractions. Nervous system signals and hormones in the blood act on the smooth muscle in arteries and arterioles, dilating or constricting these vessels and thus controlling blood flow to different body parts.

Because veins convey blood back to the heart at a lower pressure, they do not require thick walls. For a given blood vessel diameter, a vein has a wall only about a third as thick as that of an artery. Unlike arteries, veins contain valves, which maintain a unidirectional flow of blood despite the low blood pressure in these vessels.

We consider next how blood vessel diameter, vessel number, and pressure influence the velocity at which blood flows in different locations within the body.

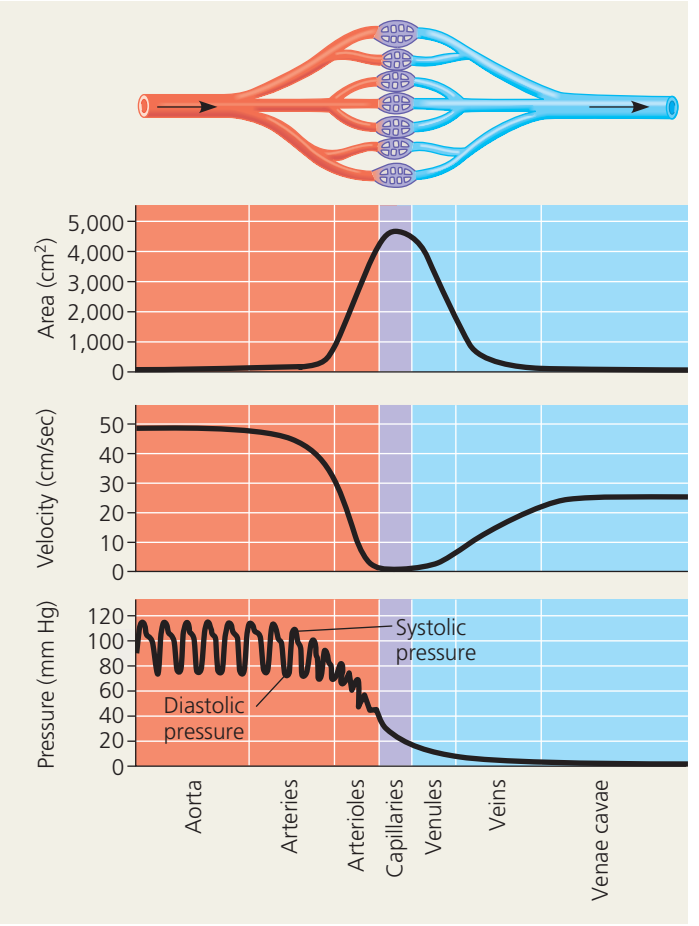


▲ **Figure 34.9 The structure of blood vessels.**

Blood Flow Velocity

To understand how blood vessel diameter influences blood flow, consider how water flows through a thick hose connected to a faucet. When the faucet is turned on, water flows at the same velocity at each point along the hose. However, if a narrow nozzle is attached to the end of the hose, the water will exit the nozzle at a much greater velocity. Because water doesn't compress under pressure, the volume of water moving through the nozzle in a given time must be the same as the volume moving through the rest of the hose. The cross-sectional area of the nozzle is smaller than that of the hose, so the water speeds up in the nozzle.

An analogous situation exists in the circulatory system, but blood *slows* as it moves from arteries to arterioles to the much narrower capillaries. Why? The reason is that the number of capillaries is enormous, roughly 7 billion in a human body. Each artery conveys blood to so many capillaries that the *total* cross-sectional area is much greater in



▲ Figure 34.10 The interrelationship of cross-sectional area of blood vessels, blood flow velocity, and blood pressure. Because total cross-sectional area increases in the arterioles and in the capillaries, blood flow velocity decreases markedly. Blood pressure, the main force driving blood from the heart to the capillaries, is highest in the aorta and other arteries.

capillary beds than in the arteries or any other part of the circulatory system **(Figure 34.10)**. The result is a dramatic decrease in velocity from the arteries to the capillaries: Blood travels 500 times more slowly in the capillaries (about 0.1 cm/sec) than in the aorta (about 48 cm/sec). After passing through the capillaries, the blood speeds up as it enters the venules and veins, which have smaller *total* cross-sectional areas than the capillaries.

Blood Pressure

Blood, like all fluids, flows from areas of higher pressure to areas of lower pressure. Contraction of a heart ventricle generates blood pressure, which exerts force in all directions. The force directed lengthwise in an artery causes the blood to flow away from the heart, the site of highest pressure. The force exerted sideways against the wall of an artery stretches the wall. Following ventricular contraction, the recoil of the elastic arterial walls plays a critical role in maintaining blood pressure, and hence blood flow, throughout the cardiac cycle. Once the blood enters the millions of tiny arterioles and capillaries, the narrow diameter of these vessels generates substantial resistance to flow. By the time the blood enters the veins, resistance dissipates much of the pressure generated by the pumping heart.

Changes in Blood Pressure During the Cardiac Cycle

Arterial blood pressure is highest during systole, the contraction phase of the cardiac cycle. The pressure at the time the ventricles contract is called *systolic pressure* (see Figure 34.10). Each spike in blood pressure caused by a contraction of a ventricle stretches the arteries. By placing your fingers on the inside of your wrist, you can feel a **pulse**—the rhythmic bulging of the artery walls with each heartbeat. The pressure surge is partly due to the narrow openings of arterioles impeding the exit of blood from the arteries. When the heart contracts, blood enters the arteries faster than it can leave, and the vessels stretch from the rise in pressure.

During diastole, the relaxation phase, the elastic walls of the arteries snap back. As a consequence, there is a lower but still substantial arterial blood pressure when the ventricles are relaxed (*diastolic pressure*). Before enough blood has flowed into the arterioles to completely relieve pressure in the arteries, the heart contracts again. Because the arteries remain pressurized throughout the cardiac cycle (see Figure 34.10), blood continuously flows into arterioles and capillaries.

To measure blood pressure, doctors or nurses often use an inflatable cuff attached to a pressure gauge. The cuff is wrapped around the upper arm and inflated until the pressure closes the artery; the cuff is then deflated gradually. When the cuff pressure drops just below that in the artery, blood begins to pulse past the cuff, making sounds that can be heard with a stethoscope. The pressure measured at this point equals the systolic pressure. As deflation continues, the cuff pressure at some point no longer constricts blood movement. The reading on the gauge when the blood begins to flow freely and silently equals the diastolic pressure. For a healthy 20-year-old human at rest, arterial blood pressure in the systemic circuit is typically about 120 millimeters of mercury (mm Hg) at systole and 70 mm Hg at diastole, expressed as 120/70. (Arterial blood pressure in the pulmonary circuit is six to ten times lower.)

Maintenance of Blood Pressure

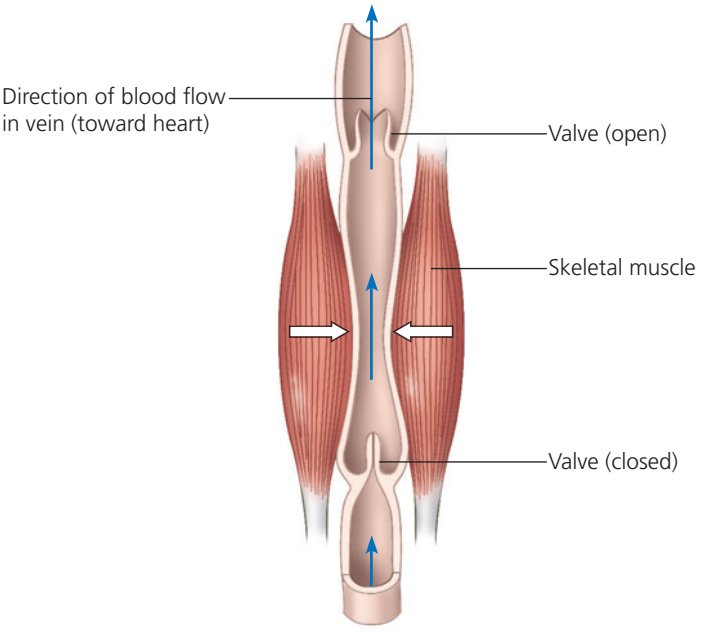
Homeostatic mechanisms regulate arterial blood pressure by altering the diameter of arterioles. As the smooth muscles in arteriole walls contract, the arterioles narrow, a process called **vasoconstriction**. Narrowing of the arterioles increases blood pressure upstream in the arteries. When the smooth muscles relax, the arterioles undergo **vasodilation**, an increase in diameter that causes blood pressure in the arteries to fall.

Researchers have identified nitric oxide (NO), a gas, as a major inducer of vasodilation and endothelin, a peptide, as the most potent inducer of vasoconstriction. Cues from the nervous and endocrine systems regulate production of NO and endothelin in blood vessels, where their activities regulate blood pressure.

Gravity also has a significant effect on blood pressure. When you are standing, for example, your head is roughly 0.35 m higher than your chest, and the arterial blood pressure in your brain is about 27 mm Hg less than that near your heart. If the blood pressure in your brain is too low to provide adequate blood flow, you will likely faint. By causing your body to collapse to the ground, fainting effectively places your head at the level of your heart, quickly increasing blood flow to your brain.

For animals with very long necks, the blood pressure required to overcome gravity is particularly high. A giraffe, for example, requires a systolic pressure of more than 250 mm Hg near the heart to get blood to its head. When a giraffe lowers its head to drink, one-way valves and sinuses, along with feedback mechanisms that reduce cardiac output, prevent this high pressure from damaging its brain.

Gravity is also a consideration for blood flow in veins, especially those in the legs. Although blood pressure in veins is relatively low, the valves inside the veins maintain a unidirectional flow of blood. The return of blood to the heart is further enhanced by rhythmic contractions of smooth muscles in the walls of venules and veins and by the contraction of skeletal muscles during exercise **(Figure 34.11)**.



▲ **Figure 34.11 Blood flow in veins.** Skeletal muscle contraction squeezes and constricts veins. Flaps of tissue within the veins act as one-way valves that keep blood moving only toward the heart. If you sit or stand too long, the lack of muscular activity may cause your feet to swell as blood pools in your veins.

Capillary Function

At any given time, only about 5–10% of the body's capillaries have blood flowing through them. Capillaries in the brain, heart, kidneys, and liver are usually filled to capacity, but at many other sites the blood supply varies over time as blood is diverted from one destination to another. For example, blood flow to the skin is regulated to help control body temperature, and blood supply to the digestive tract increases after a meal. During strenuous exercise, blood is diverted from the digestive tract and supplied more generously to skeletal muscles and skin. This is one reason why exercising heavily immediately after eating a big meal may cause indigestion.

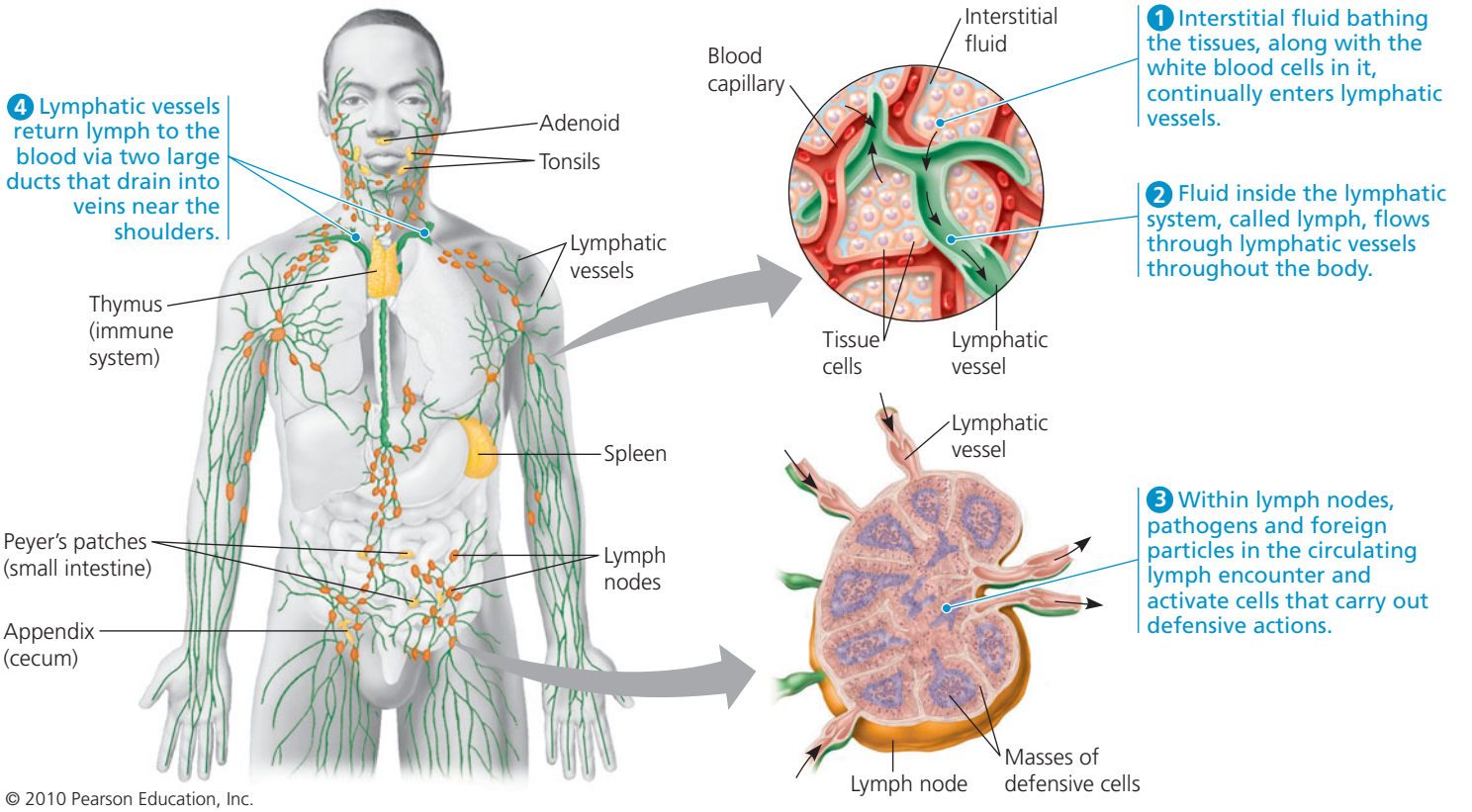
Given that capillaries lack smooth muscle, how is blood flow in capillary beds altered? One mechanism for altering blood flow is vasoconstriction or vasodilation of the arteriole that supplies a capillary bed. A second mechanism involves rings of smooth muscle located at the entrance to capillary beds. Opening and closing these muscular rings regulates and redirects the passage of blood into particular sets of capillaries.

As you have read, the critical exchange of substances between the blood and interstitial fluid takes place across the thin endothelial walls of the capillaries. Some substances are carried across the endothelium in vesicles that form on one side by endocytosis and release their contents on the opposite side by exocytosis. Small molecules, such as O_2 and CO_2, simply diffuse across the endothelial cells or, in some tissues, through microscopic pores in the capillary wall. These openings also provide the route for transport of small solutes such as sugars, salts, and urea, as well as for bulk flow of fluid into tissues driven by blood pressure within the capillary.

Two opposing forces control the movement of fluid between the capillaries and the surrounding tissues: Blood pressure tends to drive fluid out of the capillaries, and the presence of blood proteins tends to pull fluid back. Many blood proteins (and all blood cells) are too large to pass readily through the endothelium, and they remain in the capillaries. These dissolved proteins are responsible for much of the blood's *osmotic pressure* (the pressure produced by the difference in solute concentration across a membrane). The difference in osmotic pressure between the blood and the interstitial fluid opposes fluid movement out of the capillaries. On average, blood pressure is greater than the opposing forces, leading to a net loss of fluid from capillaries. The net loss is generally greatest at the arterial end of these vessels, where blood pressure is highest.

Fluid Return by the Lymphatic System

Each day, the adult human body loses approximately 4–8 L of fluid from capillaries to the surrounding tissues. There is also some leakage of blood proteins, even though the capillary wall is not very permeable to large molecules. The lost fluid and proteins return to the blood via the **lymphatic system**,



▲ Figure 34.12 The human lymphatic system. Lymph flows through lymphatic vessels (shown in green). Foreign substances carried by the lymph are trapped in lymph nodes (orange) and lymphoid organs (yellow): the adenoids, tonsils, spleen, Peyer's patches, and appendix. Steps 1–4 trace the flow of lymph and illustrate the critical role of lymph nodes in activating immune responses.

which includes a network of tiny vessels intermingled among capillaries of the cardiovascular system **(Figure 34.12)**.

After entering the lymphatic system by diffusion, the fluid lost by capillaries is called **lymph**; its composition is about the same as that of interstitial fluid. The lymphatic system drains into large veins of the circulatory system at the base of the neck. This joining of the lymphatic and circulatory systems enables lipids to be transferred from the small intestine to the blood (see Chapter 33).

The movement of lymph from peripheral tissues to the heart relies on much the same mechanisms that assist blood flow in veins. Lymph vessels, like veins, have valves that prevent the backflow of fluid. Rhythmic contractions of the vessel walls help draw fluid into the small lymphatic vessels. In addition, skeletal muscle contractions play a role in moving lymph.

Disorders that interfere with the lymphatic system highlight its role in maintaining proper fluid distribution in the body. Disruptions in the movement of lymph often cause edema, swelling that results from the excessive accumulation of fluid in tissues. Severe blockage of lymph flow, as occurs when certain parasitic worms lodge in lymph vessels, results in extremely swollen limbs or other body parts, a condition known as elephantiasis.

Along a lymph vessel are organs called **lymph nodes**. By filtering the lymph and by housing cells that attack viruses and bacteria, lymph nodes play an important role in the body's defense. When the body is fighting an infection, the white cells in lymph nodes multiply rapidly, causing swelling and tenderness (which is why your doctor may check for swollen lymph nodes in your neck, armpits, or groin when you feel sick). Because lymph nodes have filtering and surveillance functions, doctors may examine the lymph nodes of cancer patients to detect the spread of diseased cells.

In recent years, evidence has surfaced demonstrating that the lymphatic system also plays a role in harmful immune responses, such as those responsible for asthma. Because of these and other findings, the lymphatic system, given limited attention until the 1990s, has become a very active and promising area of biomedical research.

CONCEPT CHECK 34.3

1. What is the primary cause of the low velocity of blood flow in capillaries?
2. What short-term changes in cardiovascular function might best enable skeletal muscles to help an animal escape from a dangerous situation?
3. **WHAT IF?** If you had additional hearts distributed throughout your body, what would be one likely advantage and one likely disadvantage?

For suggested answers, see Appendix A.

CONCEPT 34.4

Blood components function in exchange, transport, and defense

As you read in Concept 34.1, the fluid transported by an open circulatory system is continuous with the fluid that surrounds all of the body cells and therefore has the same composition. In contrast, the fluid in a closed circulatory system can be more highly specialized, as is the case for the blood of vertebrates.

Blood Composition and Function

Vertebrate blood is a connective tissue consisting of cells suspended in a liquid matrix called **plasma**. Separating the components of blood using a centrifuge reveals that cellular elements (cells and cell fragments) occupy about 45% of the volume of blood **(Figure 34.13)**. The remainder is plasma. Dissolved in the plasma are ions and proteins that, together with the blood cells, function in osmotic regulation, transport, and defense.

Plasma

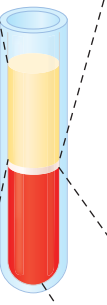
Among the many solutes in plasma are inorganic salts in the form of dissolved ions, sometimes referred to as blood electrolytes. Although plasma is about 90% water, the dissolved salts are an essential component of the blood. Some of these ions buffer the blood, which in humans normally has a pH of 7.4. Salts are also important in maintaining the osmotic balance of the blood. In addition, the concentration of ions in plasma directly affects the composition of the interstitial fluid, where many of these ions have a vital role in muscle and nerve activity. Serving all of these functions necessitates keeping plasma electrolytes within narrow concentration ranges via homeostatic mechanisms.

Plasma proteins act as buffers against pH changes and help maintain the osmotic balance between blood and interstitial fluid. Particular plasma proteins have additional functions. The immunoglobulins, or antibodies, help combat viruses and other foreign agents that invade the body (see Chapter 35). Other plasma proteins serve as escorts for lipids, which are insoluble in water and can travel in blood only when bound to proteins. Still other plasma proteins are clotting factors that help plug leaks when blood vessels are injured. (The term *serum* refers to blood plasma from which these clotting factors have been removed.)

Plasma also contains a wide variety of other substances in transit from one part of the body to another, including nutrients, metabolic wastes, respiratory gases, and hormones.

Plasma 55%

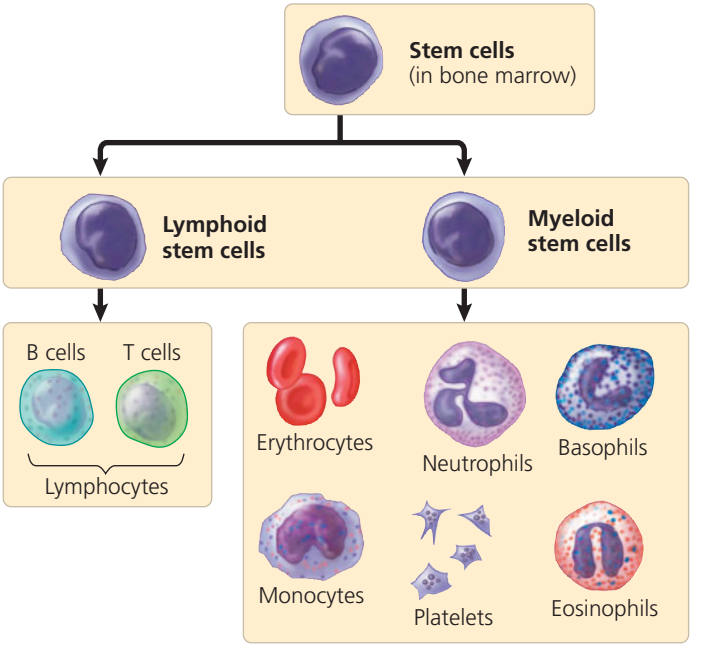
Constituent	Major functions
Water	Solvent for carrying other substances
Ions (blood electrolytes) Sodium Potassium Calcium Magnesium Chloride Bicarbonate	Osmotic balance, pH buffering, and regulation of membrane permeability
Plasma proteins	
Albumin	Osmotic balance, pH buffering
Fibrinogen	Clotting
Immunoglobulins (antibodies)	Defense
Substances transported by blood Nutrients (such as glucose, fatty acids, vitamins) Waste products of metabolism Respiratory gases (O_2 and CO_2) Hormones	



Cellular elements 45%

Cell type	Number per µL (mm^3) of blood	Functions
Leukocytes (white blood cells) Basophils Lymphocytes Eosinophils Neutrophils Monocytes	5,000–10,000	Defense and immunity
Platelets	250,000–400,000	Blood clotting
Erythrocytes (red blood cells)	5,000,000–6,000,000	Transport of O_2 and some CO_2

▲ **Figure 34.13** **The composition of mammalian blood.**



▲ Figure 34.14 Differentiation of blood cells. Some of the multipotent stem cells differentiate into lymphoid stem cells, which then develop into B cells and T cells, two types of lymphocytes that function in immunity (see Chapter 35). All other blood cells and platelets arise from myeloid stem cells.

Cellular Elements

Blood contains two classes of cells: red blood cells, which transport O_2, and white blood cells, which function in defense. Also suspended in blood plasma are **platelets**, cell fragments that are involved in the clotting process. All these cellular elements develop from multipotent **stem cells** that are dedicated to replenishing the body's blood cell populations **(Figure 34.14)**. The stem cells that produce blood cells and platelets are located in the red marrow inside bones, particularly the ribs, vertebrae, sternum, and pelvis.

Erythrocytes Red blood cells, or **erythrocytes**, are by far the most numerous blood cells. Each microliter (μL, or mm^3) of human blood contains 5–6 million red cells, and there are about 25 trillion of these cells in the body's 5 L of blood. Their main function is O_2 transport, and their structure is closely related to this function. Human erythrocytes are small disks (7–8 μm in diameter) that are biconcave—thinner in the center than at the edges. This shape increases surface area, enhancing the rate of diffusion of O_2 across the plasma membrane. Mature mammalian erythrocytes lack nuclei. This unusual characteristic leaves more space in these tiny cells for **hemoglobin**, the iron-containing protein that transports O_2 (see Figure 3.21).

Despite its small size, an erythrocyte contains about 250 million molecules of hemoglobin (Hb). Because each molecule of hemoglobin binds up to four molecules of O_2, one erythrocyte can transport about one billion O_2 molecules. As erythrocytes pass through the capillary beds of lungs, gills, or other respiratory organs, O_2 diffuses into the erythrocytes and binds to hemoglobin. In the systemic capillaries, O_2 dissociates from hemoglobin and diffuses into body cells.

In **sickle-cell disease**, an abnormal form of hemoglobin (Hb^S) polymerizes into aggregates. Because the concentration of hemoglobin in erythrocytes is so high, these aggregates are large enough to distort the erythrocyte into an elongated, curved shape that resembles a sickle. This abnormality results from an alteration in the amino acid sequence of hemoglobin at a single position (see Figure 3.22).

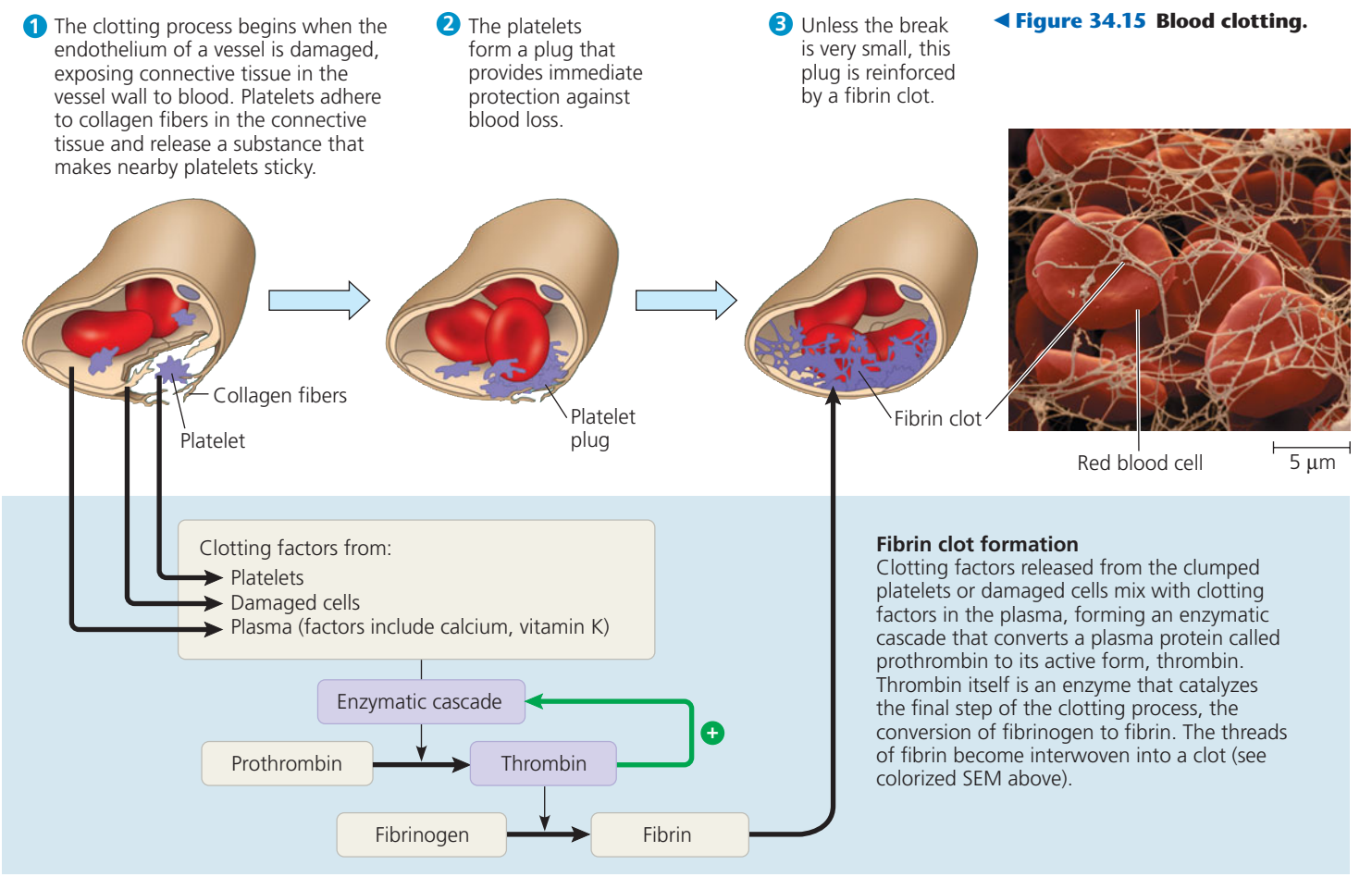
Throughout a person's life, stem cells replace the worn-out cellular elements of blood. Erythrocytes are the shortest lived, circulating for only 120 days on average before being replaced. A negative-feedback mechanism, sensitive to the amount of O_2 reaching the body's tissues via the blood, controls erythrocyte production. If the tissues do not receive enough O_2, the kidneys synthesize and secrete *erythropoietin* (*EPO*), a hormone that stimulates erythrocyte production. Today, EPO produced by recombinant DNA technology is used to treat health problems such as *anemia*, a condition of lower-than-normal erythrocyte or hemoglobin levels. Some athletes inject themselves with EPO to increase their erythrocyte levels, although this practice, a form of blood doping, has been banned by major sports organizations.

Leukocytes The blood contains five major types of white blood cells, or **leukocytes**. Their function is to fight infections. Some are phagocytic, engulfing and digesting microorganisms as well as debris from the body's own dead cells. Other leukocytes, called lymphocytes, develop into specialized B cells and T cells that mount immune responses against foreign substances (as will be discussed in Chapter 35). Normally, 1 μL of human blood contains about 5,000–10,000 leukocytes; their numbers increase temporarily whenever the body is fighting an infection. Unlike erythrocytes, leukocytes are also found outside the circulatory system, patrolling both interstitial fluid and the lymphatic system.

Platelets Platelets are pinched-off cytoplasmic fragments of specialized bone marrow cells. They are about 2–3 μm in diameter and have no nuclei. Platelets serve both structural and molecular functions in blood clotting.

Blood Clotting

The occasional cut or scrape is not life-threatening because blood components seal the broken blood vessels. A break in a blood vessel wall exposes proteins that attract platelets and initiate coagulation, the conversion of liquid components of blood to a solid clot. The coagulant, or sealant, circulates in an inactive form called fibrinogen. In response to a broken blood vessel, platelets release clotting factors that trigger reactions leading to the formation of thrombin, an enzyme that converts fibrinogen to fibrin. Newly formed fibrin aggregates into threads that form the framework of the clot. Thrombin also



◀ Figure 34.15 Blood clotting.

activates a factor that catalyzes the formation of more thrombin, driving clotting to completion through positive feedback (see Chapter 32). The steps in the production of a blood clot are diagrammed in **Figure 34.15**. Any genetic mutation that blocks a step in the clotting process can cause hemophilia, a disease characterized by excessive bleeding and bruising from even minor cuts and bumps (see Chapter 12).

Anticlotting factors in the blood normally prevent spontaneous clotting in the absence of injury. Sometimes, however, clots form within a blood vessel, blocking the flow of blood. Such a clot is called a **thrombus**. We'll explore how a thrombus forms and the danger that it poses later in this chapter.

Cardiovascular Disease

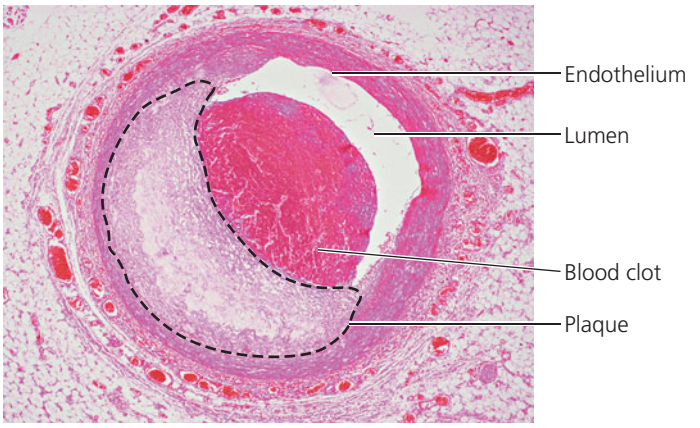
Cardiovascular diseases—disorders of the heart and blood vessels—cause more than 750,000 human deaths each year in the United States. These diseases range from a minor disturbance of vein or heart valve function to a life-threatening disruption of blood flow to the heart or brain.

Cholesterol metabolism has a central role in cardiovascular disease. In animal cell membranes this steroid is important for maintaining normal membrane fluidity (see Figure 5.5). Cholesterol travels in plasma in particles that consist of thousands of cholesterol molecules and other lipids bound to a protein. One type of particle—**low-density lipoprotein (LDL)**—delivers cholesterol to cells for membrane production. Another type—**high-density lipoprotein (HDL)**—scavenges excess cholesterol for return to the liver. A high ratio of LDL to HDL substantially increases the risk for atherosclerosis, a form of heart disease discussed below.

Another factor in cardiovascular disease is *inflammation*, the body's reaction to injury. Tissue damage leads to recruitment of two types of circulating immune cells, macrophages and leukocytes. Signals released by these cells trigger a flow of fluid out of blood vessels at the site of injury, resulting in the tissue swelling characteristic of inflammation (see Figure 35.5). Although inflammation is often a normal and healthy response to injury, it sometimes significantly disrupts circulatory function, as explained in the next section.

Atherosclerosis, Heart Attacks, and Stroke

Circulating cholesterol and inflammation can act together to produce a cardiovascular disease called **atherosclerosis**, the hardening of the arteries by fatty deposits. Healthy arteries have a smooth inner lining that reduces resistance to blood flow. Damage or infection can roughen the lining and lead to inflammation. Leukocytes are attracted to the damaged lining and begin to take up lipids, including cholesterol from LDL.



▲ Figure 34.16 Atherosclerosis. In atherosclerosis, thickening of an arterial wall by plaque formation can restrict blood flow through the artery. Fragments of ruptured plaque can travel via the bloodstream and become lodged in other arteries. If the blockage is in an artery that supplies the heart or brain, the result could be a heart attack or stroke, respectively.

A fatty deposit called a plaque, grows steadily, incorporating fibrous connective tissue and additional cholesterol. As the plaque grows, the walls of the artery become thick and stiff, and the obstruction of the artery increases, reducing the diameter available for blood flow **(Figure 34.16)**.

Untreated atherosclerosis often results in a heart attack or a stroke. A **heart attack**, also called a *myocardial infarction*, is the damage or death of cardiac muscle tissue resulting from blockage of one or more coronary arteries, which supply O_2-rich blood to the heart muscle. Because the coronary arteries are small in diameter, they are especially vulnerable to obstruction. Such blockage can destroy cardiac muscle quickly because the constantly beating heart muscle cannot survive long without O_2. If the heart stops beating, the victim may nevertheless survive if a heartbeat is restored within a few minutes by cardiopulmonary resuscitation (CPR) or some other emergency procedure.

A **stroke** is the death of nervous tissue in the brain due to a lack of O_2. Strokes usually result from rupture or blockage of arteries in the neck or head. The effects of a stroke and the individual's chance of survival depend on the extent and location of the damaged brain tissue. If a stroke results from a blocked artery, rapid administration of a clot-dissolving drug may help limit the damage.

Although atherosclerosis often isn't detected until critical blood flow is disrupted, there can be warning signs. Partial blockage of the coronary arteries may cause occasional chest pain, a condition known as angina pectoris, or more commonly angina. The pain is most likely to be felt when the heart is laboring hard during physical or emotional stress, and it signals that part of the heart is not receiving enough O_2. An obstructed coronary artery may be treated surgically, either by inserting a metal mesh tube called a stent to expand the artery or by transplanting a healthy blood vessel from the chest or a limb to bypass the blockage.

Risk Factors and Treatment of Cardiovascular Disease

Although the tendency to develop particular cardiovascular diseases is inherited, it is also strongly influenced by lifestyle. For example, exercise decreases the LDL/HDL ratio. In contrast, smoking, as well as consuming certain processed vegetable oils called *trans fats*, increases the ratio of LDL to HDL, raising the risk of cardiovascular disease. For many individuals at high risk, treatment with drugs called statins can lower LDL levels and thereby reduce the likelihood of heart attacks. In the **Scientific Skills Exercise**, you can interpret the effect of a genetic mutation on blood LDL levels.

The recognition that inflammation plays a central role in atherosclerosis and thrombus formation is also shaping the treatment of cardiovascular disease. For example, aspirin, which inhibits the inflammatory response, has been found to help prevent the recurrence of heart attacks and stroke. Researchers have also focused on C-reactive protein (CRP), which is produced by the liver and found in the blood during episodes of acute inflammation. Like a high level of LDL cholesterol, the presence of significant amounts of CRP in blood is a useful risk indicator for cardiovascular disease.

Hypertension (high blood pressure) is yet another contributor to heart attack and stroke as well as other health problems. According to one hypothesis, chronic high blood pressure damages the endothelium that lines the arteries, promoting plaque formation. The usual definition of hypertension in adults is a systolic pressure above 140 mm Hg or a diastolic pressure above 90 mm Hg. Fortunately, hypertension is simple to diagnose and can usually be controlled by dietary changes, exercise, medication, or a combination of these approaches.

CONCEPT CHECK 34.4

1. Explain why a physician might order a white cell count for a patient with symptoms of an infection.
2. Clots in arteries can cause heart attacks and strokes. Why, then, does it make sense to treat people with hemophilia by introducing clotting factors into their blood?
3. **WHAT IF?** Nitroglycerin (the key ingredient in dynamite) is sometimes prescribed for heart disease patients. Within the body, the nitroglycerin is converted to nitric oxide. Why would you expect nitroglycerin to relieve chest pain in these patients?

For suggested answers, see Appendix A.

CONCEPT 34.5

Gas exchange occurs across specialized respiratory surfaces

In the remainder of this chapter, we will focus on the process of **gas exchange**. Although this process is often called respiratory exchange or respiration, it should not be confused

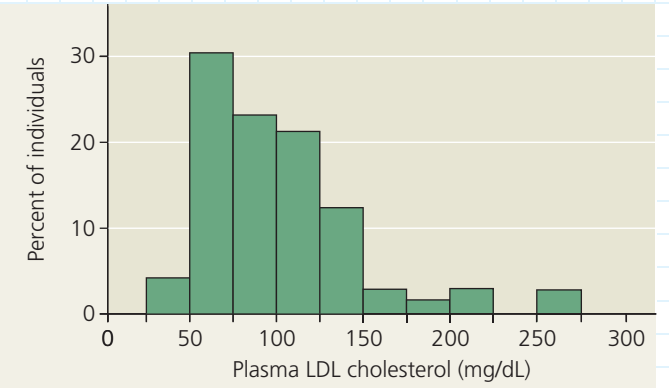
Scientific Skills Exercise

Interpreting Data in Histograms

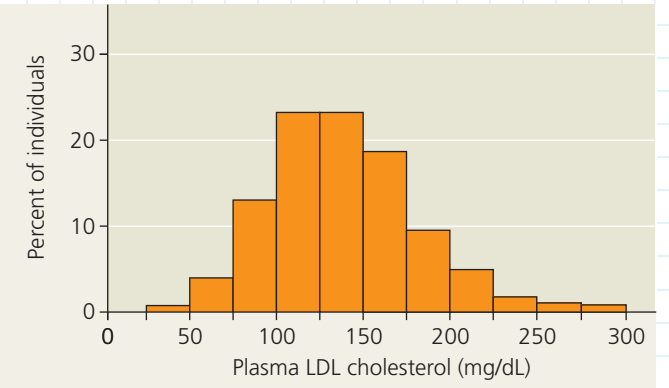
Does Inactivating the PCSK9 Enzyme Lower LDL Levels in Humans? Researchers interested in genetic factors affecting susceptibility to cardiovascular disease examined the DNA of 15,000 individuals. This screening revealed that 3% of the population sample had a mutation that inactivated one copy (allele) of the gene for PCSK9, a human liver enzyme. Because mutations that *increase* PCSK9 activity *increase* levels of LDL cholesterol in the blood, the researchers hypothesized that *inactivating* mutations in this gene would *lower* LDL levels. In this exercise, you will interpret the results of an experiment they carried out to test this hypothesis.

How the Experiment Was Done Researchers measured LDL cholesterol levels in blood plasma from 85 individuals with one copy of the *PCSK9* gene inactivated (the study group) and from 3,278 wild-type individuals (the control group).

Data from the Experiment



Individuals with an inactivating mutation in one copy of *PCSK9* gene (study group)



Individuals with two functional copies of *PCSK9* gene (control group)

Interpret the Data

1. The results are presented using a variant of bar graph called a *histogram*. In a histogram, the variable on the *x*-axis is grouped into ranges. The height of each bar in this histogram reflects the percentage of samples that fall into the range specified on the *x*-axis for that bar. For example, in the top histogram, about 4% of individuals studied had plasma LDL cholesterol levels in the 25–50 mg/dL (milligrams per deciliter) range. Add the percentages for the relevant bars to calculate the percentage of individuals in the study group and the control group with an LDL level below 100 mg/dL. (For additional information about histograms, see the Scientific Skills Review in Appendix F and in the Study Area in MasteringBiology.)
2. Given the differences between these two histograms, what conclusion can you draw?
3. Based on what you know about LDL cholesterol, would you predict that the individuals in the study group have an increased, unchanged, or reduced risk for cardiovascular disease relative to wild-type individuals? Explain.
4. Propose an explanation for the fact that the two histograms overlap as much as they do.
5. Comparing these two histograms allowed researchers to draw a conclusion regarding the effect of PCSK9 mutations on LDL cholesterol levels in blood. Suppose you now consider two individuals with a plasma LDL level of 160 mg/dL, one from the study group and one from the control group. What do you predict regarding their relative risk of cardiovascular disease? Explain how you arrived at your prediction. What role did the histograms play in making your prediction in this case?

Data from J. C. Cohen et al., Sequence variations in PCSK9, low LDL, and protection against coronary heart disease, *New England Journal of Medicine* 354:1264–1272 (2006).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.

with the energy transformations of cellular respiration. Gas exchange is the uptake of molecular O_2 from the environment and the discharge of CO_2 to the environment. The respiratory medium—the source of oxygen in the environment—is either water or air.

Partial Pressure Gradients in Gas Exchange

To understand the driving forces for gas exchange, we must calculate **partial pressure**, which is simply the pressure exerted by a particular gas in a mixture of gases. To do so, we need to know the pressure that the mixture exerts and the

fraction of the mixture represented by a particular gas. Let's consider O_2 as an example. At sea level, the atmosphere exerts a downward force equal to that of a column of mercury (Hg) 760 mm high. Atmospheric pressure at sea level is thus 760 mm Hg. Since the atmosphere is 21% O_2 by volume, the partial pressure of O_2 is 0.21×760, or about 160 mm Hg. This value is called the *partial pressure* of O_2 (abbreviated P_{O_2}) because it is the part of atmospheric pressure contributed by O_2. The partial pressure of CO_2 (abbreviated P_{CO_2}) is much less, only 0.29 mm Hg at sea level.

Partial pressures also apply to gases dissolved in a liquid, such as water. When water is exposed to air, an equilibrium is reached in which the partial pressure of each gas in the water equals the partial pressure of that gas in the air. Thus, water exposed to air at sea level has a P_{O_2} of 160 mm Hg, the same as in the atmosphere. However, the *concentrations* of O_2 in the air and water differ substantially because O_2 is much less soluble in water than in air.

Once we have calculated partial pressures, we can readily predict the net result of diffusion at gas exchange surfaces: A gas always undergoes net diffusion from a region of higher partial pressure to a region of lower partial pressure.

Respiratory Media

The conditions for gas exchange vary considerably, depending on whether the respiratory medium—the source of O_2—is air or water. As already noted, O_2 is plentiful in air, making up about 21% of Earth's atmosphere by volume. Compared to water, air is much less dense and less viscous, so it is easier to move and to force through small passageways. As a result, breathing air is relatively easy and need not be particularly efficient. Humans, for example, extract only about 25% of the O_2 in inhaled air.

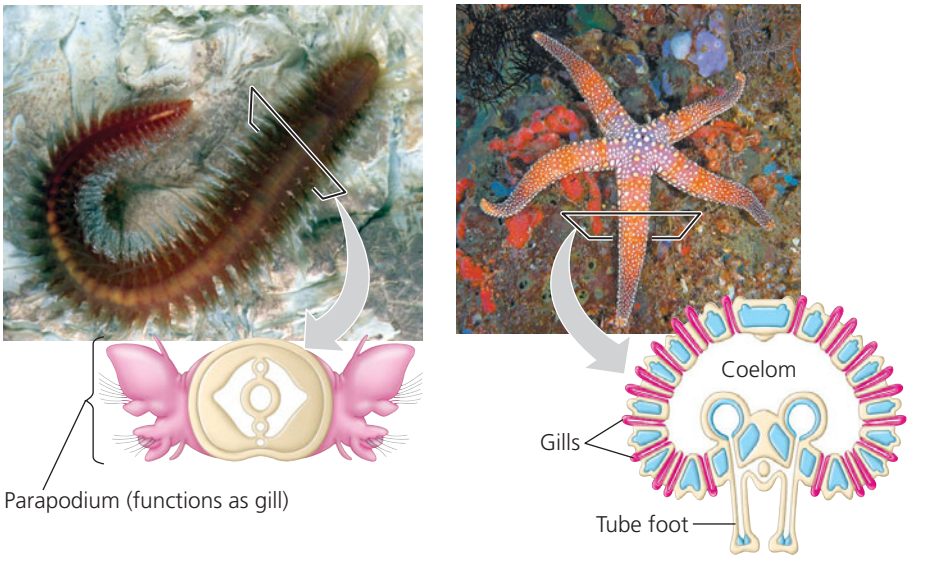
Gas exchange with water as the respiratory medium is much more demanding. The amount of O_2 dissolved in a given volume of water varies but is always less than in an equivalent volume of air: Water in many marine and freshwater habitats contains only 4–8 mL of dissolved O_2 per liter, a concentration roughly 40 times less than in air. The warmer and saltier the water is, the less dissolved O_2 it can hold. Water's lower O_2 content, greater density, and greater viscosity mean that aquatic animals such as fishes and lobsters must expend considerable energy to carry out gas exchange. In the context of these challenges, adaptations have evolved that enable most aquatic animals to be very efficient in gas exchange. Many of these adaptations involve the organization of the surfaces dedicated to exchange, as illustrated in a marine worm and a sea star **(Figure 34.17)**.

Respiratory Surfaces

Specialization for gas exchange is apparent in the structure of the respiratory surface, the part of an animal's body where gas exchange occurs. Like all living cells, the cells that carry out gas exchange have a plasma membrane that must be in contact with an aqueous solution. Respiratory surfaces are therefore always moist.

The movement of O_2 and CO_2 across respiratory surfaces takes place by diffusion. The rate of diffusion is proportional to the surface area across which it occurs and inversely proportional to the square of the distance through which molecules must move. In other words, gas exchange is fast when the area for diffusion is large and the path for diffusion is short. As a result, respiratory surfaces tend to be large and thin.

In some relatively simple animals, such as sponges, cnidarians, and flatworms, every cell in the body is close enough to the external environment that gases can diffuse quickly between any cell and the environment. In many animals, however, the bulk of the body's cells lack immediate access to the environment. The respiratory surface in these animals is a thin, moist epithelium that constitutes a respiratory organ.



(a) Marine worm. Many polychaetes (marine worms of the phylum Annelida) have a pair of flattened appendages called parapodia (singular, *parapodium*) on each body segment. The parapodia serve as gills and also function in crawling and swimming.

(b) Sea star. The gills of a sea star are simple tubular projections of the skin. The hollow core of each gill is an extension of the coelom (body cavity). Gas exchange occurs by diffusion across the gill surfaces, and fluid in the coelom circulates in and out of the gills, aiding gas transport. The surfaces of a sea star's tube feet also function in gas exchange.

▲ Figure 34.17 Diversity in the structure of gills, external body surfaces that function in gas exchange.

In some animals, including earthworms and some amphibians, the skin serves as a respiratory organ. A dense network of capillaries just below the surface facilitates the exchange of gases between the circulatory system and the environment. For most animals, however, the general body surface lacks sufficient area to exchange gases for the whole organism. The evolutionary solution to this limitation is a respiratory organ that is extensively folded or branched, thereby enlarging the available surface area for gas exchange. Gills, tracheae, and lungs are three such organs.

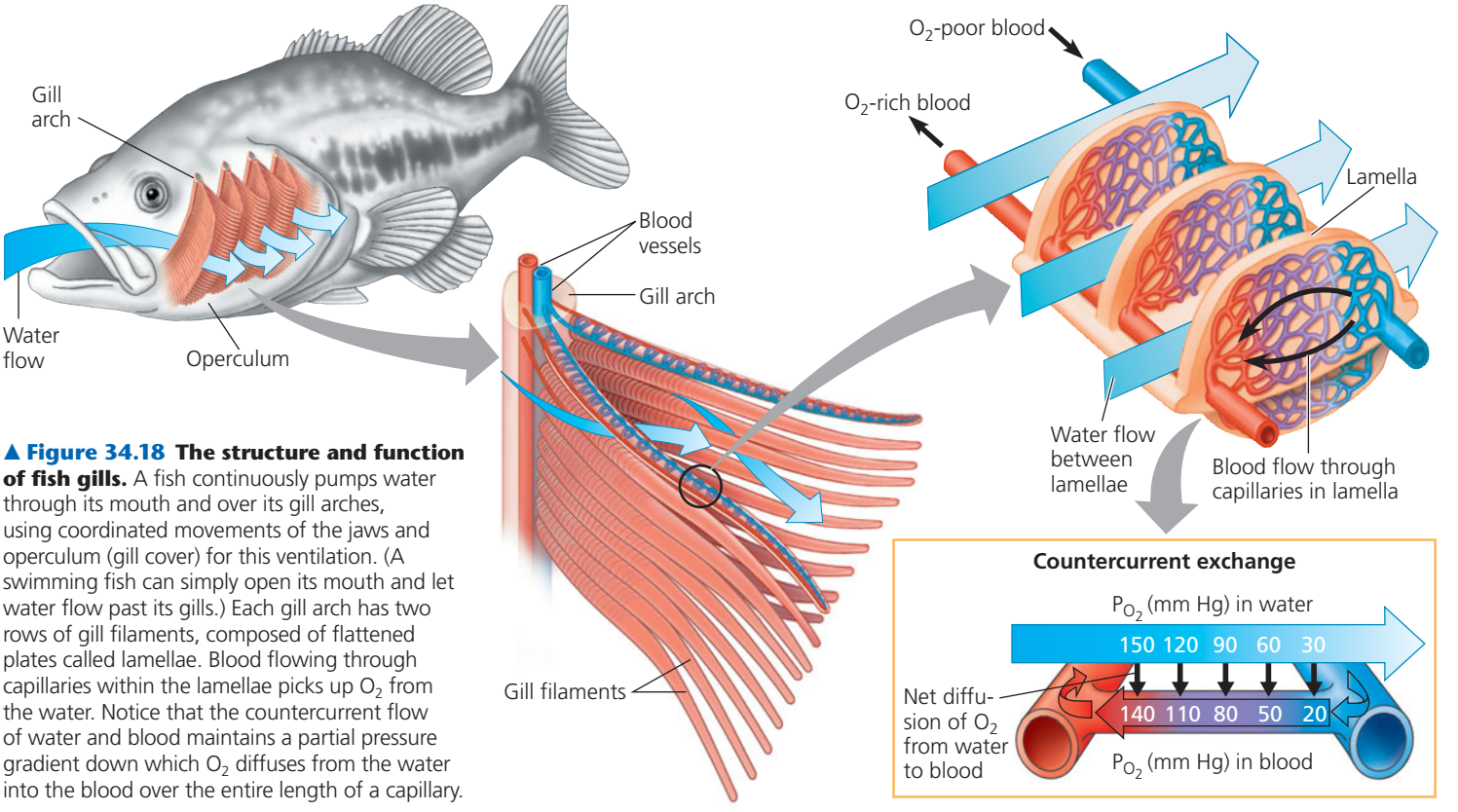
Gills in Aquatic Animals

Gills are outfoldings of the body surface that are suspended in the water. They can be localized to specialized structures, as in an axolotl (see Figure 34.1), or distributed across the body, as in a sea star or marine worm (see Figure 34.17). Movement of the respiratory medium over the respiratory surface, a process called **ventilation**, maintains the partial pressure gradients of O_2 and CO_2 across the gill that are necessary for gas exchange.

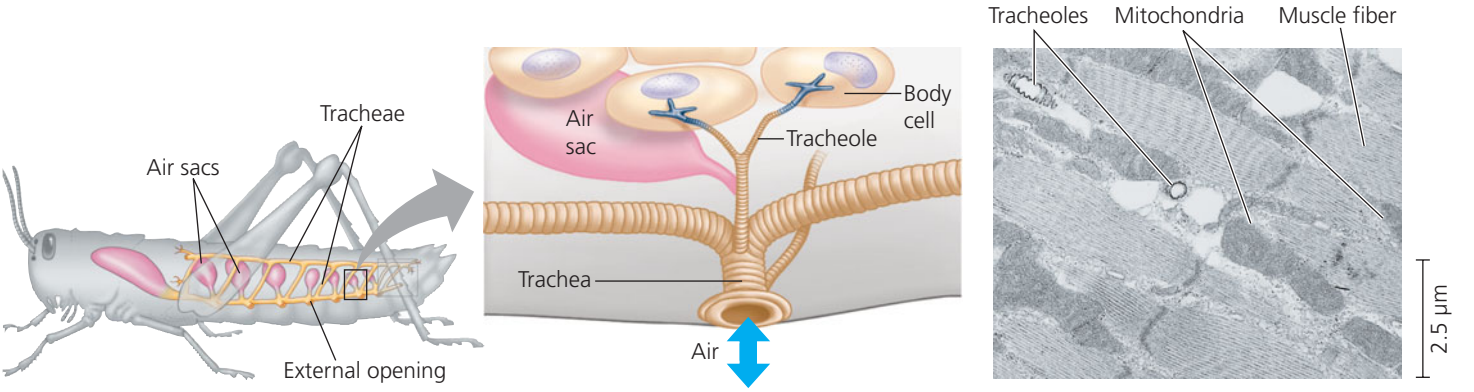
To promote ventilation, most gill-bearing animals move their gills through the water or move water over their gills. For example, crayfish and lobsters have paddle-like appendages that drive a current of water over the gills, whereas mussels and clams move water with cilia. Octopuses and squids ventilate their gills by taking in and ejecting water, with the side benefit of locomotion by jet propulsion. Fishes use the motion of swimming or movements of the mouth and gill covers to ventilate their gills. In both cases, a water current enters the mouth of the fish, passes through slits in the pharynx, flows over the gills, and exits the body **(Figure 34.18)**.

In fishes, the efficiency of gas exchange is maximized by **countercurrent exchange**, the exchange of a substance or heat between two fluids flowing in opposite directions. (Recall from Chapter 32 that countercurrent exchange also contributes to temperature regulation and kidney function.) Because blood flows in the direction opposite to that of water passing over the gills, blood is less saturated with O_2 at each point in its travel than the water it meets (see Figure 34.18). As blood enters a gill capillary, it encounters water that is completing its passage through the gill. Depleted of much of its dissolved O_2, this water nevertheless has a higher P_{O_2} than the incoming blood, and O_2 transfer takes place. As the blood continues its passage, its P_{O_2} steadily increases, but so does that of the water it encounters, since each successive position in the blood's travel corresponds to an earlier position in the water's passage over the gills. Thus, a partial pressure gradient favoring the diffusion of O_2 from water to blood exists along the entire length of the capillary.

Countercurrent exchange mechanisms are remarkably efficient. More than 80% of the O_2 dissolved in the water entering the mouth and gills of the fish is removed as it passes over the respiratory surface.



▲ Figure 34.18 The structure and function of fish gills. A fish continuously pumps water through its mouth and over its gill arches, using coordinated movements of the jaws and operculum (gill cover) for this ventilation. (A swimming fish can simply open its mouth and let water flow past its gills.) Each gill arch has two rows of gill filaments, composed of flattened plates called lamellae. Blood flowing through capillaries within the lamellae picks up O_2 from the water. Notice that the countercurrent flow of water and blood maintains a partial pressure gradient down which O_2 diffuses from the water into the blood over the entire length of a capillary.



(a) The respiratory system of an insect consists of branched internal tubes. The largest tubes, called tracheae, connect to external openings spaced along the insect's body surface. Air sacs formed from enlarged portions of the tracheae are found near organs that require a large supply of oxygen.

(b) Rings of chitin keep the tracheae open, allowing air to enter and pass into smaller tubes called tracheoles. The branched tracheoles deliver air directly to cells throughout the body. Tracheoles have closed ends filled with fluid (blue-gray). When the animal is active and using more O_2, most of the fluid is withdrawn into the body. This increases the surface area of air-filled tracheoles in contact with cells.

(c) The TEM above shows cross sections of tracheoles in a tiny piece of insect flight muscle. Each of the numerous mitochondria in the muscle cells lies within about 5 µm of a tracheole.

▲ Figure 34.19 The insect tracheal system.

Tracheal Systems in Insects

In most terrestrial animals, respiratory surfaces are enclosed within the body, exposed to the atmosphere only through narrow tubes. Although the most familiar such structure is the lung, the most common is the insect **tracheal system**, a network of air tubes that branch throughout the body. The largest tubes, called tracheae, open to the outside **(Figure 34.19a)**. The finest branches extend close to the surface of nearly every cell, where gas is exchanged by diffusion across the moist epithelium that lines the tips of the tracheal branches **(Figure 34.19b)**. Because the tracheal system brings air within a very short distance of virtually every body cell in an insect, it can transport O_2 and CO_2 without the participation of the animal's open circulatory system.

For small insects, diffusion through the tracheae brings in enough O_2 and removes enough CO_2 to support cellular respiration. Larger insects meet their higher energy demands by ventilating their tracheal systems with rhythmic body movements that compress and expand the air tubes like bellows. Insects in flight, which have a particularly high metabolic rate, have flight muscle cells that are packed with mitochondria. Tracheal tubes distributed throughout the flight muscles supply these ATP-generating organelles with ample O_2 **(Figure 34.19c)**.

Lungs

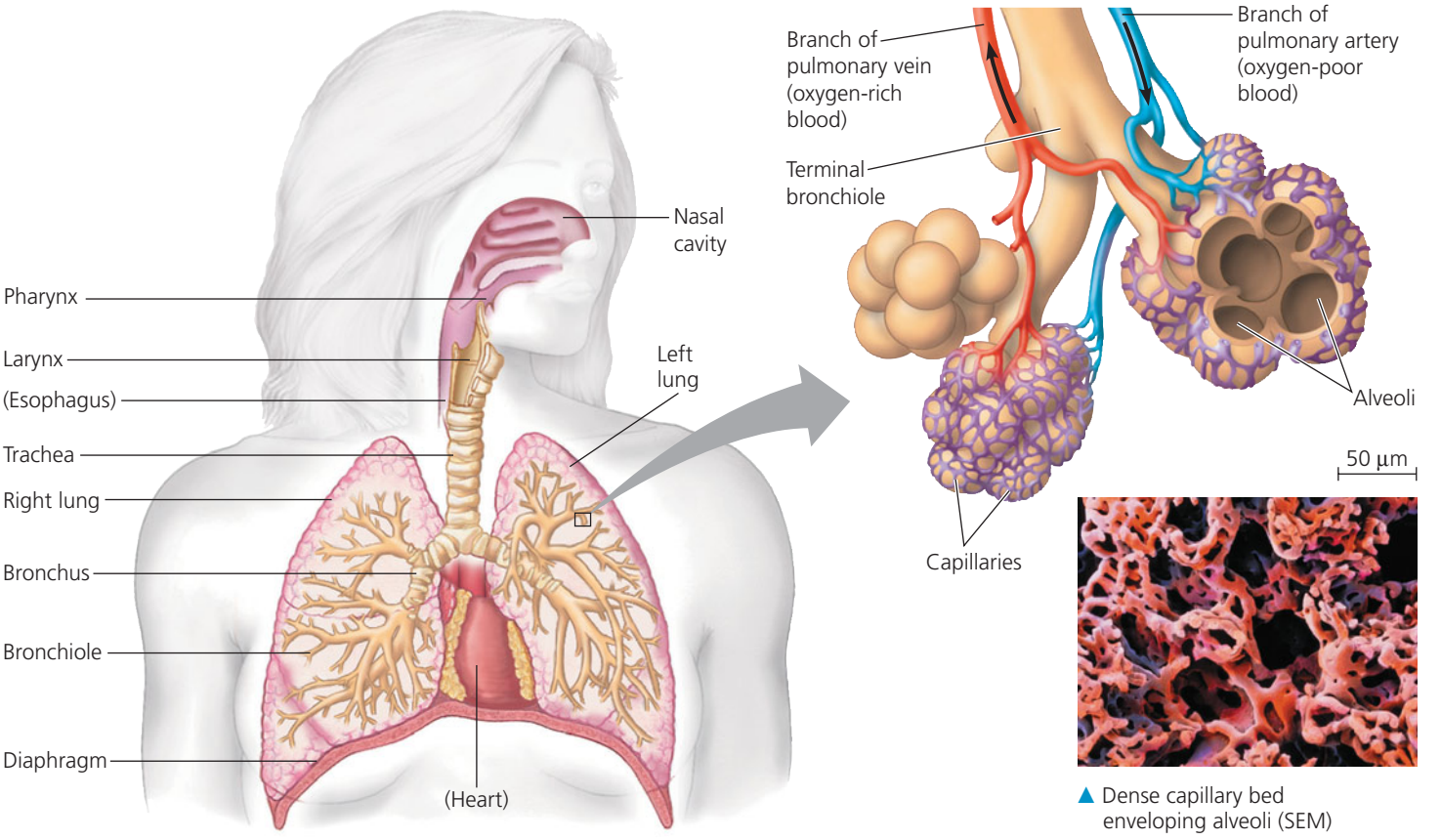
Unlike tracheal systems, which branch throughout the insect body, **lungs** are localized respiratory organs. Representing an infolding of the body surface, they are typically subdivided into numerous pockets. Because the respiratory surface of a lung is not in direct contact with all other parts of the body, the gap must be bridged by the circulatory system, which transports gases between the lungs and the rest of the body. Lungs have evolved in organisms with open circulatory systems, such as spiders and land snails, as well as in vertebrates.

Among vertebrates that lack gills, the use of lungs for gas exchange varies. Amphibians rely heavily on diffusion across body surfaces, such as the skin, to carry out gas exchange; lungs, if present, are relatively small. In contrast, most reptiles (including all birds) and all mammals depend entirely on lungs for gas exchange. Lungs and air breathing have evolved in a few aquatic vertebrates as adaptations to living in oxygen-poor water or to spending part of their time exposed to air (for instance, when the water in a pond recedes).

Mammalian Respiratory Systems: A Closer Look

In mammals, a system of branching ducts conveys air to the lungs, which are located in the thoracic cavity **(Figure 34.20)**. Air enters through the nostrils and is then filtered by hairs, warmed, humidified, and sampled for odors as it flows through a maze of spaces in the nasal cavity. The nasal cavity leads to the pharynx, an intersection where the paths for air and food cross. When food is swallowed, the **larynx** (the upper part of the respiratory tract) moves upward and tips a flap of cartilage over the opening of the **trachea**, or windpipe. This allows food to go down the esophagus to the stomach. The rest of the time, the airway is open, enabling breathing.

From the larynx, air passes into the trachea. Cartilage reinforcing the walls of both the larynx and the trachea keeps this part of the airway open. Within the larynx of most mammals, exhaled air rushes by a pair of elastic bands of muscle called vocal folds, or, in humans, vocal cords. Sounds are produced when muscles in the larynx are tensed, stretching the cords so they vibrate. High-pitched sounds result from tightly stretched cords vibrating rapidly; low-pitched sounds come from less tense cords vibrating slowly.



▲ Dense capillary bed enveloping alveoli (SEM)

▲ Figure 34.20 The mammalian respiratory system. From the nasal cavity and pharynx, inhaled air passes through the larynx, trachea, and bronchi to the bronchioles, which end in microscopic alveoli lined by a thin, moist epithelium. Branches of the pulmonary arteries convey oxygen-poor blood to the alveoli; branches of the pulmonary veins transport oxygen-rich blood from the alveoli back to the heart.

The trachea branches into two **bronchi** (singular, *bronchus*), one leading to each lung. Within the lung, the bronchi branch repeatedly into finer and finer tubes called *bronchioles*. The entire system of air ducts has the appearance of an inverted tree, the trunk being the trachea. The epithelium lining the major branches of this respiratory tree is covered by cilia and a thin film of mucus. The mucus traps dust, pollen, and other particulate contaminants, and the beating cilia move the mucus upward to the pharynx, where it can be swallowed into the esophagus. This process, sometimes referred to as the "mucus escalator," plays a crucial role in cleansing the respiratory system.

Gas exchange in mammals occurs in **alveoli** (singular, *alveolus*; see Figure 34.20), air sacs clustered at the tips of the tiniest bronchioles. Human lungs contain millions of alveoli, which together have a surface area of about 100 m^2—50 times that of the skin. Oxygen in the air entering the alveoli dissolves in the moist film lining their inner surfaces and rapidly undergoes net diffusion across the epithelium into a web of capillaries that surrounds each alveolus. Net diffusion of carbon dioxide occurs in the opposite direction, from the capillaries across the epithelium of the alveolus and into the air space.

Lacking cilia or significant air currents to remove particles from their surface, alveoli are highly susceptible to contamination. White blood cells patrol the alveoli, engulfing foreign particles. However, if too much particulate matter reaches the alveoli, the defenses can be overwhelmed, leading to inflammation and irreversible damage. For example, particulates from cigarette smoke that enter alveoli can cause a permanent reduction in lung capacity. For coal miners, inhalation of large amounts of coal dust can lead to silicosis, a disabling, irreversible, and sometimes fatal lung disease.

The film of liquid that lines alveoli is subject to surface tension, an attractive force that has the effect of minimizing a liquid's surface area (see Chapter 2). Given their tiny diameter (about 0.25 mm), why don't alveoli collapse under high surface tension? Researchers reasoned that alveoli must be coated with a material that reduces surface tension. In 1955, English biophysicist Richard Pattle obtained experimental evidence for such a material, now called a **surfactant**, for *surf*ace-*act*ive agent. In addition, he proposed that the absence of surfactant might cause respiratory distress syndrome (RDS), a disease common among preterm infants born 6 weeks or more before their due dates. In the 1950s, RDS killed 10,000 infants annually in the United States alone.

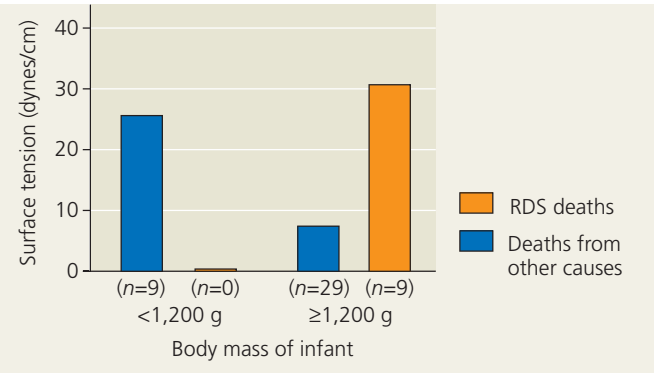
In the late 1950s, Mary Ellen Avery carried out the first experiment linking RDS to a surfactant deficiency

▼ Figure 34.21 Inquiry

What causes respiratory distress syndrome?

Experiment Mary Ellen Avery, a research fellow at Harvard University, hypothesized that a lack of surfactant caused respiratory distress syndrome (RDS) in preterm infants. To test this idea, she obtained autopsy samples of lungs from infants that had died of RDS or from other causes. She extracted material from the samples and let it form a film on water. Avery then measured the tension (in dynes per centimeter) across the water surface and recorded the lowest surface tension observed for each sample.

Results In analyzing the data, Avery noted a pattern when she grouped the samples from infants with a body mass of less than 1,200 g (2.7 lbs) and those who had grown larger.



Conclusion For infants 1,200 g and above, the samples from those that had died of causes other than RDS exhibited much lower surface tension than samples from those that had died of RDS. Avery inferred that infants' lungs normally contain a surface-tension reducing material (now called surfactant), and that a lack of this material was a likely cause of RDS. The results from infants less than 1,200 g were similar to those of infants who had died from RDS, suggesting that surfactant is not normally produced until a fetus reaches this size.

Source M. E. Avery and J. Mead, Surface properties in relation to atelectasis and hyaline membrane disease, *American Journal of Diseases of Children* 97:517–523 (1959).

WHAT IF? Suppose researchers had measured the amount of surfactant in lung samples. Describe the graph you would expect if the amount of surfactant were plotted against infant weight.

(Figure 34.21). Subsequent studies revealed that surfactant contains a mixture of phospholipids and proteins and in a full-term (38-week) pregnancy appears in the lungs about five weeks before birth. Artificial surfactants are now used routinely to treat early preterm infants. For her contributions, Avery received the National Medal of Science in 1991.

CONCEPT CHECK 34.5

1. Why is the position of lung tissues *within* the body an advantage for terrestrial animals?
2. After a heavy rain, earthworms come to the surface. How would you explain this behavior in terms of an earthworm's requirements for gas exchange?
3. **MAKE CONNECTIONS** Describe the role of countercurrent exchange in facilitating both thermoregulation (see Concept 32.1) and respiration.

For suggested answers, see Appendix A.

CONCEPT 34.6

Breathing ventilates the lungs

Having surveyed the route that air follows when we breathe, we turn now to the process of breathing itself. Like fishes, terrestrial vertebrates rely on ventilation to maintain high O_2 and low CO_2 concentrations at the gas exchange surface. The process that ventilates lungs is **breathing**, the alternating inhalation and exhalation of air. A variety of mechanisms for moving air in and out of lungs have evolved, as we will see by considering amphibians, birds, and mammals.

An amphibian such as a frog ventilates its lungs by **positive pressure breathing**, filling the lungs with forced airflow. During each cycle of ventilation, fresh air is first drawn through the nostrils into a specialized oral cavity. Next, this air-filled cavity is closed off while elastic recoil of the lungs directs stale air out through the mouth and nostrils. Finally, with the nostrils and mouth closed and the oral cavity open to the trachea, the floor of the oral cavity rises, forcing air into the lungs.

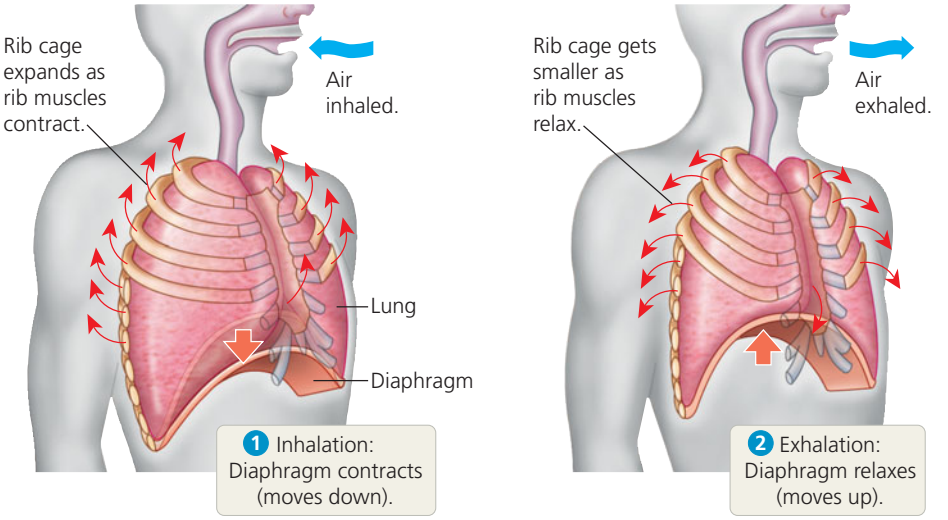
To bring fresh air to their lungs, birds use eight or nine air sacs situated on either side of the lungs. The air sacs do not function directly in gas exchange but act as bellows that keep air flowing through the lungs. Instead of alveoli, the sites of gas exchange in bird lungs are tiny channels called *parabronchi*. Passage of air through the entire system—lungs and air sacs—requires two cycles of inhalation and exhalation.

Two features of ventilation in birds make it highly efficient. First, when birds breathe, air passes over the gas exchange surface in only one direction. Second, incoming fresh air does not mix with air that has already carried out gas exchange.

How a Mammal Breathes

Mammals employ **negative pressure breathing**—pulling, rather than pushing, air into their lungs **(Figure 34.22)**. Using muscle contraction to actively expand their thoracic cavity, mammals lower air pressure in their lungs below that of the outside air. Because gas flows from a region of higher pressure to a region of lower pressure, air rushes through the nostrils and mouth and down the breathing tubes to the alveoli. During exhalation, the muscles controlling the thoracic cavity relax, and the cavity's volume is reduced. The increased air pressure in the alveoli forces air up the breathing tubes and out of the body. Thus, inhalation is always active and requires work, whereas exhalation is usually passive.

Expanding the thoracic cavity during inhalation involves rib muscles and the **diaphragm**, a sheet of skeletal muscle that forms the bottom wall of the cavity. Contracting one set of rib muscles expands the rib cage, the front wall of the thoracic cavity, by pulling the ribs upward and the sternum outward. At the same time, the diaphragm contracts, expanding the thoracic cavity downward. The effect of the descending diaphragm is similar to that of a plunger being drawn out of a syringe.



▲ Figure 34.22 Negative pressure breathing. A mammal breathes by changing the air pressure within its lungs relative to the pressure of the outside atmosphere.

Within the thoracic cavity, a double membrane surrounds the lungs. The inner layer of this membrane adheres to the outside of the lungs, and the outer layer adheres to the wall of the thoracic cavity. A thin space filled with fluid separates the two layers. Surface tension in the fluid causes the two layers to stick together like two plates of glass separated by a film of water: The layers can slide smoothly past each other, but they cannot be pulled apart easily. Consequently, the volume of the thoracic cavity and the volume of the lungs change in unison.

The volume of air inhaled and exhaled with each breath is called **tidal volume**. It averages about 500 mL in resting adult humans. The tidal volume during maximal inhalation and exhalation is the **vital capacity**, which is about 3.4 L and 4.8 L for college-age women and men, respectively. The air that remains after a forced exhalation is called the **residual volume**. As humans age, our lungs lose their resilience, and residual volume increases at the expense of vital capacity.

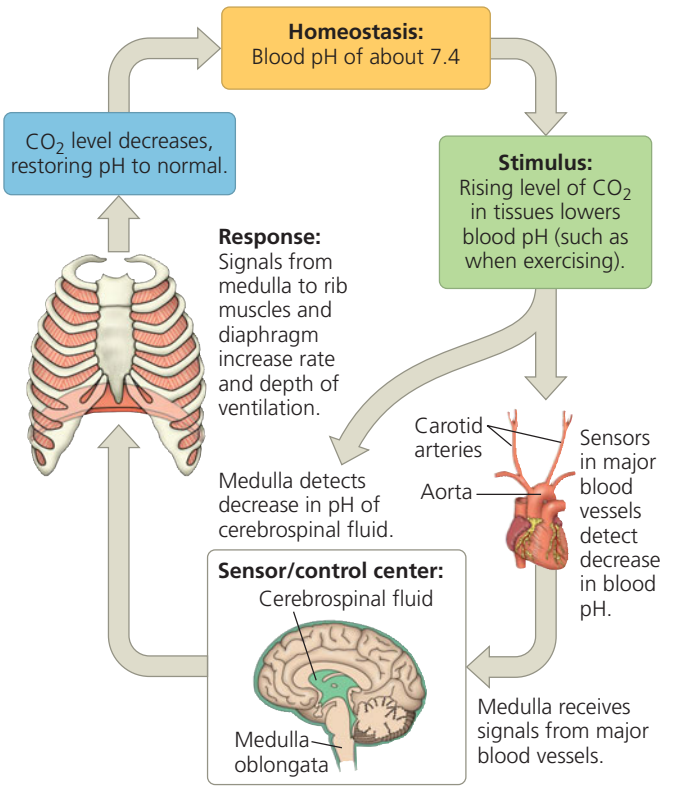
Because the lungs in mammals do not completely empty with each breath, and because inhalation occurs through the same airways as exhalation, each inhalation mixes fresh air with oxygen-depleted residual air. As a result, the maximum P_{O_2} in alveoli is always considerably less than in the atmosphere. This is one reason mammals don't function as well as birds at high altitude. For example, humans have great difficulty obtaining enough O_2 when climbing Earth's highest peaks, such as Mount Everest (8,850 m) in the Himalayas. However, bar-headed geese and several other bird species easily fly through high Himalayan passes during their migrations.

Control of Breathing in Humans

Although you can voluntarily hold your breath or breathe faster and deeper, most of the time your breathing is regulated by involuntary mechanisms. These control mechanisms ensure that gas exchange is coordinated with blood circulation and with metabolic demand.

The neurons mainly responsible for regulating breathing are in the medulla oblongata, near the base of the brain **(Figure 34.23)**. Neural circuits in the medulla form a breathing control center that establishes the breathing rhythm. When you breathe deeply, a negative-feedback mechanism prevents the lungs from overexpanding: During inhalation, sensors that detect stretching of the lung tissue send nerve impulses to the control circuits in the medulla, inhibiting further inhalation.

In regulating breathing, the medulla uses the pH of the surrounding tissue fluid as an indicator of blood CO_2 concentration. The reason pH can be used in this way is that blood CO_2 is the main determinant of the pH of cerebrospinal fluid, the fluid surrounding the brain and spinal cord. Carbon dioxide diffuses from the blood to the cerebrospinal fluid, where it reacts with water and forms carbonic acid (H_2CO_3). The



▲ Figure 34.23 Homeostatic control of breathing.

WHAT IF? *Suppose a person began breathing very rapidly while resting. Describe the effect on blood CO_2 levels and the steps by which the negative-feedback circuit would restore homeostasis.*

H_2CO_3 can then dissociate into a bicarbonate ion (HCO_3^-) and a hydrogen ion (H^+):

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Increased metabolic activity, such as occurs during exercise, increases the concentration of CO_2 in the blood, and lowers pH through the reaction shown above. Sensors in the medulla as well as in major blood vessels detect this pH change. In response, the medulla's control circuits increase the depth and rate of breathing (see Figure 34.23). Both remain high until the excess CO_2 is eliminated in exhaled air and pH returns to a normal value.

The blood O_2 level usually has little effect on the breathing control centers. However, when the O_2 level drops very low (at high altitudes, for instance), O_2 sensors in the aorta and the carotid arteries in the neck send signals to the breathing control centers, which respond by increasing the breathing rate.

Breathing control is effective only if ventilation is matched to blood flow through the capillaries in the alveoli. During exercise, for instance, such coordination couples an increased breathing rate, which enhances O_2 uptake and CO_2 removal, with an increase in cardiac output.

CONCEPT CHECK 34.6

1. How does an increase in the CO_2 concentration in the blood affect the pH of cerebrospinal fluid?
2. A drop in blood pH causes an increase in heart rate. What is the function of this control mechanism?
3. **WHAT IF?** If an injury tore a small hole in the membranes surrounding your lungs, what effect on lung function would you expect?

For suggested answers, see Appendix A.

CONCEPT 34.7

Adaptations for gas exchange include pigments that bind and transport gases

The high metabolic demands of many animals necessitate the exchange of large quantities of O_2 and CO_2. Blood molecules called respiratory pigments facilitate this exchange through their interaction with O_2 and CO_2. Before exploring how respiratory pigments function, let's summarize the basic gas exchange circuit in humans.

Coordination of Circulation and Gas Exchange

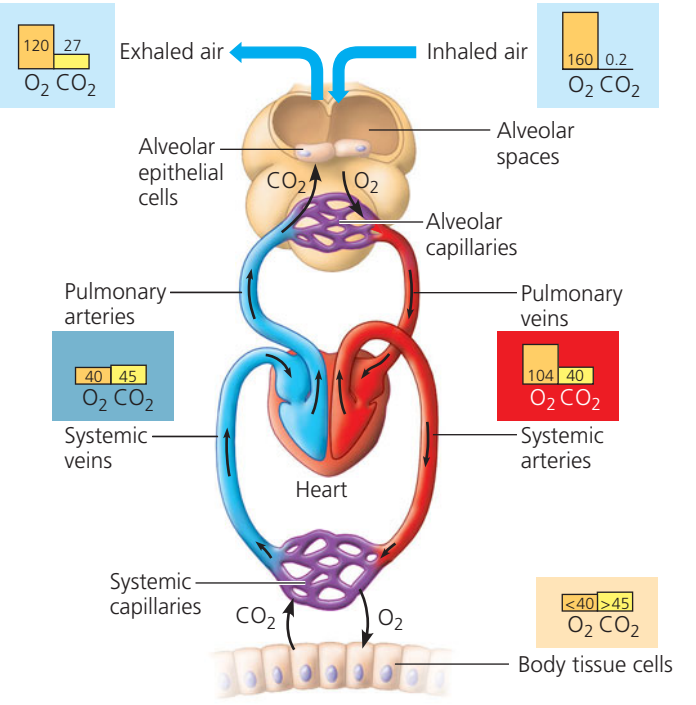
The partial pressures of O_2 and CO_2 in the blood vary at different points in the circulatory system, as shown in **Figure 34.24**. Blood flowing through the alveolar capillaries has a lower P_{O_2} and a higher P_{CO_2} than the air in the alveoli. As a result, CO_2 diffuses down its partial pressure gradient from the blood to the air in the alveoli. Meanwhile, O_2 in the air dissolves in the fluid that coats the alveolar epithelium and undergoes net diffusion into the blood. By the time the blood leaves the lungs in the pulmonary veins, its P_{O_2} has been raised and its P_{CO_2} has been lowered. After returning to the heart, this blood is pumped through the systemic circuit.

In the tissue capillaries, gradients of partial pressure favor the net diffusion of O_2 out of the blood and CO_2 into the blood. These gradients exist because cellular respiration in the mitochondria of cells near each capillary removes O_2 from and adds CO_2 to the surrounding interstitial fluid. After the blood unloads O_2 and loads CO_2, it is returned to the heart and pumped to the lungs again.

Having characterized the driving forces for gas exchange in different tissues, we will now introduce the critical role of the specialized carrier proteins—the respiratory pigments.

Respiratory Pigments

The low solubility of O_2 in water (and thus in blood) poses a problem for animals that rely on the circulatory system to deliver O_2. For example, a person requires almost 2 L of O_2 per minute during intense exercise, and all of it must be carried in the blood from the lungs to the active tissues. At normal body temperature and air pressure, however, only 4.5 mL of O_2 can dissolve into a



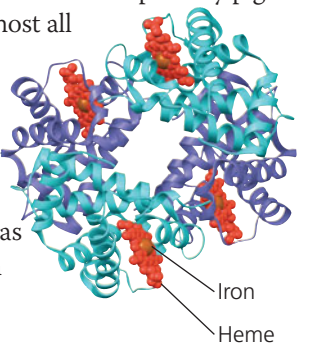
▲ Figure 34.24 Loading and unloading of respiratory gases. The colored bars indicate the partial pressures (in mm Hg) of O_2 (P_{O_2}) and CO_2 (P_{CO_2}) in different locations.

WHAT IF? *If you consciously forced more air out of your lungs each time you exhaled, how would that affect the values shown above?*

liter of blood in the lungs. Even if 80% of the dissolved O_2 were delivered to the tissues (an unrealistically high percentage), the heart would still need to pump 555 L of blood per minute!

In fact, animals transport most of their O_2 bound to proteins called **respiratory pigments**. Respiratory pigments circulate with the blood or hemolymph and are often contained within specialized cells. The pigments greatly increase the amount of O_2 that can be carried in the circulatory fluid (to about 200 mL of O_2 per liter in mammalian blood). In our example of an exercising human with an O_2 delivery rate of 80%, the presence of a respiratory pigment reduces the cardiac output necessary for O_2 transport to a manageable 12.5 L of blood per minute.

A variety of respiratory pigments have evolved among the animal taxa. With a few exceptions, these molecules have a distinctive color (hence the term *pigment*) and consist of a metal bound to a protein. One example is the blue pigment hemocyanin, which has copper as its oxygen-binding component and is found in arthropods and many molluscs. The respiratory pigment of many invertebrates and almost all vertebrates is hemoglobin.

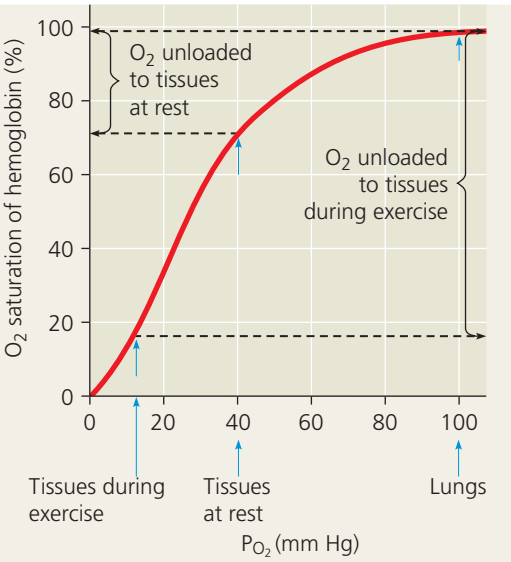


Hemoglobin

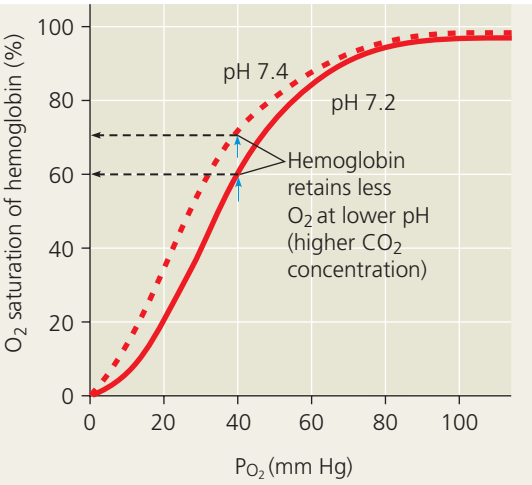
In vertebrates, hemoglobin is contained in the erythrocytes and consists of four subunits (polypeptide chains), each with a cofactor called a heme group that has an iron atom at its center. Each iron atom binds one molecule of O_2; hence, a single hemoglobin molecule can carry four molecules of O_2. Like all respiratory pigments, hemoglobin binds O_2 reversibly, loading O_2 in the lungs or gills and unloading it in other parts of the body. This process depends on cooperativity between the hemoglobin subunits (see Concept 6.5). When O_2 binds to one subunit, the others change shape slightly, increasing their affinity for O_2. Similarly, when four O_2 molecules are bound and one subunit unloads its O_2, the other three subunits more readily unload O_2, as an associated shape change lowers their affinity for O_2.

The cooperativity in both O_2 binding and release is evident in the dissociation curve for hemoglobin **(Figure 34.25a)**. Over the range of P_{O_2} where the dissociation curve has a steep slope, even a slight change in P_{O_2} causes hemoglobin to load or unload a substantial amount of O_2. Notice that the steep part of the curve corresponds to the range of P_{O_2} found in body tissues. When cells in a particular location begin working harder—during exercise, for instance—P_{O_2} dips in their vicinity as the O_2 is consumed in cellular respiration. Because of the effect of subunit cooperativity, a slight drop in P_{O_2} causes a relatively large increase in the amount of O_2 the blood unloads.

The production of CO_2 during cellular respiration promotes the unloading of O_2 by hemoglobin in active tissues. As we have seen, CO_2 reacts with water, forming carbonic acid, which lowers the pH of its surroundings. Low pH, in turn, decreases the affinity of hemoglobin for O_2, an effect called the **Bohr shift (Figure 34.25b)**. Thus, where CO_2 production is greater, hemoglobin releases more O_2, which can then be used to support more cellular respiration.



(a) P_{O_2} and hemoglobin dissociation at pH 7.4. The curve shows the relative amounts of O_2 bound to hemoglobin exposed to solutions with different P_{O_2}. At a P_{O_2} of 100 mm Hg, typical in the lungs, hemoglobin is about 98% saturated with O_2. At a P_{O_2} of 40 mm Hg, common in the vicinity of tissues at rest, hemoglobin is about 70% saturated, having unloaded nearly a third of its O_2. As shown in the above graph, hemoglobin can release much more O_2 to metabolically very active tissues, such as muscle tissue during exercise.



(b) pH and hemoglobin dissociation. Because hydrogen ions affect the shape of hemoglobin, a drop in pH shifts the O_2 dissociation curve toward the right (the Bohr shift). At a given P_{O_2}, say 40 mm Hg, hemoglobin gives up more O_2 at pH 7.2 than at pH 7.4, the normal pH of human blood. The pH is lower in very active tissues because the CO_2 produced by cellular respiration reacts with water, forming carbonic acid. There, hemoglobin releases more O_2, which supports the increased cellular respiration in the active tissues.

▲ Figure 34.25 Dissociation curves for hemoglobin at 37°C.

In addition to its role in O_2 transport, hemoglobin assists in buffering the blood—that is, preventing harmful changes in pH. It also has a minor role in CO_2 transport, the topic we will explore next.

Carbon Dioxide Transport

Only about 7% of the CO_2 released by respiring cells is transported in solution in blood plasma. The remainder diffuses from the plasma into erythrocytes and reacts with water (assisted by the enzyme carbonic anhydrase), forming H_2CO_3. The H_2CO_3 readily dissociates into H^+ and HCO_3^-. Most of the H^+ binds to hemoglobin and other proteins, minimizing the change in blood pH. Most of the HCO_3^- diffuses out of the erythrocyte and is transported to the lungs in the plasma. The remainder, about 5% of the overall CO_2, binds to hemoglobin and is transported in erythrocytes.

When blood flows through the lungs, the relative partial pressures of CO_2 favor the diffusion of CO_2 out of the blood. As CO_2 diffuses from blood into alveoli, the amount of CO_2 in the blood decreases. This decrease shifts the chemical equilibrium in favor of the conversion of HCO_3^- to CO_2, enabling further net diffusion of CO_2 into alveoli. Overall, the P_{CO_2} gradient is sufficient to reduce P_{CO_2} by about 15% during passage of blood through the lungs.

Respiratory Adaptations of Diving Mammals

EVOLUTION Animals vary greatly in their ability to temporarily inhabit environments in which there is no access to their normal respiratory medium—for example, when an air-breathing mammal swims underwater. Whereas most humans, even well-trained divers, cannot hold their breath longer than 2 or 3 minutes or swim deeper than 20 m, the Weddell seal of Antarctica routinely plunges to 200–500 m and remains there for about 20 minutes (and sometimes for more than an hour). Another diving mammal, the elephant seal, can reach depths of 1,500 m—almost a mile—and stay submerged for as long as 2 hours! What evolutionary adaptations enable these animals to perform such amazing feats?

One adaptation of diving mammals to prolonged stays underwater is an ability to store large amounts of O_2. The Weddell seal has a greater volume of blood per kilogram of body mass than a human and has a high concentration of an oxygen-storing protein called **myoglobin** in its muscles. As a result, the Weddell seal can store about twice as much O_2 per kilogram of body mass as can a human.

Diving mammals not only have a relatively large O_2 stockpile but also have adaptations that conserve O_2. They swim with little muscular effort and glide passively upward or downward by changing their buoyancy. During a dive, most blood is routed to the brain, spinal cord, eyes, adrenal glands, and, in pregnant seals, the placenta. Blood supply to the muscles is restricted or, during the longest dives, shut off altogether. During dives of more than about 20 minutes, a Weddell seal's muscles deplete the O_2 stored in myoglobin and then derive their ATP from fermentation instead of respiration.

The unusual abilities of the Weddell seal and other air-breathing divers to power their bodies during long dives showcase two related themes in our study of organisms—the response to environmental challenges over the short term by physiological adjustments and over the long term as a result of natural selection.

CONCEPT CHECK 34.7

1. What determines whether the net diffusion of O_2 and CO_2 is into or out of the capillaries? Explain.
2. How does the Bohr shift help deliver O_2 to very active tissues?
3. **WHAT IF?** A doctor might give bicarbonate (HCO_3^-) to a patient who is breathing very rapidly. What assumption is the doctor making about the blood chemistry of the patient?

For suggested answers, see Appendix A.

34 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 34.1

Circulatory systems link exchange surfaces with cells throughout the body (pp. 685–688)

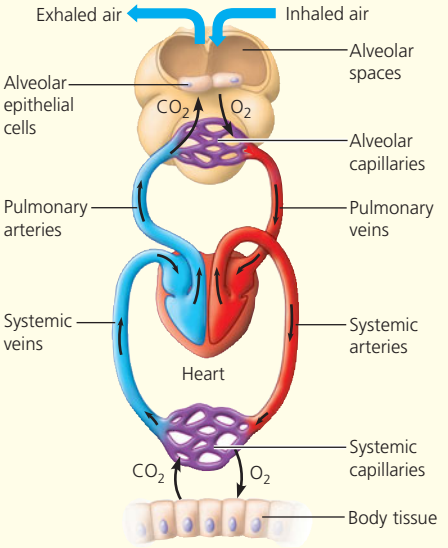
- In animals with simple body plans, a **gastrovascular cavity** mediates exchange between the environment and body cells. Because net diffusion is slow over long distances, most complex animals have a circulatory system that moves fluid between cells and the organs that carry out exchange with the environment. Arthropods and most molluscs have an **open circulatory system**, in which **hemolymph** bathes organs directly. Vertebrates have a **closed circulatory system**, in which **blood** circulates in a closed network of pumps and vessels.
- The closed circulatory system of vertebrates consists of blood, blood vessels, and a two- to four-chambered **heart**. Blood pumped by a heart **ventricle** passes to **arteries** and then to **capillaries**, the sites of chemical exchange between blood and interstitial fluid. **Veins** return blood from capillaries to an **atrium**, which passes blood to a ventricle.
- Fishes, rays, and sharks have a single pump in their circulatory systems, whereas air-breathing vertebrates have two pumps combined in a single heart. Variations between different species in ventricle number and divisions reflect adaptations to different environments and metabolic needs.

? *How does the flow of a fluid in a closed circulatory system differ from the movement of molecules between cells and their environment with regard to distance traveled, direction traveled, and driving force?*

CONCEPT 34.2

Coordinated cycles of heart contraction drive double circulation in mammals (pp. 689–690)

- The right ventricle pumps blood to the lungs, where it loads O_2 and unloads CO_2. Oxygen-rich blood from the lungs enters the heart at the left atrium and is pumped to the body tissues by the left ventricle. Blood returns to the heart through the right atrium.



- The **cardiac cycle**, one complete sequence of the heart's pumping and filling, consists of a period of contraction, called **systole**, and a period of relaxation, called **diastole**. The heartbeat originates with impulses at the **sinoatrial (SA) node** (pacemaker) of the right atrium. The impulses trigger atrial contraction, are delayed at the **atrioventricular (AV) node**, and then cause ventricular contraction. The nervous system, hormones, and body temperature influence pacemaker activity.

? *What changes in cardiac function might you expect after surgical replacement of a defective heart valve?*

CONCEPT 34.3

Patterns of blood pressure and flow reflect the structure and arrangement of blood vessels (pp. 690–694)

- Blood vessels have structures well adapted to function. Capillaries have narrow diameters and thin walls that facilitate exchange. Arteries contain thick elastic walls that maintain blood pressure. Veins contain one-way valves that contribute to the return of blood to the heart. Blood pressure is altered by changes in cardiac output and by variable constriction of arterioles.
- The velocity of blood flow is lowest in the capillary beds as a result of their large total cross-section area. Fluid leaks out of capillaries and is returned to blood by the **lymphatic system**, which also plays a vital role in defense against infection.

? *If you rest your forearm on the top of your head rather than by your side, how, if at all, is blood pressure in that arm affected? Explain.*

CONCEPT 34.4

Blood components function in exchange, transport, and defense (pp. 695–698)

- Whole blood consists of cells and cell fragments (**platelets**) suspended in a liquid matrix called **plasma**. Plasma proteins influence blood pH, osmotic pressure, and viscosity, and they function in lipid transport, immunity (antibodies), and blood clotting (fibrinogen). Red blood cells, or **erythrocytes**, transport O_2. White blood cells, or **leukocytes**, function in defense against microbes and foreign substances. Platelets function in blood clotting.
- A variety of diseases impair function of the circulatory system. In **sickle-cell disease**, an aberrant form of **hemoglobin** disrupts erythrocyte shape and function. In cardiovascular disease, inflammation of the arterial lining enhances deposition of lipids and cells, resulting in the potential for life-threatening damage to the heart or brain.

? *In the absence of infection, what percentage of cells in human blood are leukocytes?*

CONCEPT 34.5

Gas exchange occurs across specialized respiratory surfaces (pp. 698–704)

- At all sites of **gas exchange**, a gas undergoes net diffusion from where its **partial pressure** is higher to where it is lower. Air is more conducive to gas exchange than water because air has a higher O_2 content, lower density, and lower viscosity.
- Gills are outfoldings of the body specialized for gas exchange in water. The effectiveness of gas exchange in some gills, including those of fishes, is increased by **ventilation** and **countercurrent exchange** between blood and water. Gas exchange in insects relies on a **tracheal system**, a branched network of tubes that brings O_2 directly to cells. Spiders, land snails, and most terrestrial vertebrates have **lungs**. In mammals, inhaled air passes through the pharynx into the **trachea, bronchi,** bronchioles, and dead-end **alveoli**, where gas exchange occurs.

? *Why does altitude have almost no effect on an animal's ability to rid itself of CO_2 through gas exchange?*

CONCEPT 34.6

Breathing ventilates the lungs (pp. 704–706)

- Breathing mechanisms vary substantially among vertebrates. An amphibian ventilates its lungs by **positive pressure breathing**, which forces air down the trachea. Birds use a system of air sacs as bellows to keep air flowing through the lungs in one direction only. Mammals ventilate their lungs by **negative pressure breathing**, which pulls air into the lungs. Lung volume increases as the rib muscles and **diaphragm** contract. Incoming and outgoing air mix, decreasing the efficiency of ventilation.
- Control centers in the brain regulate the rate and depth of breathing. Sensors detect the pH of cerebrospinal fluid (reflecting CO_2 concentration in the blood), and the medulla adjusts breathing rate and depth to match metabolic demands. Secondary control is exerted by sensors in the aorta and carotid arteries that monitor blood levels of O_2 as well as CO_2 (via blood pH).

? *How does air in the lungs differ from the fresh air that enters the body during inspiration?*

CONCEPT 34.7

Adaptations for gas exchange include pigments that bind and transport gases (pp. 706–708)

- In the lungs, gradients of partial pressure favor the net diffusion of O_2 into the blood and CO_2 out of the blood. The opposite situation exists in the rest of the body. **Respiratory pigments**, such as hemoglobin, bind O_2, greatly increasing the amount of O_2 transported by the circulatory system.
- Evolutionary adaptations enable some animals to satisfy extraordinary O_2 demands. Deep-diving air-breathers stockpile O_2 in blood and other tissues and deplete it slowly.

? *In what way is the role of a respiratory pigment like that of an enzyme?*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

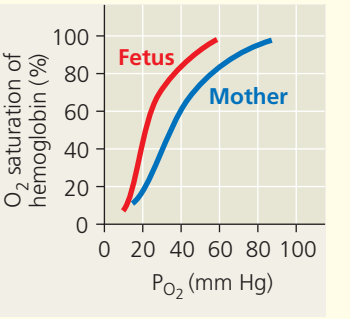
1. Which of the following respiratory systems is not closely associated with a blood supply?
   a. the lungs of a vertebrate
   b. the gills of a fish
   c. the tracheal system of an insect
   d. the skin of an earthworm
   e. the parapodia of a polychaete worm
2. Blood returning to the mammalian heart in a pulmonary vein drains first into the
   a. vena cava.
   b. left atrium.
   c. right atrium.
   d. left ventricle.
   e. right ventricle.
3. Pulse is a direct measure of
   a. blood pressure.
   b. stroke volume.
   c. cardiac output.
   d. heart rate.
   e. breathing rate.
4. When you hold your breath, which of the following blood gas changes first leads to the urge to breathe?
   a. rising O_2
   b. falling O_2
   c. rising CO_2
   d. falling CO_2
   e. rising CO_2 and falling O_2

Level 2: Application/Analysis

5. If a molecule of CO_2 released into the blood in your left toe is exhaled from your nose, it must pass through all of the following *except*
   a. the pulmonary vein.
   b. an alveolus.
   c. the trachea.
   d. the right atrium.
   e. the right ventricle.
6. Compared with the interstitial fluid that bathes active muscle cells, blood reaching these cells in arteries has a
   a. higher P_{O_2}.
   b. higher P_{CO_2}.
   c. greater bicarbonate concentration.
   d. lower pH.
   e. lower osmotic pressure.
7. Which of the following would *increase* the amount of oxygen undergoing net diffusion from the lungs into the blood?
   a. increasing the binding of oxygen to hemoglobin
   b. increasing the water vapor content of air in the lungs
   c. increasing the partial pressure of oxygen in the blood
   d. decreasing the red blood cell count of the blood
   e. decreasing the partial pressure of oxygen in the lung

Level 3: Synthesis/Evaluation

8. **DRAW IT** Plot blood pressure against time for one cardiac cycle in humans, drawing separate lines for the pressure in the aorta, the left ventricle, and the right ventricle. Below the time axis, add a vertical arrow pointing to the time when you expect a peak in atrial blood pressure.
9. **SCIENTIFIC INQUIRY**
   The hemoglobin of a human fetus differs from adult hemoglobin. Compare the dissociation curves of the two hemoglobins in the graph at right. Propose a hypothesis to explain the benefit of this difference between these two hemoglobins.



10. **FOCUS ON EVOLUTION**
    One of the many mutant opponents of the movie monster Godzilla is Mothra, a giant mothlike creature with a wingspan of several dozen meters. However, the largest known insects were Paleozoic dragonflies with half-meter wingspans. Focusing on respiration and gas exchange, explain why truly giant insects are improbable.
11. **FOCUS ON INTERACTIONS**
    Some athletes prepare for competition at sea level by sleeping in a tent in which P_{O_2} is kept artificially low. When climbing very high peaks, some mountaineers breathe from bottles of pure O_2. Relate these behaviors to humans' physiological interactions with our gaseous environment and control mechanisms governing oxygen delivery within the body.

For selected answers, see Appendix A.

35 The Immune System

KEY CONCEPTS

35.1 In innate immunity, recognition and response rely on traits common to groups of pathogens

35.2 In adaptive immunity, receptors provide pathogen-specific recognition

35.3 Adaptive immunity defends against infection of body fluids and body cells

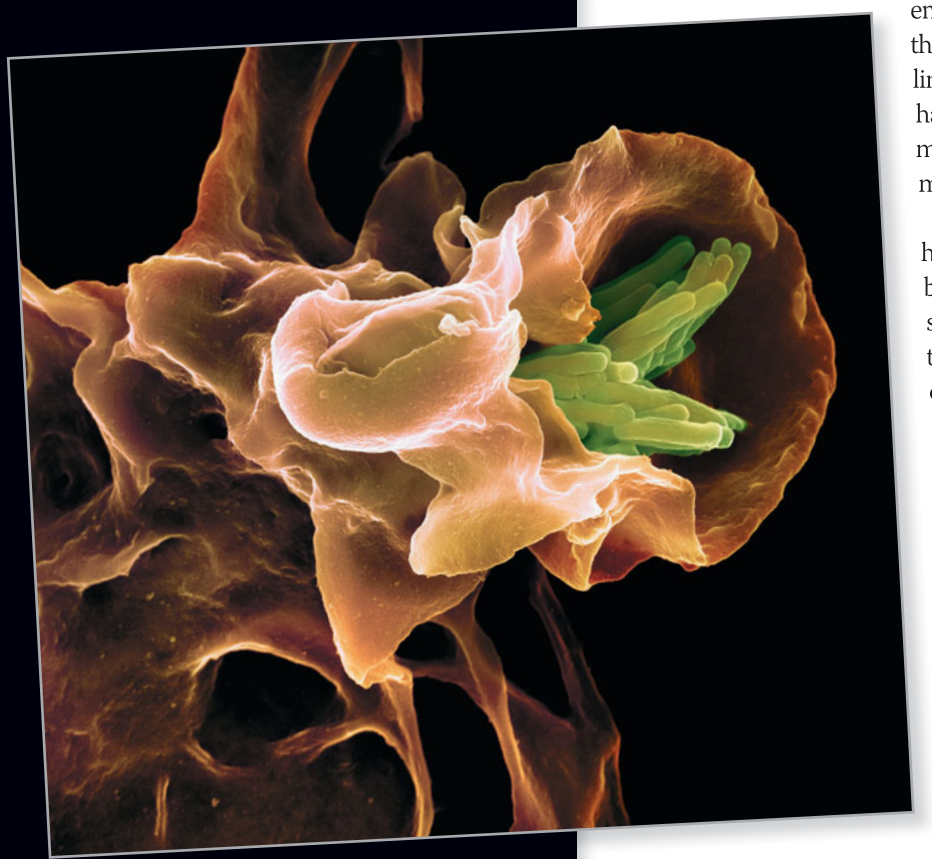
OVERVIEW

Recognition and Response

For a **pathogen**—a bacterium, fungus, virus, or other disease-causing agent—the internal environment of an animal is a nearly ideal habitat. The animal body offers a ready source of nutrients, a protected setting for growth and reproduction, and a means of transport to new environments. From the perspective of a cold or flu virus, we are wonderful hosts. From our vantage point, the situation is not so ideal. Fortunately, adaptations have arisen over the course of evolution that protect animals against many invaders.

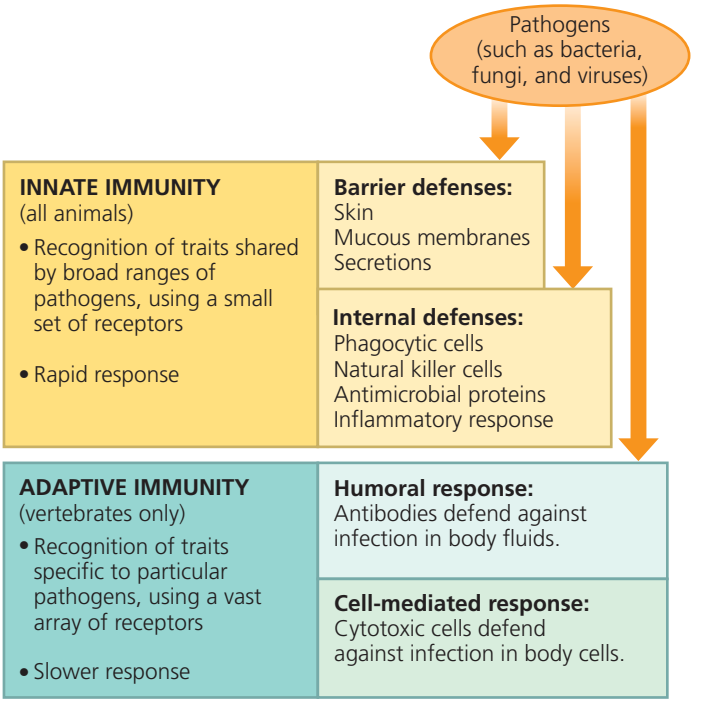
Dedicated immune cells in the body fluids and tissues of most animals specifically interact with and destroy pathogens. For example, **Figure 35.1** shows an immune cell called a macrophage (brown) surrounding and engulfing a clump of bacteria (green). Immune cells also release defense molecules into body fluids, including proteins that punch holes in bacterial membranes or block viruses from entering body cells. Together, the body's defenses make up the **immune system**, which enables an animal to avoid or limit many infections. A foreign molecule or cell doesn't have to be pathogenic (disease-causing) to elicit an immune response, but we'll focus in this chapter on the immune system's role in defending against pathogens.

▼ **Figure 35.1** What triggered this attack by an immune cell on a clump of rod-shaped bacteria?



The first lines of defense offered by immune systems help prevent pathogens from gaining entrance to the body. For example, an outer covering, such as a shell or skin, blocks entry by many microbes. Sealing off the entire body surface is impossible, however, because gas exchange, nutrition, and reproduction require openings to the environment. Secretions that trap or kill microbes guard the body's entrances and exits, while the linings of the digestive tract, airway, and other exchange surfaces provide additional barriers to infection.

If a pathogen breaches barrier defenses and enters the body, the problem of how to fend off attack changes substantially. Housed within body fluids and tissues, the invader is no longer an outsider. To fight infections, an animal's immune system must detect foreign particles and cells within the body. In other words, a properly functioning immune system distinguishes nonself from self. How is this accomplished? Immune cells produce receptor molecules that bind specifically to molecules from foreign cells or viruses and activate defense responses. The specific binding of immune receptors to foreign molecules is a type of *molecular recognition* and is the central event in identifying nonself particles and cells.



▲ Figure 35.2 Overview of animal immunity. Immune responses can be divided into innate and adaptive immunity. Some components of innate immunity help activate adaptive immune defenses.

Animal immune systems rely on either one or two major components for molecular recognition and defense. All animals have the component called **innate immunity**, which includes barrier defenses. Besides innate immunity, an additional component, called **adaptive immunity**, is found only in vertebrates. **Figure 35.2** provides an overview of the basic components of both innate and adaptive immunity.

Molecular recognition in innate immunity relies on a small set of receptors that bind to molecules or structures that are absent from animal bodies but common to a group of viruses, bacteria, or other microbes. Binding of an innate immune receptor to a foreign molecule activates internal defenses, enabling responses to a very broad range of pathogens.

In adaptive immunity, molecular recognition relies on a vast arsenal of receptors, each of which recognizes a feature typically found only on a particular part of a particular molecule in a particular pathogen. As a result, recognition and response in adaptive immunity occur with tremendous specificity.

The adaptive immune response, also known as the acquired immune response, is activated after the innate immune response and develops more slowly. The names *adaptive* and *acquired* reflect the fact that this immune response is enhanced by previous exposure to the infecting pathogen. Examples of adaptive responses include the synthesis of proteins that inactivate a bacterial toxin and the targeted killing of a virus-infected body cell.

In this chapter, we'll examine how each type of immunity protects animals from disease. You'll also learn how pathogens can avoid or overwhelm the immune system and how defects in the immune system can imperil an animal's health.

CONCEPT 35.1

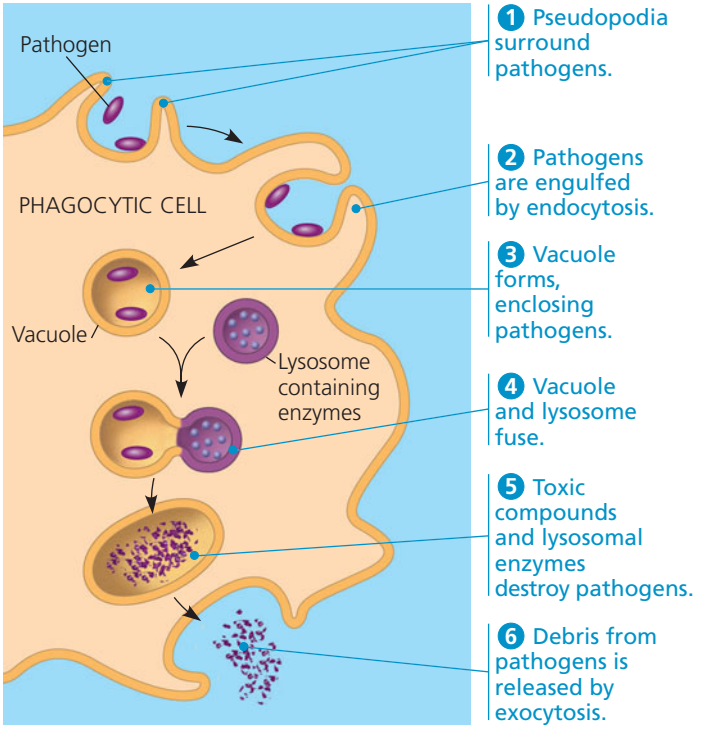
In innate immunity, recognition and response rely on traits common to groups of pathogens

Innate immunity is found in all animals (as well as in plants). In exploring innate immunity, we'll begin with invertebrates, which repel and fight infection with only this type of immunity. We'll then turn to vertebrates, in which innate immunity serves both as an immediate defense against infection and as the foundation for adaptive immune defenses.

Innate Immunity of Invertebrates

The great success of insects in terrestrial and freshwater habitats teeming with diverse microbes highlights the effectiveness of invertebrate innate immunity. In each of these environments, insects rely on their exoskeleton as a first line of defense against infection. Within the digestive system, **lysozyme**, an enzyme that breaks down bacterial cell walls, acts as a chemical barrier against pathogens ingested with food.

Any pathogen that breaches an insect's barrier defenses encounters a number of internal immune defenses. Immune cells called *hemocytes* travel throughout the body in the hemolymph, the insect circulatory fluid. Some hemocytes ingest and break down bacteria and other foreign substances, a process known as **phagocytosis (Figure 35.3)**. Other hemocytes



▲ Figure 35.3 Phagocytosis. This schematic depicts events in the ingestion and destruction of a microbe by a typical phagocytic cell.

release chemicals that kill pathogens and help entrap large invaders, such as *Plasmodium*, the parasite of mosquitoes that causes malaria in humans. One major class of defense molecules consists of antimicrobial peptides, which circulate throughout the body and inactivate or kill fungi and bacteria by disrupting their plasma membranes.

Immune cells of insects bind to molecules found only in the outer layers of fungi or bacteria. Fungal cell walls contain certain unique polysaccharides, whereas bacterial cell walls have polymers containing combinations of sugars and amino acids not found in animal cells. Such macromolecules serve as "identity tags" in the process of pathogen recognition. Insect immune cells secrete recognition proteins, each of which binds to a macromolecule characteristic of a broad class of bacteria or fungi. Once bound to a macromolecule, the recognition protein triggers an innate immune response specific for that class.

Innate Immunity of Vertebrates

Among jawed vertebrates, innate immune defenses coexist with the more recently evolved system of adaptive immunity. Because most of the recent discoveries regarding vertebrate innate immunity have come from studies of mice and humans, we'll focus here on mammals. We'll consider first the innate defenses that are similar to those found among invertebrates: barrier defenses, phagocytosis, and antimicrobial peptides. We'll then examine some unique aspects of vertebrate innate immunity, such as natural killer cells, interferons, and the inflammatory response.

Barrier Defenses

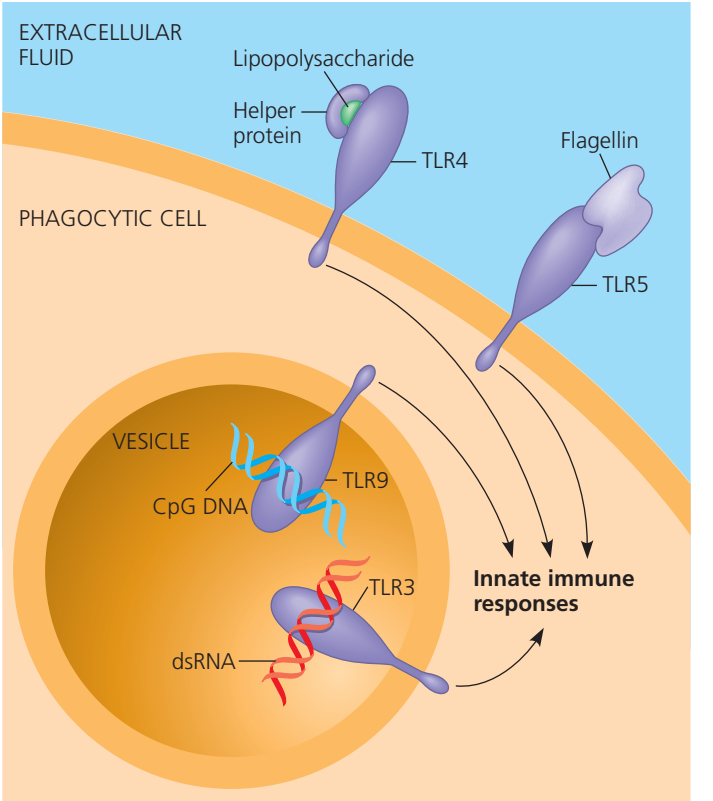
In mammals, barrier defenses block the entry of many pathogens. These defenses include the skin and the mucous membranes lining the digestive, respiratory, urinary, and reproductive tracts. The mucous membranes produce *mucus*, a viscous fluid that traps microbes and other particles. In the airway, ciliated epithelial cells sweep mucus and any entrapped microbes upward, helping prevent infection of the lungs.

Beyond their physical role in inhibiting microbial entry, body secretions create an environment that is hostile to many microbes. Lysozyme in tears, saliva, and mucous secretions destroys the cell walls of susceptible bacteria as they enter the openings around the eyes or the upper respiratory tract. Microbes in food or water and those in swallowed mucus must also contend with the acidic environment of the stomach, which kills most of them before they can enter the intestines. Similarly, secretions from oil and sweat glands give human skin a pH ranging from 3 to 5, acidic enough to prevent the growth of many bacteria.

Cellular Innate Defenses

Pathogens entering the mammalian body are engulfed by phagocytic cells that detect fungal or bacterial components using several types of receptors. Some mammalian receptors are very similar to Toll, a key activator of innate immunity in insects. Each mammalian **Toll-like receptor (TLR)** binds to fragments of molecules characteristic of a set of pathogens **(Figure 35.4)**. For example, TLR3 binds to double-stranded RNA, a form of nucleic acid characteristic of certain viruses. Similarly, TLR4 recognizes lipopolysaccharide, a molecule found on the surface of many bacteria, and TLR5 recognizes flagellin, the main protein of bacterial flagella. In each case, the recognized macromolecule is normally absent from the vertebrate body and is an essential component of certain groups of pathogens.

As in invertebrates, detection of invading pathogens in mammals triggers phagocytosis and destruction. The two main types of phagocytic cells in the mammalian body are neutrophils and macrophages. **Neutrophils**, which circulate in the blood, are attracted by signals from infected tissues. **Macrophages** ("big eaters") are larger phagocytic cells. Some migrate throughout the body, whereas others reside in organs and tissues where they are likely to encounter pathogens. For example, some macrophages are located in the spleen, where pathogens in the blood become trapped.



▲ Figure 35.4 TLR signaling. Each mammalian Toll-like receptor (TLR) recognizes a molecular pattern characteristic of a group of pathogens. Lipopolysaccharide, flagellin, CpG DNA (DNA containing unmethylated CG sequences), and double-stranded RNA (dsRNA) are all found in bacteria, fungi, or viruses, but not in animal cells. Together with other recognition and response factors, TLR proteins trigger internal innate immune defenses.

? *Some TLR proteins are on the cell surface, whereas others are inside vesicles. Suggest a possible benefit of this distribution.*

Two other types of cells—dendritic cells and eosinophils—provide additional functions in innate defense. *Dendritic cells* mainly populate tissues, such as skin, that contact the environment. They stimulate adaptive immunity against pathogens they encounter and engulf, as we'll explore shortly. *Eosinophils*, often found beneath mucous membranes, are important in defending against multicellular invaders, such as parasitic worms. Upon encountering such parasites, eosinophils discharge destructive enzymes.

Cellular innate defenses in vertebrates also involve **natural killer cells**. These cells circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells. Natural killer cells do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.

Many cellular innate defenses in vertebrates involve the lymphatic system (see Figure 34.12). Some macrophages reside in lymph nodes, where they engulf pathogens that have entered the lymph from the interstitial fluid. Dendritic cells reside outside the lymphatic system but migrate to the lymph nodes after interacting with pathogens. Within the lymph nodes, dendritic cells interact with other immune cells, stimulating adaptive immunity.

Antimicrobial Peptides and Proteins

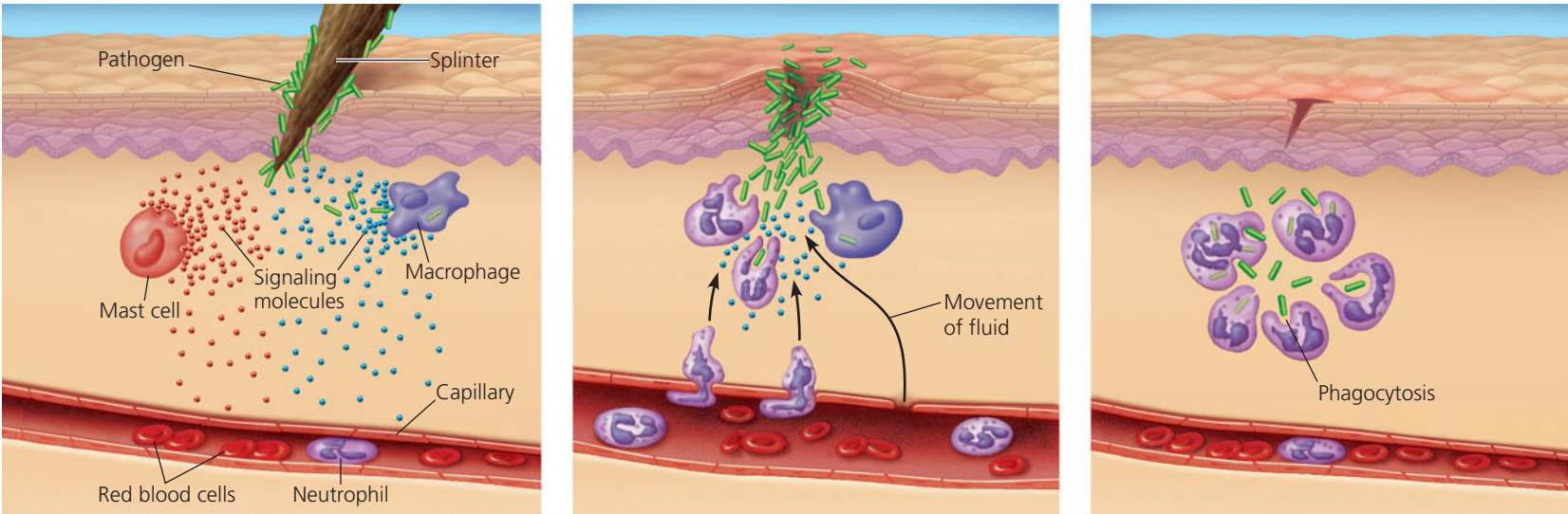
In mammals, pathogen recognition triggers the production and release of a variety of peptides and proteins that attack pathogens or impede their reproduction. Some of these defense molecules function like the antimicrobial peptides of insects, damaging broad groups of pathogens by disrupting membrane integrity. Others, including the interferons and complement proteins, are unique to vertebrate immune systems.

Interferons are proteins that provide innate defense by interfering with viral infections. Virus-infected body cells secrete interferons, which induce nearby uninfected cells to produce substances that inhibit viral reproduction. In this way, interferons limit the cell-to-cell spread of viruses in the body, helping control viral infections such as colds and influenza. Some white blood cells secrete a different type of interferon that helps activate macrophages, enhancing their phagocytic ability. Pharmaceutical companies now use recombinant DNA technology to mass-produce interferons to help treat certain viral infections, such as hepatitis C.

The infection-fighting **complement system** consists of roughly 30 proteins in blood plasma. These proteins circulate in an inactive state and are activated by substances on the surface of many microbes. Activation results in a cascade of biochemical reactions that can lead to lysis (bursting) of invading cells. The complement system also functions in the inflammatory response, our next topic, as well as in the adaptive defenses discussed later in the chapter.

Inflammatory Response

The pain and swelling that alert you to a splinter under your skin are the result of a local **inflammatory response**, the changes brought about by signaling molecules released upon injury or infection **(Figure 35.5)**. One important inflammatory signaling molecule is **histamine**, which is stored in the granules (vesicles) of **mast cells**, found in connective tissue. Histamine released at sites of damage triggers nearby blood vessels to dilate and become more permeable. Activated macrophages and neutrophils discharge **cytokines**, signaling molecules that in an immune response promote blood flow to the site of injury or infection. The increase in local blood supply causes the



1 At the injury site, mast cells release histamines, and macrophages secrete cytokines. These signaling molecules cause nearby capillaries to dilate.

2 Capillaries widen and become more permeable, allowing fluid containing antimicrobial peptides to enter the tissue. Signals released by immune cells attract neutrophils.

3 Neutrophils digest pathogens and cell debris at the site, and the tissue heals.

▲ Figure 35.5 Major events in a local inflammatory response.

redness and increased skin temperature typical of the inflammatory response (from the Latin *inflammare*, to set on fire). Blood-engorged capillaries leak fluid into neighboring tissues, causing swelling.

During inflammation, cycles of signaling and response transform the site. Activated complement proteins promote further release of histamine, attracting more phagocytic cells that enter injured tissues (see Figure 35.5) and carry out additional phagocytosis. At the same time, enhanced blood flow to the site helps deliver antimicrobial peptides. The result is an accumulation of pus, a fluid rich in white blood cells, dead pathogens, and cell debris from damaged tissue.

A minor injury or infection causes a local inflammatory response, but severe tissue damage or infection may lead to a response that is systemic (throughout the body). Cells in injured or infected tissue often secrete molecules that stimulate the release of additional neutrophils from the bone marrow. In a severe infection, such as meningitis or appendicitis, the number of white blood cells in the blood may increase several-fold within a few hours.

Another systemic inflammatory response is fever. In response to certain pathogens, substances released by activated macrophages cause the body's thermostat to reset to a higher temperature (see Concept 32.1). The benefits of the resulting fever are still a subject of debate. One hypothesis is that an elevated body temperature may enhance phagocytosis and, by speeding up chemical reactions, accelerate tissue repair.

Certain bacterial infections can induce an overwhelming systemic inflammatory response, leading to a life-threatening condition called *septic shock*. Characterized by very high fever, low blood pressure, and poor blood flow through capillaries, septic shock occurs most often in the very old and the very young. It is fatal in more than one-third of cases and kills more than 90,000 people each year in the United States alone.

Chronic (ongoing) inflammation can also threaten human health. For example, millions of individuals worldwide suffer from Crohn's disease and ulcerative colitis, often debilitating disorders in which an unregulated inflammatory response disrupts intestinal function.

Evasion of Innate Immunity by Pathogens

Adaptations have evolved in some pathogens that enable them to avoid destruction by phagocytic cells. For example, the outer capsule that surrounds certain bacteria interferes with molecular recognition and phagocytosis. One such bacterium, *Streptococcus pneumoniae*, played a critical role in the discovery that DNA can convey genetic information (see Figure 13.2). Other bacteria, after being engulfed by a host cell, resist breakdown within lysosomes. An example is the bacterium that causes tuberculosis (TB). Rather than being destroyed within host cells, this bacterium grows and reproduces, effectively hidden from the body's innate immune defenses. These and other mechanisms that prevent destruction by the innate immune system make certain fungi and bacteria substantial pathogenic threats. Indeed, TB kills more than a million people a year worldwide.

CONCEPT CHECK 35.1

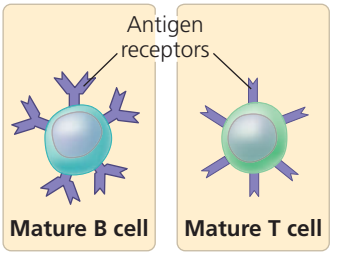
1. Although pus is often seen simply as a sign of infection, it is also an indicator of immune defenses in action. Explain.
2. **MAKE CONNECTIONS** How do the molecules that activate the vertebrate TLR signal transduction pathway differ from the ligands in most other signaling pathways (see Concept 5.6)?
3. **WHAT IF?** Suppose humans were the major host for a bacterial species. What temperature would you predict would be optimal for growth of this species? Explain.

For suggested answers, see Appendix A.

CONCEPT 35.2

In adaptive immunity, receptors provide pathogen-specific recognition

Vertebrates are unique in having adaptive immunity in addition to innate immunity. The adaptive response relies on T cells and B cells, which are types of white blood cells called **lymphocytes**. Like all blood cells, lymphocytes originate from stem cells in the bone marrow. Some lymphocytes migrate from the bone marrow to the **thymus**, an organ in the thoracic cavity above the heart (see Figure 34.12). These lymphocytes mature into **T cells**. Lymphocytes that remain and mature in the bone marrow develop as **B cells**.



Any substance that elicits a response from a B cell or T cell is called an **antigen**. In adaptive immunity, recognition occurs when a B cell or T cell binds to an antigen, such as a bacterial or viral protein, via a protein called an **antigen receptor**. An antigen receptor is specific enough to bind to just one part of one molecule from a particular pathogen, such as a species of bacteria or strain of virus. Although the cells of the immune system produce millions of different antigen receptors, all of the antigen receptors made by a single B or T cell are identical. Infection by a virus, bacterium, or other pathogen triggers activation of B and T cells with antigen receptors specific for parts of that pathogen. B and T cells are shown in this text with only a few antigen receptors, but there are actually about 100,000 antigen receptors on the surface of a single B or T cell.

Antigens are usually foreign and are typically large molecules, either proteins or polysaccharides. The small, accessible portion of an antigen that binds to an antigen receptor is called an **epitope**, or *antigenic determinant*. An example is a group of amino acids in a particular protein. A single antigen usually has several different epitopes, each of which binds to a receptor with a different specificity. Because all antigen receptors

produced by a single B cell or T cell are identical, they bind to the same epitope. Each B or T cell thus displays *specificity* for a particular epitope, enabling it to respond to any pathogen that produces molecules containing that same epitope.

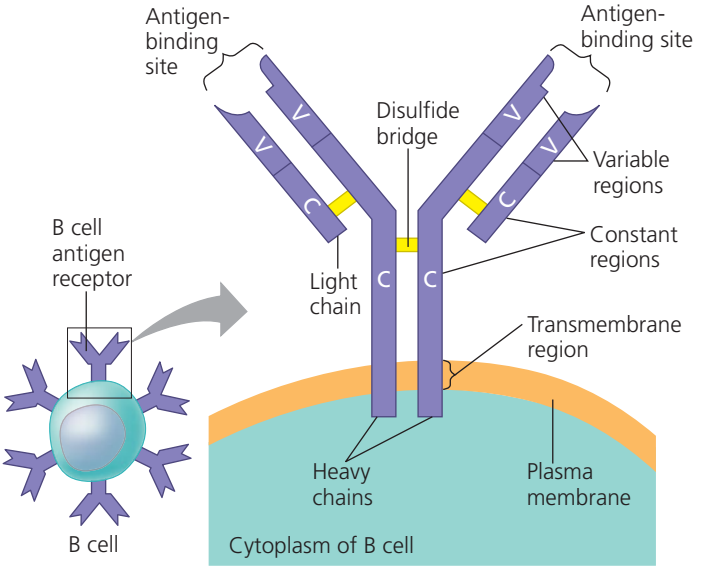
The antigen receptors of B cells and T cells have similar components, but they encounter antigens in different ways. We'll consider the two processes in turn.

Antigen Recognition by B Cells and Antibodies

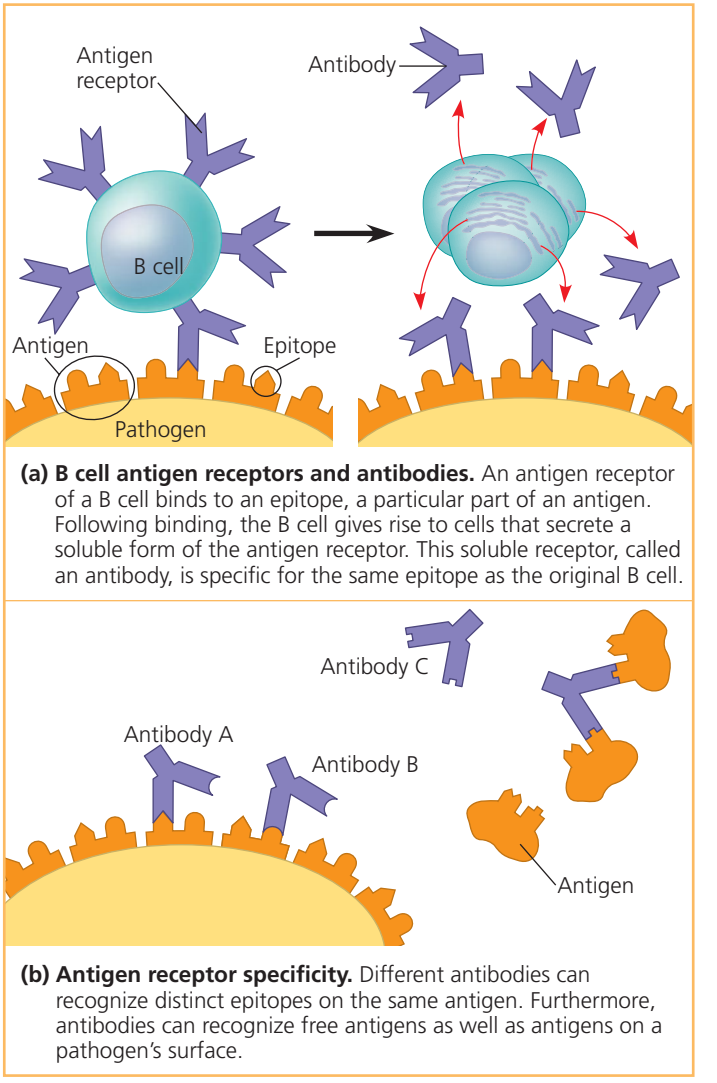
Each B cell antigen receptor is a Y-shaped molecule consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains**, with disulfide bridges linking the chains together **(Figure 35.6)**. A transmembrane region near one end of each heavy chain anchors the receptor in the cell's plasma membrane. A short tail region at the end of the heavy chain extends into the cytoplasm.

The light and heavy chains each have a *constant (C) region*, where amino acid sequences vary little among the receptors on different B cells. Within the two tips of the Y shape (see Figure 35.6), each chain has a *variable (V) region*, so named because its amino acid sequence varies extensively from one B cell to another. Together, parts of a heavy-chain V region and a light-chain V region form an asymmetric binding site for an antigen. As shown in Figure 35.6, each B cell antigen receptor has two identical antigen-binding sites.

The binding of a B cell antigen receptor to an antigen is an early step in B cell activation, leading eventually to formation of cells that secrete a soluble form of the receptor **(Figure 35.7a)**. This secreted protein is called an **antibody**, or **immunoglobulin (Ig)**. Antibodies have the same Y-shaped organization as B cell antigen receptors, but they are secreted rather than membrane-bound. It is the antibodies, rather than the B cells themselves, that actually help defend against pathogens.



▲ **Figure 35.6 The structure of a B cell antigen receptor.**



(a) B cell antigen receptors and antibodies. An antigen receptor of a B cell binds to an epitope, a particular part of an antigen. Following binding, the B cell gives rise to cells that secrete a soluble form of the antigen receptor. This soluble receptor, called an antibody, is specific for the same epitope as the original B cell.

(b) Antigen receptor specificity. Different antibodies can recognize distinct epitopes on the same antigen. Furthermore, antibodies can recognize free antigens as well as antigens on a pathogen's surface.

▲ **Figure 35.7 Antigen recognition by B cells and antibodies.**

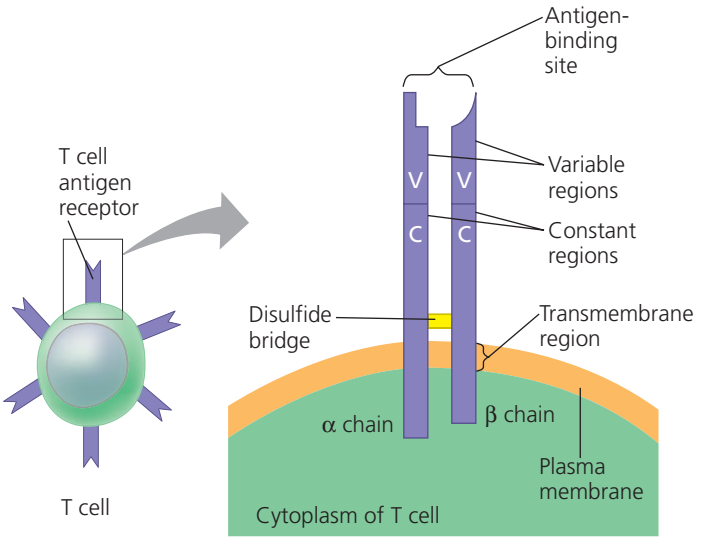
MAKE CONNECTIONS *The interactions depicted here involve a highly specific binding between antigen and receptor. How is antigen-antibody binding similar to an enzyme-substrate interaction (see Figures 3.20 and 6.14)?*

The antigen-binding site of a membrane-bound receptor or antibody has a unique shape that provides a lock-and-key fit for a particular epitope. Many noncovalent bonds between an epitope and the binding surface provide a stable and specific interaction. Differences in the amino acid sequences of variable regions provide the variation in binding surfaces that enables this highly specific binding.

B cell antigen receptors and antibodies bind to intact antigens in the blood and lymph. As illustrated in **Figure 35.7b** for antibodies, they can bind to antigens on the surface of pathogens or free in body fluids.

Antigen Recognition by T Cells

For a T cell, the antigen receptor consists of two different polypeptide chains, an *α chain* and a *β chain*, linked by a disulfide bridge **(Figure 35.8)**. Near the base of the T cell antigen receptor

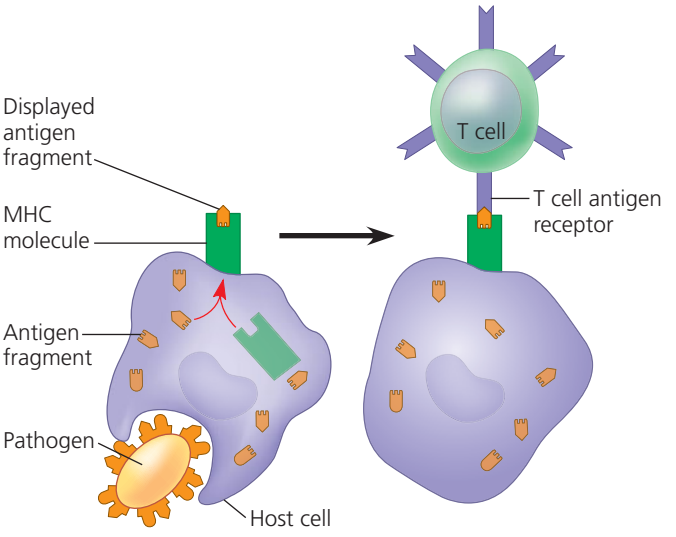


▲ Figure 35.8 The structure of a T cell antigen receptor.

(often called simply a T cell receptor) is a transmembrane region that anchors the molecule in the cell's plasma membrane. At the outer tip of the molecule, the variable (V) regions of α and β chains together form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

Whereas the antigen receptors of B cells bind to epitopes of intact antigens on pathogens or circulating in body fluids, those of T cells bind only to fragments of antigens that are displayed, or presented, on the surface of host cells. The host protein that displays the antigen fragment on the cell surface is called a **major histocompatibility complex (MHC) molecule**.

Recognition of protein antigens by T cells begins when a pathogen or part of a pathogen either infects or is taken in by a host cell **(Figure 35.9)**. Inside the host cell, enzymes in the cell



▲ Figure 35.9 Antigen recognition by T cells. Inside the host cell, an antigen fragment from a pathogen binds to an MHC molecule and is brought up to the cell surface, where it is displayed. The combination of MHC molecule and antigen fragment is recognized by a T cell.

cleave the antigen into smaller peptides. Each peptide, called an *antigen fragment*, then binds to an MHC molecule inside the cell. Movement of the MHC molecule and bound antigen fragment to the cell surface results in **antigen presentation**, the display of the antigen fragment in an exposed groove of the MHC protein.

In effect, antigen presentation advertises the fact that a host cell contains a foreign substance. If the cell displaying an antigen fragment encounters a T cell with the right specificity, the antigen receptor on the T cell can bind to both the antigen fragment and the MHC molecule. This interaction of an MHC molecule, an antigen fragment, and an antigen receptor is necessary for a T cell to participate in an adaptive immune response, as you'll see later.

B Cell and T Cell Development

Now that you know how B cells and T cells recognize antigens, let's consider four major characteristics of adaptive immunity. First, there is an immense diversity of lymphocytes and receptors, enabling the immune system to detect pathogens never before encountered. Second, adaptive immunity normally has self-tolerance, the lack of reactivity against an animal's own molecules and cells. Third, cell proliferation triggered by activation greatly increases the number of B and T cells specific for an antigen. Fourth, there is a stronger and more rapid response to an antigen encountered previously, due to a feature known as immunological memory.

Receptor diversity and self-tolerance arise as a lymphocyte matures. Cell proliferation and the formation of immunological memory occur later, after a mature lymphocyte encounters and binds to a specific antigen. We'll consider these four characteristics in the order in which they develop.

Generation of B Cell and T Cell Diversity

Each person makes more than 1 million different B cell antigen receptors and 10 million different T cell antigen receptors. Yet there are only about 20,000 protein-coding genes in the human genome. How, then, do we generate such remarkable diversity in antigen receptors? The answer lies in combinations. Think of selecting a car with a choice of three interior colors and six exterior colors. There are 18 (3×6) color combinations to consider. Similarly, by combining variable elements, the immune system assembles many different receptors from a much smaller collection of parts.

To understand the origin of receptor diversity, let's consider an immunoglobulin (Ig) gene that encodes the light chain of both secreted antibodies (immunoglobulins) and membrane-bound B cell antigen receptors. Although we'll analyze only a single Ig light-chain gene, all B and T cell antigen receptor genes undergo very similar transformations.

The capacity to generate diversity is built into the structure of Ig genes. A receptor light chain is encoded by three gene segments: a variable (*V*) segment, a joining (*J*) segment, and a

constant (*C*) segment. The *V* and *J* segments together encode the variable region of the receptor chain, while the *C* segment encodes the constant region. The light-chain gene contains a single *C* segment, 40 different *V* segments, and 5 different *J* segments. These alternative copies of the *V* and *J* segments are arranged within the gene in a series **(Figure 35.10)**. Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 different ways (40 $V \times 5\ J \times 1\ C$). The number of different heavy-chain combinations is even greater, resulting in even more diversity.

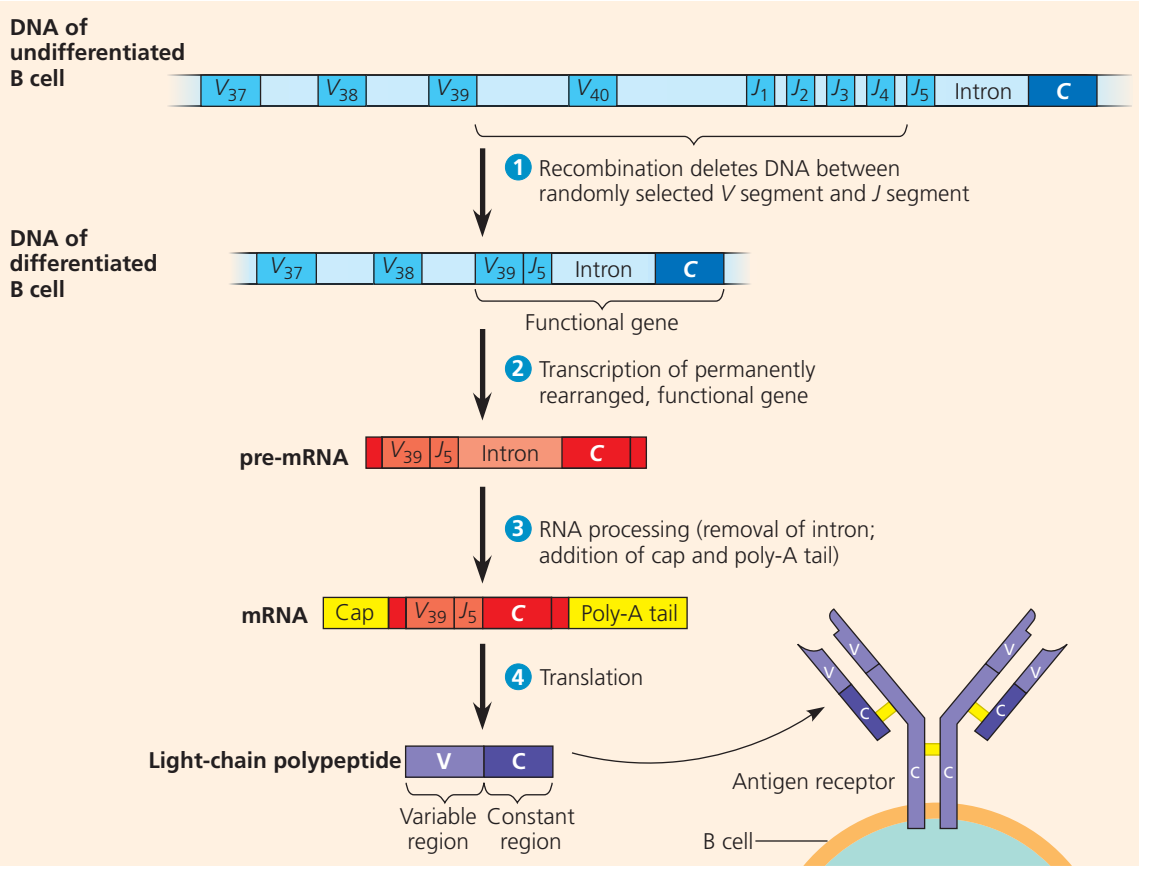
Assembling a functional Ig gene requires rearranging the DNA. Early in B cell development, an enzyme complex called *recombinase* links one light-chain *V* gene segment to one *J* gene segment. This recombination event eliminates the long stretch of DNA between the segments, forming a single exon that is part *V* and part *J*. Because there is only an intron between the *J* and *C* DNA segments, no further DNA rearrangement is required. Instead, the *J* and *C* segments of the RNA transcript will be joined when splicing removes the intervening RNA (see Figure 14.12 to review RNA splicing).

Recombinase acts randomly, linking any one of the 40 *V* gene segments to any one of the 5 *J* gene segments. Heavy-chain genes undergo a similar rearrangement. In any given cell, however, only one allele of a light-chain gene and one allele of a heavy-chain gene are rearranged. Furthermore, the rearrangements are permanent and are passed on to the daughter cells when the lymphocyte divides.

After both a light-chain and a heavy-chain gene have rearranged, antigen receptors can be synthesized. The rearranged genes are transcribed, and the transcripts are processed for translation. Following translation, the light chain and heavy chain assemble together, forming an antigen receptor (see Figure 35.10). Each pair of randomly rearranged heavy and light chains results in a different antigen-binding site. For the total population of B cells in a human body, the number of such combinations has been calculated as 3.5×10^6. Furthermore, mutations introduced during *VJ* recombination add additional variation, making the number of possible antigen-binding specificities even greater.

Origin of Self-Tolerance

In adaptive immunity, how does the body distinguish self from nonself? Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the organism's own molecules. If these self-reactive lymphocytes were not eliminated or inactivated, the immune system could not distinguish self from nonself and would attack body proteins, cells, and tissues. Instead, as lymphocytes mature in the bone marrow or thymus, their antigen receptors are tested for self-reactivity. Some B and T cells with receptors specific for the body's own molecules are destroyed by programmed cell death. The remaining self-reactive lymphocytes are typically rendered nonfunctional, leaving only those lymphocytes that react to foreign molecules. Since the



▶ Figure 35.10 Immunoglobulin (antibody) gene rearrangement. The joining of randomly selected *V* and *J* gene segments (V_{39} and J_5 in this example) results in a functional gene that encodes the light-chain polypeptide of a B cell antigen receptor. Transcription, splicing, and translation result in a light chain that combines with a polypeptide produced from an independently rearranged heavy-chain gene to form a functional receptor. Mature B cells (and T cells) are exceptions to the generalization that all nucleated cells in the body have exactly the same DNA.

MAKE CONNECTIONS

Both alternative splicing and joining of V and J segments by recombination generate diverse gene products from a limited set of gene segments. How do these processes differ (see Figure 15.12)?

body normally lacks mature lymphocytes that can react against its own components, the immune system is said to exhibit self-tolerance.

Proliferation of B Cells and T Cells

Despite the enormous variety of antigen receptors, only a tiny fraction are specific for a given epitope. How, then, does an effective adaptive response develop? To begin with, an antigen is presented to a steady stream of lymphocytes in the lymph nodes (see Figure 34.12) until a match is made. A successful match then triggers changes in cell number and activity for the lymphocyte to which an antigen has bound.

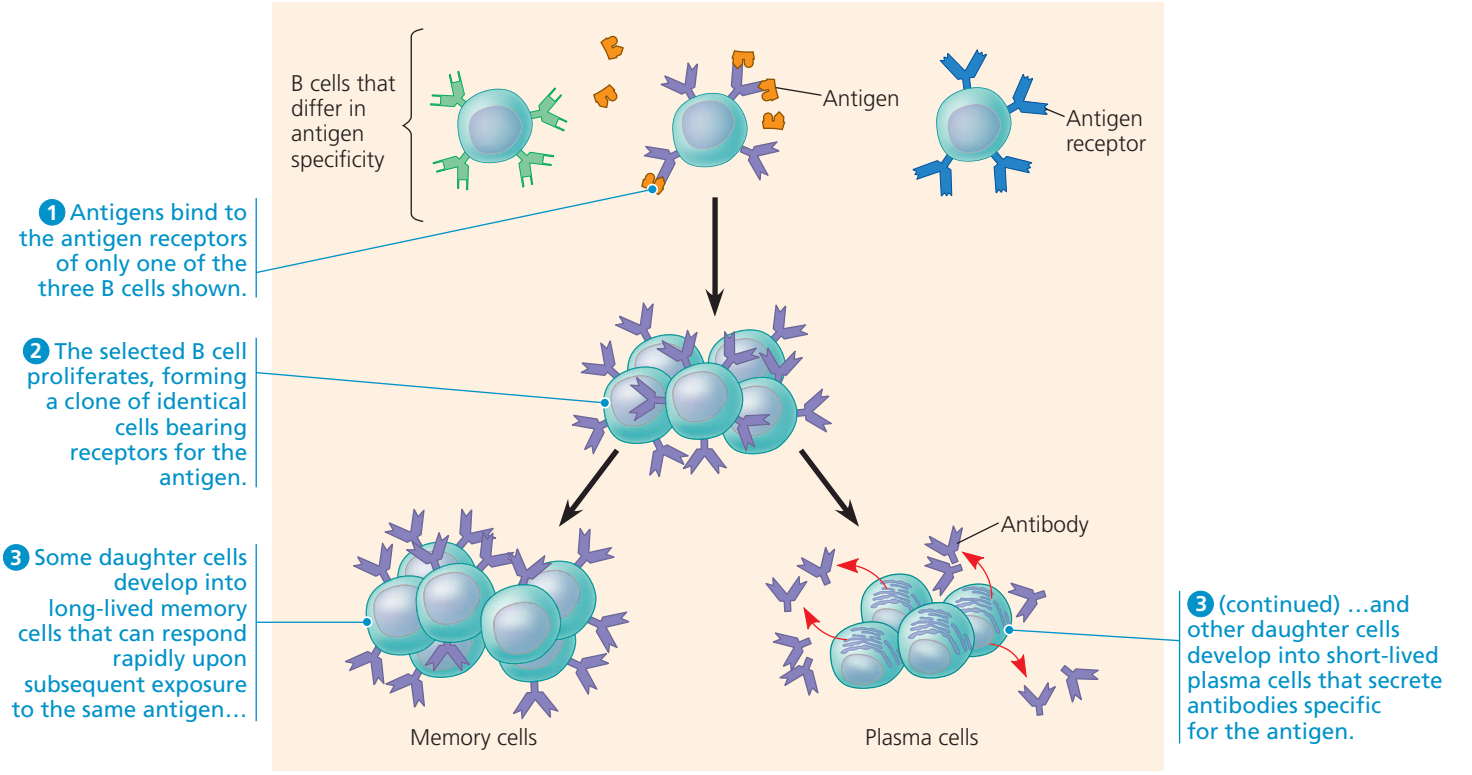
The binding of an antigen receptor to an epitope initiates events that activate the lymphocyte. Once activated, a B cell or T cell undergoes multiple cell divisions. For each activated cell, the result of this proliferation is a clone, a population of cells that are identical to the original cell. Some cells from this clone become **effector cells**, short-lived cells that take effect immediately against the antigen and any pathogens producing that antigen. The effector forms of B cells are **plasma cells**, which secrete antibodies. The effector forms of T cells are helper T cells and cytotoxic T cells, whose roles we'll explore in Concept 35.3. The remaining cells in the clone become **memory cells**, long-lived cells that can give rise to effector cells if the same antigen is encountered later in the animal's life.

Figure 35.11 summarizes the proliferation of a lymphocyte into a clone of cells in response to binding to an antigen, using B cells as an example. This process is called **clonal selection** because an encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells specific for a particular epitope.

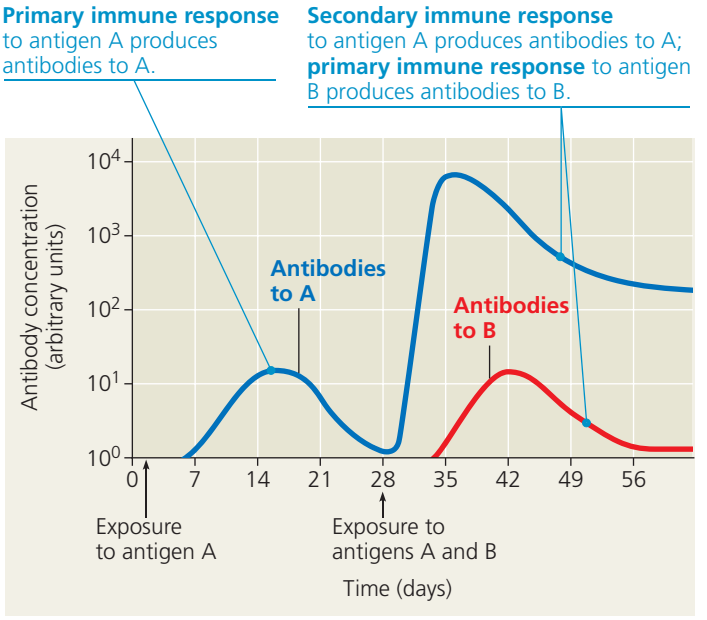
Immunological Memory

Immunological memory is responsible for the long-term protection that a prior infection provides against many diseases, such as chickenpox. This type of protection was noted almost 2,400 years ago by the Greek historian Thucydides. He observed that individuals who had recovered from the plague could safely care for those who were sick or dying, "for the same man was never attacked twice—never at least fatally."

Prior exposure to an antigen alters the speed, strength, and duration of the immune response. The production of effector cells from a clone of lymphocytes during the first exposure to an antigen is the basis for the **primary immune response**. The primary response peaks about 10–17 days after the initial exposure. During this time, selected B cells and T cells give rise to their effector forms. If an individual is exposed again to the same antigen, the response is faster (typically peaking only 2–7 days after exposure), of greater magnitude, and more prolonged. This is the **secondary immune response**, a hallmark of adaptive, or acquired, immunity. Because selected



▲ **Figure 35.11 Clonal selection.** This figure illustrates clonal selection, using B cells as an example. In response to a specific antigen and to immune cell signals (not shown), one B cell divides and forms a clone of cells. The remaining B cells, which have antigen receptors specific for other antigens, do not respond. The clone of cells formed by the selected B cell gives rise to memory B cells and antibody-secreting plasma cells. T cells also undergo clonal selection, generating memory T cells and effector T cells (cytotoxic T cells and helper T cells).



▲ Figure 35.12 The specificity of immunological memory. Long-lived memory cells generated in the primary response to antigen A give rise to a heightened secondary response to the same antigen, but do not affect the response to a different antigen (B).

B cells give rise to antibody-secreting effector cells, measuring the concentrations of specific antibodies in blood over time distinguishes the primary and secondary immune responses **(Figure 35.12)**.

The secondary immune response relies on the reservoir of T and B memory cells generated following initial exposure to an antigen. Because these cells are long-lived, they provide the basis for immunological memory, which can span many decades. (Effector cells have much shorter life spans, which is why the immune response diminishes after an infection is overcome.) If an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of clones of thousands of effector cells also specific for that antigen, thus generating a greatly enhanced immune defense.

Although the processes for antigen recognition, clonal selection, and immunological memory are similar for B cells and T cells, these two classes of lymphocytes fight infection in different ways and in different settings, as we'll explore next.

CONCEPT CHECK 35.2

1. **DRAW IT** Sketch a B cell antigen receptor. Label the V and C regions of the light and heavy chains. Label the antigen-binding sites, disulfide bridges, and transmembrane region. Where are these features located relative to the V and C regions?
2. Explain two advantages of having memory cells when a pathogen is encountered for a second time.
3. **WHAT IF?** If both copies of a light-chain gene and a heavy-chain gene recombined in each (diploid) B cell, how would this affect B cell development and function?

For suggested answers, see Appendix A.

CONCEPT 35.3

Adaptive immunity defends against infection of body fluids and body cells

Having considered how clones of lymphocytes arise, we now explore how these cells help fight infections and minimize damage by pathogens. The defenses provided by B and T lymphocytes can be divided into a humoral immune response and a cell-mediated immune response. The **humoral immune response** occurs in the blood and lymph (once called body humors, or fluids). In the humoral response, antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph. In the **cell-mediated immune response**, specialized T cells destroy infected host cells. Both responses include a primary immune response and a secondary immune response, with memory cells enabling the secondary response.

Helper T Cells: A Response to Nearly All Antigens

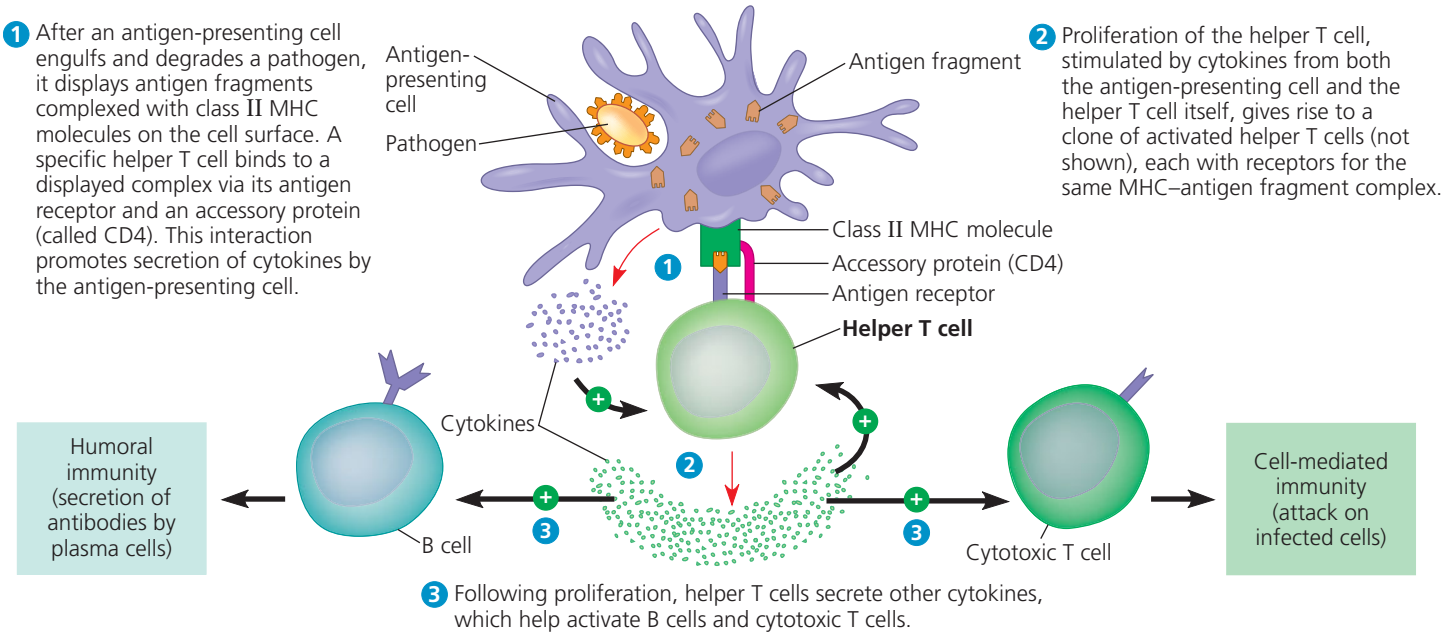
A type of T cell called a **helper T cell** triggers both the humoral and cell-mediated immune responses. Helper T cells themselves do not carry out those responses. Instead, signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells.

Two requirements must be met for a helper T cell to activate adaptive immune responses. First, a foreign molecule must be present that can bind specifically to the antigen receptor of the T cell. Second, this antigen must be displayed on the surface of an **antigen-presenting cell**. The antigen-presenting cell can be a dendritic cell, macrophage, or B cell.

When host cells are infected, they, too, display antigens on their surface. What, then, distinguishes an antigen-presenting cell? The answer lies in the existence of two classes of MHC molecules. Most body cells have only class I MHC molecules, but antigen-presenting cells have both class I and class II MHC molecules. The class II molecules provide a molecular signature by which an antigen-presenting cell is recognized.

A helper T cell and the antigen-presenting cell displaying its specific epitope have a complex interaction **(Figure 35.13)**. The antigen receptors on the surface of the helper T cell bind to the antigen fragment and to the class II MHC molecule displaying that fragment on the antigen-presenting cell. At the same time, an accessory protein called CD4 on the helper T cell surface binds to the class II MHC molecule, helping keep the cells joined. As the two cells interact, signals in the form of cytokines are exchanged.

Antigen-presenting cells interact with helper T cells in several different contexts. Antigen presentation by a dendritic cell or macrophage activates a helper T cell, which then proliferates, forming a clone of activated cells. B cells present antigens



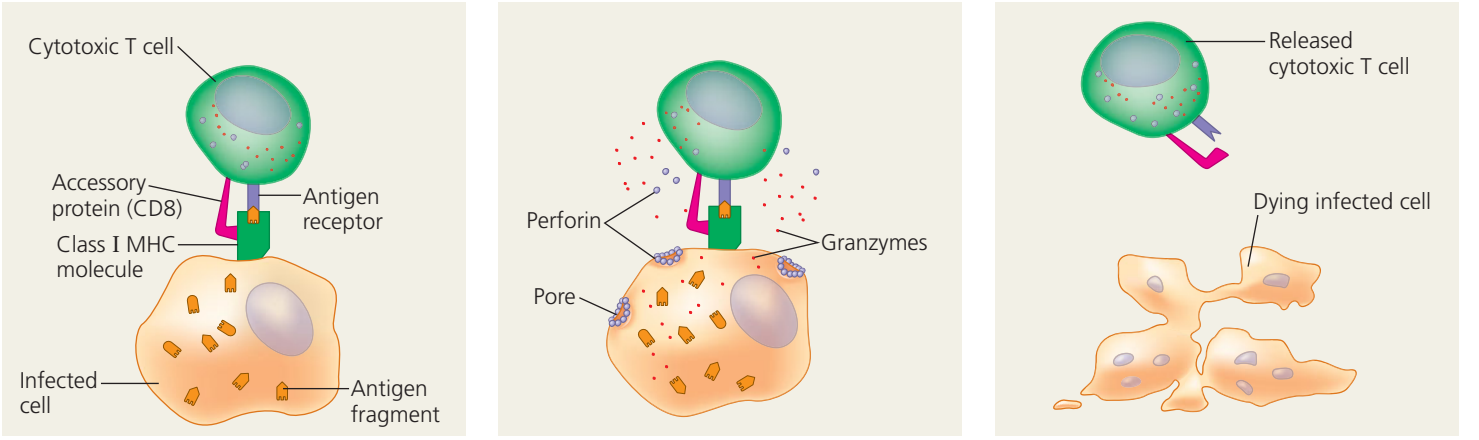
▲ Figure 35.13 The central role of helper T cells in humoral and cell-mediated immune responses. In this example, a helper T cell responds to a dendritic cell displaying a microbial antigen.

to *already* activated helper T cells, which in turn activate the B cells themselves. Activated helper T cells also help stimulate cytotoxic T cells, as we'll discuss next.

Cytotoxic T Cells: A Response to Infected Cells

In the cell-mediated immune response, **cytotoxic T cells** use toxic proteins to kill cells infected by viruses or other intracellular pathogens. To become active, cytotoxic T cells require signals from helper T cells and interaction with an antigen-presenting cell. Fragments of foreign proteins produced in infected host cells associate with class I MHC molecules and are displayed on the cell surface, where they can be recognized by activated cytotoxic T cells **(Figure 35.14)**. As with helper T cells, cytotoxic T cells have an accessory protein that binds to the MHC molecule. This accessory protein, called CD8, helps keep the two cells in contact while the cytotoxic T cell is activated.

The targeted destruction of an infected host cell by a cytotoxic T cell involves the secretion of proteins that disrupt membrane integrity and trigger cell death (see Figure 35.14). The death of the infected cell not only deprives the pathogen of a place to reproduce, but also exposes cell contents to circulating antibodies, which mark released antigens for disposal.

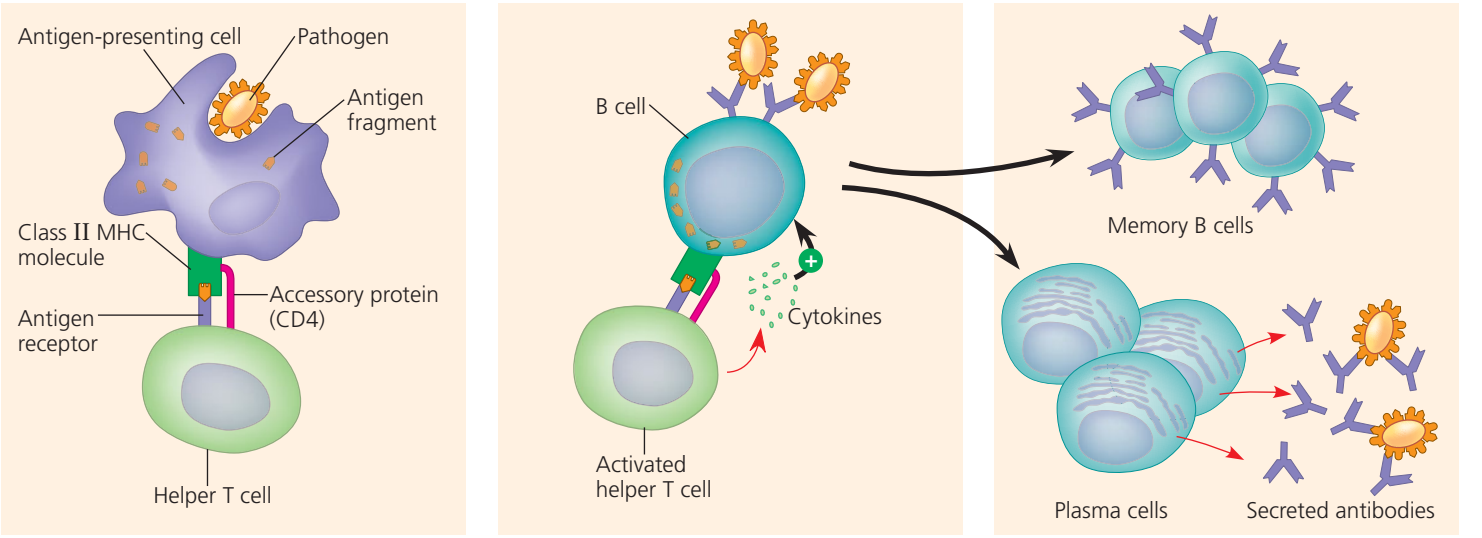


1 An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on an infected cell via its antigen receptor and an accessory protein (called CD8).

2 The T cell releases perforin molecules, which form pores in the infected cell membrane, and granzymes, enzymes that break down proteins. Granzymes enter the infected cell by endocytosis.

3 The granzymes initiate apoptosis within the infected cell, leading to fragmentation of the nucleus and cytoplasm and eventual cell death. The released cytotoxic T cell can attack other infected cells.

▲ Figure 35.14 The killing action of cytotoxic T cells on an infected host cell. An activated cytotoxic T cell releases molecules that make pores in an infected cell's membrane and enzymes that break down proteins, promoting the cell's death.



1 After an antigen-presenting cell engulfs and degrades a pathogen, it displays an antigen fragment complexed with a class II MHC molecule. A helper T cell that recognizes the complex is activated with the aid of cytokines secreted from the antigen-presenting cell.

2 When a B cell with receptors for the same epitope internalizes the antigen, it displays an antigen fragment on the cell surface in a complex with a class II MHC molecule. An activated helper T cell bearing receptors specific for the displayed fragment binds to and activates the B cell.

3 The activated B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells. The secreted antibodies are specific for the same antigen that initiated the response.

▲ Figure 35.15 Activation of a B cell in the humoral immune response. Most protein antigens require activated helper T cells to trigger a humoral response. A macrophage (shown here) or a dendritic cell can activate a helper T cell, which in turn can activate a B cell to give rise to antibody-secreting plasma cells.

? *What function do cell-surface antigen receptors play for memory B cells?*

B Cells and Antibodies: A Response to Extracellular Pathogens

The secretion of antibodies by clonally selected B cells is the hallmark of the humoral immune response. As illustrated in **Figure 35.15**, activation of B cells involves both helper T cells and proteins on the surface of pathogens. Stimulated by both an antigen and cytokines, the B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells.

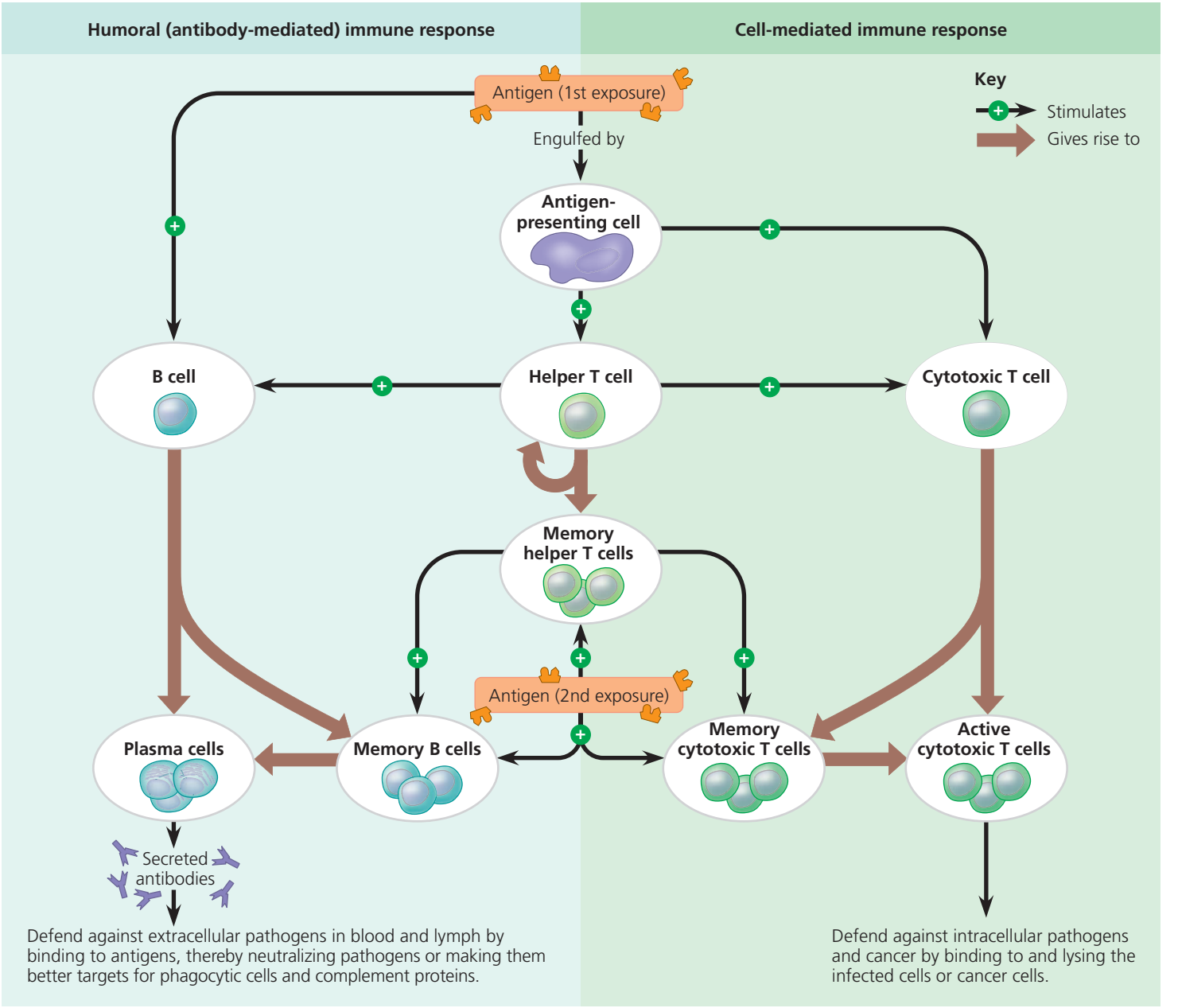
A single activated B cell gives rise to thousands of identical plasma cells. Each plasma cell secretes approximately 2,000 antibodies every second during its 4- to 5-day life span. The antibodies do not kill pathogens, but by binding to antigens, they mark pathogens in various ways for inactivation or destruction. In the simplest of these activities, *neutralization*, antibodies bind to proteins on the surface of a virus (see Figure 35.7b). The bound antibodies prevent infection of a host cell, thus neutralizing the virus. Similarly, antibodies sometimes bind to toxins released in body fluids, preventing the toxins from entering body cells. Because each antibody has two antigen-binding sites, antibodies can also facilitate phagocytosis by linking bacterial cells, viruses, or other foreign substances into aggregates.

Antibodies sometimes work together with the proteins of the complement system. (The name *complement* reflects the fact that these proteins increase the effectiveness of antibody-directed attacks on bacteria.) Binding of a complement protein to an antigen-antibody complex on a foreign cell triggers events leading to formation of a pore in the membrane of the cell. Ions and water rush into the cell, causing it to swell and lyse.

B cells can express five different types of immunoglobulin. For a given B cell, each type has an identical antigen-binding specificity but a distinct heavy-chain C region. One type of B cell Ig, the B cell antigen receptor, is membrane bound. The other four Ig types consist of soluble antibodies, including those found in blood, tears, saliva, and breast milk.

Summary of the Humoral and Cell-Mediated Immune Responses

As noted earlier, both the humoral and cell-mediated responses can include primary as well as secondary immune responses. Memory cells of each type—helper T cell, B cell, and cytotoxic T cell—enable the secondary response. For example, when body fluids are reinfected by a pathogen encountered previously, memory B cells and memory helper T cells initiate a secondary humoral response. **Figure 35.16** reviews the events that initiate humoral and cell-mediated immune responses, highlights the central role of the helper T cell, and serves as a helpful summary of adaptive immunity.



▲ Figure 35.16 An overview of the adaptive immune response.

? *Identify each black or brown arrow as representing part of the primary or secondary response.*

ANIMATION

BioFlix Visit the Study Area in **MasteringBiology** for the BioFlix® 3-D Animation on Immunology.

Active and Passive Immunization

Our discussion of adaptive immunity has focused to this point on **active immunity**, the defenses that arise when a pathogen infects the body. A different type of immunity results when, for example, antibodies in the blood of a pregnant female cross the placenta to her fetus. This protection is called **passive immunity** because the antibodies in the recipient (in this case, the fetus) are produced by another individual (the mother). Antibodies present in breast milk provide additional passive immunity to the infant's digestive tract while the infant's immune system develops. Because passive immunity does not involve the recipient's B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months).

Both active immunity and passive immunity can be induced artificially. Active immunity is induced when antigens are introduced into the body in *vaccines*, which may be made from inactivated bacterial toxins, killed or weakened pathogens, or even genes encoding microbial proteins. This process, called **immunization** (or vaccination), induces a primary immune response and immunological memory. As a result, any subsequent encounter with the pathogen from which the vaccine was derived triggers a rapid and strong secondary immune response (see Figure 35.12).

Misinformation about vaccine safety and disease risk has led to a substantial and growing public health problem. Consider measles as just one example. Side effects of immunization are remarkably rare, with fewer than one in a million children suffering a significant allergic reaction to the measles vaccine. The disease, however, is quite dangerous, killing more than 200,000 people each year. Declining vaccination rates in parts of the United Kingdom, Russia, and the United States have resulted in a number of recent measles outbreaks and many preventable deaths.

In artificial passive immunization, antibodies from an immune animal are injected into a nonimmune animal. For example, humans bitten by venomous snakes are sometimes treated with antivenin, serum from sheep or horses that have been immunized against a snake venom. When injected immediately after a snakebite occurs, the antibodies in antivenin can neutralize toxins in the venom before the toxins do massive damage.

Antibodies as Tools

Antibodies produced after exposure to an antigen are *polyclonal*: They are the products of many different clones of plasma cells, each specific for a different epitope. Antibodies can also be prepared from a clone of B cells grown in culture. The **monoclonal antibodies** produced by such a culture are identical and specific for the same epitope on an antigen.

Monoclonal antibodies have provided the basis for many recent advances in medical diagnosis and treatment. For example, home pregnancy test kits use monoclonal antibodies to detect human chorionic gonadotropin (hCG). Because hCG is produced as soon as an embryo implants in the uterus (see Chapter 36), the presence of this hormone in a woman's urine is a reliable indicator for a very early stage of pregnancy. Monoclonal antibodies are also produced in large amounts and injected as a therapy for a number of human diseases.

Immune Rejection

Like pathogens, cells from another person can be recognized as foreign and attacked by immune defenses. For example, skin transplanted from one person to a genetically nonidentical person will look healthy for a week or so but will then be destroyed (rejected) by the recipient's immune response. Carbohydrates on the surface of transfused blood cells can also be recognized as foreign by the recipient's immune system, triggering an immediate and devastating reaction. To avoid this danger, the so-called ABO blood groups of the donor and recipient must be taken into account.

In the case of tissue and organ transplants, or grafts, MHC molecules stimulate the immune response that leads to rejection. Each vertebrate species has many alleles for each MHC gene, enabling presentation of antigen fragments that vary in shape and net electrical charge. This diversity of MHC molecules almost guarantees that no two people, except identical twins, will have exactly the same set. Thus, in the vast majority of graft and transplant recipients, some MHC molecules on the donated tissue are foreign to the recipient. To minimize rejection, physicians use donor tissue bearing MHC molecules that match those of the recipient as closely as possible. In addition, the recipient takes medicines that suppress immune responses (but as a result leave the recipient more susceptible to infections).

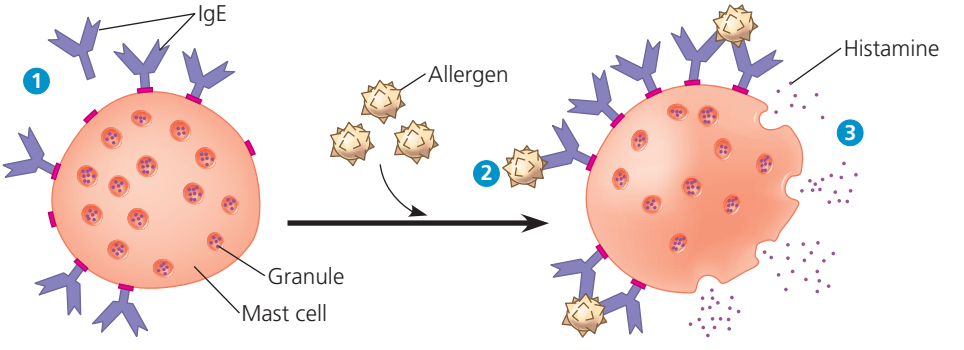
Disruptions in Immune System Function

Although adaptive immunity offers significant protection against a wide range of pathogens, it is not fail-safe. Here we'll examine some of the ways the adaptive immune system fails to protect the host organism.

Allergies

Allergies are exaggerated (hypersensitive) responses to certain antigens called **allergens**. Hay fever, for instance, occurs when plasma cells secrete antibodies specific for antigens on the surface of pollen grains, as illustrated in **Figure 35.17**. The interaction of pollen grains and these antibodies triggers immune cells in connective tissue to release histamine and other inflammatory chemicals. The results can include sneezing, teary eyes, and smooth muscle contractions in the lungs that inhibit effective breathing. Drugs called antihistamines block receptors for histamine, diminishing allergy symptoms (and inflammation).

In some instances, an acute allergic response leads to a life-threatening reaction called *anaphylactic shock*. Inflammatory chemicals trigger abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure, as well as constriction of bronchioles. Death may occur within minutes due to lack of blood

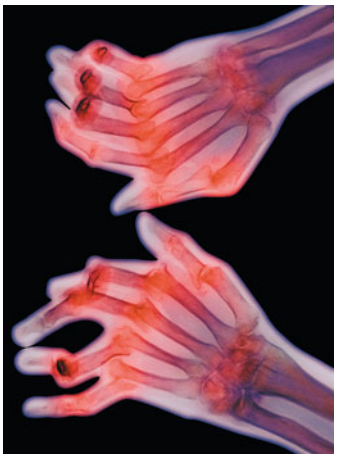


1 IgE antibodies produced in response to initial exposure to an allergen bind to receptors on mast cells.

2 On subsequent exposure to the same allergen, IgE molecules attached to a mast cell recognize and bind the allergen.

3 Cross-linking of adjacent IgE molecules triggers release of histamine and other chemicals, leading to allergy symptoms.

▲ **Figure 35.17 Mast cells and the allergic response.** In this example, pollen grains act as the allergen, and the immunoglobulins that mediate the response are of a type called IgE.



▶ Figure 35.18 Colored X-ray of hands deformed by rheumatoid arthritis.

flow and the inability to breathe. Substances that can cause anaphylactic shock in allergic individuals include bee venom, penicillin, peanuts, and shellfish. People with severe hypersensitivities often carry syringes containing the hormone epinephrine, which counteracts this allergic response.

Autoimmune Diseases

In some people, the immune system is active against particular molecules of the body, causing an **autoimmune disease**. In systemic lupus erythematosus, commonly called lupus, the immune system generates antibodies against histones and DNA. Other targets of autoimmunity are the insulin-producing beta cells of the pancreas (in type 1 diabetes) and the myelin sheaths that encase many neurons (in multiple sclerosis).

Gender, genetics, and environment all influence susceptibility to autoimmune disorders. For example, many autoimmune diseases afflict females more often than males. Women are nine times as likely as men to suffer from lupus and two to three times as likely to develop rheumatoid arthritis, a damaging and painful inflammation of the cartilage and bone in joints **(Figure 35.18)**. The cause of this sex bias, as well as the rise in autoimmune disease frequency in industrialized countries, are areas of active research and debate.

Immune System Avoidance

EVOLUTION Just as immune systems that ward off pathogens have evolved in animals, mechanisms that thwart immune responses have evolved in pathogens. In one such mechanism, a pathogen alters how it appears to the immune system. If a pathogen changes the epitopes it expresses to ones that a host has not previously encountered, it can reinfect or remain in the host without triggering the rapid and robust response mediated by memory cells. Such changes in epitope expression are called *antigenic variation*. The parasite that causes sleeping sickness provides an extreme example, periodically switching at random among 1,000 different versions of the protein found over its entire surface. In the **Scientific Skills Exercise**, you will interpret data related to this example of antigenic variation and the body's response.

Antigenic variation is the major reason the influenza, or "flu," virus remains a major public health problem. As it replicates in one human host after another, the human flu virus undergoes frequent mutations. Because any change that lessens recognition by the immune system provides a selective advantage, the virus steadily accumulates such alterations. These changes are the reason that a new flu vaccine must be distributed each year. In addition, the human flu virus occasionally exchanges genes with influenza viruses that infect domesticated animals, such as pigs or chickens. If the new strain expresses surface epitopes of the animal rather than the human virus, it may not be recognized by any of the memory cells in the human population. The resulting outbreak can be deadly: The 1918–1919 influenza outbreak killed more than 20 million people.

Some viruses avoid an immune response by infecting cells and then entering a largely inactive state called *latency*. The viral genome integrates into the chromosome of the host cell, which ceases making most viral proteins and typically releases no free viruses. Latency typically persists until conditions arise that are favorable for viral transmission or unfavorable for host survival.

Herpes simplex viruses provide a good example of latency. The type 1 virus causes most oral herpes infections, whereas the sexually transmitted type 2 virus is responsible for most cases of genital herpes. These viruses remain latent in sensory neurons until a stimulus such as fever, emotional stress, or menstruation reactivates the viruses. Activation of the type 1 virus can result in blisters around the mouth that are inaccurately called "cold" sores. Infections of the type 2 virus pose a serious threat to the babies of infected mothers and can increase transmission of HIV.

The **human immunodeficiency virus (HIV)**, the pathogen that causes AIDS (acquired immune deficiency syndrome), both escapes and attacks the adaptive immune response. Once introduced into the body, HIV infects helper T cells with high efficiency. Although the body responds to HIV with an immune response sufficient to eliminate most viral infections, some HIV invariably escapes. One reason HIV persists is that it has a very high mutation rate. Altered proteins on the surface of some mutated viruses reduce interaction with antibodies and cytotoxic T cells. Such viruses survive, proliferate, and mutate further. The virus thus evolves within the body. The continued presence of HIV is also helped by latency.

Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it. Viral reproduction and cell death triggered by the virus lead to loss of helper T cells, impairing both humoral and cell-mediated immune responses. The result is a progression to AIDS, characterized by susceptibility to infections and cancers that a healthy immune system would usually defeat. For example, *Pneumocystis carinii*, a common fungus that does not cause disease in healthy individuals, can result in severe pneumonia in people with AIDS. Such opportunistic diseases, as well as nerve damage and wasting, are the primary causes of death from AIDS, not HIV itself.

Scientific Skills Exercise

Comparing Two Variables on a Common x-Axis

How Does the Immune System Respond to a Changing Pathogen? Natural selection favors parasites that are able to maintain a low-level infection in a host for a long time. *Trypanosoma*, the unicellular parasite that causes sleeping sickness, is one example (see Figure 25.12). The glycoproteins covering a trypanosome's surface are encoded by a gene that is duplicated more than a thousand times in the organism's genome. Each copy is slightly different. By periodically switching among these genes, the trypanosome can change the molecular structure of its surface glycoproteins. In this exercise, you will interpret two data sets to explore hypotheses about the benefits of the trypanosome's ever-shifting surface glycoproteins and the host's immune response.

Part A: Data from a Study of Parasite Levels This study measured the abundance of parasites in the blood of one human patient during the first few weeks of a chronic infection.

Day	Number of Parasites (in millions) per mL of Blood
4	0.1
6	0.3
8	1.2
10	0.2
12	0.2
14	0.9
16	0.6
18	0.1
20	0.7
22	1.2
24	0.2

Part A: Interpret the Data

1. Plot the data in the above table as a line graph. Which column is the independent variable, and which is the dependent variable? Put the independent variable on the *x*-axis. (For additional information about graphs, see the Scientific Skills Review in Appendix F and in the Study Area in MasteringBiology.)
2. Visually displaying data in a graph can help make patterns in the data more noticeable. Describe any patterns revealed by your graph.
3. Assume that a drop in parasite abundance reflects an effective immune response by the host. Formulate a hypothesis to explain the pattern you described in question 2.

Part B: Data from a Study of Antibody Levels Many decades after scientists first observed the pattern of *Trypanosoma* abundance over the course of infection, researchers identified antibodies specific to different forms of the parasite's surface glycoprotein. The table below lists the relative abundance of two such antibodies during the early period of chronic infection, using an index ranging from 0 to 1.

Day	Antibody Specific to Glycoprotein Variant A	Antibody Specific to Glycoprotein Variant B
4	0	0
6	0	0
8	0.2	0
10	0.5	0
12	1	0
14	1	0.1
16	1	0.3
18	1	0.9
20	1	1
22	1	1
24	1	1

Part B: Interpret the Data

4. Note that these data were collected over the same period of infection (days 4–24) as the parasite abundance data you graphed in Part A. Therefore, you can incorporate these new data into your first graph, using the same *x*-axis. However, since the antibody level data are measured in a different way than the parasite abundance data, add a second set of *y*-axis labels on the right side of your graph. Then, using different colors or sets of symbols, add the data for the two antibody types. Labeling the *y*-axis two different ways enables you to compare how two dependent variables change relative to a shared independent variable.
5. Describe any patterns you observe by comparing the two data sets over the same period. Do these patterns support your hypothesis from Part A? Do they prove that hypothesis? Explain.
6. Scientists can now also distinguish the abundance of trypanosomes recognized specifically by antibodies type A and type B. How would incorporating such information change your graph?

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.

HIV transmission requires the transfer of virus particles or infected cells via body fluids such as semen, blood, or breast milk. Unprotected sex (that is, without a condom) and transmission via HIV-contaminated needles (often among intravenous drug users) account for the vast majority of HIV infections. People infected with HIV can transmit the disease in the first few weeks of infection, *before* they express HIV-specific antibodies that can be detected in a blood test. Although HIV infection cannot be cured, drugs have been developed that can significantly slow HIV replication and the progression to AIDS. New drugs continue to be needed as HIV's high mutation rate results in the frequent appearance of drug-resistant strains.

Cancer and Immunity

When adaptive immunity is inactivated, the frequency of certain cancers increases dramatically. For example, the risk of developing Kaposi's sarcoma is 20,000 times greater for untreated AIDS patients than for healthy people. This observation was unanticipated. If the immune system recognizes only nonself, it should fail to recognize the uncontrolled growth of self cells that is the hallmark of cancer. It turns out, however, that viruses are involved in about 15–20% of all human cancers. Because the immune system can recognize viral proteins as foreign, it can act as a defense against viruses that can cause cancer and against cancer cells that harbor viruses.

Scientists have identified six viruses that can cause cancer in humans. The Kaposi's sarcoma herpesvirus is one such virus. Hepatitis B virus, which can trigger liver cancer, is another. A vaccine introduced in 1986 for hepatitis B virus was the first vaccine shown to help prevent a specific human cancer. Rapid progress on developing vaccines for virus-induced cancers continues. In 2006, the release of a vaccine against cervical cancer, specifically human papillomavirus (HPV), marked a major victory against a disease that afflicts more than half a million women worldwide every year.

CONCEPT CHECK 35.3

1. In the condition known as myasthenia gravis, antibodies bind to and block certain receptors on muscle cells, preventing muscle contraction. What type of disorder does this reflect?
2. If a child were born without a thymus, what cells and functions would be deficient? Explain.
3. **WHAT IF?** Suppose that a snake handler bitten by a particular venomous snake species was treated with antivenin. Why might the same treatment for a second such bite a year later have different results?

For suggested answers, see Appendix A.

35 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 35.1

In innate immunity, recognition and response rely on traits common to groups of pathogens (pp. 712–715)

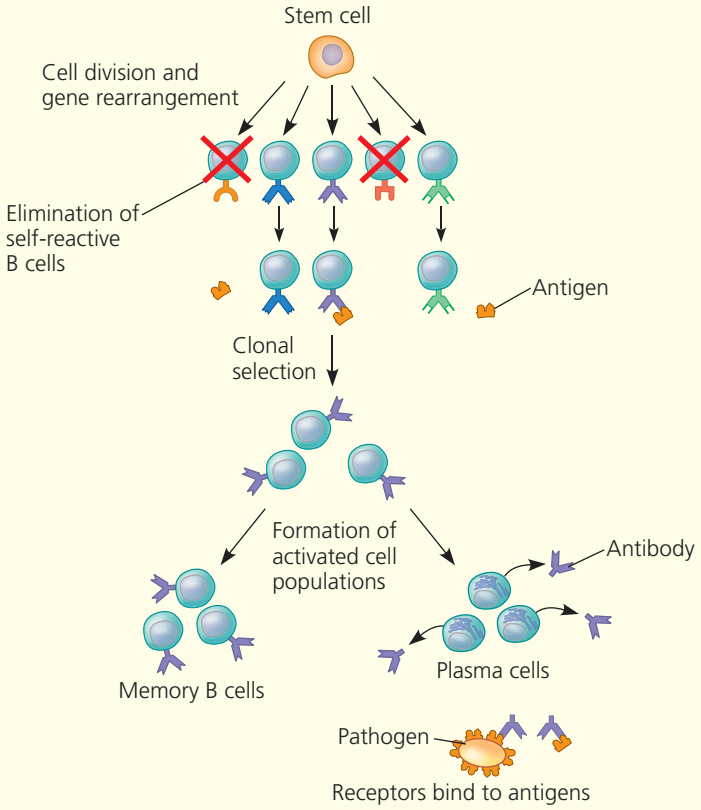
- In both invertebrates and vertebrates, **innate immunity** is mediated by physical and chemical barriers as well as cell-based defenses. Activation of innate immune responses relies on recognition proteins specific for broad classes of pathogens. Microbes that penetrate barrier defenses are ingested by phagocytic cells, which in vertebrates include **macrophages** and **dendritic cells**. In the **inflammatory response**, **histamine** and other chemicals released at the injury site promote changes in blood vessels that enhance immune cell access and action.

? *In what ways does innate immunity protect the mammalian digestive tract?*

CONCEPT 35.2

In adaptive immunity, receptors provide pathogen-specific recognition (pp. 715–720)

- **Adaptive immunity** relies on two types of **lymphocytes** that arise from stem cells in the bone marrow: **T cells** and **B cells**. Lymphocytes have cell-surface **antigen receptors** for foreign molecules (**antigens**). Some T cells help other lymphocytes; others kill infected host cells. B cells called **plasma cells** produce soluble receptor proteins called **antibodies**, which bind to foreign molecules and cells. Activated T and B lymphocytes called **memory cells** defend against future infections by the same pathogen.
- Recognition of foreign molecules involves the binding of variable regions of receptors to an **epitope**, a small region of an antigen. B cells and antibodies recognize epitopes on the surface of antigens. T cells recognize protein epitopes in small antigen fragments (peptides) that are presented on the surface of host cells by proteins called **major histocompatibility complex (MHC) molecules**.
- The four major characteristics of B and T cell development are the generation of cell diversity, self-tolerance, proliferation, and immunological memory. Proliferation and memory are both based on **clonal selection**, illustrated here for B cells.



? *Why is the adaptive immune response to an initial infection slower than the innate response?*

CONCEPT 35.3

Adaptive immunity defends against infection of body fluids and body cells (pp. 720–727)

- **Helper T cells** interact with antigen fragments displayed by class II MHC molecules on the surface of **antigen-presenting cells:** dendritic cells, macrophages, and B cells. Activated helper T cells secrete **cytokines** that stimulate other lymphocytes. In the **cell-mediated immune response**, activated **cytotoxic T cells** trigger destruction of infected cells. In the **humoral immune response**, antibodies help eliminate antigens by phagocytosis and complement-mediated lysis.

- **Active immunity** develops in response to infection or to **immunization**. The transfer of antibodies in **passive immunity** provides immediate, short-term protection.
- In tissue grafts and organ transplants, MHC molecules stimulate immune rejection.
- In allergies, such as hay fever, the interaction of antibodies and **allergens** triggers immune cells to release histamine and other mediators that cause vascular changes and allergic symptoms. Loss of self-tolerance can lead to **autoimmune diseases**, such as multiple sclerosis.
- Antigenic variation, latency, and direct assault on the immune system allow some pathogens to thwart immune responses. **HIV** infection destroys helper T cells, leaving the patient prone to disease. Immune defense against cancer appears to primarily involve action against viruses that can cause cancer and cancer cells that harbor viruses.

? *Do natural infection and immunization result in different types of immunological memory? Explain.*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. Which of these is not part of insect immunity?
   a. activation of microbe-killing chemicals
   b. activation of natural killer cells
   c. phagocytosis by hemocytes
   d. production of antimicrobial peptides
   e. a protective exoskeleton
2. An epitope associates with which part of an antigen receptor or antibody?
   a. the disulfide bridge
   b. the heavy-chain constant regions only
   c. variable regions of a heavy chain and light chain combined
   d. the light-chain constant regions only
   e. the tail
3. Which statement best describes the difference in responses of effector B cells (plasma cells) and cytotoxic T cells?
   a. B cells confer active immunity; cytotoxic T cells confer passive immunity.
   b. B cells kill pathogens directly; cytotoxic T cells kill host cells.
   c. B cells secrete antibodies against a pathogen; cytotoxic T cells kill pathogen-infected host cells.
   d. B cells carry out the cell-mediated response; cytotoxic T cells carry out the humoral response.
   e. B cells respond the first time a pathogen is present; cytotoxic T cells respond subsequent times.

Level 2: Application/Analysis

4. Which of the following statements is *not* true?
   a. An antibody has more than one antigen-binding site.
   b. An antigen can have different epitopes.
   c. A pathogen makes more than one antigen.
   d. A lymphocyte has receptors for multiple different antigens.
   e. A liver cell makes one class of MHC molecule.
5. Which of the following should be the same in identical twins?
   a. the set of antibodies produced
   b. the set of MHC molecules produced
   c. the set of T cell antigen receptors produced
   d. the susceptibility to a particular virus
   e. the set of immune cells eliminated as self-reactive

Level 3: Synthesis/Evaluation

6. Vaccination increases the number of
   a. different receptors that recognize a pathogen.
   b. lymphocytes with receptors that can bind to the pathogen.
   c. epitopes that the immune system can recognize.
   d. macrophages specific for a pathogen.
   e. MHC molecules that can present an antigen.
7. Which of the following would *not* help a virus avoid triggering an adaptive immune response?
   a. having frequent mutations in genes for surface proteins
   b. infecting cells that produce very few MHC molecules
   c. producing proteins very similar to those of other viruses
   d. infecting and killing helper T cells
   e. building the viral shell from host proteins
8. **DRAW IT** Consider a pencil-shaped protein with two epitopes, Y (the "eraser" end) and Z (the "point" end). They are recognized by antibodies A1 and A2, respectively. Draw and label a picture showing the antibodies linking proteins into a complex that could trigger endocytosis by a macrophage.
9. **MAKE CONNECTIONS** Contrast the clonal selection of lymphocytes with Lamarck's idea for the inheritance of acquired characteristics (see Concept 19.1).
10. **SCIENTIFIC INQUIRY**
    A diagnostic test for tuberculosis (TB) involves injecting antigen (from the bacterium that causes TB) under the skin and then waiting a few days for a reaction to appear. This test is *not* useful for diagnosing TB in AIDS patients. Why?
11. **FOCUS ON EVOLUTION**
    Describe one invertebrate defense mechanism and discuss how it is an evolutionary adaptation retained in vertebrates.
12. **FOCUS ON INFORMATION**
    Among all nucleated body cells, only B and T cells lose DNA during their development and maturation. In a short essay (100–150 words), discuss the relationship between this loss and the theme of DNA as heritable biological information, focusing on similarities between cellular and organismal generations.

For selected answers, see Appendix A.

36 Reproduction and Development

▼ **Figure 36.1** How can each of these sea slugs be both male and female?

KEY CONCEPTS

OVERVIEW

Pairing Up for Sexual Reproduction

The sea slugs, or nudibranchs (*Nembrotha chamberlaini*), in **Figure 36.1** are mating. If not disturbed, these marine molluscs may remain joined for hours as sperm are transferred and eggs are fertilized. A few weeks later, new individuals will hatch, and sexual reproduction will be complete–but which parent is the mother of these offspring? The answer is simple yet probably unexpected: both. In fact, each sea slug produces eggs *and* sperm, and so is both a mother and a father to the next generation.

As humans, we tend to think of reproduction in terms of the mating of males and females and the fusion of sperm and eggs. Across the animal kingdom, however, reproduction takes many forms. In some species, individuals change their sex during their lifetime; in other species, such as sea slugs, an individual is both male and female. There are animals that can fertilize their own eggs, as well as others that can reproduce without any form of sex. In certain species, such as honeybees, only a few members of a large population reproduce.

A population outlives its members only by reproduction, the generation of new individuals from existing ones. In this chapter, we'll compare the diverse reproductive mechanisms that have evolved in the animal kingdom. Then we'll examine details of reproduction in mammals, with particular emphasis on the intensively studied example of humans. Lastly, we'll explore fundamental events in the earliest stages of an animal's development.

CONCEPT 36.1

Both asexual and sexual reproduction occur in the animal kingdom

There are two modes of animal reproduction—sexual and asexual. In **sexual reproduction**, the fusion of haploid gametes forms a diploid cell, the **zygote**. The animal that develops from a zygote can in turn give rise to gametes by meiosis (see Figure 10.8). The female gamete, the **egg**, is large and nonmotile, whereas the male gamete, the **sperm**, is generally much smaller and motile. In contrast, in **asexual reproduction**, new individuals are generated without the

▲ Figure 36.2 Asexual reproduction of a sea anemone (*Anthopleura elegantissima*). The large individual in the center of this photograph is undergoing fission, a type of asexual reproduction. Two smaller individuals will form as the parent divides approximately in half. Each offspring will be a genetic copy of the parent.

fusion of egg and sperm. For most asexual animals, reproduction relies entirely on mitotic cell division.

Mechanisms of Asexual Reproduction

Several simple forms of asexual reproduction are found only among invertebrates. One of these is *budding*, in which new individuals arise from outgrowths of existing ones (see Figure 10.2). In stony corals, for example, buds form and remain attached to the parent. The eventual result is a colony more than 1 m across, consisting of thousands of connected individuals. Also common among invertebrates is *fission*, the separation of a parent organism into two individuals of approximately equal size **(Figure 36.2)**.

Asexual reproduction can also be a two-step process: *fragmentation*, the breaking of the body into several pieces, followed by *regeneration*, the regrowth of lost body parts. If more than one piece grows and develops into a complete animal, the net effect is reproduction. For example, certain annelid worms can split their body into several fragments, each regenerating a complete worm in less than a week. Many sponges, cnidarians, bristle worms, and sea squirts also reproduce by fragmentation and regeneration.

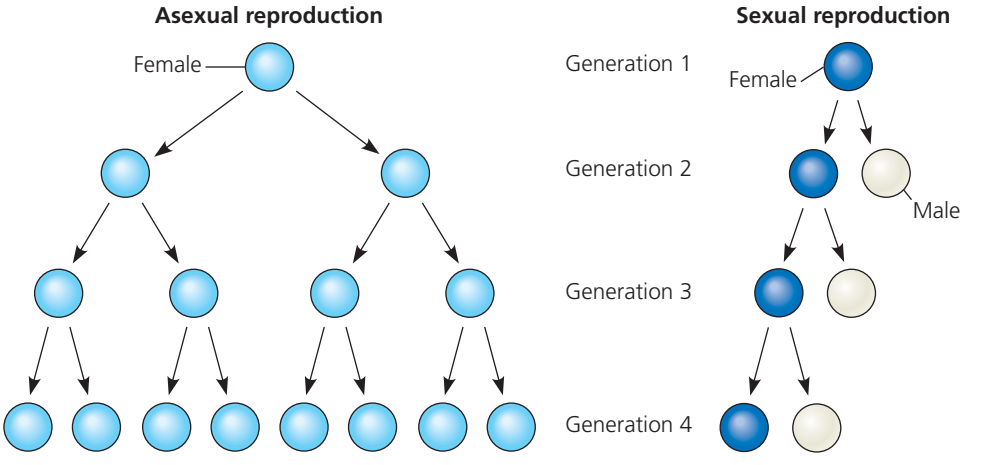
A particularly intriguing form of asexual reproduction is **parthenogenesis**, in which an egg develops without being fertilized. Among invertebrates, parthenogenesis occurs in certain species of bees, wasps, and ants. The progeny can be either haploid or diploid. If haploid, the offspring develop into adults that produce eggs or sperm without meiosis. Among vertebrates, parthenogenesis has been observed in about one in every thousand species. Recently, zookeepers discovered evidence of parthenogenesis in Komodo dragons and in a species of hammerhead shark: In both cases, females had been kept completely isolated from males of their species but nevertheless produced offspring.

The rest of this chapter focuses on sexual reproduction, the existence of which is in fact puzzling, at least from an evolutionary perspective.

Sexual Reproduction: An Evolutionary Enigma

EVOLUTION Sex must enhance reproductive success or survival because it would otherwise rapidly disappear. To see why, consider an animal population in which half the females reproduce sexually and half reproduce asexually **(Figure 36.3)**. We'll assume that the number of offspring per female is a constant, two in this case. The two offspring of an asexual female will both be daughters that will each give birth to two more daughters that can reproduce. In contrast, on average, half of a sexual female's offspring will be male. The number of sexual offspring will remain the same at each generation, because both a male and a female are required to reproduce. Thus, the asexual condition will increase in frequency at each generation. Yet despite this "twofold cost," sex is maintained even in animal species that can also reproduce asexually.

What advantage does sex provide? The answer remains elusive. Most hypotheses focus on the unique combinations of parental genes formed during meiotic recombination and fertilization. By producing offspring of varied genotypes, sexual reproduction may enhance the reproductive success of parents when environmental factors, such as pathogens, change relatively rapidly. In contrast, we would expect asexual reproduction to be most advantageous in stable, favorable environments because it perpetuates successful genotypes precisely.



▲ Figure 36.3 The "reproductive handicap" of sex. These diagrams contrast the reproductive output of females (blue spheres) over four generations for asexual versus sexual reproduction, assuming two surviving offspring per female. The asexual portion of the population rapidly outgrows the sexual one.

▲ Figure 36.4 Caribou (*Rangifer tarandus*) mother and calf. As a result of warming due to global climate change, the number of caribou offspring in a West Greenland study site has fallen fourfold.

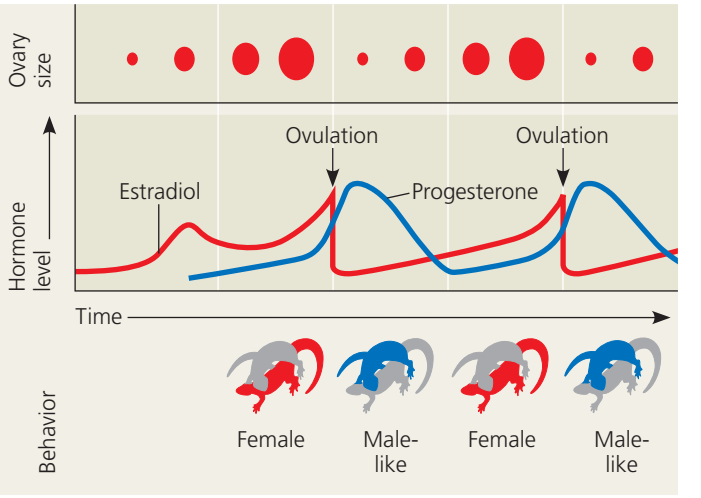
Reproductive Cycles

Most animals exhibit cycles in reproductive activity, often related to changing seasons. These cycles are controlled by hormones, whose secretion in turn is regulated by environmental cues. In this way, animals conserve resources, reproducing only when sufficient energy sources or stores are available and when environmental conditions favor the survival of offspring.

Because seasonal temperature is often an important cue for reproduction, climate change can decrease reproductive success. Researchers have demonstrated just such an effect on caribou (wild reindeer) in Greenland. In spring, caribou migrate to calving grounds to eat sprouting green plants, give birth, and care for their calves **(Figure 36.4)**. Prior to 1993, the arrival of caribou at the calving grounds coincided with the brief period during which the plants were nutritious and digestible. From 1993 to 2006, however, average spring temperatures in the calving grounds increased by more than 4°C, and the plants now sprout two weeks earlier. Because caribou migration is triggered by day length, not temperature, there is a mismatch between the timing of new plant growth and caribou birthing. Without adequate nutrition for the nursing females, production of caribou offspring has declined by 75% since 1993.

A different kind of reproductive cycle occurs in some species of whiptail lizards in the genus *Aspidoscelis*, in which members of breeding pairs alternate roles. In these species, reproduction is exclusively asexual, and there are no males. Nevertheless, these lizards have courtship and mating behaviors very similar to those of sexual species of *Aspidoscelis*. During the breeding season, one female of each mating pair mimics a male **(Figure 36.5a)**. Each member of the pair alternates roles two or three times during the season. An individual adopts female behavior prior to ovulation, when the level of the female sex hormone estradiol is high, and then switches to male-like behavior after ovulation, when the level of progesterone is high **(Figure 36.5b)**. Ovulation is more likely to occur if the individual is mounted during the critical time of the hormone cycle; isolated lizards lay fewer eggs than those that go through the motions of sex. These observations support the hypothesis that these parthenogenetic lizards evolved from species having two sexes and still require certain sexual stimuli for maximum reproductive success.

(a) Both lizards in this photograph are *A. uniparens* females. The one on top is playing the role of a male. Every two or three weeks during the breeding season, individuals switch sex roles.



(b) The sexual behavior of *A. uniparens* is correlated with the cycle of ovulation mediated by sex hormones. As the blood level of estradiol rises, the ovaries grow, and the lizard behaves as a female. After ovulation, the estradiol level drops abruptly, and the progesterone level rises; these hormone levels correlate with male-like behavior.

▲ Figure 36.5 Sexual behavior in parthenogenetic lizards. The desert-grassland whiptail lizard (*Aspidoscelis uniparens*) is an all-female species. These reptiles reproduce by parthenogenesis, the development of an unfertilized egg. Nevertheless, ovulation is stimulated by mating behavior.

Variation in Patterns of Sexual Reproduction

For many animals, finding a partner for sexual reproduction can be challenging. Adaptations that arose during the evolution of some species meet this challenge in a novel way—by blurring the strict distinction between male and female. One

such adaptation arose among sessile (stationary) animals, such as barnacles; burrowing animals, such as clams; and some parasites, including tapeworms. Largely lacking mobility, these animals have little opportunity to find a mate. The evolutionary solution in this case is **hermaphroditism**, in which each individual has both male and female reproductive systems (the term *hermaphrodite* merges the names Hermes and Aphrodite, a Greek god and goddess). Because each hermaphrodite reproduces as both a male and a female, *any* two individuals can mate. Each animal donates and receives sperm during mating, as the sea slugs in Figure 36.1 are doing. In some species, hermaphrodites are also capable of self-fertilization, allowing a form of sexual reproduction that doesn't require any partner.

The bluehead wrasse (*Thalassoma bifasciatum*) provides an example of a quite different variation in sexual reproduction. These coral reef fish live in harems, each consisting of a single male and several females. When the lone male dies, the opportunity for sexual reproduction would appear lost. Instead, the largest female in the harem transforms into a male and within a week begins to produce sperm instead of eggs. What selective pressure in the evolution of the bluehead wrasse resulted in sex reversal for that female with the largest body? Because it is the male wrasse that defends a harem against intruders, a larger size may be particularly important for a male in ensuring successful reproduction.

External and Internal Fertilization

Sexual reproduction requires **fertilization**, the union of sperm and egg. In species with **external fertilization**, the female releases eggs into the environment, where the male then fertilizes them. Other species have **internal fertilization**: Sperm are deposited in or near the female reproductive tract, and fertilization occurs within the tract.

A moist habitat is almost always required for external fertilization, both to prevent the gametes from drying out and to allow the sperm to swim to the eggs. Many aquatic invertebrates simply shed their eggs and sperm into the surroundings, and fertilization occurs without the parents making physical contact. However, timing is crucial to ensure that mature sperm and eggs encounter one another.

Among some species with external fertilization, individuals clustered in the same area release their gametes into the water at the same time, a process known as *spawning*. In some cases, chemical signals generated by one individual as it releases gametes trigger other individuals to release gametes. In other cases, environmental cues, such as temperature or day length, cause a whole population to release gametes at one time. For example, the palolo worm, native to coral reefs of the South Pacific, coordinates its spawning to both the season and the lunar cycle. Sometime in spring when the moon is in its last quarter, palolo worms break in half, releasing tail segments engorged with sperm or eggs. These packets rise to the ocean surface and burst in such vast numbers that the sea appears milky with gametes.

▲ **Figure 36.6 External fertilization.** Many species of amphibians reproduce by external fertilization. In most of these species, behavioral adaptations ensure that a male is present when the female releases eggs. Here, a female frog (on bottom) has released a mass of eggs in response to being clasped by a male. The male released sperm (not visible) at the same time, and external fertilization has already occurred in the water.

The sperm quickly fertilize the floating eggs, and within hours, the palolo's once-a-year reproductive frenzy is complete.

When external fertilization is not synchronous across a population, individuals may exhibit specific "courtship" behaviors leading to the fertilization of the eggs of one female by one male **(Figure 36.6)**. By triggering the release of both sperm and eggs, these behaviors increase the probability of successful fertilization.

Internal fertilization is an adaptation that enables sperm to reach an egg efficiently, even when the environment is dry. It typically requires cooperative behavior that leads to copulation, as well as sophisticated and compatible reproductive systems. The male copulatory organ delivers sperm, and the female reproductive tract often has receptacles for storage and delivery of sperm to mature eggs.

No matter how fertilization occurs, the mating animals may make use of *pheromones*, chemicals released by one organism that can influence the physiology and behavior of other individuals of the same species. Pheromones are small, volatile or water-soluble molecules that disperse into the environment and, like hormones, are active in tiny amounts. Many pheromones function as mate attractants, enabling some female insects to be detected by males more than a kilometer away.

Ensuring the Survival of Offspring

Internal fertilization typically is associated with the production of fewer gametes than external fertilization but results in the survival of a higher fraction of zygotes. Better zygote survival is due in part to the fact that eggs fertilized internally are sheltered from potential predators. However, internal fertilization is also more often associated with mechanisms that provide

▲ Figure 36.7 Parental care in an invertebrate. Compared with many other insects, giant water bugs of the genera *Abedus* and *Belostoma* produce relatively few offspring, but offer much greater parental protection. Following internal fertilization, the female glues her fertilized eggs to the back of the male (shown here). The male carries them for days, frequently fanning water over them to keep the eggs moist, aerated, and free of parasites.

greater protection of the embryos and parental care of the young. For example, the eggs of birds and other reptiles have calcium- and protein-containing shells and internal membranes that protect against water loss and physical damage (see Figure 27.25). In contrast, the eggs of fishes and amphibians have only a gelatinous coat and lack internal membranes.

Rather than secreting a protective eggshell, some animals retain the embryo for a portion of its development within the female's reproductive tract. Embryos of marsupial mammals, such as kangaroos and opossums, spend only a short period in the uterus; the embryos then crawl out and complete fetal development attached to a mammary gland in the mother's pouch. Embryos of eutherian (placental) mammals, such as humans, remain in the uterus throughout fetal development. There they are nourished by the mother's blood supply through a temporary organ, the placenta. The embryos of some fishes and sharks also complete development internally.

When an eagle hatches out of an egg or when a human is born, the newborn is not yet capable of independent existence. Instead, adult birds feed their young and adult mammals nurse their offspring. Parental care is in fact widespread among animals, including invertebrate species **(Figure 36.7)**.

CONCEPT CHECK 36.1

1. How does internal fertilization facilitate life on land?
2. **WHAT IF?** If a hermaphrodite self-fertilizes, will the offspring be identical to the parent? Explain.
3. **MAKE CONNECTIONS** What examples of plant reproduction are most similar to asexual reproduction in animals? (See Concept 30.2.)

For suggested answers, see Appendix A.

CONCEPT 36.2

Reproductive organs produce and transport gametes

Sexual reproduction in animals relies on sets of cells that are precursors for eggs and sperm. A group of cells dedicated to this function is often established early in the formation of the embryo and remains inactive while the body takes shape. Cycles of growth and mitosis then increase, or *amplify*, the number of cells available for making eggs or sperm.

Variation in Reproductive Systems

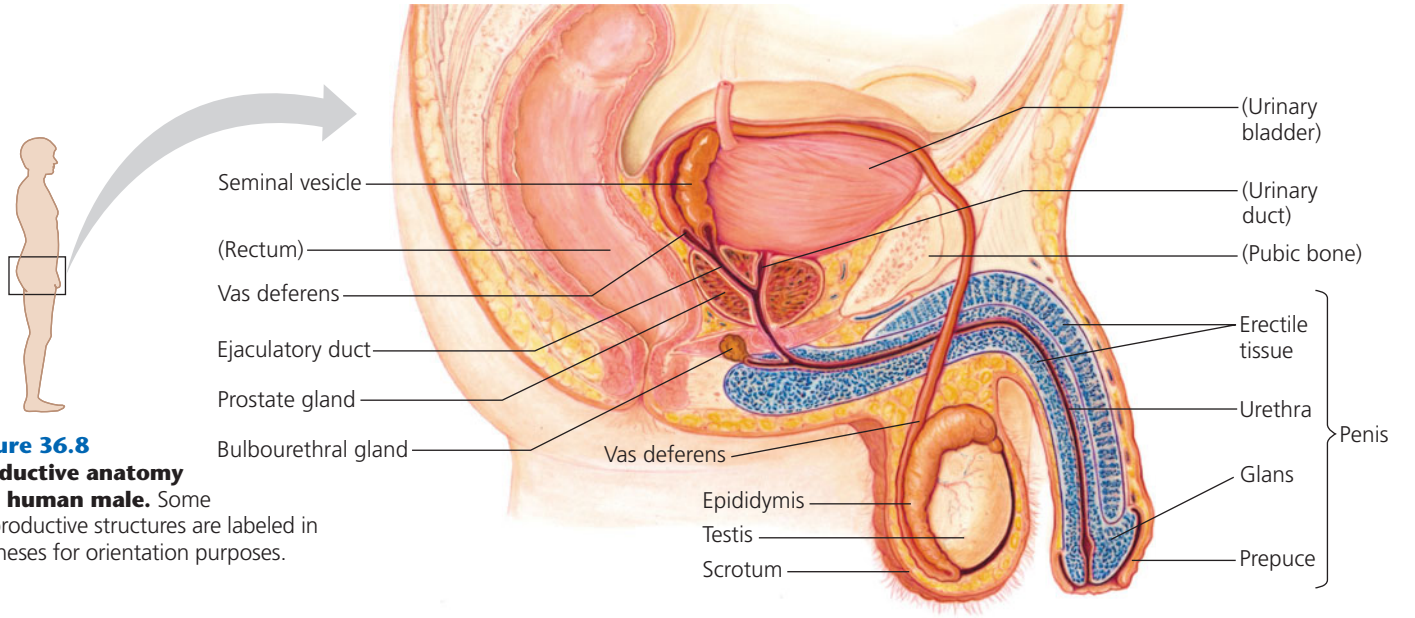
In producing gametes and making them available for fertilization, animals employ a variety of reproductive systems. **Gonads**, organs that produce gametes, are found in many but not all animals. Exceptions include the palolo worm, discussed earlier. The palolo and most other polychaete worms (phylum Annelida; see Figure 27.11) have separate sexes but lack distinct gonads; rather, the eggs and sperm develop from undifferentiated cells lining the coelom (body cavity). As the gametes mature, they are released from the body wall and fill the coelom. Depending on the species, mature gametes in these worms may be shed through the excretory opening, or the swelling mass of eggs may split a portion of the body open, spilling the eggs into the environment.

More elaborate reproductive systems include sets of accessory tubes and glands that carry, nourish, and protect the gametes and sometimes the developing embryos. Most insects, for example, have separate sexes with complex reproductive systems. In many insect species, the female reproductive system includes one or more *spermathecae*, sacs in which sperm may be stored for extended periods, a year or more in some species. Because the female releases male gametes from the spermathecae only in response to the appropriate stimuli, fertilization occurs under conditions likely to be well suited to embryonic development.

Vertebrate reproductive systems display limited but significant variations. In many nonmammalian vertebrates, the digestive, excretory, and reproductive systems have a common opening to the outside, the **cloaca**, a structure probably present in the ancestors of all vertebrates. Males of these species lack a well-developed penis and release sperm by turning the cloaca inside out.

In contrast, mammals generally lack a cloaca and have a separate opening for the digestive tract. Most female mammals also have separate openings for the excretory and reproductive systems. In some vertebrates, the uterus is divided into two chambers; in others, including humans and birds, it is a single structure.

Having surveyed some general features of animal reproduction, we turn now to human reproduction, beginning with the reproductive anatomy of males.



▶ Figure 36.8
Reproductive anatomy of the human male. Some nonreproductive structures are labeled in parentheses for orientation purposes.

Human Male Reproductive Anatomy

The human male's external reproductive organs are the scrotum and penis. The internal reproductive organs consist of gonads that produce both sperm and reproductive hormones, accessory glands that secrete products essential to sperm movement, and ducts that carry the sperm and glandular secretions **(Figure 36.8)**.

Testes

The male gonads, or **testes** (singular, *testis*), produce sperm in highly coiled tubes called **seminiferous tubules**. Most mammals produce sperm properly only when the testes are cooler than the rest of the body. In humans and many other mammals, the **scrotum**, a fold of the body wall, maintains testis temperature about 2°C below the core body temperature.

The testes develop in the abdominal cavity and descend into the scrotum just before birth (a testis within a scrotum is a *testicle*). In many rodents, the testes are drawn back into the cavity between breeding seasons, interrupting sperm maturation. Some mammals whose body temperature is low enough to allow sperm maturation—such as whales and elephants—retain the testes in the abdominal cavity at all times.

Ducts

From the seminiferous tubules of a testis, the sperm pass into the coiled duct of an **epididymis**. In humans, it takes 3 weeks for sperm to travel the 6 m length of this duct, during which time the sperm complete maturation and become motile. During **ejaculation**, the sperm are propelled from each epididymis through a muscular duct, the **vas deferens**. Each vas deferens (one from each epididymis) extends around and behind the urinary bladder, where it joins a duct from the seminal vesicle, forming a short **ejaculatory duct**. The ejaculatory ducts open into the **urethra**, the outlet tube for both the excretory system and the reproductive system. The urethra runs through the penis and opens to the outside at the tip of the penis.

Accessory Glands

Three sets of accessory glands—the seminal vesicles, the prostate gland, and the bulbourethral glands—produce secretions that combine with sperm to form **semen**, the fluid that is ejaculated. Two **seminal vesicles** contribute about 60% of the volume of semen. The fluid from the seminal vesicles is thick, yellowish, and alkaline. It contains mucus, the sugar fructose (which provides most of the sperm's energy), a coagulating enzyme, ascorbic acid, and local regulators called prostaglandins.

The **prostate gland** secretes its products into the urethra through small ducts. This fluid is thin and milky; it contains anticoagulant enzymes and citrate (a sperm nutrient). This gland undergoes benign (noncancerous) enlargement in more than half of all men over age 40 and in almost all men over 70. In addition, prostate cancer, which most often afflicts men 65 and older, is one of the most common human cancers.

The *bulbourethral glands* are a pair of small glands along the urethra below the prostate. Before ejaculation, they secrete clear mucus that neutralizes any acidic urine remaining in the urethra. Bulbourethral fluid also carries some sperm released before ejaculation, which is one reason for the high failure rate of the withdrawal method of birth control (coitus interruptus).

Penis

The human **penis** contains the urethra as well as three cylinders of spongy erectile tissue. During sexual arousal, the erectile tissue, which is derived from modified veins and capillaries, fills with blood from the arteries. As this tissue fills, the increasing pressure seals off the veins that drain the penis, causing it to engorge with blood. The resulting erection enables the penis to be inserted into the vagina. Alcohol consumption, certain drugs, emotional issues, and aging all can cause an inability to achieve an erection (erectile dysfunction). For individuals with long-term erectile dysfunction, drugs such as Viagra promote the vasodilating action of nitric oxide; the resulting relaxation of smooth muscles in the blood

vessels of the penis enhances blood flow into the erectile tissues. Although all mammals rely on penile erection for mating, the penis of rodents, raccoons, walruses, whales, and several other mammals also contains a bone, the baculum, which is thought to further stiffen the penis for mating.

The main shaft of the penis is covered by relatively thick skin. The head, or **glans**, of the penis has a much thinner covering and is consequently more sensitive to stimulation. The human glans is covered by a fold of skin called the **prepuce**, or foreskin, which is removed when a male is circumcised.

Human Female Reproductive Anatomy

The human female's external reproductive structures are the clitoris and two sets of labia, which surround the clitoris and vaginal opening. The internal organs are the gonads, which produce both eggs and reproductive hormones, and a system of ducts and chambers, which receive and carry gametes and house the embryo and fetus **(Figure 36.9)**.

Ovaries

The female gonads are a pair of **ovaries** that flank the uterus and are held in place in the abdominal cavity by ligaments. The outer layer of each ovary is packed with **follicles**, each consisting of an **oocyte**, a partially developed egg, surrounded by support cells. The surrounding cells nourish and protect the oocyte during much of its formation and development.

Oviducts and Uterus

An **oviduct**, or fallopian tube, extends from the uterus toward a funnel-like opening at each ovary. The dimensions of this tube vary along its length, with the inside diameter near the uterus being as narrow as a human hair. Upon **ovulation**, the release of a mature egg, cilia on the epithelial lining of the oviduct help collect the egg by drawing fluid from the body cavity into the oviduct. Together with wavelike contractions of the oviduct, the cilia convey the egg down the duct to the **uterus**, also known as the womb. The uterus is a thick, muscular organ that can expand during pregnancy to accommodate a 4-kg fetus. The inner lining of the uterus, the **endometrium**, is richly supplied with blood vessels. The neck of the uterus, called the **cervix**, opens into the vagina.

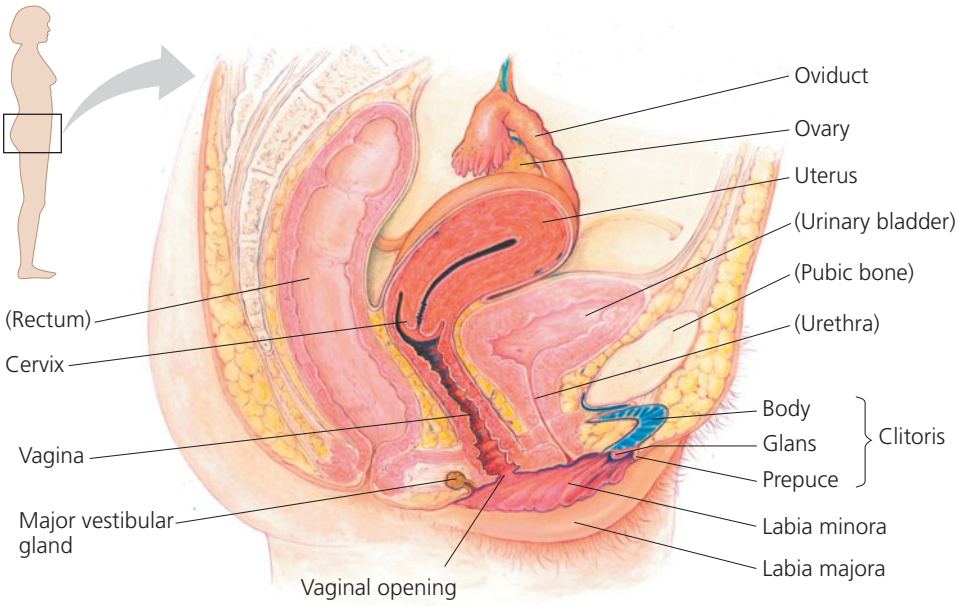
Vagina and Vulva

The **vagina** is a muscular but elastic chamber that is the site for insertion of the penis and deposition of sperm during copulation. The vagina, which also serves as the birth canal through which a baby is born, opens to the outside at the **vulva**, the collective term for the external female genitalia.

A pair of thick, fatty ridges, the **labia majora**, encloses and protects the rest of the vulva. The vaginal opening and the separate opening of the urethra are located within a cavity bordered by a pair of slender skin folds, the **labia minora**. A thin piece of tissue called the **hymen** partly covers the vaginal opening in humans at birth and usually until sexual intercourse or vigorous physical activity ruptures it. Located at the top of the labia minora, the **clitoris** consists of erectile tissue supporting a rounded glans, or head, covered by a small hood of skin, the prepuce. During sexual arousal, the clitoris, vagina, and labia minora all engorge with blood and enlarge. Richly supplied with nerve endings, the clitoris is one of the most sensitive points of sexual stimulation. Sexual arousal also induces the vestibular glands near the vaginal opening to secrete lubricating mucus, thereby facilitating intercourse.

Mammary Glands

The **mammary glands** are present in both sexes, but they normally produce milk only in females. Though not part of the reproductive system, the female mammary glands are important to reproduction. Within the glands, small sacs of epithelial tissue secrete milk, which drains into a series of ducts that open at the nipple. The breasts contain connective and fatty (adipose) tissue in addition to the mammary glands. Because the low level of the hormone estradiol in males limits the development of the fat deposits, male breasts usually remain small.



▲ **Figure 36.9** **Reproductive anatomy of the human female.** Some nonreproductive structures are labeled in parentheses for orientation purposes.

Gametogenesis

With this overview of reproductive anatomy in mind, we turn now to **gametogenesis**, the production of gametes. **Figure 36.10** compares this process in human males and females, highlighting the close relationship between the gonads' structure and their function.

Spermatogenesis, the formation and development of sperm, is continuous and

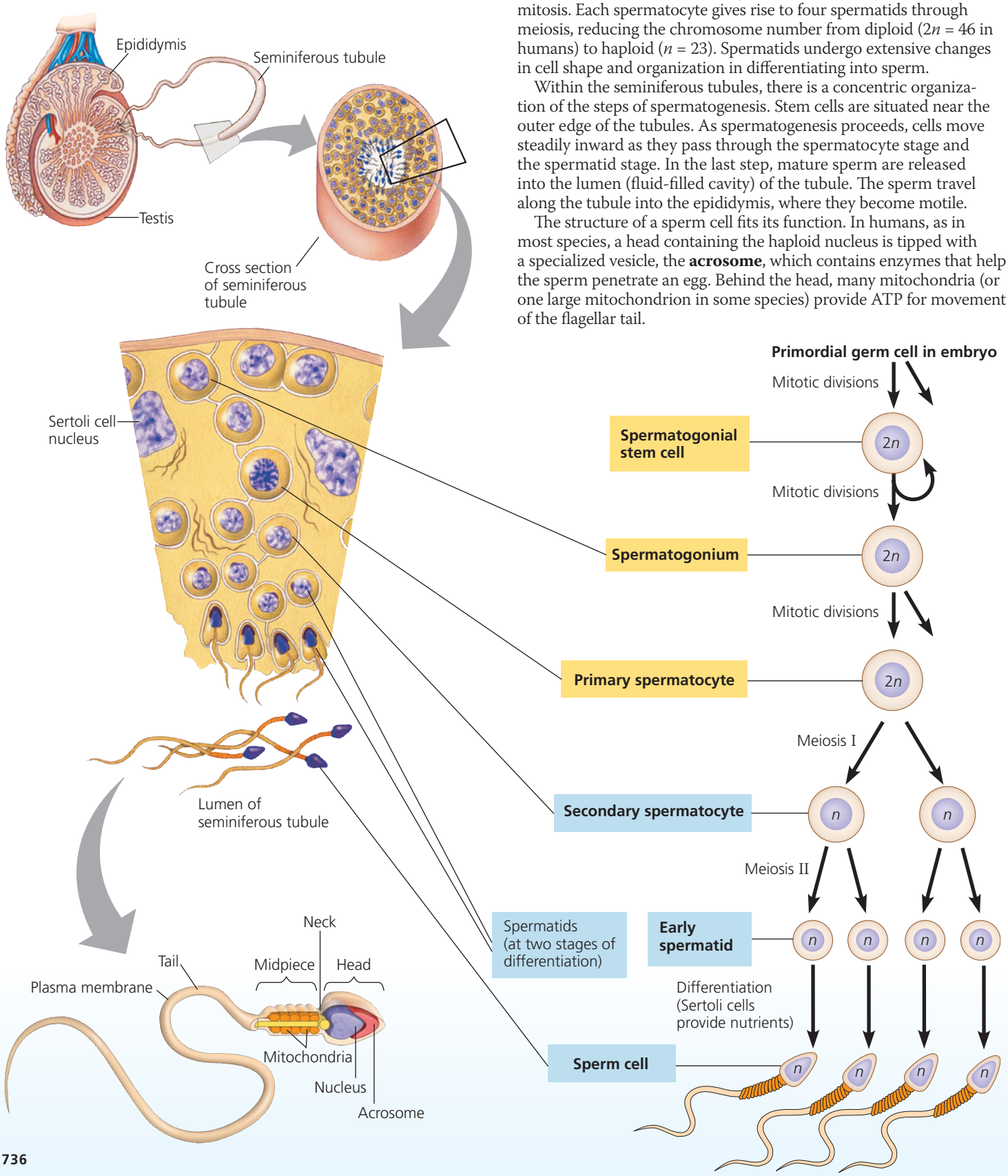
Spermatogenesis

These drawings correlate the mitotic and meiotic divisions in sperm development with the microscopic structure of seminiferous tubules.

The initial, or *primordial,* germ cells of the embryonic testes divide and differentiate into stem cells that divide by mitosis to form **spermatogonia**, which in turn generate spermatocytes, also by mitosis. Each spermatocyte gives rise to four spermatids through meiosis, reducing the chromosome number from diploid ($2n = 46$ in humans) to haploid ($n = 23$). Spermatids undergo extensive changes in cell shape and organization in differentiating into sperm.

Within the seminiferous tubules, there is a concentric organization of the steps of spermatogenesis. Stem cells are situated near the outer edge of the tubules. As spermatogenesis proceeds, cells move steadily inward as they pass through the spermatocyte stage and the spermatid stage. In the last step, mature sperm are released into the lumen (fluid-filled cavity) of the tubule. The sperm travel along the tubule into the epididymis, where they become motile.

The structure of a sperm cell fits its function. In humans, as in most species, a head containing the haploid nucleus is tipped with a specialized vesicle, the **acrosome**, which contains enzymes that help the sperm penetrate an egg. Behind the head, many mitochondria (or one large mitochondrion in some species) provide ATP for movement of the flagellar tail.

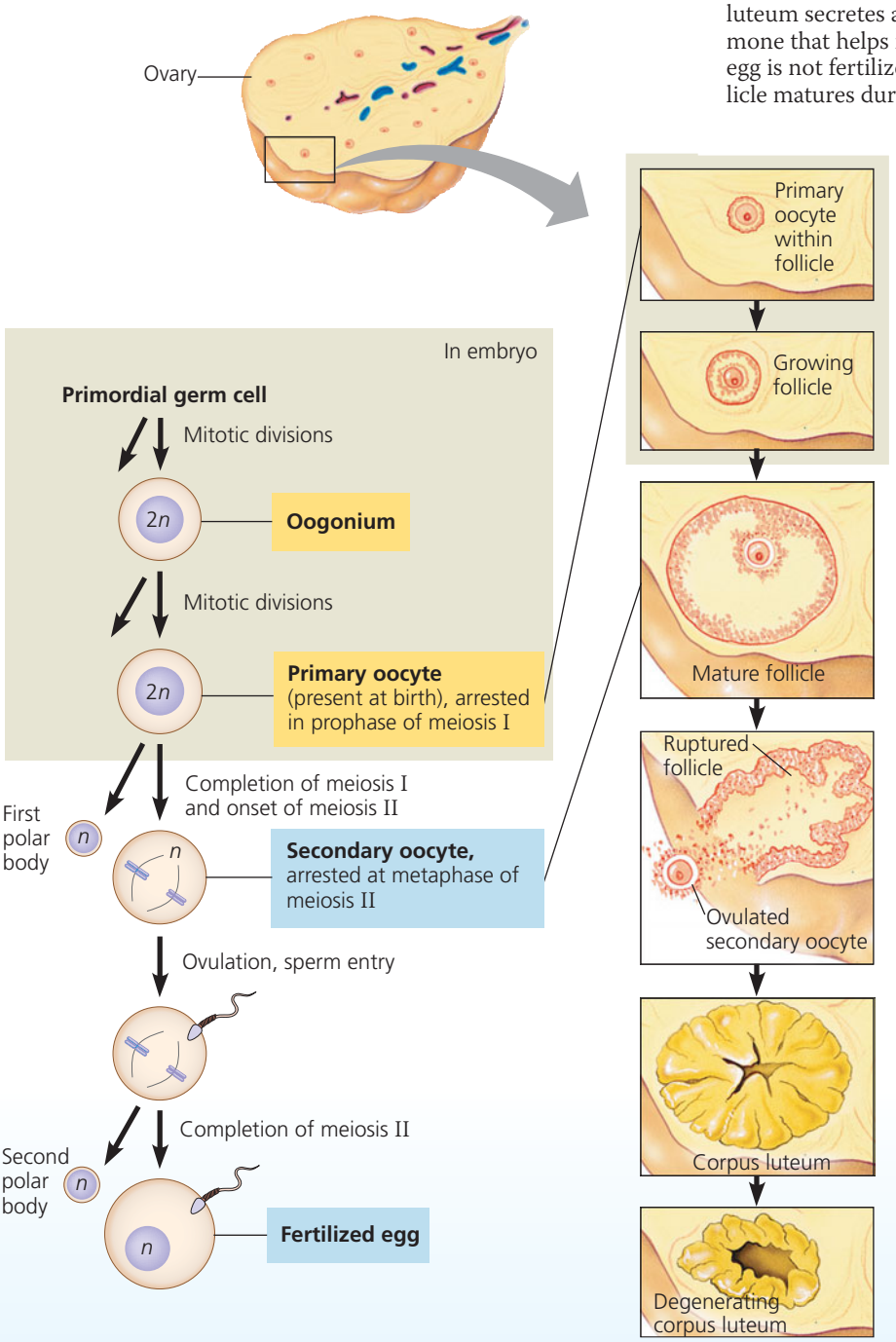


Oogenesis

Oogenesis begins in the female embryo with the production of **oogonia** from primordial germ cells. The oogonia divide by mitosis to form cells that begin meiosis, but stop the process at prophase I before birth. These developmentally arrested cells, called **primary oocytes**, each reside within a small follicle, a cavity lined with protective cells. Beginning at puberty, follicle-stimulating hormone (FSH) periodically stimulates a small group of follicles to resume growth and development. Cells of the follicle produce the primary female sex hormone, estradiol (a type of estrogen). Typically, only one follicle fully matures each month, with its primary oocyte completing meiosis I. The second meiotic division begins, but stops at metaphase. Thus arrested in meiosis II, the **secondary oocyte** is released at ovulation, when its follicle breaks open. Only if a sperm penetrates the oocyte does meiosis II resume. (In other animal species, the sperm may enter the oocyte at the same stage, earlier, or later.) Each of the two meiotic divisions involves unequal cytokinesis, with the smaller cells becoming polar bodies that eventually degenerate (the first polar body may or may not divide again). Thus, the functional product of complete oogenesis is a single mature egg already containing a sperm head; fertilization is defined strictly as the fusion of the haploid nuclei of the sperm and secondary oocyte, although we often use it loosely to mean the entry of the sperm head into the egg.

The ruptured follicle left behind after ovulation develops into a mass called the **corpus luteum** ("yellow body"). The corpus luteum secretes additional estradiol as well as progesterone, a hormone that helps maintain the uterine lining during pregnancy. If the egg is not fertilized, the corpus luteum degenerates, and a new follicle matures during the next cycle.

At birth, the ovaries together contain 1–2 million primary oocytes, of which about 500 fully mature between puberty and menopause. To the best of our current knowledge, women are born with all the primary oocytes they will ever have. It is worth noting, however, that a similar conclusion regarding most other mammals was overturned in 2004 when researchers discovered that the ovaries of adult mice contain multiplying oogonia that develop into oocytes. If the same is true of humans, then the marked decline in fertility that occurs as women age might result from both a depletion of oogonia and the degeneration of aging oocytes.



WHAT IF? *Suppose you are analyzing the DNA from the polar bodies formed during human oogenesis. If the mother has a mutation in a known disease gene, would analyzing the polar body DNA allow you to infer whether the mutation is present in the mature oocyte? Explain.*

prolific in adult males. To produce hundreds of millions of sperm each day, cell division and maturation occur throughout the seminiferous tubules coiled within the two testes. For a single sperm, the process takes about 7 weeks from start to finish.

Oogenesis, the development of mature oocytes (eggs), is a prolonged process in the human female. Immature eggs form in the ovary of the female embryo but do not complete their development until years, and often decades, later.

Spermatogenesis differs from oogenesis in three significant ways:

- Only in spermatogenesis do all four products of meiosis develop into mature gametes. In oogenesis, cytokinesis during meiosis is unequal, with almost all the cytoplasm segregated to a single daughter cell. This large cell is destined to become the egg; the other products of meiosis, smaller cells called polar bodies, degenerate.
- Spermatogenesis occurs throughout adolescence and adulthood. In contrast, the mitotic divisions of oogenesis in human females are thought to be complete before birth, and the production of mature gametes ceases at about age 50.
- Spermatogenesis produces mature sperm from precursor cells in a continuous sequence, whereas oogenesis has long interruptions.

CONCEPT CHECK 36.2

1. In what ways are a second polar body and an early spermatid similar? In what ways are they dissimilar?
2. Why might using a hot tub frequently make it harder for a couple to conceive a child?
3. **MAKE CONNECTIONS** How are the uterus of an insect and the ovary of a flowering plant similar in function? How are they different? (See Figure 30.7.)
4. **WHAT IF?** If each vas deferens in a male was surgically sealed off, what changes would you expect in sexual response and ejaculate composition?

For suggested answers, see Appendix A.

CONCEPT 36.3

The interplay of tropic and sex hormones regulates reproduction in mammals

In both male and female humans, the coordinated actions of hormones from the hypothalamus, anterior pituitary, and gonads govern reproduction. The hypothalamus secretes *gonadotropin-releasing hormone (GnRH)*, which directs the anterior pituitary to secrete **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. FSH and LH are **tropic hormones**, meaning that they act on endocrine tissues to trigger the release of other hormones. They are called *gonadotropins* because the endocrine tissues they act on are in the gonads.

▲ Figure 36.11 Androgen-dependent male anatomy and behavior in a lizard. A male anole (*Norops ortoni*) extends his dewlap, a brightly colored skinflap beneath the throat. Testosterone is required in the male both for the dewlap to develop and for the anole to display it to attract mates and guard his territory.

FSH and LH regulate gametogenesis by targeting tissues in the gonads and by regulating sex hormone production.

The principal sex hormones are steroid hormones that include *androgens*, *estrogens*, and **progesterone**. The major androgen is **testosterone**; the major estrogen is **estradiol**. Males and females both produce androgens and estrogens, but differ in their blood concentrations of particular hormones. Testosterone levels are about 10 times higher in males than in females, whereas estradiol levels are about 10 times higher in females than in males. The gonads are the major source of sex hormones, with much smaller amounts being produced by the adrenal gland.

Like gonadotropins, the sex hormones regulate gametogenesis both directly and indirectly, but they have other actions as well. For example, androgens are responsible for the male vocalizations of many vertebrates, such as the territorial songs of birds and the courtship displays of lizards **(Figure 36.11)**. In human embryos, androgens promote the appearance of the primary sex characteristics of males, the structures directly involved in reproduction. These include the seminal vesicles and associated ducts, as well as external reproductive structures. In the **Scientific Skills Exercise**, you can interpret the results of an experiment investigating the development of reproductive structures in mammals.

At puberty, sex hormones in both male and female humans induce formation of secondary sex characteristics, the physical and behavioral features that are not directly related to the reproductive system. In males, androgens cause the voice to deepen, facial and pubic hair to develop, and muscles to grow (by stimulating protein synthesis). Androgens also promote specific sexual behaviors and sex drive, as well as an increase in general aggressiveness. Estrogens similarly have multiple effects in females. At puberty, estradiol stimulates breast and pubic hair development. Estradiol also influences female sexual behavior, induces fat deposition in the breasts and hips, increases water retention, and alters calcium metabolism.

Scientific Skills Exercise

Making Inferences and Designing an Experiment

What Role Do Hormones Play in Making a Mammal Male or Female? In non-egg-laying mammals, females have two X chromosomes, whereas males have one X chromosome and one Y chromosome. In the 1940s, French physiologist Alfred Jost wondered whether development of mammalian embryos as female or male in accord with their chromosome set requires instructions in the form of hormones produced by the gonads. In this exercise, you will interpret the results of an experiment that Jost performed to answer this question.

How the Experiment Was Done Working with rabbit embryos still in the mother's uterus at a stage before sex differences are observable, Jost surgically removed the portion of each embryo that would form the ovaries or testes. When the baby rabbits were born, he made note of their chromosomal sex and whether their genital structures were male or female.

Data from the Experiment

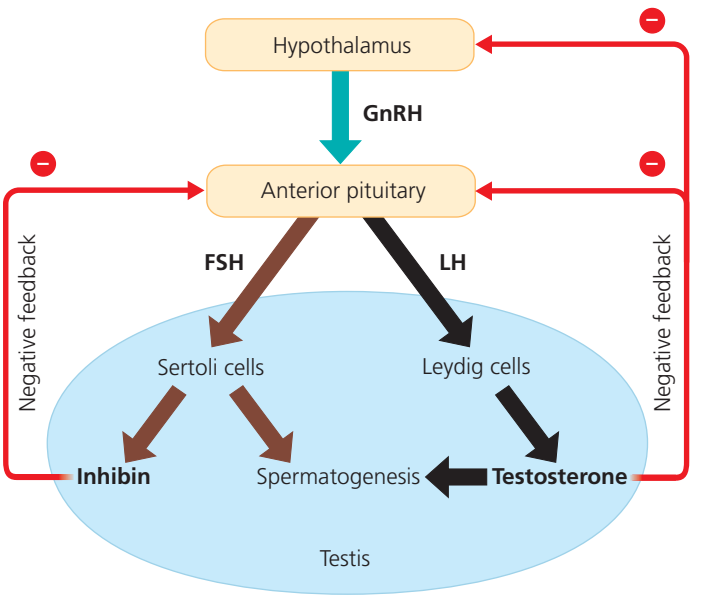
Chromosome Set	Appearance of Genitalia	
	No Surgery	Embryonic Gonad Removed
XY (male)	Male	Female
XX (female)	Female	Female

Interpret the Data

1. This experiment is an example of a research approach in which scientists infer how something works normally based on what happens when the normal process is blocked. What normal process was blocked in Jost's experiment? From the results, what inference can you make about the role of the gonads in controlling the development of mammalian genitalia?
2. The data in Jost's experiment could be explained if some aspect of the surgery other than gonad removal caused female genitalia to develop. If you were to repeat Jost's experiment, how might you test the validity of such an explanation?
3. What result would Jost have obtained if female development also required a signal from the gonad?
4. Design another experiment to determine whether the signal that controls male development is a hormone. Make sure to identify your hypothesis, prediction, data collection plan, and controls.

Data from A. Jost, Recherches sur la differenciation sexuelle de l'embryon de lapin (Studies on the sexual differentiation of the rabbit embryo), *Archives d'Anatomie Microscopique et de Morphologie Experimentale* 36:271–316 (1947).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.



▲ **Figure 36.12 Hormonal control of the testes.**

We turn now to the role of gonadotropins and sex hormones in gametogenesis, beginning with males.

Hormonal Control of the Male Reproductive System

FSH and LH, released by the anterior pituitary in response to GnRH secretion by the hypothalamus, act on different types of cells in the testes to direct spermatogenesis **(Figure 36.12)**. **Sertoli cells**, located within the seminiferous tubules, respond to FSH by nourishing developing sperm (see Figure 36.10). **Leydig cells**, scattered in connective tissue between the tubules, respond to LH by producing testosterone and other androgens, which promote spermatogenesis in the tubules.

Two negative-feedback mechanisms control sex hormone production in males (see Figure 36.12). Testosterone regulates blood levels of GnRH, FSH, and LH through inhibitory effects on the hypothalamus and anterior pituitary. In addition, *inhibin*, a hormone that in males is produced by Sertoli cells, acts on the anterior pituitary gland to reduce FSH secretion. Together, these negative-feedback circuits maintain androgen production at optimal levels.

Hormonal Control of Female Reproductive Cycles

Whereas human males produce sperm continuously, human females produce eggs in cycles. Ovulation occurs only after the endometrium (lining of the uterus) has started to thicken and develop a rich blood supply, preparing the uterus for the possible implantation of an embryo. If pregnancy does not occur, the uterine lining is sloughed off, and another cycle begins. The cyclic shedding of the blood-rich endometrium from the uterus, a process that occurs in a flow through the cervix and vagina, is called **menstruation**.

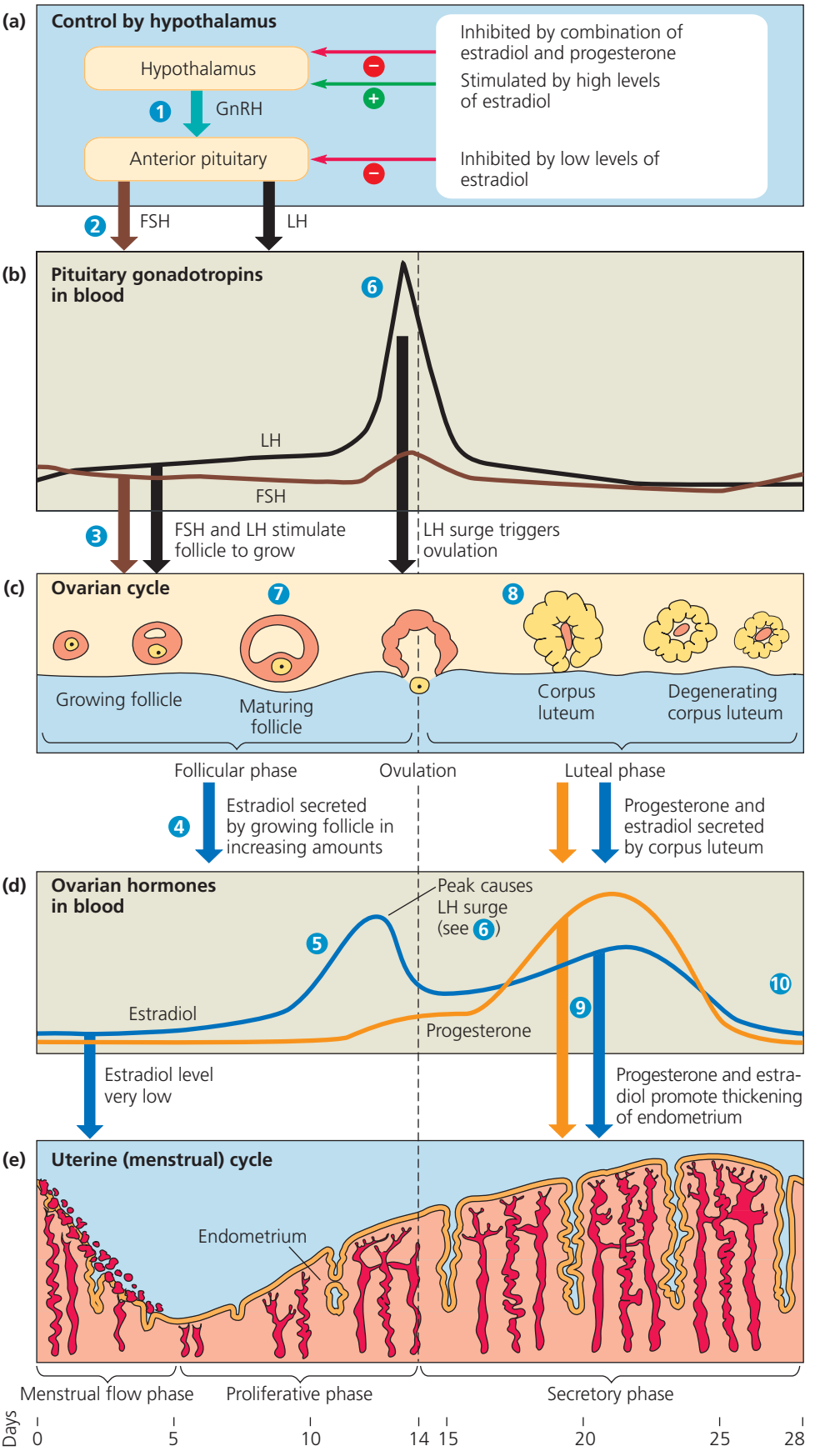
There are two closely linked reproductive cycles in human females. Changes in the uterus define the **menstrual cycle**, also called the **uterine cycle**. Menstrual cycles average 28 days (although cycles vary, ranging from about 20 to 40 days). The cyclic events in the ovaries define the **ovarian cycle**. Hormone activity links the two cycles to each other, synchronizing ovarian follicle growth and ovulation with the establishment of a uterine lining that can support embryonic development.

Figure 36.13 outlines the major events of the female reproductive cycles, illustrating the close coordination across different tissues in the body.

The Ovarian Cycle

The ovarian cycle begins 1 with the release from the hypothalamus of GnRH, which stimulates the anterior pituitary to 2 secrete small amounts of FSH and LH. 3 Follicle-stimulating hormone (as its name implies) stimulates follicle growth, aided by LH, and 4 the cells of the growing follicles start to make estradiol. There is a slow rise in estradiol secreted during most of the **follicular phase**, the part of the ovarian cycle during which follicles grow and oocytes mature. (Several follicles begin to grow with each cycle, but usually only one matures; the others disintegrate.) The low levels of estradiol inhibit secretion of the pituitary hormones, keeping the levels of FSH and LH relatively low. During this portion of the cycle, regulation of the hormones controlling reproduction closely parallels the regulation observed in males.

5 When estradiol secretion by the growing follicle begins to rise steeply, 6 the FSH and LH levels increase markedly. Whereas a low level of estradiol inhibits the secretion of pituitary gonadotropins, a high concentration has the opposite effect: It stimulates gonadotropin secretion by acting on the hypothalamus to increase its output of GnRH. The effect is greater for LH because the high concentration of estradiol increases the GnRH sensitivity of LH-releasing cells in the pituitary. In addition, follicles respond more



▲ **Figure 36.13** **The reproductive cycles of the human female.** This figure shows how **(c)** the ovarian cycle and **(e)** the uterine (menstrual) cycle are regulated by changing hormone levels in the blood, depicted in parts **(a)**, **(b)**, and **(d)**. The time scale at the bottom of the figure applies to parts **(b)–(e)**.

strongly to LH at this stage because more of their cells have receptors for this hormone.

The increase in LH concentration caused by increased estradiol secretion from the growing follicle is an example of positive feedback. The result is final maturation of the follicle. (7) The maturing follicle, containing a fluid-filled cavity, enlarges, forming a bulge near the surface of the ovary. The follicular phase ends at ovulation, about a day after the LH surge. In response to the peak in LH levels, the follicle and adjacent wall of the ovary rupture, releasing the secondary oocyte. There is sometimes a distinctive pain in the lower abdomen at or near the time of ovulation; this pain is felt on the left or right side, corresponding to whichever ovary has matured a follicle during that cycle.

The *luteal phase* of the ovarian cycle follows ovulation. (8) LH stimulates the follicular tissue left behind in the ovary to transform into a corpus luteum, a glandular structure. Under continued stimulation by LH, the corpus luteum secretes progesterone and estradiol, which in combination exert negative feedback on the hypothalamus and pituitary. This feedback reduces the secretion of LH and FSH to very low levels, preventing another egg from maturing when a pregnancy may already be under way.

Near the end of the luteal phase, low gonadotropin levels cause the corpus luteum to disintegrate, triggering a sharp decline in estradiol and progesterone concentrations. The decreasing levels of ovarian steroid hormones liberate the hypothalamus and pituitary from the negative-feedback effect of these hormones. The pituitary can then begin to secrete enough FSH to stimulate the growth of new follicles in the ovary, initiating the next ovarian cycle.

The Uterine (Menstrual) Cycle

Prior to ovulation, ovarian steroid hormones stimulate the uterus to prepare for support of an embryo. Estradiol secreted in increasing amounts by growing follicles signals the endometrium to thicken. In this way, the follicular phase of the ovarian cycle is coordinated with the *proliferative phase* of the uterine cycle. After ovulation, (9) the estradiol and progesterone secreted by the corpus luteum stimulate maintenance of the uterine lining, as well as further development, including enlargement of arteries and growth of endometrial glands. These glands secrete a nutrient fluid that can sustain an early embryo even before it implants in the uterine lining. Thus, the luteal phase of the ovarian cycle is coordinated with what is called the *secretory phase* of the uterine cycle.

Once the corpus luteum has disintegrated, (10) the rapid drop in ovarian hormone levels causes arteries in the endometrium to constrict. Deprived of its circulation, the uterine lining largely disintegrates, and the uterus, in response to prostaglandin secretion, contracts. Small endometrial blood vessels constrict, releasing blood that is shed along with endometrial tissue and fluid. The result is menstruation—the *menstrual flow phase* of the uterine cycle. During this phase, which usually lasts a few days, a new group of ovarian follicles begin to grow. By convention, the first day of flow is designated day 1 of the new uterine (and ovarian) cycle.

Overall, the hormonal cycles in females coordinate egg maturation and release with changes in the uterus, the organ that must accommodate an embryo if the egg cell is fertilized. If an embryo has not implanted in the endometrium by the end of the secretory phase, a new menstrual flow commences, marking the start of the next cycle. Later in the chapter, you'll learn about override mechanisms that prevent disintegration of the endometrium in pregnancy.

Menopause

After about 500 cycles, a woman undergoes **menopause**, the cessation of ovulation and menstruation. Menopause usually occurs between the ages of 46 and 54. During this interval, the ovaries lose their responsiveness to FSH and LH, resulting in a decline in estradiol production.

Menopause is an unusual phenomenon. In most other species, females and males retain their reproductive capacity throughout life. Is there an evolutionary explanation for menopause? One intriguing hypothesis proposes that during early human evolution, undergoing menopause after bearing several children allowed a mother to provide better care for her children and grandchildren, thereby increasing the survival of individuals who share much of her genetic makeup.

Menstrual Versus Estrous Cycles

In all female mammals, the endometrium thickens before ovulation, but only humans and some other primates have menstrual cycles. Other mammals have **estrous cycles**, in which in the absence of a pregnancy, the uterus reabsorbs the endometrium and no extensive fluid flow occurs. Whereas human females may engage in sexual activity throughout the menstrual cycle, mammals with estrous cycles usually copulate only during the period surrounding ovulation. This period, called estrus (from the Latin *oestrus*, frenzy, passion), is the only time the female is receptive to mating. It is often called "heat," and the female's temperature does increase slightly.

The length and frequency of estrous cycles vary widely among mammals. Bears and wolves have one estrous cycle per year; elephants typically have multiple cycles lasting 14–16 weeks each. Rats have estrous cycles throughout the year, each lasting only 5 days.

Human Sexual Response

In humans, the arousal of sexual interest is complex, involving a variety of psychological as well as physical factors. Although many reproductive structures in the male and female are quite different in appearance, they often serve similar functions in arousal, reflecting their shared developmental origin. For example, the same embryonic tissues give rise to the glans of the penis and the clitoris, to the scrotum and the labia majora, and

to the skin on the penis and the labia minora. Furthermore, the general pattern of human sexual response is similar in males and females. Two types of physiological reactions predominate in both sexes: *vasocongestion*, the filling of a tissue with blood, and *myotonia*, increased muscle tension.

The sexual response cycle can be divided into four phases: excitement, plateau, orgasm, and resolution. An important function of the excitement phase is to prepare the vagina and penis for *coitus* (sexual intercourse). During this phase, vasocongestion is particularly evident in erection of the penis and clitoris; and in enlargement of the testicles, labia, and breasts. The vagina becomes lubricated and myotonia may occur, resulting in nipple erection or tension of the arms and legs.

In the plateau phase, these responses continue as a result of direct stimulation of the genitalia. In females, the outer third of the vagina becomes vasocongested, while the inner two-thirds slightly expands. This change, coupled with the elevation of the uterus, forms a depression for receiving sperm at the back of the vagina. Breathing increases and heart rate rises, sometimes to 150 beats per minute—not only in response to the physical effort of sexual activity, but also as an involuntary response to stimulation of the autonomic nervous system (see Chapter 38).

Orgasm is characterized by rhythmic, involuntary contractions of the reproductive structures in both sexes. Male orgasm has two stages. The first, emission, occurs when the glands and ducts of the reproductive tract contract, forcing semen into the urethra. Expulsion, or ejaculation, occurs when the urethra contracts and the semen is expelled. During female orgasm, the uterus and outer vagina contract, but the inner two-thirds of the vagina does not. Orgasm is the shortest phase of the sexual response cycle, usually lasting only a few seconds. In both sexes, contractions occur at about 0.8-second intervals and may also involve the anal sphincter and several abdominal muscles.

The resolution phase completes the cycle and reverses the responses of the earlier stages. Vasocongested organs return to their normal size and color, and muscles relax. Most of the changes of resolution are completed within 5 minutes, but some may take as long as an hour. Following orgasm, the male typically enters a refractory period, lasting anywhere from a few minutes to hours, during which erection and orgasm cannot be achieved. Females do not have a refractory period, making possible multiple orgasms within a short period of time.

CONCEPT CHECK 36.3

1. FSH and LH get their names from events of the female reproductive cycle, but they also function in males. How are their functions in females and males similar?
2. How does an estrous cycle differ from a menstrual cycle, and in what animals are the two types of cycles found?
3. **WHAT IF?** If a human female were to take estradiol and progesterone immediately after the start of a new menstrual cycle, how would ovulation be affected? Explain.

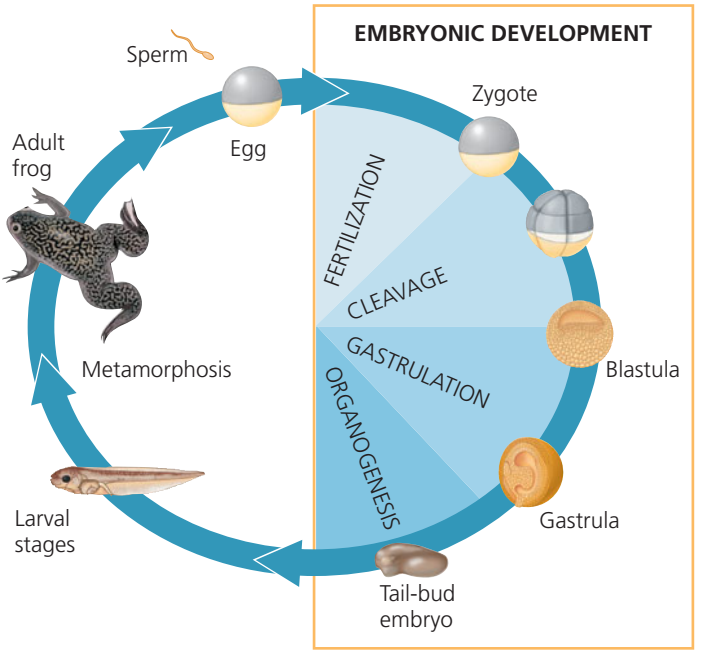
For suggested answers, see Appendix A.

CONCEPT 36.4

Fertilization, cleavage, and gastrulation initiate embryonic development

Having explored gamete production and mating, we turn our attention now to development. Across a range of animal species, embryonic development involves common stages that occur in a set order. As shown in **Figure 36.14**, the first is fertilization, which forms a zygote. Development proceeds with the cleavage stage, during which a series of mitoses divide, or cleave, the zygote into a many-celled embryo. These cleavage divisions, which typically are rapid and lack accompanying cell growth, convert the embryo to a hollow ball of cells called a blastula. Next, the blastula folds in on itself, rearranging into a three-layered embryo, the gastrula, in a process called gastrulation. During organogenesis, the last major stage of embryonic development, local changes in cell shape and large-scale changes in cell location generate the rudimentary organs from which adult structures grow.

With this overview of embryonic development in mind, let's take a brief look at the early events of development—fertilization, cleavage, and gastrulation—in sea urchins (phylum Echinodermata; see Figure 27.11). Why sea urchins? Their gametes are easy to collect, and they have external fertilization; as a result, researchers can observe fertilization and subsequent events simply by combining eggs and sperm in seawater. Sea urchins are one example of a model organism, a species chosen for in-depth research in part because it is easy to study in the laboratory.



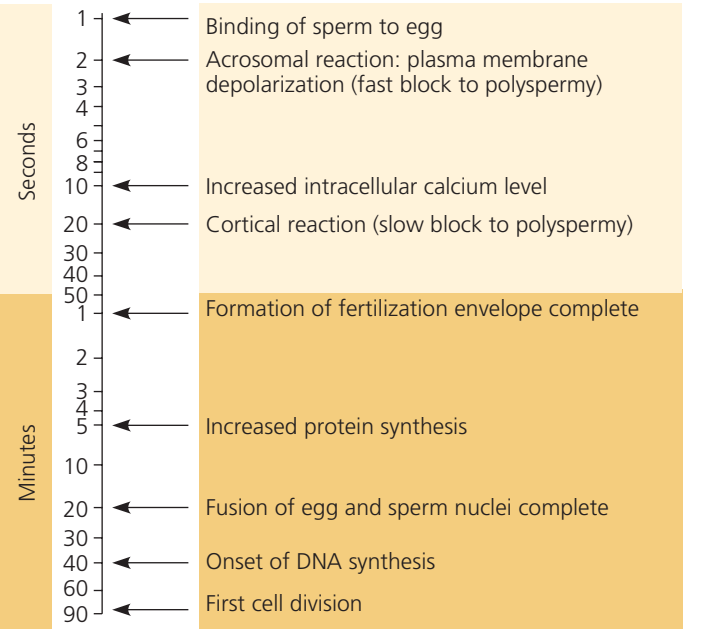
▲ **Figure 36.14** **Developmental events in the life cycle of a frog.**

Fertilization

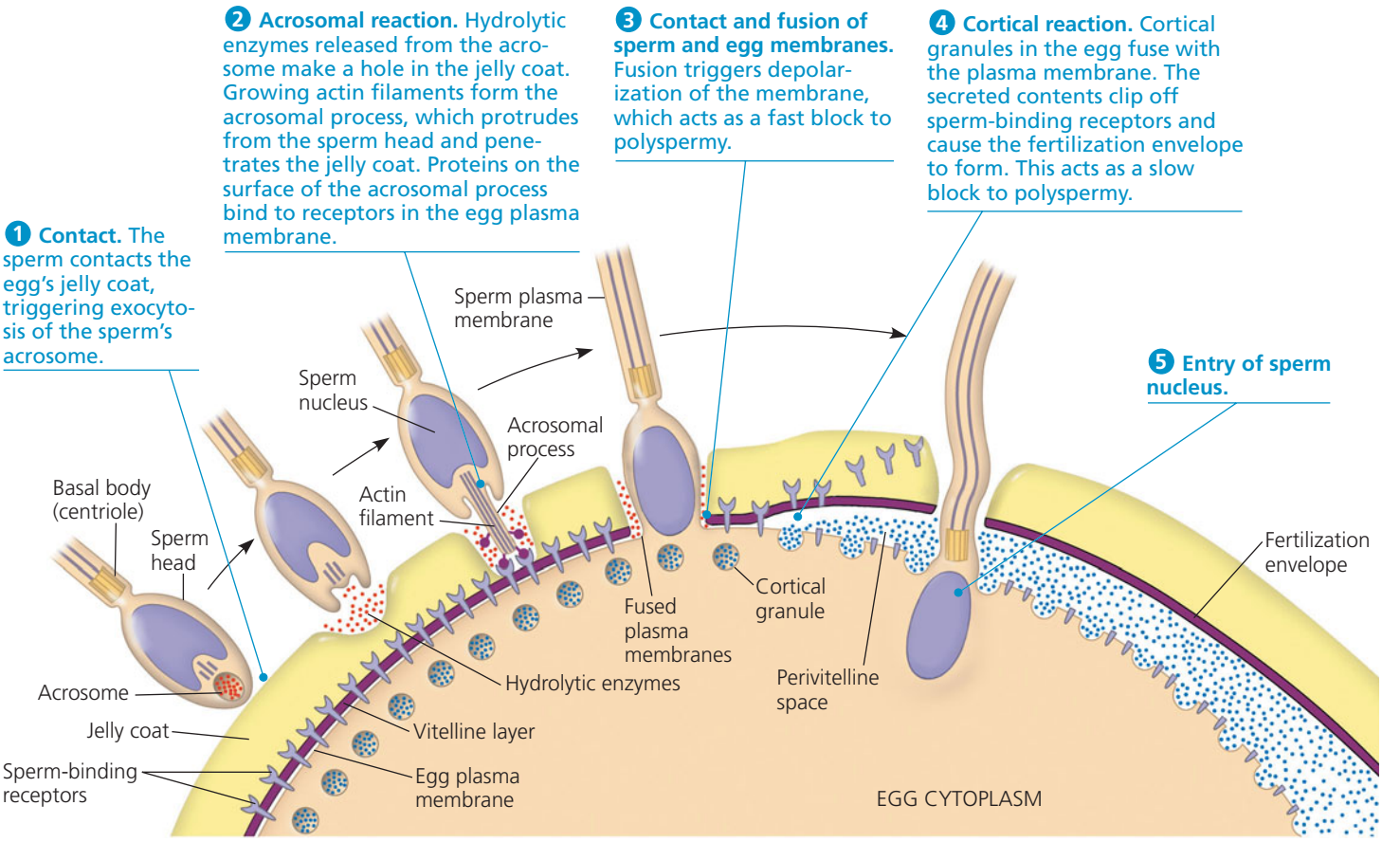
Molecules and events at the egg surface play a crucial role in each step of fertilization. First, sperm dissolve or penetrate any protective layer surrounding the egg to reach the plasma membrane. Next, molecules on the sperm surface bind to receptors on the egg, helping ensure that a sperm of the same species fertilizes the egg. Finally, changes at the surface of the egg prevent **polyspermy**, the entry of multiple sperm nuclei into the egg. If polyspermy were to occur, the resulting abnormal number of chromosomes in the embryo would be lethal. **Figure 36.15** illustrates the events that provide a fast and slow block to polyspermy in sea urchins, ensuring that only one sperm nucleus crosses the egg plasma membrane.

A major function of fertilization is combining haploid sets of chromosomes from two individuals into a single diploid cell, the zygote. However, the events of fertilization also initiate metabolic reactions that trigger the onset of embryonic development, thus "activating" the egg. As shown in **Figure 36.16**, activation leads to a number of events, such as an increase in protein synthesis, that precede the formation of a diploid nucleus.

What triggers egg activation? Studies show that sperm entry triggers release of internal Ca^{2+} stores into the egg cytoplasm and that injecting Ca^{2+} into an unfertilized egg activates



▲ **Figure 36.16 Timeline for the fertilization of sea urchin eggs.** The process begins when a sperm cell binds the egg (top of chart). Notice that the scale is logarithmic.



▲ **Figure 36.15 The acrosomal and cortical reactions during sea urchin fertilization.** The events following contact of a single sperm and egg ensure that the nucleus of only one sperm enters the egg cytoplasm.

egg metabolism. Other experiments indicate that the rise in Ca^{2+} concentration also causes the cortical reaction that provides the slow block to polyspermy (see Figure 36.15).

Fertilization in other species shares many features with the process in sea urchins. However, the timing of events differs, as does the stage of meiosis the egg has reached by the time it is fertilized. Sea urchin eggs have already completed meiosis when they are released from the female. In other species, eggs are arrested at a specific stage of meiosis and do not complete the meiotic divisions until fertilization occurs. Human eggs, for example, are arrested at metaphase of meiosis II prior to fertilization (see Figure 36.10).

Cleavage and Gastrulation

Once fertilization is complete, many animal species undergo a succession of rapid cell divisions that characterize the **cleavage** stage of early development. During cleavage, the cell cycle consists primarily of the S (DNA synthesis) and M (mitosis) phases (for a review of the cell cycle, see Figure 9.6). Cells essentially skip the G_1 and G_2 (gap) phases, and little or no protein synthesis occurs. As a result, cleavage partitions the cytoplasm of the large fertilized egg into many smaller cells. The first five to seven cleavage divisions produce a hollow ball of cells, the **blastula**, surrounding a fluid-filled cavity called the **blastocoel** **(Figure 36.17)**.

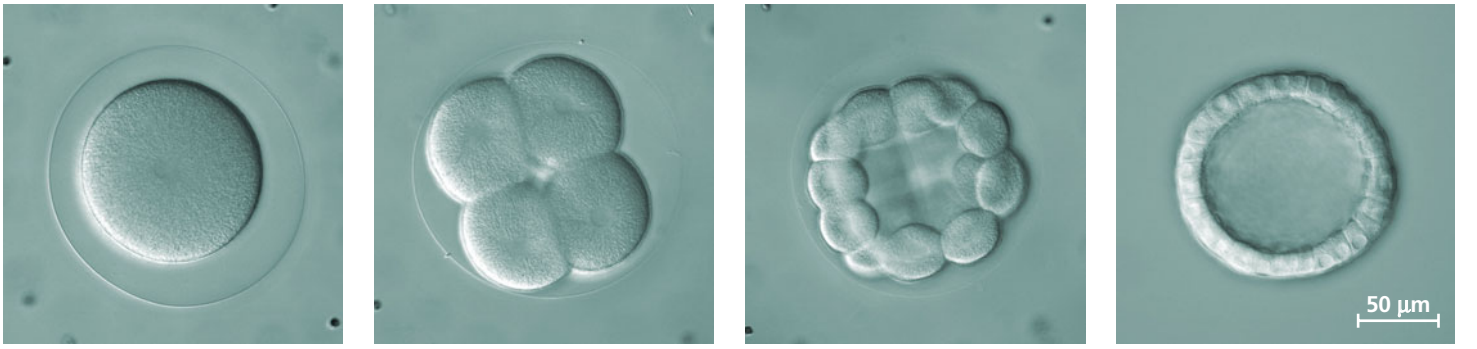
After cleavage, the rate of cell division slows considerably as the normal cell cycle is restored. The remaining stages of embryonic development are responsible for **morphogenesis**, the cellular and tissue-based processes by which the animal body takes shape.

During **gastrulation**, a set of cells at or near the surface of the blastula moves to an interior location, cell layers are established, and a primitive digestive tube is formed. Gastrulation reorganizes the hollow blastula into a two-layered or three-layered embryo called a **gastrula**. The cell layers produced by gastrulation are collectively called the embryonic *germ layers* (from the Latin *germen*, to sprout or germinate). In the late gastrula, **ectoderm** forms the outer layer and **endoderm** lines the embryonic digestive compartment or tract. In vertebrates and other animals with bilateral symmetry, a third germ layer, the **mesoderm**, forms between the ectoderm and the endoderm.

Gastrulation in the sea urchin begins at the vegetal pole of the blastula **(Figure 36.18)**. There, *mesenchyme cells* individually detach from the blastocoel wall and enter the blastocoel. The remaining cells near the vegetal pole flatten slightly and cause that end of the embryo to buckle inward. This process—the infolding of a sheet of cells into the embryo—is called *invagination*. Extensive rearrangement of cells transforms the shallow depression into a deeper, narrower, blind-ended tube called the *archenteron*. The open end of the archenteron, which will become the anus, is called the *blastopore*. A second opening, which will become the mouth, forms when the opposite end of the archenteron touches the inside of the ectoderm and the two layers fuse, producing a rudimentary digestive tube.

The cell movements and interactions that form the germ layers vary considerably among species. One basic distinction is whether the mouth develops from the first opening that forms in the embryo (protostomes) or the second (deuterostomes). Sea urchins and other echinoderms are deuterostomes, as are chordates like ourselves and other vertebrates.

Each germ layer contributes to a distinct set of structures in the adult animal, as shown for vertebrates in **Figure 36.19**. Note that some organs and many organ systems of the adult



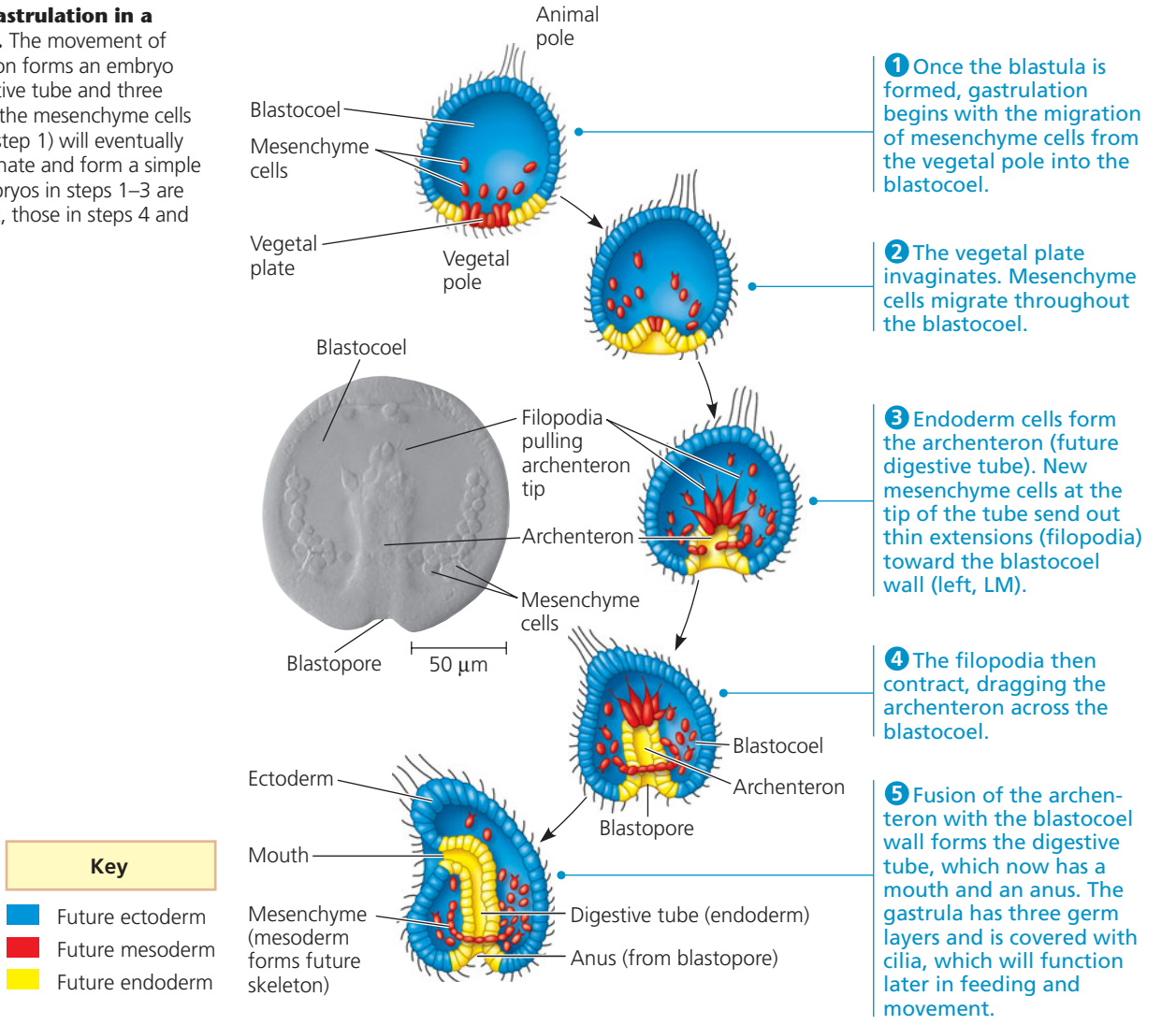
(a) Fertilized egg. Shown here is the zygote shortly before the first cleavage division, surrounded by the fertilization envelope.

(b) Four-cell stage. Remnants of the mitotic spindle can be seen between the two pairs of cells that have just completed the second cleavage division.

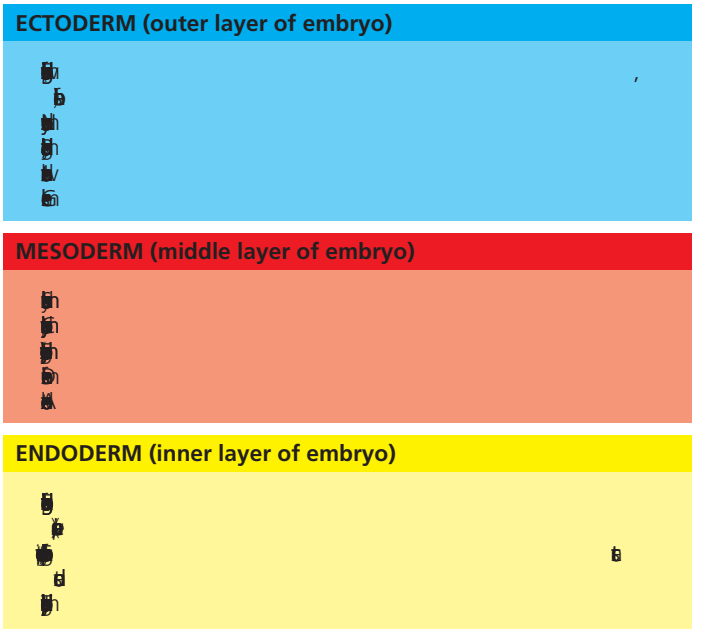
(c) Early blastula. After further cleavage divisions, the embryo is a multicellular ball that is still surrounded by the fertilization envelope. The blastocoel has begun to form in the center.

(d) Later blastula. A single layer of cells surrounds a large blastocoel. Although not visible here, the fertilization envelope is still present; the embryo will soon hatch from it and begin swimming.

▲ Figure 36.17 Cleavage in an echinoderm embryo. Cleavage is a series of mitotic cell divisions that transform the zygote into a blastula, a hollow ball of cells called blastomeres. These light micrographs show the embryonic stages of a sand dollar, which are virtually identical to those of a sea urchin.



▶ Figure 36.18 Gastrulation in a sea urchin embryo. The movement of cells during gastrulation forms an embryo with a primitive digestive tube and three germ layers. Some of the mesenchyme cells that migrate inward (step 1) will eventually secrete calcium carbonate and form a simple internal skeleton. Embryos in steps 1–3 are viewed from the front, those in steps 4 and 5 from the side.



▲ Figure 36.19 Major derivatives of the three embryonic germ layers in vertebrates.

derive from more than one germ layer. For example, the adrenal glands have both ectodermal and mesoderm tissue, and many other endocrine glands contain endodermal tissue.

Having introduced the developmental stages of fertilization, cleavage, and gastrulation, using the sea urchin as the primary example, we now return to our consideration of human reproduction.

Human Conception, Embryonic Development, and Birth

During human copulation, the male delivers 2–5 mL of semen containing hundreds of millions of sperm. When first ejaculated, the semen coagulates, which may serve to keep the ejaculate in place until sperm reach the cervix. Soon after, anticoagulants liquefy the semen, and the sperm begin swimming through the uterus and oviducts. Fertilization—also called **conception** in humans—occurs when a sperm fuses with an

egg (mature oocyte) in the oviduct **(Figure 36.20a)**. As in sea urchin fertilization, sperm binding triggers a cortical reaction, which results in a slow block to polyspermy. (No fast block to polyspermy has been identified in mammals.)

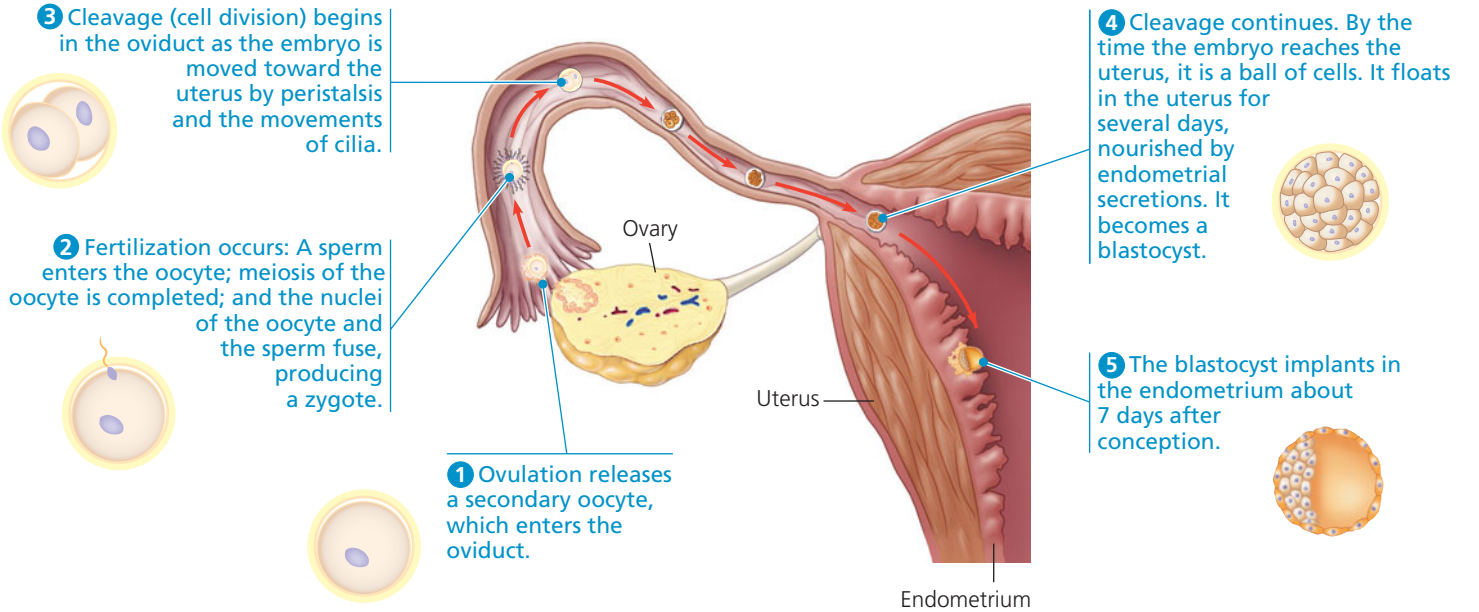
The zygote begins cleavage about 24 hours after fertilization and produces a blastocyst after an additional 4 days. A few days later, the embryo implants into the endometrium of the uterus **(Figure 36.20b)**. The condition of carrying one or more embryos in the uterus is called *pregnancy*, or **gestation**. Human pregnancy averages 266 days (38 weeks) from fertilization of the egg, or 40 weeks from the start of the last menstrual cycle. In comparison, gestation averages 21 days in many rodents, 270 days in cows, and more than 600 days in elephants.

Human gestation can be divided for convenience into three *trimesters* of about three months each. During the first trimester, the implanted embryo secretes hormones that signal its presence and regulate the mother's reproductive system. One embryonic hormone, *human chorionic gonadotropin (hCG)*, acts like LH in maintaining secretion of progesterone and estrogens by the corpus luteum through the first few months of pregnancy. Some hCG passes from the maternal blood to the urine; detecting hCG in the urine is the basis of the most common early pregnancy test.

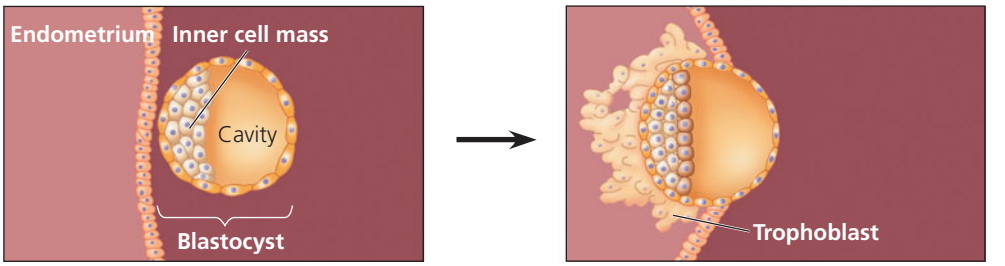
Occasionally, the embryo splits during the first month of development, resulting in identical, or *monozygotic* (one-egg), twins. Fraternal, or *dizygotic*, twins arise in a very different way: Two follicles mature in a single cycle, are independently fertilized, and implant as two genetically distinct embryos.

Not all embryos are capable of completing development. Many spontaneously stop developing as a result of chromosomal or developmental abnormalities. Such spontaneous abortion, or *miscarriage*, occurs in as many as one-third of all pregnancies, often before the woman is even aware she is pregnant.

During its first 2–4 weeks of development, the embryo obtains nutrients directly from the endometrium. Meanwhile, the outer layer, called the **trophoblast**, grows outward and mingles with the endometrium, eventually helping form the **placenta**. This disk-shaped organ, containing both embryonic and maternal blood vessels, can weigh close to 1 kg. Material diffusing between the maternal and embryonic circulatory systems supplies nutrients, provides immune protection,

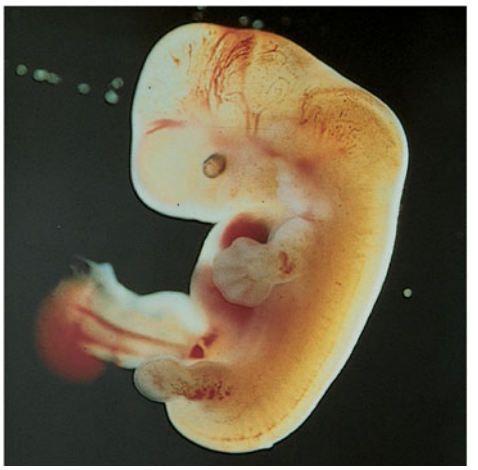


(a) From ovulation to implantation

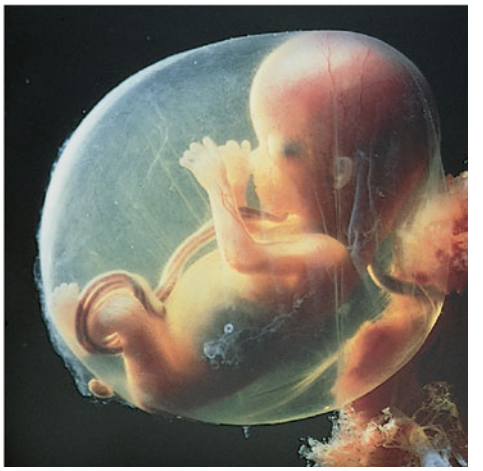


(b) Implantation of blastocyst

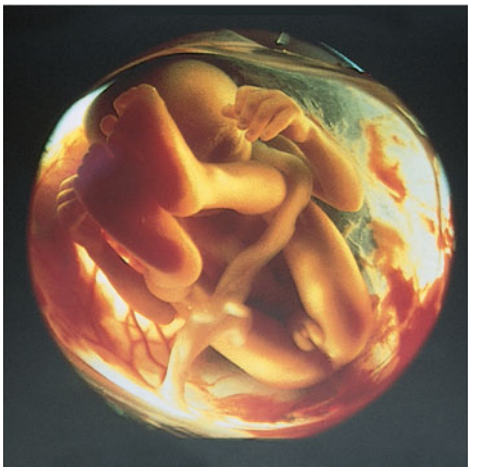
▲ Figure 36.20 Formation of a human zygote and early postfertilization events.



(a) 5 weeks. Limb buds, eyes, the heart, the liver, and rudiments of all other organs have started to develop in the embryo, which is only about 1 cm long.



(b) 14 weeks. Growth and development of the offspring, now called a fetus, continue during the second trimester. This fetus is about 6 cm long.



(c) 20 weeks. Growth to nearly 20 cm in length requires adoption of the fetal position (head at knees) due to the limited space available.

▲ Figure 36.21 Human fetal development.

exchanges respiratory gases, and disposes of metabolic wastes for the embryo.

The first trimester is the main period of **organogenesis**, the development of the body organs. During organogenesis, the embryo is particularly susceptible to damage. For example, alcohol that passes through the placenta and reaches the developing central nervous system of the embryo can cause fetal alcohol syndrome, a disorder that can result in mental retardation and other serious birth defects. At 8 weeks, all the major structures of the adult are present in rudimentary form, and the embryo is called a **fetus**. The heart begins beating by the fourth week; a heartbeat can be detected at 8–10 weeks. At the end of the first trimester, the fetus, although well differentiated, is only 5 cm long **(Figure 36.21)**.

During the second trimester, the fetus grows to about 30 cm in length and is very active. The mother may feel fetal movements as early as one month into the second trimester. During the third trimester, the fetus grows to about 3–4 kg in weight and 50 cm in length. Fetal activity may decrease as the fetus fills the available space.

Childbirth begins with *labor*, a series of strong, rhythmic uterine contractions that push the fetus and placenta out of the body. Once labor begins, local regulators (prostaglandins) and hormones (chiefly estradiol and oxytocin) induce and regulate further contractions of the uterus. A positive-feedback loop (see Chapter 32) is central to this regulation: Uterine contractions stimulate secretion of oxytocin, which in turn stimulates further contractions.

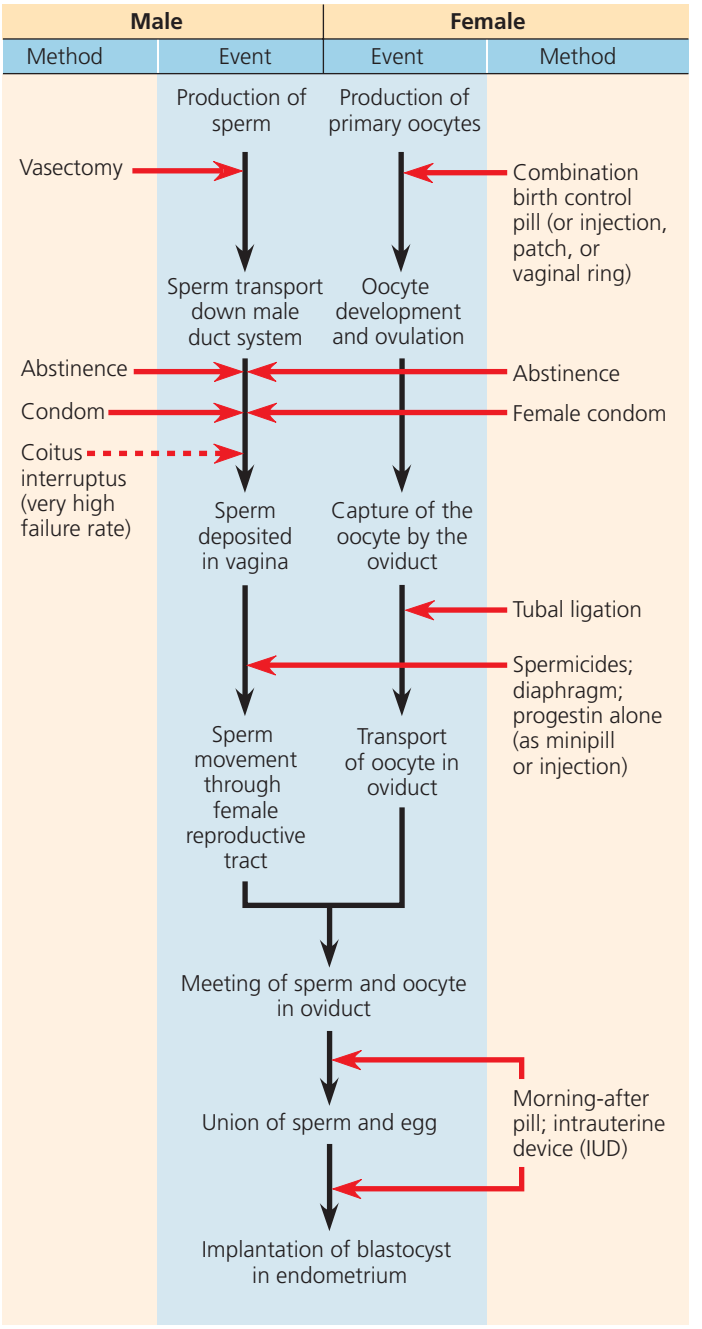
One aspect of postnatal care unique to mammals is *lactation*, the production of mother's milk. In response to suckling by the newborn, as well as changes in estradiol levels after birth, the hypothalamus signals the anterior pituitary to secrete prolactin, which stimulates the mammary glands to produce milk. Suckling also stimulates the secretion of oxytocin from the posterior pituitary, which triggers milk release from the mammary glands (see Figure 32.12).

Contraception

Contraception, the deliberate prevention of pregnancy, can be achieved in a number of ways. Some contraceptive methods prevent gamete development or release from female or male gonads; others prevent fertilization by keeping sperm and egg apart; and still others prevent implantation of an embryo. For complete information on contraceptive methods, you should consult a health-care provider. The following brief introduction to the biology of the most common methods and the corresponding diagram in **Figure 36.22** make no pretense of being a contraception manual.

Fertilization can be prevented by abstinence from sexual intercourse or by any of several barriers that keep live sperm from contacting the egg. Temporary abstinence, often called the *rhythm method* of birth control or *natural family planning*, depends on refraining from intercourse when conception is most likely. Because the egg can survive in the oviduct for 24–48 hours and sperm for up to 5 days, a couple practicing temporary abstinence should not engage in intercourse for a significant number of days before and after ovulation. Contraceptive methods based on fertility awareness require that the couple be knowledgeable about physiological indicators associated with ovulation, such as changes in cervical mucus. Note that a pregnancy rate of 10–20% is typically reported for couples practicing natural family planning. (Pregnancy rate is the average number of women who become pregnant during a year for every 100 women using a particular pregnancy prevention method, expressed as a percentage.)

As a method of preventing fertilization, *coitus interruptus*, or withdrawal (removal of the penis from the vagina before



▲ Figure 36.22 Mechanisms of several contraceptive methods. Red arrows indicate where these methods, devices, or products interfere with events from the production of sperm and primary oocytes to an implanted, developing embryo.

ejaculation), is unreliable. Sperm from a previous ejaculate may be transferred in secretions that precede ejaculation. Furthermore, a split-second lapse in timing or willpower can result in tens of millions of sperm being transferred before withdrawal.

Used properly, several barrier methods of contraception that block the sperm from meeting the egg have pregnancy rates of less than 10%. The *condom* is a thin, latex rubber or natural membrane sheath that fits over the penis to collect the semen. For sexually active individuals, latex condoms are the only contraceptives that are highly effective in preventing the spread of sexually transmitted diseases, including AIDS. (This protection is, however, not absolute.) Another common barrier device is the *diaphragm*, a dome-shaped rubber cap inserted into the upper portion of the vagina before intercourse. Both devices have lower pregnancy rates when used in conjunction with a spermicidal (sperm-killing) foam or jelly. Other barrier devices include the vaginal pouch, or "female condom."

Except for complete abstinence from sexual intercourse, the most effective means of birth control are sterilization, intrauterine devices (IUDs), and hormonal contraceptives. Sterilization (vasectomy in males or tubal ligation in females) is almost 100% effective. The IUD has a pregnancy rate of 1% or less and is the most commonly used reversible method of birth control outside the United States. Placed in the uterus by a doctor, the IUD interferes with fertilization and implantation. Hormonal contraceptives, most often in the form of *birth control pills*, also have pregnancy rates of 1% or less.

The most commonly prescribed hormonal contraceptives are a combination of a synthetic estrogen and a synthetic progestin (progesterone-like hormone). This combination mimics negative feedback in the ovarian cycle, stopping the release of GnRH by the hypothalamus and thus of FSH and LH by the pituitary. The prevention of LH release blocks ovulation. In addition, the inhibition of FSH secretion by the low dose of estrogens in the pills prevents follicles from developing. Such combination birth control pills can also act as "morning-after" pills. Taken within 3 days after unprotected intercourse, they prevent fertilization or implantation with an effectiveness of about 75%.

A different type of hormonal contraceptive contains only progestin. Progestin causes a woman's cervical mucus to thicken so that it blocks sperm from entering the uterus. Progestin also decreases the frequency of ovulation and causes changes in the endometrium that may interfere with implantation if fertilization occurs. Progestin can be administered as injections that last for three months or as a tablet ("minipill") taken daily. Pregnancy rates for progestin treatment are very low.

Hormonal contraceptives have both beneficial and harmful side effects. Women who regularly smoke cigarettes face a three to ten times greater risk of dying from cardiovascular disease if they also use oral contraceptives. Among nonsmokers, birth control pills slightly raise a woman's risk of abnormal blood clotting, high blood pressure, heart attack, and stroke. Although oral contraceptives increase the risk for these cardiovascular disorders, they eliminate the dangers of pregnancy; women on birth control pills have mortality rates about one-half those of pregnant women. Also, the pill decreases the risk of ovarian and endometrial cancers.

Infertility and *In Vitro* Fertilization

Infertility—an inability to conceive offspring—is quite common, affecting about one in ten couples both in the United States and worldwide. The causes of infertility are varied, and the likelihood of a reproductive defect is nearly the same for

men and women. Among preventable causes of infertility, the most significant is *sexually transmitted disease* (*STD*). In women 15–24 years old, approximately 700,000 cases of chlamydia and gonorrhea are reported annually in the United States. The actual number infected is considerably higher because most women with these STDs have no symptoms and are therefore unaware of their infection. Up to 40% of women who remain untreated for chlamydia or gonorrhea develop an inflammatory disorder that can lead to infertility or to potentially fatal complications during pregnancy.

Some forms of infertility are treatable. Hormone therapy can sometimes increase sperm or egg production, and surgery can often correct ducts that have failed to form properly or have become blocked. In some cases, doctors recommend ***in vitro* fertilization (IVF)**, which involves mixing oocytes and sperm in culture dishes. Fertilized eggs are incubated until they have formed at least eight cells and are then transferred to the woman's uterus for implantation. If mature sperm are defective or low in number, a sperm nucleus is sometimes injected directly into an oocyte. Though costly, IVF procedures have enabled more than a million couples to conceive children.

CONCEPT CHECK 36.4

1. Where does fertilization occur in the human female?
2. Which of the three germ layers contributes least to tissues lining the interior or exterior of the body?
3. **WHAT IF?** If an STD led to complete blockage of both oviducts, what effect would you expect on the menstrual cycle and on fertility?

For suggested answers, see Appendix A.

36 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 36.1

Both asexual and sexual reproduction occur in the animal kingdom (pp. 729–733)

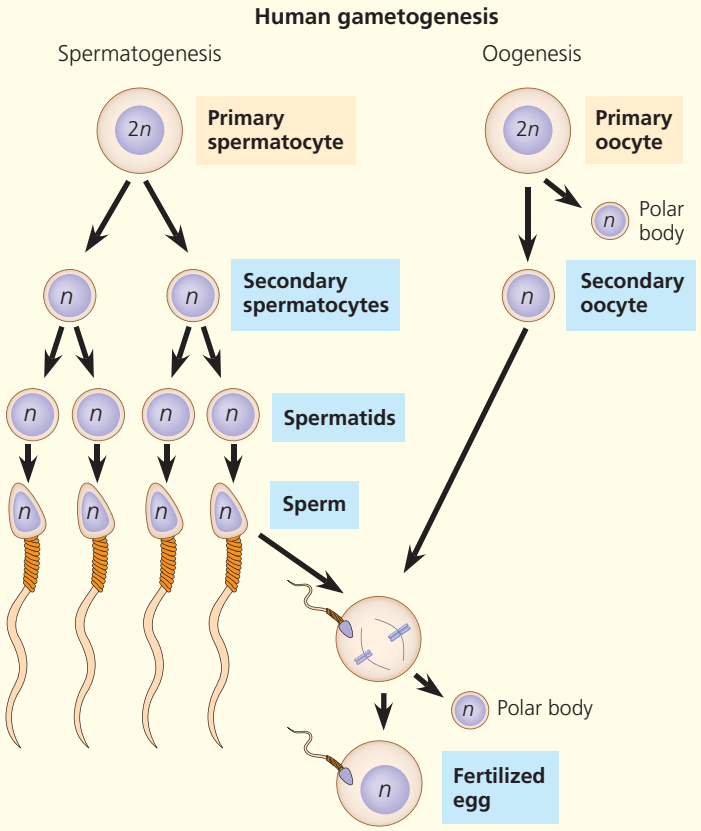
- **Sexual reproduction** requires the fusion of male and female gametes, forming a diploid **zygote**. **Asexual reproduction** is the production of offspring without gamete fusion. Mechanisms of asexual reproduction include budding, fission, and fragmentation with regeneration. Variations on the mode of reproduction are achieved through **parthenogenesis**, **hermaphroditism**, and sex reversal. Hormones and environmental cues control reproductive cycles.
- **Fertilization**, whether external or internal, requires coordinated timing, which may be mediated by environmental cues, pheromones, or courtship behavior. **Internal fertilization** is typically often associated both with fewer offspring and with greater protection of offspring by the parents.

? *Would a pair of haploid offspring produced by parthenogenesis be genetically identical? Explain.*

CONCEPT 36.2

Reproductive organs produce and transport gametes (pp. 733–738)

- Systems for gamete production and delivery range from undifferentiated cells in the body cavity to complex **gonads** with accessory tubes and glands that carry and protect gametes and embryos. In human males, **sperm** are produced in **testes**, which are suspended outside the body in the **scrotum**. Ducts connect the testes to internal accessory glands and to the **penis**. The reproductive system of the human female consists principally of the **ovaries**, **oviducts**, **uterus**, and **vagina** internally and the **labia** and the **glans** of the **clitoris** externally. **Eggs** are produced in the ovaries and upon fertilization develop in the uterus.
- **Gametogenesis**, or gamete production, consists of **spermatogenesis** in males and **oogenesis** in females. Meiosis generates one large egg in oogenesis, but four sperm in spermatogenesis. In humans, sperm develop continuously, whereas oocyte maturation is discontinuous and cyclic.



? *How does the difference in size and cellular contents between sperm and eggs relate to their specific functions?*

CONCEPT 36.3

The interplay of tropic and sex hormones regulates reproduction in mammals (pp. 738–742)

- In mammals, GnRH from the hypothalamus regulates the release of **FSH** and **LH** from the anterior pituitary, which in turn orchestrates gametogenesis. In males, secretion of androgens (chiefly

testosterone) and sperm production are both controlled by FSH and LH. In the female **menstrual cycle**, cyclic secretion of FSH and LH brings about changes in the ovary and uterus via estrogens, primarily **estradiol**, and **progesterone**. The follicle and corpus luteum also secrete hormones, with positive and negative feedback coordinating the uterine and ovarian cycles.
- In **estrous cycles**, the endometrial lining is reabsorbed, and sexual receptivity is limited to a heat period.

? *Why do anabolic steroids lead to reduced sperm count?*

CONCEPT 36.4

Fertilization, cleavage, and gastrulation initiate embryonic development (pp. 742–749)

- Fertilization brings together the nuclei of sperm and egg, forming a diploid zygote, and activates the egg, initiating embryonic development. Changes at the egg surface triggered by sperm entry help block **polyspermy** in many animals.
- Fertilization is followed by **cleavage**, a period of rapid cell division without growth, which results in the production of a large number of cells. In many species, cleavage creates a multicellular ball called the **blastula**, which contains a fluid-filled cavity, the **blastocoel**.
- **Gastrulation** converts the blastula to a **gastrula**, which has a primitive digestive cavity and three germ layers: **ectoderm**, **mesoderm**, and **endoderm**.
- The mammalian zygote develops into a blastocyst before implantation in the **endometrium**. All major organs start developing by 8 weeks.
- **Contraception** may prevent release of gametes from the gonads, fertilization, or embryo implantation. Infertile couples may be helped by hormonal methods or ***in vitro* fertilization**.

? *How does the fertilization envelope form in sea urchins? What is its function?*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. Which of the following characterizes parthenogenesis?
   a. An individual may change its sex during its lifetime.
   b. Specialized groups of cells grow into new individuals.
   c. An organism is first a male and then a female.
   d. An egg develops without being fertilized.
   e. Both mates have male and female reproductive organs.
2. The cortical reaction of sea urchin eggs functions directly in
   a. the formation of a fertilization envelope.
   b. the production of a fast block to polyspermy.
   c. the release of hydrolytic enzymes from the sperm.
   d. the generation of an electrical impulse by the egg.
   e. the fusion of egg and sperm nuclei.
3. Which of the following is *not* properly paired?
   a. seminiferous tubule—cervix
   b. Sertoli cells—follicle cells
   c. testosterone—estradiol
   d. scrotum—labia majora
   e. vas deferens—oviduct
4. Peaks of LH and FSH production occur during
   a. the menstrual flow phase of the uterine cycle.
   b. the beginning of the follicular phase of the ovarian cycle.
   c. the period just before ovulation.
   d. the end of the luteal phase of the ovarian cycle.
   e. the secretory phase of the menstrual cycle.
5. During human gestation, rudiments of all organs develop
   a. in the first trimester.
   b. in the second trimester.
   c. in the third trimester.
   d. while the embryo is in the oviduct.
   e. during the blastocyst stage.

Level 2: Application/Analysis

6. Which of the following is a true statement?
   a. All mammals have menstrual cycles.
   b. The endometrial lining is shed in menstrual cycles but reabsorbed in estrous cycles.
   c. Estrous cycles are more frequent than menstrual cycles.
   d. Estrous cycles are not controlled by hormones.
   e. Ovulation occurs before the endometrium thickens in estrous cycles.
7. For which is the number the same in males and females?
   a. interruptions in meiotic divisions
   b. functional gametes produced by meiosis
   c. meiotic divisions required to produce each gamete
   d. gametes produced in a given time period
   e. different cell types produced by meiosis
8. Which statement about human reproduction is false?
   a. Fertilization occurs in the oviduct.
   b. Effective hormonal contraceptives are currently available only for females.
   c. An oocyte completes meiosis after a sperm penetrates it.
   d. The earliest stages of spermatogenesis occur closest to the lumen of the seminiferous tubules.
   e. Spermatogenesis and oogenesis require different temperatures.

Level 3: Synthesis/Evaluation

9. **DRAW IT** In human spermatogenesis, mitosis of a stem cell gives rise to one cell that remains a stem cell and one cell that becomes a spermatogonium. (a) Draw four rounds of mitosis for a stem cell, and label the daughter cells. (b) For one spermatogonium, draw the cells it would produce from one round of mitosis followed by meiosis. Label the cells, and label mitosis and meiosis. (c) What would happen if stem cells divided like spermatogonia?
10. **SCIENTIFIC INQUIRY**
    Suppose that you discover a new egg-laying worm species. You dissect four adults and find both oocytes and sperm in each. Cells outside the gonad contain five chromosome pairs. Lacking genetic variants, how would you determine whether the worms can self-fertilize?
11. **FOCUS ON EVOLUTION**
    Hermaphroditism is often found in animals that are fixed to a surface. Motile species are less often hermaphroditic. Why?
12. **FOCUS ON ENERGY AND MATTER**
    In a short essay (100–150 words), discuss how investments of energy by females contribute to the reproductive success of a frog (see Figure 36.6) and of a human.

For selected answers, see Appendix A.

37 Neurons, Synapses, and Signaling

KEY CONCEPTS

37.1 Neuron structure and organization reflect function in information transfer
37.2 Ion pumps and ion channels establish the resting potential of a neuron
37.3 Action potentials are the signals conducted by axons
37.4 Neurons communicate with other cells at synapses

OVERVIEW

Lines of Communication

The tropical cone snail (*Conus geographus*) in **Figure 37.1** is both beautiful and dangerous. A carnivore, this marine snail hunts, kills, and dines on fish. Injecting venom with a hollow, harpoon-like tooth, the cone snail paralyzes its free-swimming prey in seconds. The venom is so deadly that unlucky scuba divers have died from just a single injection. What makes cone snail venom so fast acting and lethal? The answer is its mixture of toxins, each with a specific mechanism of disabling **neurons**, the nerve cells that transfer information within the body. Because the venom almost instantaneously disrupts neuronal control of locomotion and respiration, an animal attacked by the cone snail cannot escape, defend itself, or otherwise survive.

▼ **Figure 37.1** What makes this snail such a deadly predator?

Communication by neurons largely consists of long-distance electrical signals and short-distance chemical signals. The specialized structure of neurons allows them to use pulses of electrical current to receive, transmit, and regulate the flow of information over long distances within the body. In transferring information from one cell to another, neurons often rely on chemical signals that act over very short distances. The mixture of molecules in a cone snail's venom is particularly potent because it interferes with both electrical signaling and chemical signaling by neurons.

All neurons transmit electrical signals within the cell in an identical manner. Thus a neuron transmitting sensory input encodes information in the same way as a neuron involved in processing information or coordinating movement. What distinguishes the type of information being transmitted is the connections made by the active neuron. Interpreting signals in the nervous system therefore involves sorting those signals according to neuronal paths and connections. In more complex animals, this higher-order processing is carried out largely in groups of neurons organized into a **brain** or into simpler clusters called **ganglia**.

In this chapter, we'll examine the structure of a neuron and explore the molecules and physical principles that govern signaling by neurons. In Chapter 38, we'll examine how nervous systems are organized for processing information, as well as how organisms gather information through receptors that are sensitive to stimuli such as light or sound. Then, in Chapter 39, we'll study how organisms respond to stimuli through movement and other forms of behavior.

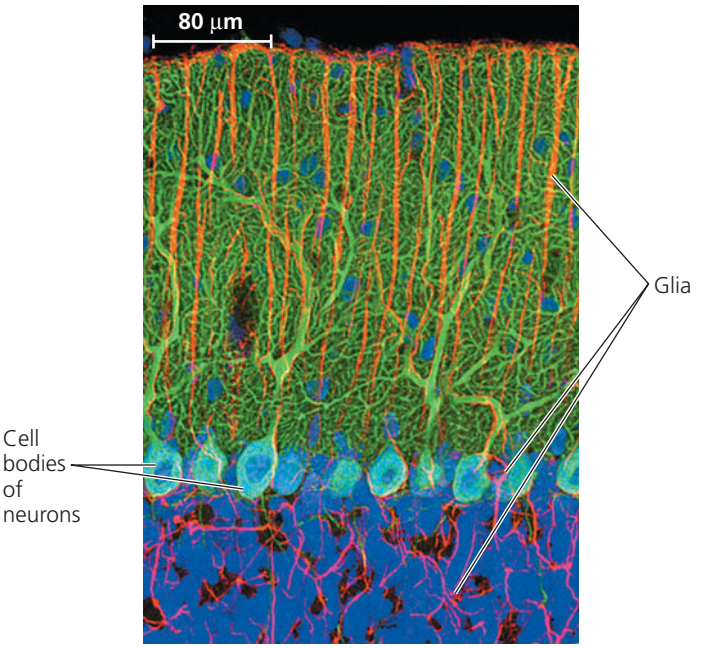
CONCEPT 37.1

Neuron structure and organization reflect function in information transfer

Our starting point for exploring the nervous system is the neuron, a cell type exemplifying the close fit of form and function that often arises over the course of evolution.

Neuron Structure and Function

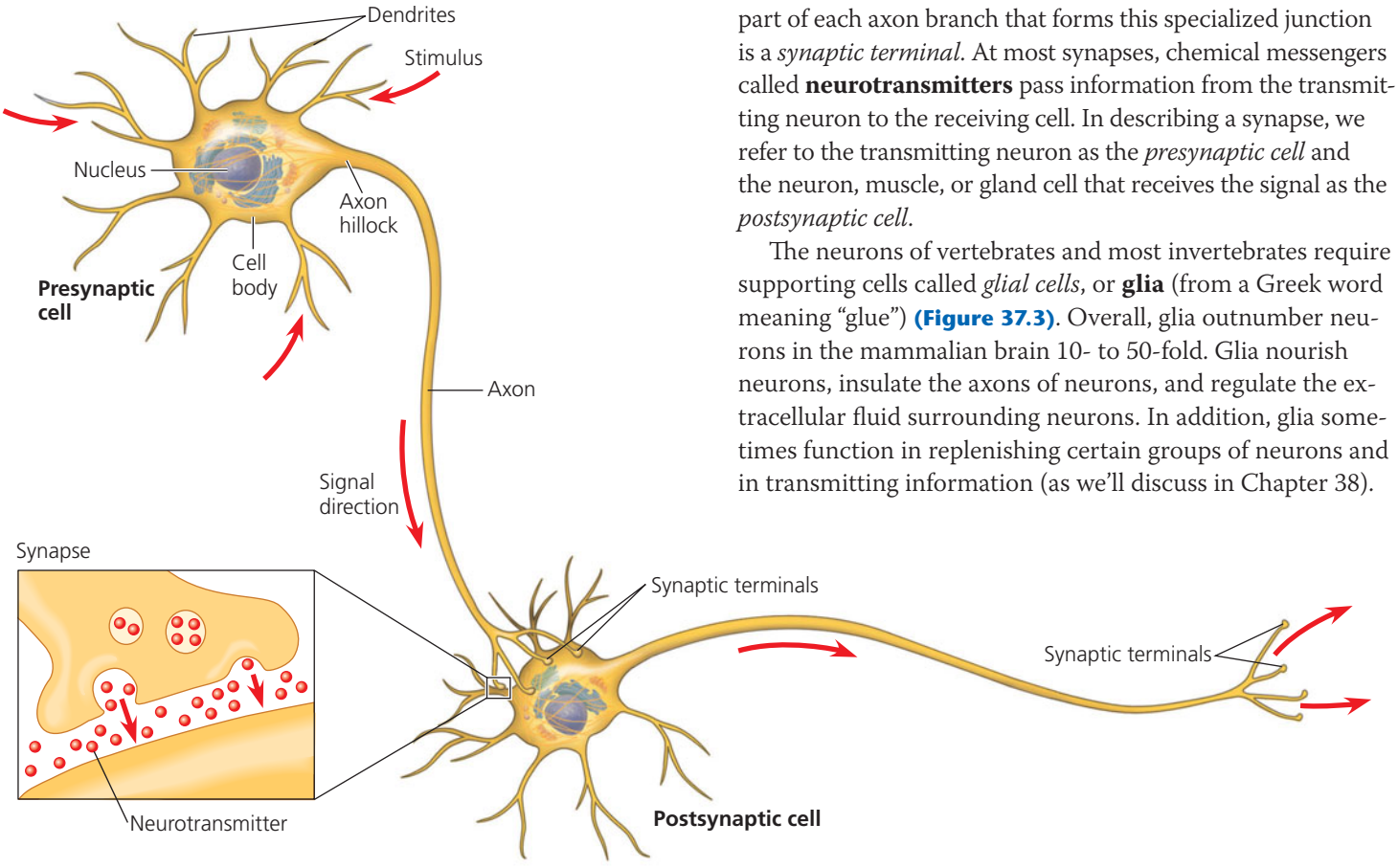
The ability of a neuron to receive and transmit information is based on a highly specialized cellular organization **(Figure 37.2)**. Most of a neuron's organelles, including its nucleus, are located in the **cell body**. A typical neuron has numerous highly branched extensions called **dendrites** (from the Greek *dendron*, tree). Together with the cell body, the dendrites *receive* signals from other neurons. A neuron also has a single **axon**, an extension that *transmits* signals to other cells. Axons are often much longer than dendrites, and some, such as those that reach from the spinal cord of a giraffe to the muscle cells in its feet, are over a meter long. The cone-shaped base of an axon, called the axon hillock, is typically where signals that travel down the axon are generated. Near its other end, an axon usually divides into many branches.



▲ **Figure 37.3 Glia in the mammalian brain.** This micrograph (a fluorescently labeled laser confocal image) shows a region of the rat brain packed with glia and interneurons. Glia are labeled red, DNA in nuclei is labeled blue, and dendrites of neurons are labeled green.

Each branched end of an axon transmits information to another cell at a junction called a **synapse** (see Figure 37.2). The part of each axon branch that forms this specialized junction is a *synaptic terminal*. At most synapses, chemical messengers called **neurotransmitters** pass information from the transmitting neuron to the receiving cell. In describing a synapse, we refer to the transmitting neuron as the *presynaptic cell* and the neuron, muscle, or gland cell that receives the signal as the *postsynaptic cell*.

The neurons of vertebrates and most invertebrates require supporting cells called *glial cells*, or **glia** (from a Greek word meaning "glue") **(Figure 37.3)**. Overall, glia outnumber neurons in the mammalian brain 10- to 50-fold. Glia nourish neurons, insulate the axons of neurons, and regulate the extracellular fluid surrounding neurons. In addition, glia sometimes function in replenishing certain groups of neurons and in transmitting information (as we'll discuss in Chapter 38).

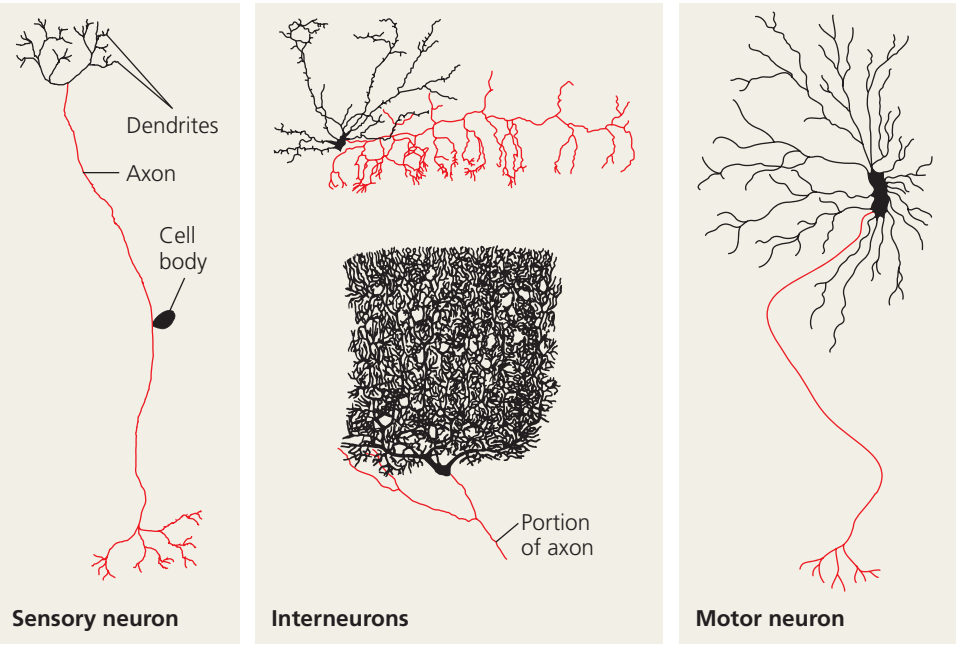


▲ **Figure 37.2 Neuron structure.**

Introduction to Information Processing

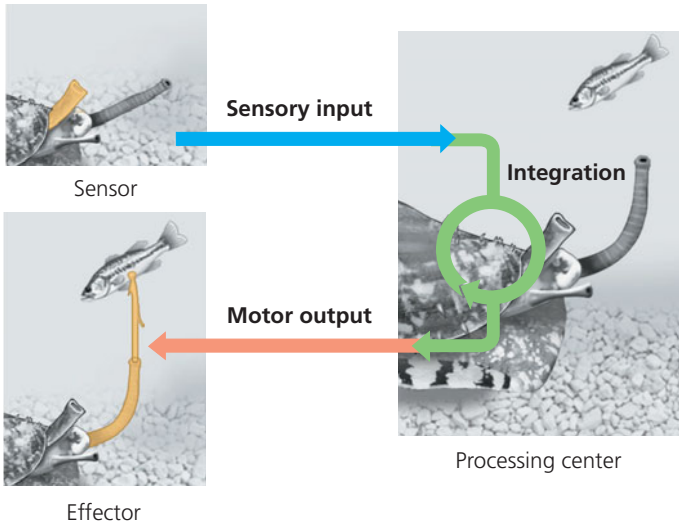
Information processing by a nervous system occurs in three stages: sensory input, integration, and motor output. As an example, let's consider how a cone snail like the one in Figure 37.1 identifies and attacks its prey **(Figure 37.4)**. Sensory input is generated as the snail surveys its environment with its tube-like siphon, sampling scents that might reveal a nearby fish. During the integration stage, the snail's nervous system processes this information to determine if a fish is in fact present and, if so, where the fish is located. Motor output then initiates attack, activating neurons that trigger release of the harpoon-like tooth toward the prey.

In all but the simplest animals, specialized populations of neurons handle each stage of information processing.



▲ **Figure 37.5 Structural diversity of neurons.** In these drawings of neurons, cell bodies and dendrites are black and axons are red.

- **Sensory neurons**, like those in the snail's siphon, transmit information to processing centers in the brain or ganglia. Some sensors detect external stimuli such as light, sound, touch, or smell, whereas others monitor internal conditions such as blood pressure or muscle tension.
- Neurons in the brain or ganglia integrate (analyze and interpret) the sensory input, taking into account the immediate context and the animal's experience. The vast majority of neurons in the brain are **interneurons**, which form the local circuits connecting neurons in the brain.
- Neurons that extend out of the processing centers trigger output in the form of muscle or gland activity. For example, **motor neurons** transmit signals to muscle cells, causing them to contract.



▲ **Figure 37.4 Summary of information processing.** The cone snail's siphon (highlighted in gold in the top left panel) acts as a sensor and transfers sensory information to neuronal circuits in the snail's head (right panel). If the scent of prey is detected, these circuits issue motor commands that trigger release of a harpoon-like tooth from the proboscis (in gold in the lower left panel).

In many animals, the neurons that carry out integration are organized in a **central nervous system (CNS)**, which includes the brain and a longitudinal nerve cord. The neurons that carry information into and out of the CNS constitute the **peripheral nervous system (PNS)**. When bundled together, such neurons form **nerves**.

Depending on its role in information processing, the shape of a neuron can vary from simple to quite complex **(Figure 37.5)**. Neurons that transmit information to many target cells have highly branched axons. Similarly, neurons with highly branched dendrites can receive input through large numbers of synapses, as many as 100,000 in the case of some interneurons.

CONCEPT CHECK 37.1

1. Compare and contrast the structure and function of axons and dendrites.
2. Describe the basic pathway of information flow through neurons that causes you to turn your head when someone calls your name.
3. **WHAT IF?** How might increased branching of an axon help coordinate responses to signals communicated by the nervous system?

For suggested answers, see Appendix A.

CONCEPT 37.2

Ion pumps and ion channels establish the resting potential of a neuron

In continuing our exploration of neuron function, we turn now to the essential role of ions in neuronal signaling. In a neuron, as in other cells, ions are unequally distributed between the cell interior and the surrounding extracellular fluid (see Chapter 5). As a result, the inside of a cell is negatively charged relative to the outside. Because the attraction of opposite charges across the plasma membrane is a source of potential energy, this charge difference, or voltage, is called the **membrane potential**. For a resting neuron—one that is not sending a signal—the membrane potential is called the **resting potential** and is typically between −60 and −80 mV (millivolts).

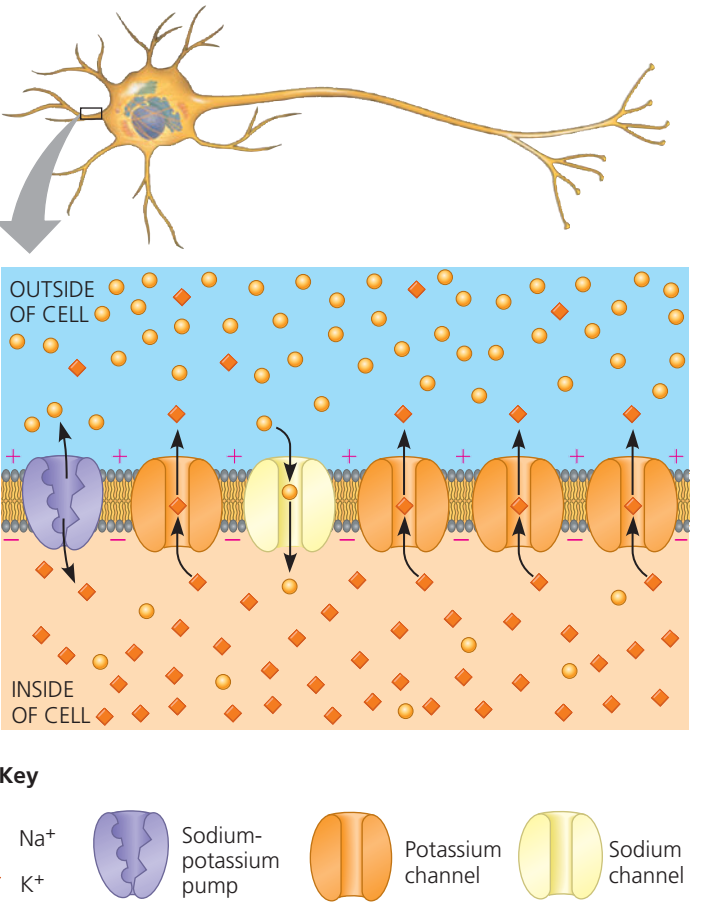
Inputs from other neurons or specific stimuli cause changes in the neuron's membrane potential that act as signals, transmitting information. Fundamentally, rapid changes in membrane potential are what enable us to see the intricate structure of a spiderweb, read a biology textbook, or ride a bicycle. Thus, to understand how neurons function, we first need to examine how chemical and electrical forces form, maintain, and alter membrane potentials.

Formation of the Resting Potential

Potassium ions (K^+) and sodium ions (Na^+) play an essential role in the formation of the resting potential. Each type of ion has a concentration gradient across the plasma membrane of a neuron **(Table 37.1)**. For most neurons, the concentration of K^+ is higher inside the cell, while the concentration of Na^+ is higher outside. These Na^+ and K^+ gradients are maintained by the **sodium-potassium pump** (see Chapter 5). This ion pump uses the energy of ATP hydrolysis to actively transport Na^+ out of the cell and K^+ into the cell **(Figure 37.6)**. There are also concentration gradients for chloride ions (Cl^-) and other anions, as shown in Table 37.1, but we can ignore these for the moment.

Table 37.1 Ion Concentrations Inside and Outside of Mammalian Neurons

Ion	Intracellular Concentration (m*M*)	Extracellular Concentration (m*M*)
Potassium (K^+)	140	5
Sodium (Na^+)	15	150
Chloride (Cl^-)	10	120
Large anions (A^-) inside cell, such as proteins	100	(not applicable)



▲ Figure 37.6 The basis of the membrane potential. The sodium-potassium pump generates and maintains the ionic gradients of Na^+ and K^+ shown in Table 37.1. (Many such pump molecules are located in the plasma membrane of each cell.) Although there is a substantial concentration gradient of sodium across the membrane, very little net diffusion of Na^+ occurs because there are very few open sodium channels. In contrast, the large number of open potassium channels allow a significant net outflow of K^+. Because the membrane is only weakly permeable to chloride and other anions, this outflow of K^+ results in a net negative charge inside the cell.

The sodium-potassium pump transports three Na^+ out of the cell for every two K^+ that it transports in. Although this pumping generates a net export of positive charge, the resulting voltage difference is only a few millivolts. Why, then, is there a voltage difference of 60 to 80 mV in a resting neuron? The answer lies in ion movement through **ion channels**, pores formed by clusters of specialized proteins that span the membrane. Ion channels allow ions to diffuse back and forth across the membrane. As ions diffuse through channels, they carry with them units of electrical charge. Any resulting *net* movement of positive or negative charge will generate a membrane potential, or voltage across the membrane.

The concentration gradients of K^+ and Na^+ across the plasma membrane represent a chemical form of potential energy. The ion channels that convert this chemical potential energy to electrical potential energy can do so because they have *selective permeability*—they allow only certain ions to pass.

For example, a potassium channel allows K^+ to diffuse freely across the membrane, but not other ions, such as Na^+.

Diffusion of K^+ through potassium channels that are always open (sometimes called leak channels) is critical for establishing the resting potential. The K^+ concentration is 140 m*M* inside the cell, but only 5 m*M* outside. The chemical concentration gradient thus favors a net outflow of K^+. Furthermore, a resting neuron has many open potassium channels, but very few open sodium channels (see Figure 37.6). Because Na^+ and other ions can't readily cross the membrane, K^+ outflow leads to a net negative charge inside the cell. This buildup of negative charge within the neuron is the major source of the membrane potential.

What stops the buildup of negative charge? The excess negative charges inside the cell exert an attractive force that opposes the flow of additional positively charged potassium ions out of the cell. The separation of charge (voltage) thus results in an electrical gradient that counterbalances the chemical concentration gradient of K^+.

Modeling the Resting Potential

The net flow of K^+ out of a neuron proceeds until the chemical and electrical forces are in balance. How well do these two forces account for the resting potential in a mammalian neuron? Consider a simple model consisting of two chambers separated by an artificial membrane **(Figure 37.7a)**. To begin, imagine that the membrane contains many open ion channels, all of which allow only K^+ to diffuse across. To produce a K^+ concentration gradient like that of a mammalian neuron, we place a solution of 140 m*M* potassium chloride (KCl) in the inner chamber and 5 m*M* KCl in the outer chamber. The K^+ will diffuse down its concentration gradient into the outer chamber. But because the chloride ions (Cl^-) lack a means of crossing the membrane, there will be an excess of negative charge in the inner chamber.

When our model neuron reaches equilibrium, the electrical gradient will exactly balance the chemical gradient, so that no further net diffusion of K^+ occurs across the membrane. The magnitude of the membrane voltage at equilibrium for a particular ion is called that ion's **equilibrium potential** (E_{ion}). For a membrane permeable to a single type of ion, E_{ion} can be calculated using a formula called the Nernst equation. At human body temperature (37°C) and for an ion with a net charge of 1+, such as K^+ or Na^+, the Nernst equation is

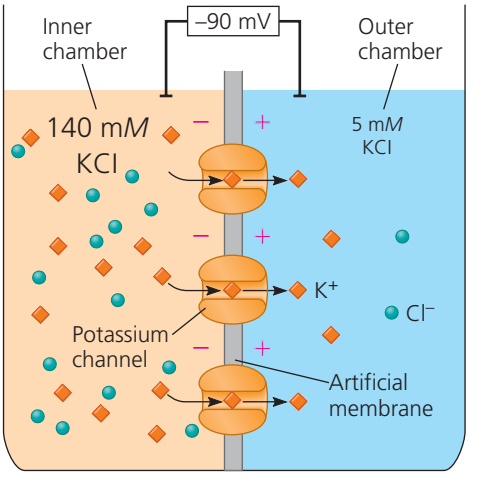
$$E_{ion} = 62\ mV\left(\log\frac{[ion]_{outside}}{[ion]_{inside}}\right)$$

Plugging in the K^+ concentrations reveals that the equilibrium potential for K^+ (E_K) is −90 mV (see Figure 37.7a). The minus sign indicates that K^+ is at equilibrium when the inside of the membrane is 90 mV more negative than the outside.

Whereas the equilibrium potential for K^+ is −90 mV, the resting potential of a mammalian neuron is somewhat less negative. This difference reflects the small but steady movement of Na^+ across the few open sodium channels in a resting neuron. The concentration gradient of Na^+ has a direction opposite to that of K^+ (see Table 37.1). Na^+ therefore diffuses into the cell, making the inside of the cell less negative. If we model a membrane in which the only open channels are selectively permeable to Na^+, we find that a tenfold higher concentration of Na^+ in the outer chamber results in an equilibrium potential (E_{Na}) of +62 mV **(Figure 37.7b)**. In an actual neuron, the resting potential (−60 to −80 mV) is much closer to E_K than to E_{Na} because there are many open potassium channels but only a small number of open sodium channels.

▶ Figure 37.7 Modeling a mammalian neuron. Each container is divided into two chambers by an artificial membrane. Ion channels allow free diffusion for particular ions, resulting in the net ion flow represented by arrows. **(a)** The presence of open potassium channels makes the membrane selectively permeable to K^+, and the inner chamber contains a 28-fold higher concentration of K^+ than the outer chamber; at equilibrium, the inside of the membrane is −90 mV relative to the outside. **(b)** The membrane is selectively permeable to Na^+, and the inner chamber contains a tenfold lower concentration of Na^+ than the outer chamber; at equilibrium, the inside of the membrane is +62 mV relative to the outside.

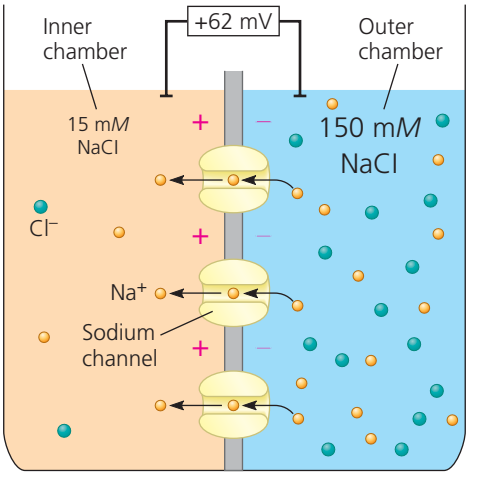
WHAT IF? *Consider the effect of adding potassium or chloride channels to the membrane in (b) in place of sodium channels. How would the membrane potential be affected in each case?*



(a) Membrane selectively permeable to K^+

Nernst equation for K^+ equilibrium potential at 37°C:

$$E_K = 62\ mV\left(\log\frac{5\ mM}{140\ mM}\right) = -90\ mV$$



(b) Membrane selectively permeable to Na^+

Nernst equation for Na^+ equilibrium potential at 37°C:

$$E_{Na} = 62\ mV\left(\log\frac{150\ mM}{15\ mM}\right) = +62\ mV$$

Because neither K^+ nor Na^+ is at equilibrium in a resting neuron, there is a net flow of each ion (a current) across the membrane. The resting potential remains steady, which means that the K^+ and Na^+ currents are equal and opposite. Ion concentrations on either side of the membrane also remain steady. Why? The resting potential arises from the net movement of far fewer ions than would be required to alter the concentration gradients.

Under conditions that allow Na^+ to cross the membrane more readily, the membrane potential will move toward E_{Na} and away from E_K. As you'll see in the next section, this is precisely what happens during the generation of a nerve impulse.

CONCEPT CHECK 37.2

1. Under what circumstances could ions flow through an ion channel from a region of lower concentration to a region of higher ion concentration?
2. **WHAT IF?** Suppose a cell's membrane potential shifts from −70 mV to −50 mV. What changes in the cell's permeability to K^+ or Na^+ could cause such a shift?
3. **MAKE CONNECTIONS** Figure 5.9 illustrates diffusion by dye molecules. Could diffusion eliminate the concentration gradient of a dye that has a net charge? Explain.

For suggested answers, see Appendix A.

CONCEPT 37.3

Action potentials are the signals conducted by axons

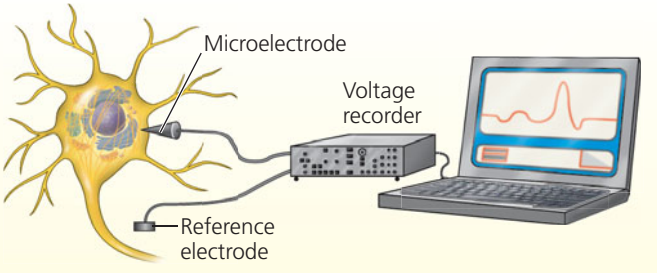
When a neuron responds to a stimulus, the membrane potential changes. Using intracellular recording **(Figure 37.8)**, researchers can record these changes as a function of time. Changes in the membrane potential occur because neurons contain **gated ion channels**, ion channels that open or close in response to stimuli. The opening or closing of gated ion channels alters the membrane's permeability to particular ions **(Figure 37.9)**, which in turn alters the membrane potential.

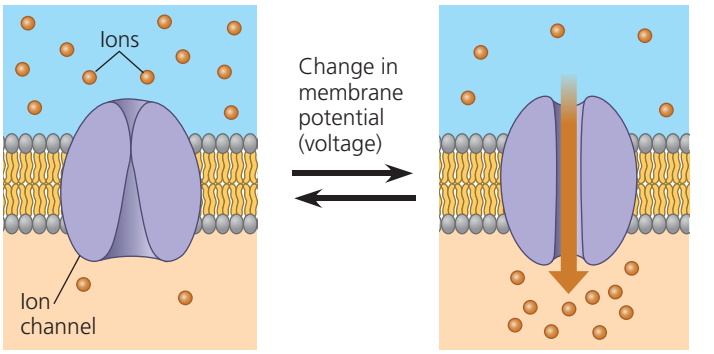
▼ Figure 37.8 Research Method

Intracellular Recording

Application Electrophysiologists use intracellular recording to measure the membrane potential of neurons and other cells.

Technique A microelectrode is made from a glass capillary tube filled with an electrically conductive salt solution. One end of the tube tapers to an extremely fine tip (diameter < 1 μm). While looking through a microscope, the experimenter uses a micropositioner to insert the tip of the microelectrode into a cell. A voltage recorder (usually an oscilloscope or a computer-based system) measures the voltage between the microelectrode tip inside the cell and a reference electrode placed in the solution outside the cell.





(a) Gate closed: No ions flow across membrane.

(b) Gate open: Ions flow through channel.

▲ Figure 37.9 Voltage-gated ion channel. A change in the membrane potential in one direction (indicated by the right-pointing arrow) opens the channel. The opposite change (left-pointing arrow) closes the channel.

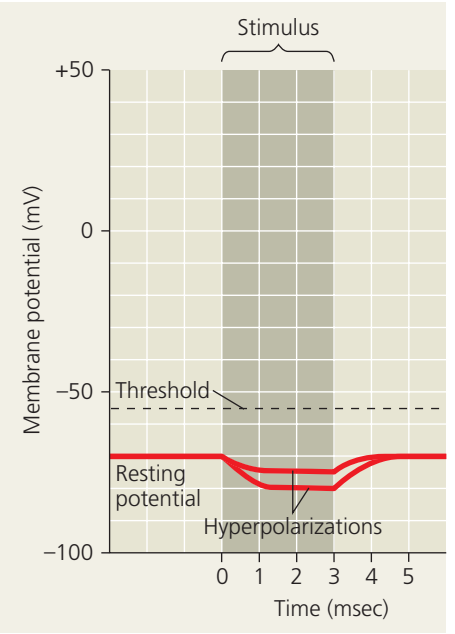
Hyperpolarization and Depolarization

To explore how the membrane potential changes, let's consider what happens when gated potassium channels that are closed in a resting neuron are stimulated to open. Opening these potassium channels increases the membrane's permeability to K^+. Net diffusion of K^+ out of the neuron increases, shifting the membrane potential toward E_K (−90 mV at 37°C). This increase in the magnitude of the membrane potential, called a **hyperpolarization**, makes the inside of the membrane more negative **(Figure 37.10a)**. In a resting neuron, hyperpolarization results from any stimulus that increases the outflow of positive ions or the inflow of negative ions.

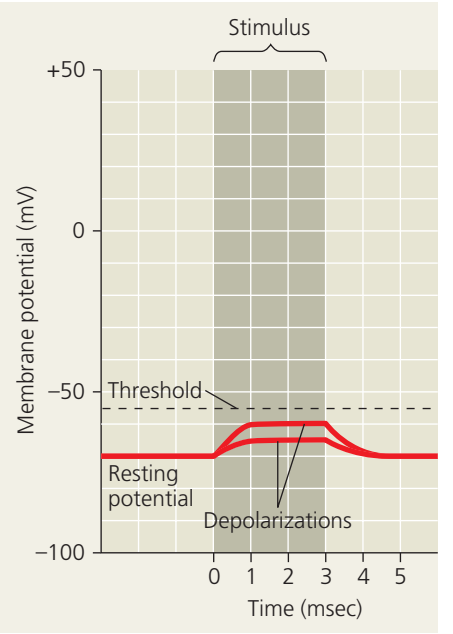
Although opening potassium channels in a resting neuron causes hyperpolarization, opening some other types of ion channels has an opposite effect, making the inside of the membrane less negative **(Figure 37.10b)**. A reduction in the magnitude of the membrane potential is called a **depolarization**. Depolarization in neurons often involves gated sodium channels. If a stimulus causes the gated sodium channels in a resting neuron to open, the membrane's permeability to Na^+ increases. Na^+ diffuses into the cell along its concentration gradient, causing a depolarization as the membrane potential shifts toward E_{Na} (+62 mV at 37°C).

Graded Potentials and Action Potentials

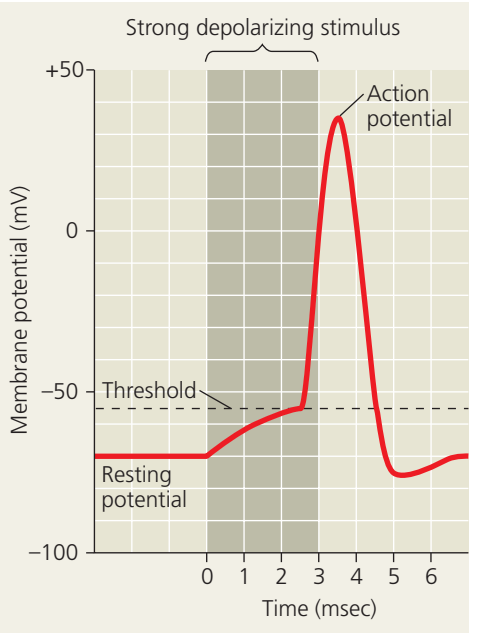
Sometimes, the response to hyperpolarization or depolarization is simply a shift in the membrane potential. This shift, called a **graded potential**, has a magnitude that varies with



(a) Graded hyperpolarizations produced by two stimuli that increase membrane permeability to K^+. The larger stimulus produces a larger hyperpolarization.



(b) Graded depolarizations produced by two stimuli that increase membrane permeability to Na^+. The larger stimulus produces a larger depolarization.



(c) Action potential triggered by a depolarization that reaches the threshold.

▲ Figure 37.10 Graded potentials and an action potential in a neuron.

DRAW IT *Redraw the graph in part (c), extending the y-axis. Then label the positions of* E_K *and* E_{Na}.

the strength of the stimulus: A larger stimulus causes a greater change in the membrane potential. Graded potentials induce a small electrical current that leaks out of the neuron as it flows along the membrane. Graded potentials thus decay with distance from their source.

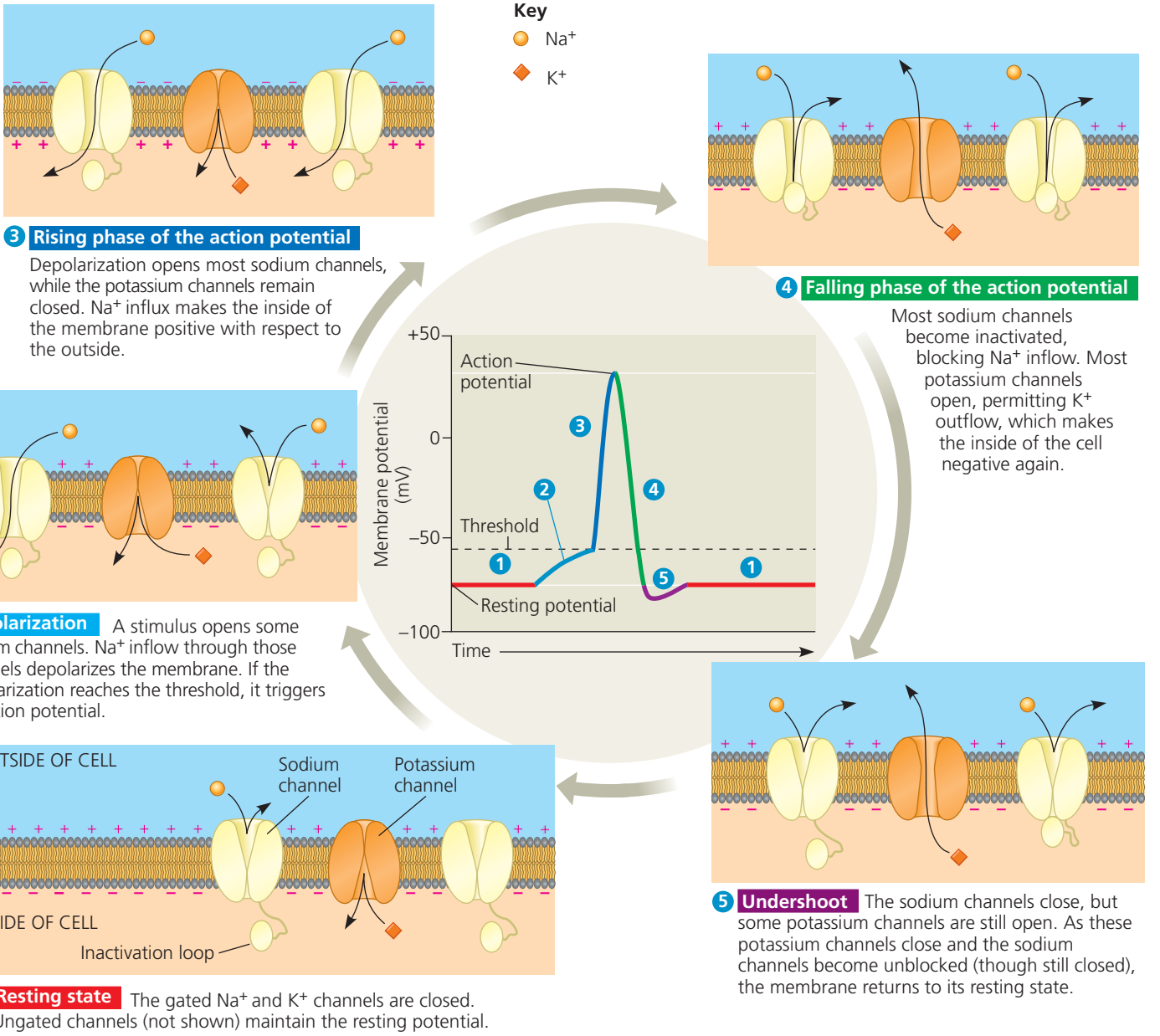
If a depolarization shifts the membrane potential sufficiently, the result is a massive change in membrane voltage called an **action potential**. Unlike graded potentials, action potentials have a constant magnitude and can regenerate in adjacent regions of the membrane. Action potentials can therefore spread along axons, making them well suited for transmitting a signal over long distances.

Action potentials arise because some of the ion channels in neurons are **voltage-gated ion channels**, opening or closing when the membrane potential passes a particular level (see Figure 37.9). If a depolarization opens voltage-gated sodium channels, the resulting flow of Na^+ into the neuron results in further depolarization. Because the sodium channels are voltage gated, the increased depolarization causes more sodium channels to open, leading to an even greater flow of current. The result is a process of positive feedback that triggers a very rapid opening of many voltage-gated sodium channels and the marked temporary change in membrane potential that defines an action potential **(Figure 37.10c)**.

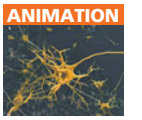
Action potentials occur whenever a depolarization increases the membrane voltage to a particular value, called the **threshold**. For many mammalian neurons, the threshold is a membrane potential of about −55 mV. Once initiated, the action potential has a magnitude that is independent of the strength of the triggering stimulus. Because action potentials either occur fully or do not occur at all, they represent an *all-or-none* response to stimuli. This all-or-none property reflects the fact that depolarization opens voltage-gated sodium channels, and the opening of sodium channels causes further depolarization. The positive-feedback loop of depolarization and channel opening triggers an action potential whenever the membrane potential reaches threshold.

Generation of Action Potentials: *A Closer Look*

The characteristic shape of the graph of an action potential (see Figure 37.10c) reflects the large change in membrane potential resulting from ion movement through voltage-gated sodium and potassium channels. Membrane depolarization opens both types of channels, but they respond independently and sequentially. Sodium channels open first, initiating the action potential. As the action potential proceeds, the sodium channels become inactivated: A loop of the channel protein moves, blocking ion flow through the opening. Sodium channels remain inactivated until after the membrane returns to the resting potential and the channels close. In contrast, potassium channels open more slowly than sodium channels, but remain open and functional until the end of the action potential.



▲ Figure 37.11 The role of voltage-gated ion channels in the generation of an action potential. The circled numbers on the graph in the center and the colors of the action potential phases correspond to the five diagrams showing voltage-gated sodium and potassium channels in a neuron's plasma membrane. (Ungated ion channels are not illustrated.)



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To understand further how voltage-gated channels shape the action potential, consider the process as a series of stages, as depicted in **Figure 37.11**. 1 When the membrane of the axon is at the resting potential, most voltage-gated sodium channels are closed. Some potassium channels are open, but most voltage-gated potassium channels are closed. 2 When a stimulus depolarizes the membrane, some gated sodium channels open, allowing more Na^+ to diffuse into the cell. The Na^+ inflow causes further depolarization, which opens still more gated sodium channels, allowing even more Na^+ to diffuse into the cell. 3 Once the threshold is crossed, the positive-feedback cycle rapidly brings the membrane potential close to E_{Na}. This stage of the action potential is called the *rising phase*. 4 Two events prevent the membrane potential from actually reaching E_{Na}: Voltage-gated sodium channels inactivate soon after opening, halting Na^+ inflow; and most voltage-gated potassium channels open, causing a rapid outflow of K^+. Both events quickly bring the membrane potential back toward E_K. This stage is called the *falling phase*. 5 In the final phase of an action potential, called the *undershoot*, the membrane's permeability to K^+ is higher than at rest, so the membrane potential is closer to E_K than it is at the resting potential. The gated potassium channels eventually close, and the membrane potential returns to the resting potential.

The sodium channels remain inactivated during the falling phase and the early part of the undershoot. As a result, if a second depolarizing stimulus occurs during this period, it will be unable to trigger an action potential. The "downtime" when a second action potential cannot be initiated is called the **refractory period**. One consequence of the refractory period is to limit the maximum frequency at which action potentials can be generated. As we will discuss shortly, the refractory period also ensures that all signals in an axon travel in one direction, from the cell body to the axon terminals.

Note that the refractory period is due to the inactivation of sodium channels, not to a change in the ion gradients across the plasma membrane. The flow of charged particles during an action potential involves far too few ions to change the concentration on either side of the membrane significantly.

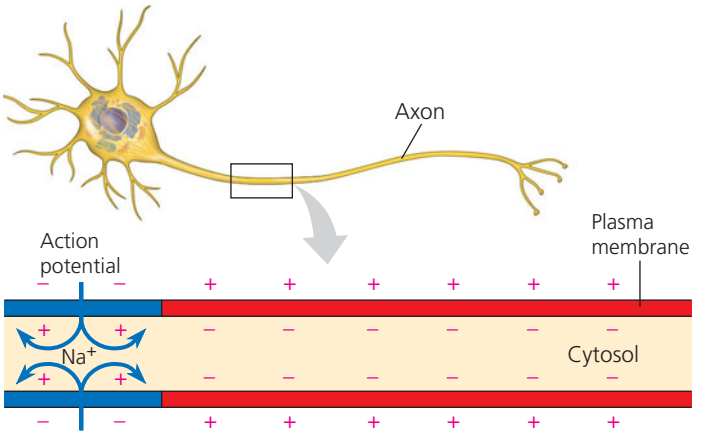
For most neurons, the interval between the onset of an action potential and the end of the refractory period is only 1–2 milliseconds (msec). Because action potentials are so brief, a neuron can produce them as rapidly as several hundred per second. Furthermore, the rate at which action potentials are produced conveys information about the strength of the input signal. In hearing, for example, louder sounds result in more frequent action potentials in neurons connecting the ear to the brain. Differences in the number of action potentials in a given time are in fact the only variable in how information is encoded and transmitted along an axon.

Gated ion channels and action potentials have a central role in nervous system activity. As a consequence, mutations in genes that encode ion channel proteins can cause disorders affecting the nerves or brain—or the muscles or heart, depending largely on where in the body the gene for the ion channel protein is expressed. For example, mutations affecting sodium channels in skeletal muscle can cause periodic muscle spasms, or myotonia. Mutations affecting sodium channels in the brain can cause epilepsy, in which groups of nerve cells fire simultaneously and excessively, producing seizures.

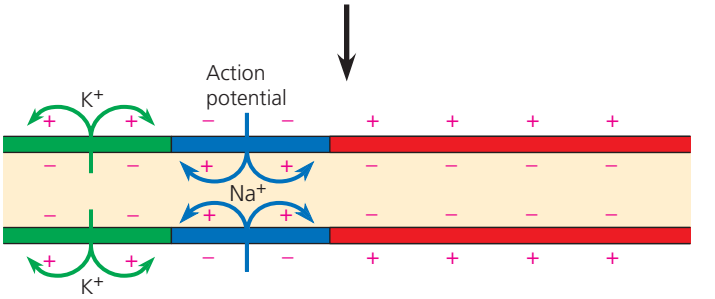
Conduction of Action Potentials

Now that we've described the events that occur in a single action potential, we'll look at how a series of action potentials moves a signal along an axon. At the site where an action potential is initiated (usually the axon hillock), Na^+ inflow during the rising phase creates an electrical current that depolarizes the neighboring region of the axon membrane **(Figure 37.12)**. The depolarization is large enough to reach threshold, causing an action potential in the neighboring region. This process is repeated many times along the length of the axon. Because an action potential is an all-or-none event, the magnitude and duration of the action potential are the same at each position along the axon. The net result is the movement of a nerve impulse from the cell body to the synaptic terminals, much like the cascade of events triggered by knocking over the first domino in a line.

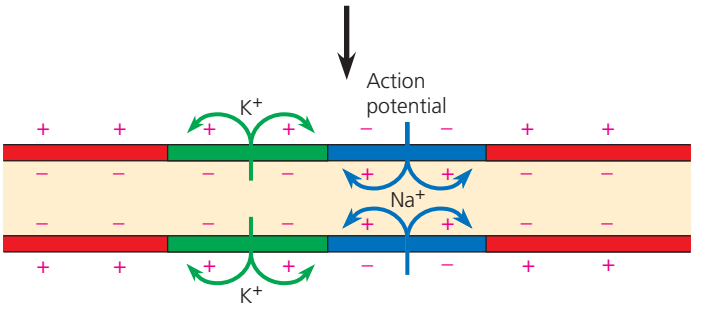
An action potential that starts at the axon hillock moves along the axon only toward the synaptic terminals. Why? Immediately behind the traveling zone of depolarization caused by Na^+ inflow is a zone of repolarization caused by K^+ outflow. In the repolarized zone, the sodium channels remain inactivated. Consequently, the inward current that depolarizes the axon membrane *ahead* of the action potential cannot produce another action potential *behind* it. This prevents action potentials from traveling back toward the cell body.



1 An action potential is generated as Na^+ flows inward across the membrane at one location.

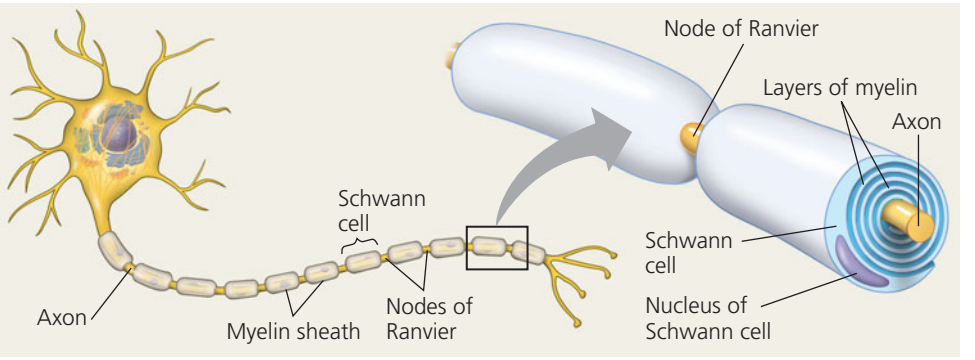


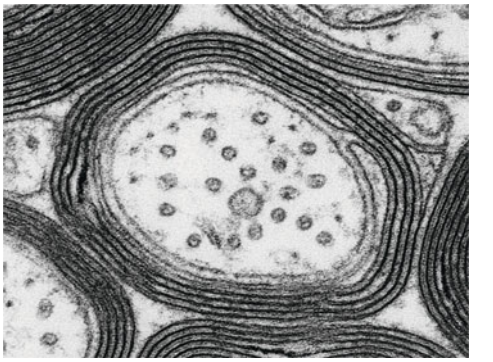
2 The depolarization of the action potential spreads to the neighboring region of the membrane, reinitiating the action potential there. To the left of this region, the membrane is repolarizing as K^+ flows outward.



3 The depolarization-repolarization process is repeated in the next region of the membrane. In this way, local currents of ions *across* the plasma membrane cause the action potential to be propagated *along* the length of the axon.

▲ Figure 37.12 Conduction of an action potential. This figure shows events at three successive times as an action potential passes from left to right. At each point along the axon, voltage-gated ion channels go through the sequence of changes depicted in Figure 37.11. Membrane colors correspond to the action potential phases in Figure 37.11.





▲ Figure 37.13 Schwann cells and the myelin sheath. In the PNS, glia called Schwann cells wrap themselves around axons, forming layers of myelin. Gaps between adjacent Schwann cells are called nodes of Ranvier. The TEM shows a cross section through a myelinated axon.

Evolutionary Adaptations of Axon Structure

EVOLUTION The rate at which the axons within nerves conduct action potentials governs how rapidly an animal can react to danger or opportunity. As a consequence, natural selection often results in anatomical adaptations that increase conduction speed. One such adaptation is a wider axon. Axon width matters because resistance to electrical current flow is inversely proportional to the cross-sectional area of a conductor (such as a wire or an axon). In the same way that a wide hose offers less resistance to the flow of water than does a narrow hose, a wide axon provides less resistance to the current associated with an action potential than does a narrow axon.

In invertebrates, conduction speed varies from several centimeters per second in very narrow axons to approximately 30 m/sec in the giant axons of some arthropods and molluscs. These giant axons (up to 1 mm wide) function in rapid behavioral responses, such as the muscle contraction that propels a hunting squid toward its prey.

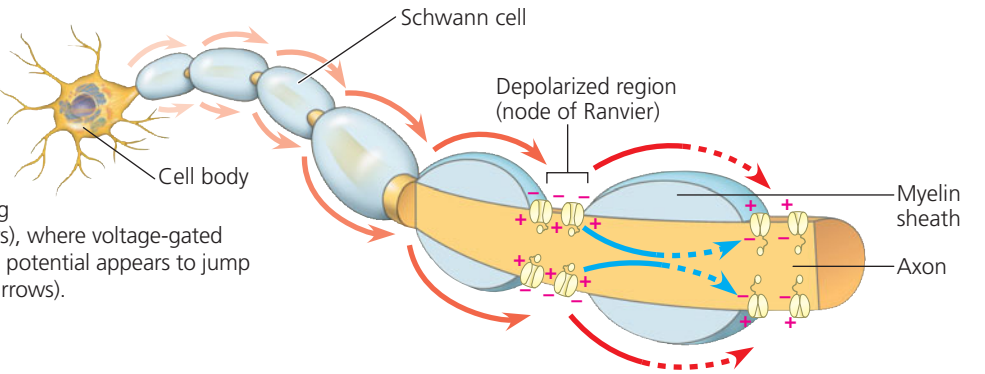
Vertebrate axons have narrow diameters but can still conduct action potentials at high speed. How is this possible? The evolutionary adaptation that enables fast conduction in vertebrate axons is electrical insulation, analogous to the plastic insulation that encases many electrical wires. Insulation causes the depolarizing current associated with an action potential to spread farther along the axon interior, bringing more distant regions to the threshold sooner.

The electrical insulation that surrounds vertebrate axons is called a **myelin sheath** **(Figure 37.13)**. Myelin sheaths are produced by two types of glia—**oligodendrocytes** in the CNS and **Schwann cells** in the PNS. During development, these specialized glia wrap axons in many layers of membrane. The membranes forming these layers are mostly lipid, which is a poor conductor of electrical current.

In myelinated axons, voltage-gated sodium channels are restricted to gaps in the myelin sheath called **nodes of Ranvier** (see Figure 37.13). The extracellular fluid is in contact with the axon membrane only at the nodes. As a result, action potentials are not generated in the regions between the nodes. Rather, the inward current produced during the rising phase of the action potential at a node travels all the way to the next node, where it depolarizes the membrane and regenerates the action potential **(Figure 37.14)**. Thus, the time-consuming process of opening and closing ion channels occurs at only a limited number of positions along the axon. This mechanism for propagating action potentials is called **saltatory conduction** (from the Latin *saltare*, to leap) because the action potential appears to jump along the axon from node to node.

The major selective advantage of myelination is its space efficiency. A myelinated axon 20 µm in diameter has a conduction speed faster than that of a squid giant axon with a diameter 40 times greater. Furthermore, more than 2,000 of those myelinated axons can be packed into the space occupied by just one giant axon.

For any axon, myelinated or not, the conduction of an action potential to the end of the axon sets the stage for the next step in neuronal signaling—the transfer of information to another cell. This information handoff occurs at synapses, the topic of the next section.



▶ Figure 37.14 Saltatory conduction. In a myelinated axon, the depolarizing current during an action potential at one node of Ranvier spreads along the interior of the axon to the next node (blue arrows), where voltage-gated sodium channels enable reinitiation. Thus, the action potential appears to jump from node to node as it travels along the axon (red arrows).

CONCEPT CHECK 37.3

1. How do action potentials and graded potentials differ?
2. In multiple sclerosis (from the Greek *skleros*, hard), a person's myelin sheaths harden and deteriorate. How would this affect nervous system function?
3. **WHAT IF?** Suppose a mutation caused gated sodium channels to remain inactivated longer after an action potential. How would this affect the frequency at which action potentials could be generated? Explain.

For suggested answers, see Appendix A.

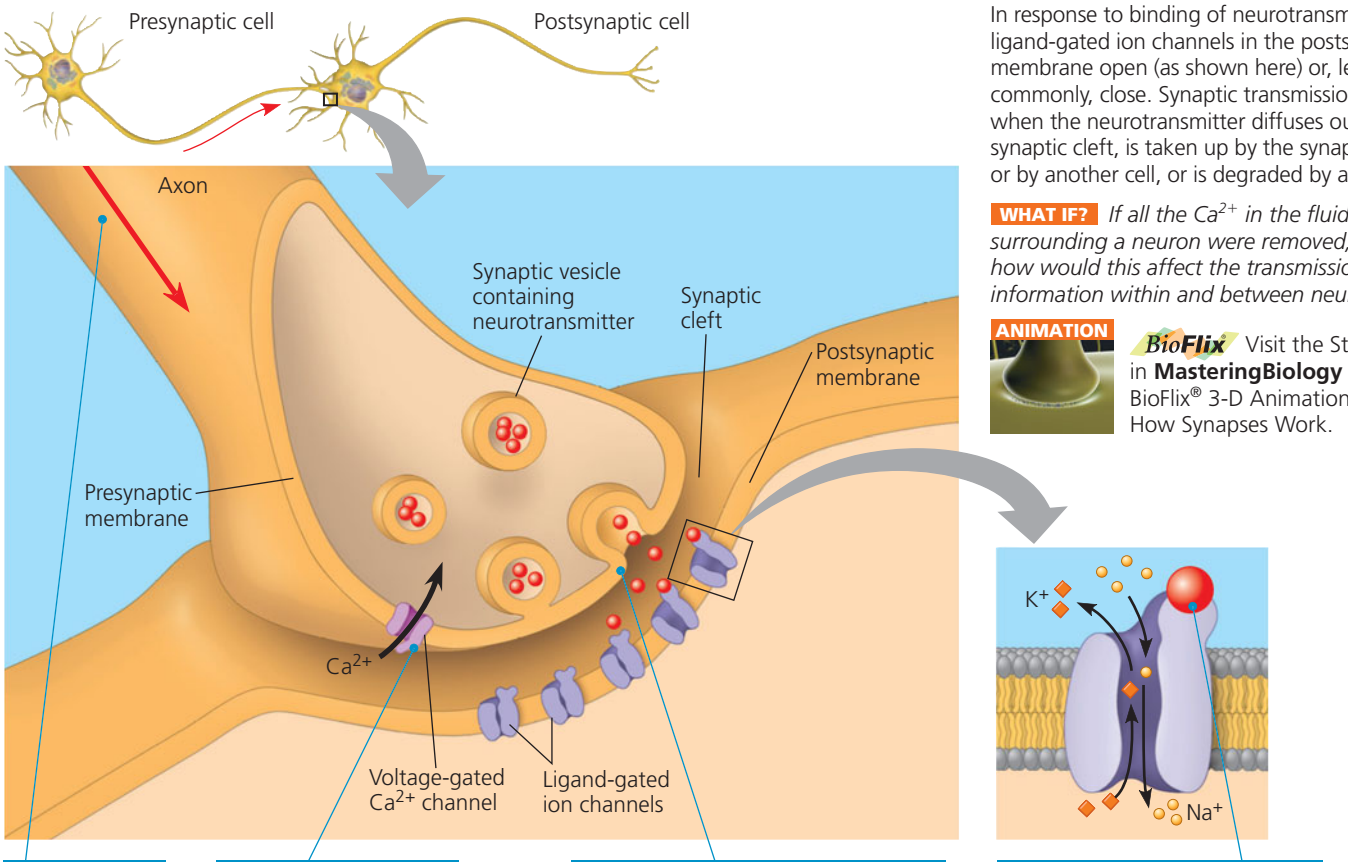
CONCEPT 37.4

Neurons communicate with other cells at synapses

In most cases, action potentials are not transmitted from neurons to other cells. However, information is transmitted, and this transmission occurs at the synapses. Some synapses, called electrical synapses, contain gap junctions (see Figure 4.27), which *do* allow electrical current to flow directly from one neuron to another. In both vertebrates and invertebrates, electrical synapses synchronize the activity of neurons responsible for certain rapid, unvarying behaviors. For example, electrical synapses associated with the giant axons of squids and lobsters facilitate swift escapes from danger. There are also many electrical synapses in the vertebrate brain.

The majority of synapses are chemical synapses, which involve the release of a chemical neurotransmitter by the presynaptic neuron. At each terminal, the presynaptic neuron synthesizes the neurotransmitter and packages it in multiple membrane-enclosed compartments called *synaptic vesicles*. The arrival of an action potential at a synaptic terminal depolarizes the plasma membrane, opening voltage-gated channels that allow Ca^{2+} to diffuse into the terminal **(Figure 37.15)**. The resulting rise in Ca^{2+} concentration in the terminal causes some of the synaptic vesicles to fuse with the terminal membrane, releasing the neurotransmitter.

Once released, the neurotransmitter diffuses across the *synaptic cleft*, the gap that separates the presynaptic neuron



◀ Figure 37.15 A chemical synapse. This figure illustrates the sequence of events that transmits a signal across a chemical synapse. In response to binding of neurotransmitter, ligand-gated ion channels in the postsynaptic membrane open (as shown here) or, less commonly, close. Synaptic transmission ends when the neurotransmitter diffuses out of the synaptic cleft, is taken up by the synaptic terminal or by another cell, or is degraded by an enzyme.

WHAT IF? *If all the Ca^{2+} in the fluid surrounding a neuron were removed, how would this affect the transmission of information within and between neurons?*

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from the postsynaptic cell. Diffusion time is very short because the gap is less than 50 nm across. Upon reaching the postsynaptic membrane, the neurotransmitter binds to and activates a specific receptor in the membrane, which in turn triggers a response in the postsynaptic cell.

Information transfer is much more readily modified at chemical synapses than at electrical synapses. A variety of factors can affect the amount of neurotransmitter that is released or the responsiveness of the postsynaptic cell. Such modifications underlie an animal's ability to alter its behavior in response to change and form the basis for learning and memory (as we will discuss in Chapter 38).

Generation of Postsynaptic Potentials

At many chemical synapses, the receptor protein that binds and responds to neurotransmitters is a **ligand-gated ion channel**, often called an *ionotropic receptor*. These receptors are clustered in the membrane of the postsynaptic cell, directly opposite the synaptic terminal. Binding of the neurotransmitter (the receptor's ligand) to a particular part of the receptor opens the channel and allows specific ions to diffuse across the postsynaptic membrane. The result is a *postsynaptic potential*, a graded potential in the postsynaptic cell.

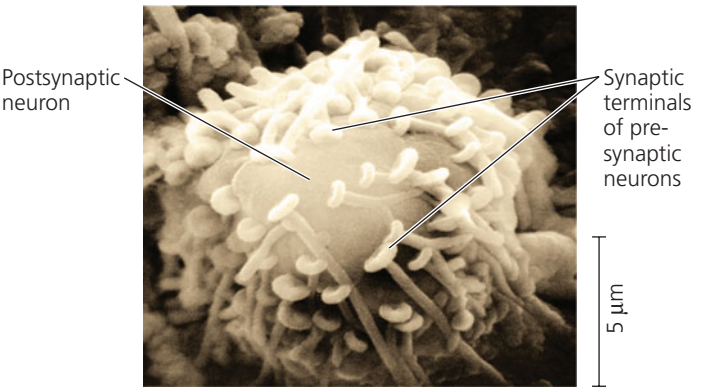
At some synapses, the ligand-gated ion channel is permeable to both K^+ and Na^+ (see Figure 37.15). When this channel opens, the membrane potential depolarizes toward a value roughly midway between E_K and E_{Na}. Because such a depolarization brings the membrane potential toward threshold, it is called an **excitatory postsynaptic potential (EPSP)**.

At other synapses, the ligand-gated ion channel is selectively permeable for only K^+ or Cl^-. When such a channel opens, the postsynaptic membrane hyperpolarizes. A hyperpolarization produced in this manner is an **inhibitory postsynaptic potential (IPSP)** because it moves the membrane potential further from threshold.

Various mechanisms limit the duration of postsynaptic potentials by rapidly clearing neurotransmitter molecules from the synaptic cleft. Some neurotransmitters are recaptured into presynaptic neurons, to be repackaged into synaptic vesicles, or into glia, to be metabolized as fuel or recycled to neurons. Other neurotransmitters are removed from the synaptic cleft by simple diffusion or by an enzyme that catalyzes hydrolysis of the neurotransmitter.

Summation of Postsynaptic Potentials

The cell body and dendrites of one postsynaptic neuron may receive inputs from chemical synapses formed with hundreds or even thousands of synaptic terminals **(Figure 37.16)**. The magnitude of the postsynaptic potential at any one synapse varies with a number of factors, including the amount of neurotransmitter released by the presynaptic neuron. As a graded potential, a postsynaptic potential becomes smaller with distance from the synapse. Therefore, by the time a single EPSP reaches the axon hillock, it is usually too small to trigger an action potential in a postsynaptic neuron **(Figure 37.17a)**.



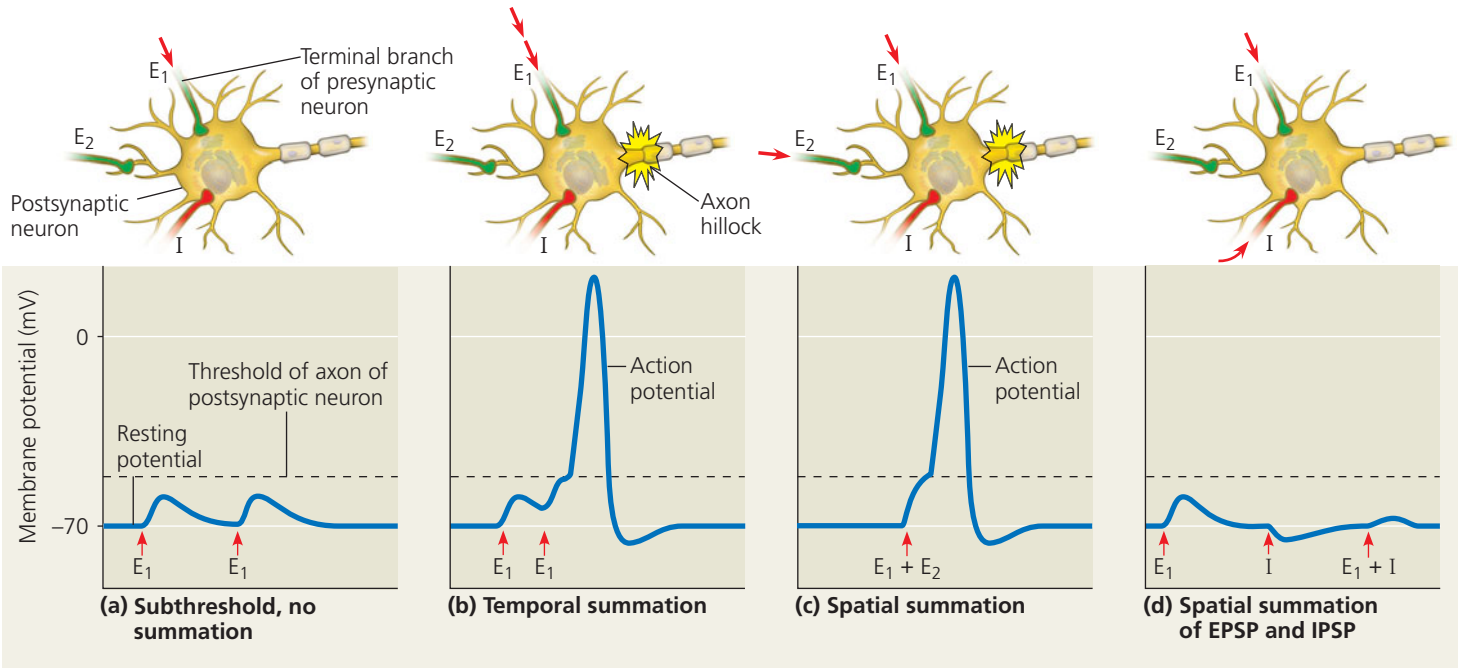
▲ Figure 37.16 Synaptic terminals on the cell body of a postsynaptic neuron (colorized SEM).

On some occasions, two EPSPs occur at a single synapse in such rapid succession that the postsynaptic neuron's membrane potential has not returned to the resting potential before the arrival of the second EPSP. When that happens, the EPSPs add together, an effect called **temporal summation (Figure 37.17b)**. Moreover, EPSPs produced nearly simultaneously by *different* synapses on the same postsynaptic neuron can also add together, an effect called **spatial summation (Figure 37.17c)**. Through spatial and temporal summation, several EPSPs can combine to depolarize the membrane at the axon hillock to threshold, causing the postsynaptic neuron to produce an action potential. Summation applies as well to IPSPs: Two or more IPSPs occurring nearly simultaneously at synapses in the same region or in rapid succession at the same synapse have a larger hyperpolarizing effect than a single IPSP. Through summation, an IPSP can also counter the effect of an EPSP **(Figure 37.17d)**.

The interplay between multiple excitatory and inhibitory inputs is the essence of integration in the nervous system. The axon hillock is the neuron's integrating center, the region where the membrane potential at any instant represents the summed effect of all EPSPs and IPSPs. Whenever the membrane potential at the axon hillock reaches threshold, an action potential is generated and travels along the axon to its synaptic terminals. After the refractory period, the neuron may produce another action potential, provided the membrane potential at the axon hillock once again reaches threshold.

Modulated Signaling at Synapses

So far, we have focused on synapses where a neurotransmitter binds directly to an ion channel, causing the channel to open. However, there are also synapses in which the receptor for the neurotransmitter is *not* part of an ion channel. At these synapses, the neurotransmitter binds to a *metabotropic receptor*, so called because the resulting opening or closing of ion channels depends on one or more metabolic steps. Binding of a neurotransmitter



▲ Figure 37.17 Summation of postsynaptic potentials. These graphs trace changes in the membrane potential at a postsynaptic neuron's axon hillock. The arrows indicate times when postsynaptic potentials occur at two excitatory synapses (E_1 and E_2, green in the diagrams above the graphs) and at one inhibitory synapse (I, red). Like most EPSPs, those produced at E_1 or E_2 do not reach the threshold at the axon hillock without summation.

to a metabotropic receptor activates a signal transduction pathway in the postsynaptic cell involving a second messenger (see Chapter 5). Compared with the postsynaptic potentials produced by ligand-gated channels, the effects of these second-messenger systems have a slower onset but last longer (minutes or even hours). Second messengers modulate the responsiveness of postsynaptic neurons to inputs in diverse ways, such as by altering the number of open potassium channels.

A variety of signal transduction pathways play a role in modulating synaptic transmission. One of the best-studied pathways involves cyclic AMP (cAMP) as a second messenger. For example, when the neurotransmitter norepinephrine binds to its metabotropic receptor, the neurotransmitter-receptor complex activates a G protein, which in turn activates adenylyl cyclase, the enzyme that converts ATP to cAMP (see Figure 5.25). Cyclic AMP activates protein kinase A, which phosphorylates specific ion channel proteins in the postsynaptic membrane, causing them to open or close. Because of the amplifying effect of the signal transduction pathway, the binding of a neurotransmitter molecule to a metabotropic receptor can open or close many channels.

Neurotransmitters

Signaling at a synapse brings about a response that depends on both the neurotransmitter released from the presynaptic membrane and the receptor produced at the postsynaptic membrane. A single neurotransmitter may bind specifically to more than a dozen different receptors, including ionotropic and metabotropic types. Indeed, a particular neurotransmitter can excite postsynaptic cells expressing one receptor and inhibit postsynaptic cells expressing a different receptor. As an example, let's examine **acetylcholine**, a common neurotransmitter in both invertebrates and vertebrates.

Acetylcholine

Acetylcholine is vital for nervous system functions that include muscle stimulation, memory formation, and learning. In vertebrates, there are two major classes of acetylcholine receptor. One type is a ligand-gated ion channel. We know the most about its function at the vertebrate *neuromuscular junction*, the site where a motor neuron forms a synapse with a skeletal muscle cell. When acetylcholine released by motor neurons binds this receptor, the ion channel opens, producing an EPSP. This excitatory activity is soon terminated by acetylcholinesterase, an enzyme in the synaptic cleft that hydrolyzes the neurotransmitter into an inactive form.

The acetylcholine receptor active at the neuromuscular junction is also found elsewhere in the PNS, as well as in the CNS. There this ionotropic receptor can bind nicotine, a chemical found in tobacco and tobacco smoke. Nicotine's effects as a physiological and psychological stimulant result from its binding to this receptor.

A metabotropic acetylcholine receptor is found at locations that include the vertebrate CNS and heart. In heart muscle, acetylcholine released by neurons activates a signal transduction pathway. The G proteins in the pathway inhibit adenylyl cyclase and open potassium channels in the muscle cell membrane. Both effects reduce the rate at which the heart pumps. Thus, the effect of acetylcholine in heart muscle is inhibitory rather than excitatory.

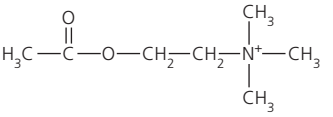
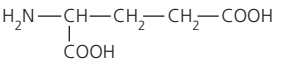
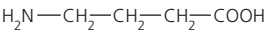
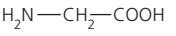
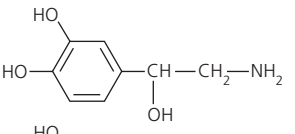
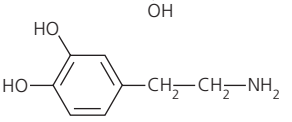
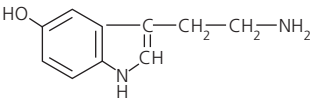
A number of toxins disrupt neurotransmission by acetylcholine. For example, the nerve gas sarin inhibits acetylcholinesterase, causing a buildup of acetylcholine to levels that trigger paralysis and typically death. In contrast, certain bacteria produce a toxin that inhibits presynaptic release of acetylcholine. This toxin causes a rare but often fatal form of food poisoning called botulism. Today, injections of the botulinum toxin, known by the trade name Botox, are used cosmetically to minimize wrinkles around the eyes or mouth by blocking transmission at synapses that control particular facial muscles.

Although acetylcholine has many roles, it is just one of more than 100 known neurotransmitters. As shown by the examples in **Table 37.2**, the rest fall into four classes: amino acids, biogenic amines, neuropeptides, and gases.

Amino Acids

Glutamate is one of several amino acids that can act as a neurotransmitter. In invertebrates, glutamate, rather than acetylcholine, is the neurotransmitter at the neuromuscular junction. In vertebrates, glutamate is the most common neurotransmitter in the CNS. Synapses at which glutamate is the neurotransmitter have a key role in the formation of long-term memory (as we'll discuss in Chapter 38).

Table 37.2 Major Neurotransmitters

Neurotransmitter	Structure
Acetylcholine	
Amino Acids	
Glutamate	
GABA (gamma-aminobutyric acid)	
Glycine	
Biogenic Amines	
Norepinephrine	
Dopamine	
Serotonin	
Neuropeptides (a very diverse group, only two of which are shown)	
Substance P	Arg—Pro—Lys—Pro—Gln—Gln—Phe—Phe—Gly—Leu—Met
Met-enkephalin (an endorphin)	Tyr—Gly—Gly—Phe—Met
Gases	
Nitric oxide	N=O

The amino acid **gamma-aminobutyric acid (GABA)** is the neurotransmitter at most inhibitory synapses in the brain. Binding of GABA to receptors in postsynaptic cells increases membrane permeability to Cl^-, resulting in an IPSP. The widely prescribed drug diazepam (Valium) reduces anxiety through binding to a site on a GABA receptor.

A third amino acid, glycine, acts at inhibitory synapses in parts of the CNS that lie outside of the brain. There, glycine binds to an ionotropic receptor that is inhibited by strychnine, a chemical often used as a rat poison.

Biogenic Amines

The neurotransmitters grouped as **biogenic amines** are synthesized from amino acids and include **norepinephrine**, which is made from tyrosine. Norepinephrine is an excitatory neurotransmitter in the autonomic nervous system, a branch of the PNS. Outside the nervous system, norepinephrine has distinct but related functions as a hormone, as does the chemically similar biogenic amine *epinephrine* (see Chapter 32).

The biogenic amines **dopamine**, made from tyrosine, and **serotonin**, made from tryptophan, are released at many sites in the brain and affect sleep, mood, attention, and learning. Some psychoactive drugs, including LSD and mescaline, apparently produce their hallucinatory effects by binding to brain receptors for these neurotransmitters.

Biogenic amines have a central role in a number of nervous system disorders and treatments (see Chapter 38). The degenerative illness Parkinson's disease is associated with a lack of dopamine in the brain. In addition, depression is often treated with drugs that increase the brain concentrations of biogenic amines. Prozac, for instance, enhances the effect of serotonin by inhibiting its reuptake after release.

Neuropeptides

Several **neuropeptides**, relatively short chains of amino acids, serve as neurotransmitters that operate via metabotropic receptors. Such peptides are typically produced by cleavage of much larger protein precursors. The neuropeptide *substance P* is a key excitatory neurotransmitter that mediates our perception of pain. Other neuropeptides, called **endorphins**, function as natural analgesics, decreasing pain perception.

Endorphins are produced in the brain during times of physical or emotional stress, such as childbirth. In addition to relieving pain, they reduce urine output, decrease respiration, and produce euphoria, as well as other emotional effects. Opiates (drugs such as morphine and heroin) mimic endorphins and produce many of the same physiological effects (see Figure 2.14). In the **Scientific Skills Exercise**, you can interpret data from an experiment designed to search for opiate receptors in the brain.

Gases

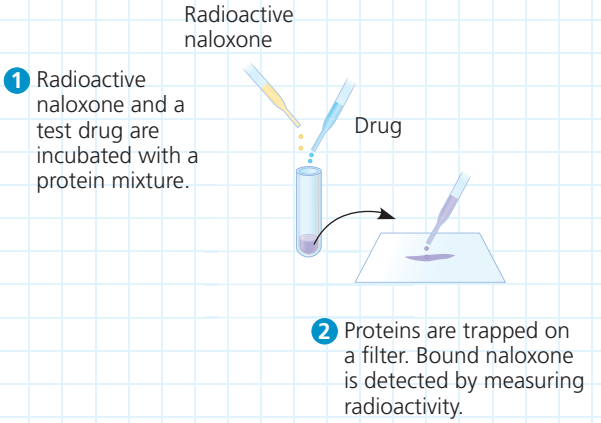
In common with many other types of cells, some vertebrate neurons release dissolved gases, notably nitric oxide (NO), that act as local regulators (see Concept 5.6). In human males, for example, certain neurons release NO into the erectile tissue

Scientific Skills Exercise

Interpreting Data Values Expressed in Scientific Notation

Does the Brain Have Specific Protein Receptors for Opiates?
A team of researchers were looking for opiate receptors in the mammalian brain. Knowing that the drug naloxone blocks the analgesic effect of opiates, they hypothesized that naloxone acts by binding tightly to brain opiate receptors without activating them. In this exercise, you will interpret the results of an experiment that the researchers conducted to test their hypothesis.

How the Experiment Was Done The researchers added radioactive naloxone to a protein mixture prepared from rodent brains. If the mixture contained opiate receptors or other proteins that could bind naloxone, the radioactivity would stably associate with the mixture. To determine whether the binding was due to specific opiate receptors, they tested other drugs, opiate and non-opiate, for their ability to block naloxone binding.



Data from the Experiment

Drug	Opiate	Lowest Concentration That Blocked Naloxone Binding
Morphine	Yes	$6 \times 10^{-9}\ M$
Methadone	Yes	$2 \times 10^{-8}\ M$
Levorphanol	Yes	$2 \times 10^{-9}\ M$
Phenobarbital	No	No effect at $10^{-4}\ M$
Atropine	No	No effect at $10^{-4}\ M$
Serotonin	No	No effect at $10^{-4}\ M$

Interpret the Data

1. The data from this experiment are expressed using scientific notation: a numerical factor times a power of 10. Remember that a negative power of 10 means a number less than 1. For example, the concentration $10^{-1}\ M$ (molar) can also be written as 0.1 *M*. Write the concentrations in the table above for morphine and atropine in this alternative format.
2. Compare the concentrations listed in the table for methadone and phenobarbital. Which concentration is higher? By how much?
3. Would phenobarbital, atropine, or serotonin have blocked naloxone binding at a concentration of $10^{-5}\ M$? Explain why or why not.
4. Which drugs blocked naloxone binding in this experiment? What do these results indicate about the brain receptors for naloxone?
5. When the researchers repeated the experiment using tissue from mammalian intestinal muscles rather than brains, they found no naloxone binding. What does that suggest about opiate receptors in mammalian muscle tissue?

Data from C. B. Pert and S. H. Snyder, Opiate receptor: Demonstration in nervous tissue, *Science*, 179:1011–1014 (1973).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.

of the penis during sexual arousal. The resulting relaxation of smooth muscle in the blood vessel walls allows the spongy erectile tissue to fill with blood, producing an erection. The erectile dysfunction drug Viagra works by inhibiting an enzyme that terminates the action of NO.

Unlike most neurotransmitters, NO is not stored in cytoplasmic vesicles but is instead synthesized on demand. NO diffuses into neighboring target cells, produces a change, and is broken down—all within a few seconds. In many of its targets, including smooth muscle cells, NO works like many hormones, stimulating an enzyme to synthesize a second messenger that directly affects cellular metabolism.

Although inhaling air containing the gas carbon monoxide (CO) can be deadly, the vertebrate body produces small amounts of CO, some of which acts as a neurotransmitter. Carbon monoxide is generated by the enzyme heme oxygenase, one form of which is found in certain populations of neurons in the brain and PNS. In the brain, CO regulates the release of hypothalamic hormones. In the PNS, it acts as an inhibitory neurotransmitter that hyperpolarizes the plasma membrane of intestinal smooth muscle cells.

In the next chapter, we'll consider how the cellular and biochemical mechanisms we have discussed contribute to nervous system function on the system level.

CONCEPT CHECK 37.4

1. How is it possible for a particular neurotransmitter to produce opposite effects in different tissues?
2. Organophosphate pesticides work by inhibiting acetylcholinesterase, the enzyme that breaks down the neurotransmitter acetylcholine. Explain how these toxins would affect EPSPs produced by acetylcholine.
3. **MAKE CONNECTIONS** Name one or more membrane activities that are common to fertilization and neurotransmitter release (see Figure 36.14).

For suggested answers, see Appendix A.

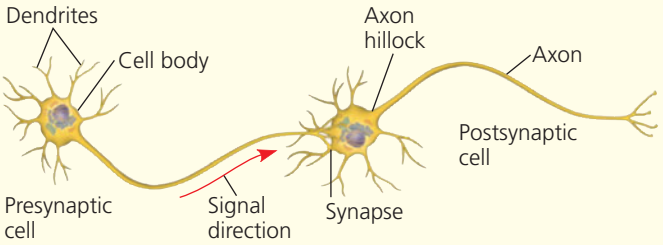
37 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 37.1

Neuron structure and organization reflect function in information transfer (pp. 752–753)

- Most neurons have branched **dendrites** that receive signals from other neurons and an **axon** that transmits signals to other cells at **synapses**. Neurons rely on **glia** for functions that include nourishment, insulation, and regulation.



- A **central nervous system (CNS)** and a **peripheral nervous system (PNS)** process information in three stages: sensory input, integration, and motor output to effector cells.

? *How would severing an axon affect the flow of information in a neuron?*

CONCEPT 37.2

Ion pumps and ion channels establish the resting potential of a neuron (pp. 754–756)

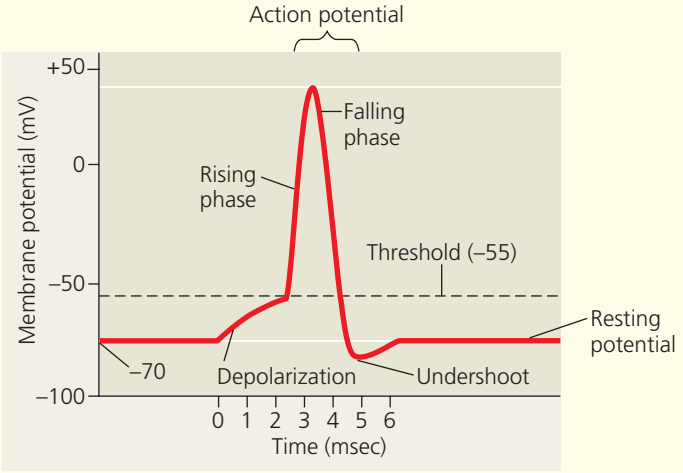
- Ionic gradients generate a voltage difference, or **membrane potential**, across the plasma membrane of cells. The concentration of Na^+ is higher outside than inside; the reverse is true for K^+. In resting neurons, the plasma membrane has many open potassium channels but few open sodium channels. Diffusion of ions, principally K^+, through channels generates a **resting potential**, with the inside more negative than the outside.

? *Suppose you placed an isolated neuron in a solution similar to extracellular fluid and later transferred the neuron to a solution lacking any sodium ions. What change would you expect in the resting potential?*

CONCEPT 37.3

Action potentials are the signals conducted by axons (pp. 756–761)

- Neurons have gated ion channels that open or close in response to stimuli, leading to changes in the membrane potential. An increase in the magnitude of the membrane potential is a **hyperpolarization**; a decrease is a **depolarization**. Changes in membrane potential that vary continuously with the strength of a stimulus are known as **graded potentials**.
- An **action potential** is a brief, all-or-none depolarization of a neuron's plasma membrane. When a graded depolarization brings the membrane potential to **threshold**, many **voltage-gated ion channels** open, triggering an inflow of Na^+ that rapidly brings the membrane potential to a positive value. A negative membrane potential is restored by the inactivation of sodium channels and by the opening of many voltage-gated potassium channels, which increases K^+ outflow. A **refractory period** follows, corresponding to the interval when the sodium channels remain inactivated.



- A nerve impulse travels from the axon hillock to the synaptic terminals by propagating a series of action potentials along the axon. The speed of conduction increases with the diameter of the axon and, in many vertebrate axons, with **myelination**. Action potentials in myelinated axons jump between the **nodes of Ranvier**, a process called **saltatory conduction**.

? *In what ways do both positive and negative feedback contribute to the shape of an action potential?*

CONCEPT 37.4

Neurons communicate with other cells at synapses (pp. 761–765)

- In an electrical **synapse**, electrical current flows directly from one cell to another. In a chemical synapse, depolarization causes synaptic vesicles to fuse with the terminal membrane and release **neurotransmitter** into the synaptic cleft.
- At many synapses, the neurotransmitter binds to **ligand-gated ion channels** in the postsynaptic membrane, producing an **excitatory** or **inhibitory postsynaptic potential** (**EPSP** or **IPSP**). The neurotransmitter then diffuses out of the cleft, is taken up by surrounding cells, or is degraded by enzymes. **Temporal** and **spatial summation** at the axon hillock determines whether a neuron generates an action potential.
- Different receptors for the same neurotransmitter produce different effects. Some neurotransmitter receptors activate signal transduction pathways, which can produce long-lasting changes in postsynaptic cells. Major neurotransmitters include **acetylcholine**; the amino acids **GABA**, **glutamate**, and glycine; **biogenic amines**; **neuropeptides**; and gases such as NO.

? *Why are many drugs that are used to treat nervous system diseases or to affect brain function targeted to specific receptors rather than particular neurotransmitters?*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

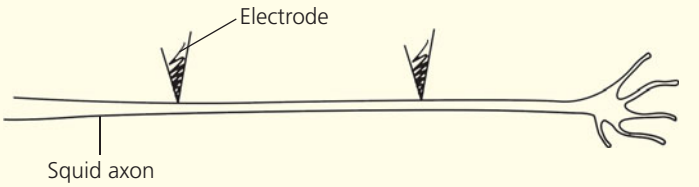
1. What happens when a resting neuron's membrane depolarizes?
   a. There is a net diffusion of Na^+ out of the cell.
   b. The equilibrium potential for K^+ (E_K) becomes more positive.
   c. The neuron's membrane voltage becomes more positive.
   d. The neuron is less likely to generate an action potential.
   e. The cell's inside is more negative than the outside.
2. A common feature of action potentials is that they
   a. cause the membrane to hyperpolarize and then depolarize.
   b. can undergo temporal and spatial summation.
   c. are triggered by a depolarization that reaches threshold.
   d. move at the same speed along all axons.
   e. require the diffusion of Na^+ and K^+ through ligand-gated channels to propagate.
3. Where are neurotransmitter receptors located?
   a. the nuclear membrane
   b. the nodes of Ranvier
   c. the postsynaptic membrane
   d. synaptic vesicle membranes
   e. the myelin sheath

Level 2: Application/Analysis

4. Why are action potentials usually conducted in one direction?
   a. The nodes of Ranvier conduct potentials in one direction.
   b. The brief refractory period prevents reopening of voltage-gated Na^+ channels.
   c. The axon hillock has a higher membrane potential than the terminals of the axon.
   d. Ions can flow along the axon in only one direction.
   e. Voltage-gated channels for both Na^+ and K^+ open in only one direction.
5. Which of the following is a *direct* result of depolarizing the presynaptic membrane of an axon terminal?
   a. Voltage-gated calcium channels in the membrane open.
   b. Synaptic vesicles fuse with the membrane.
   c. The postsynaptic cell produces an action potential.
   d. Ligand-gated channels open, allowing neurotransmitters to enter the synaptic cleft.
   e. An EPSP or IPSP is generated in the postsynaptic cell.
6. Suppose a particular neurotransmitter causes an IPSP in postsynaptic cell X and an EPSP in postsynaptic cell Y. A likely explanation is that
   a. the threshold value in the postsynaptic membrane is different for cell X and cell Y.
   b. cell Y forms chemical synapses, whereas cell X forms electrical synapses.
   c. the axon of cell X is myelinated, but that of cell Y is not.
   d. only cell Y produces an enzyme that terminates the activity of the neurotransmitter.
   e. cells X and Y express different receptor molecules for this particular neurotransmitter.

Level 3: Synthesis/Evaluation

7. **WHAT IF?** Ouabain, a plant substance used in some cultures to poison hunting arrows, disables the sodium-potassium pump. What change in the resting potential would you expect to see if you treated a neuron with ouabain? Explain.
8. **WHAT IF?** If a drug mimicked the activity of GABA in the CNS, what general effect on behavior might you expect? Explain.
9. **DRAW IT** Suppose a researcher inserts a pair of electrodes at two different positions along the middle of an axon dissected out of a squid. By applying a depolarizing stimulus, the researcher brings the plasma membrane at both positions to threshold. Using the drawing below as a model, create one or more drawings that illustrate where each action potential would terminate.



10. **SCIENTIFIC INQUIRY**
    From what you know about action potentials and synapses, propose two or three hypotheses for how various anesthetics might block pain.
11. **FOCUS ON EVOLUTION**
    An action potential is an all-or-none event. This on/off signaling is an evolutionary adaptation of animals that must sense and act in a complex environment. It is possible to imagine a nervous system in which the action potentials are graded, with the amplitude depending on the size of the stimulus. What evolutionary advantage might on/off signaling have over a graded (continuously variable) kind of signaling?
12. **FOCUS ON ORGANIZATION**
    In a short essay (100–150 words), describe how the structure and electrical properties of vertebrate neurons reflect similarities and differences with other animal cells.

For selected answers, see Appendix A.

38 Nervous and Sensory Systems

KEY CONCEPTS

38.1 Nervous systems consist of circuits of neurons and supporting cells

38.2 The vertebrate brain is regionally specialized

38.3 The cerebral cortex controls voluntary movement and cognitive functions

38.4 Sensory receptors transduce stimulus energy and transmit signals to the central nervous system

38.5 The mechanoreceptors responsible for hearing and equilibrium detect moving fluid or settling particles

38.6 The diverse visual receptors of animals depend on light-absorbing pigments

▼ **Figure 38.1** Of what use is a star-shaped nose?

OVERVIEW

Sense and Sensibility

Tunneling beneath the wetlands of eastern North America, the star-nosed mole (*Condylura cristata*) lives in almost total darkness. Virtually blind, the mole is nonetheless a remarkably quick predator, capable of detecting and eating its prey in as little as 120 milliseconds (msec). Central to the mole's hunting prowess are 11 pairs of appendages that protrude from its nose, forming a prominent star **(Figure 38.1)**. Although they look a bit like fingers, these appendages are not used in grasping. Nor are they used to detect odors. Instead, they are specialized for detecting physical contact. Just below their surface lie 25,000 touch-sensitive receptors, more than are found in your whole hand. Over 100,000 neurons relay tactile information from these receptors to the mole's brain.

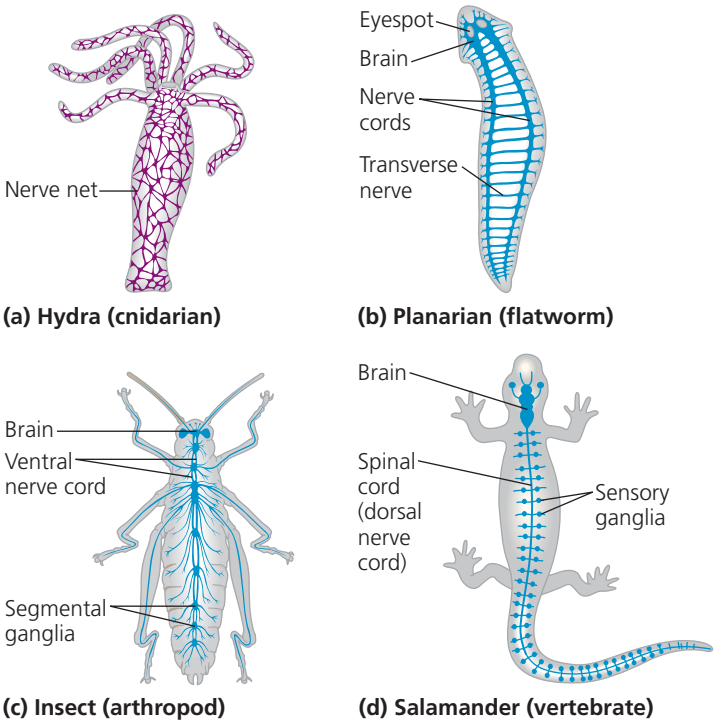
Gathering, processing, and organizing information are essential functions of all nervous systems. In this chapter, we'll begin by examining the basic organization of nervous systems. Next, we'll consider specialization in regions of the vertebrate brain and how brain activity makes information storage and organization possible. Finally, we'll investigate the sensory processes that convey information about an animal's external and internal environments to its brain.

CONCEPT 38.1

Nervous systems consist of circuits of neurons and supporting cells

The ability to sense and react originated billions of years ago in prokaryotes, enhancing survival and reproductive success in changing environments. Later in evolution, modified forms of these recognition and response processes provided a basis for communication between cells in an animal body. By the time of the Cambrian explosion more than 500 million years ago (see Concept 27.2), specialized systems of neurons had appeared that enabled animals to sense their surroundings and respond rapidly.

Hydras, jellies, and other cnidarians are the simplest animals with nervous systems. In most cnidarians, interconnected nerve cells form a diffuse **nerve net**



(a) Hydra (cnidarian) **(b) Planarian (flatworm)**

(c) Insect (arthropod) **(d) Salamander (vertebrate)**

▲ **Figure 38.2** **Nervous system organization. (a)** A hydra's nervous system contains individual neurons (purple) organized in a diffuse nerve net. **(b–d)** More complicated nervous systems have groups of neurons (blue) organized into nerves and often ganglia and a brain.

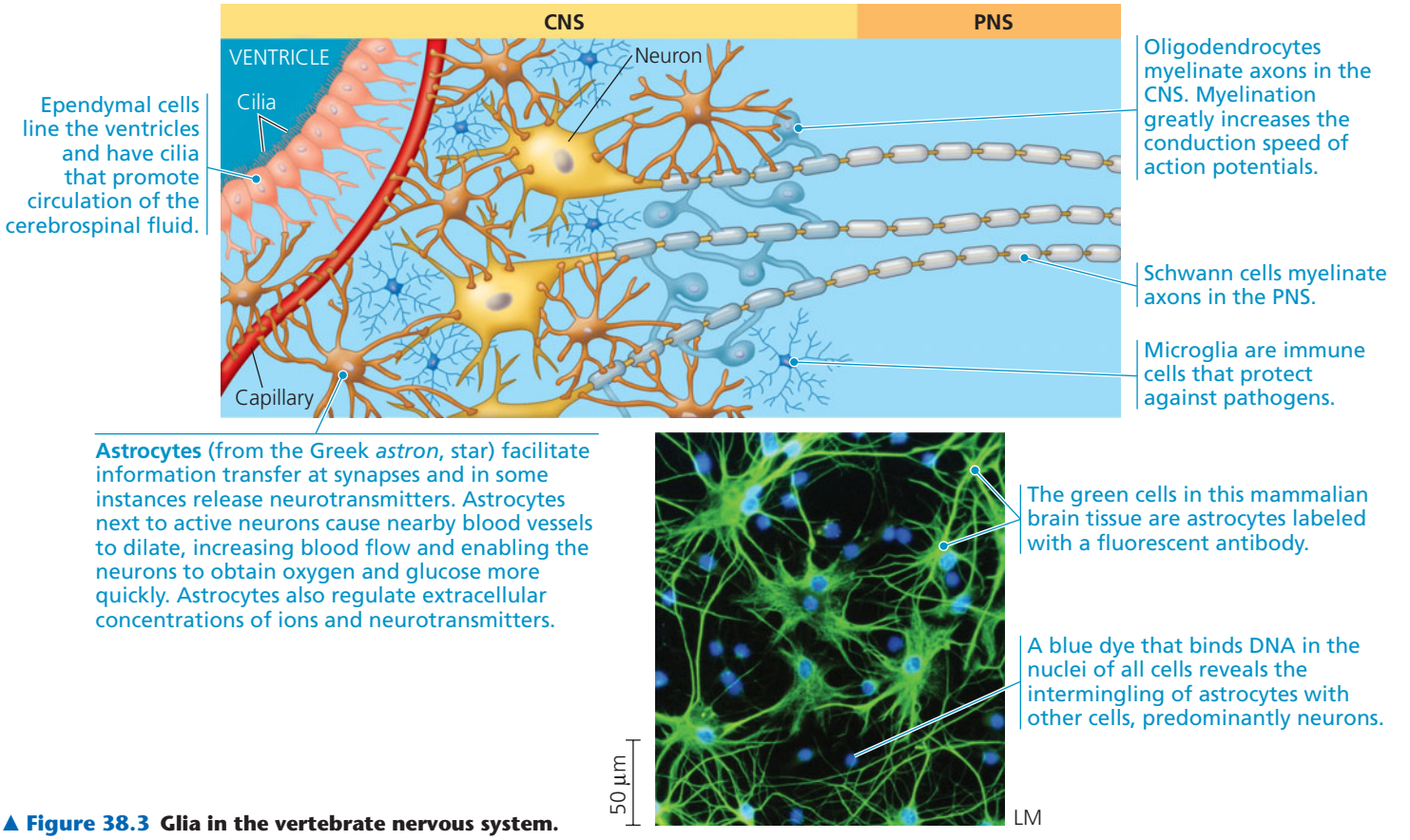
(Figure 38.2a), which controls the contraction and expansion of the gastrovascular cavity. In more complex animals, the axons of multiple nerve cells are often bundled together, forming **nerves**. These fibrous structures channel and organize information flow along specific routes through the nervous system.

Animals that have elongated, bilaterally symmetric bodies have even more specialized nervous systems. The organization of neurons in such animals reflects *cephalization*, an evolutionary trend toward a clustering of sensory neurons and interneurons at the anterior (front) end of the body. These anterior neurons communicate with cells elsewhere in the body, including neurons located in one or more nerve cords extending toward the posterior (rear) end. In nonsegmented worms, such as the planarian shown in **Figure 38.2b**, a small brain and longitudinal nerve cords constitute the simplest clearly defined **central nervous system (CNS)**. More complex invertebrates, such as arthropods **(Figure 38.2c)**, have more complicated brains and ventral nerve cords that contain *ganglia*, segmentally arranged clusters of neurons.

In vertebrates **(Figure 38.2d)**, the brain and spinal cord form the CNS; nerves and ganglia form the **peripheral nervous system (PNS)**.

Glia

Throughout the vertebrate brain and spinal cord, glia nourish, support, and regulate the functioning of neurons. **Figure 38.3** illustrates the major types of glia in an adult vertebrate.



▲ **Figure 38.3** **Glia in the vertebrate nervous system.**

The essential functions of glia include their role in the development of the nervous system. In embryos, cells called *radial glia* form tracks along which newly formed neurons migrate from the neural tube, the structure that gives rise to the CNS. Later, star-shaped glia called **astrocytes** induce cells that line the capillaries in the CNS to form tight junctions (see Figure 4.27). The result is the *blood-brain barrier*, a separation between the extracellular environment of the CNS and the circulatory system that restricts the movement of most substances from the blood to the brain.

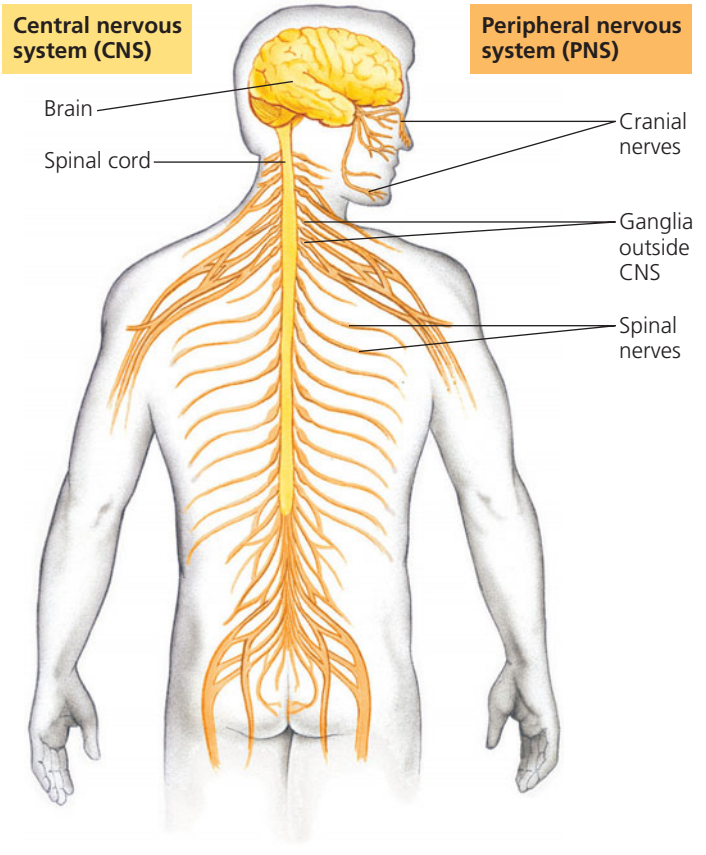
Glial cells not only support neurons, but also can contribute to the formation of new neurons. It was long thought that adult brains do not create new neurons; however, in 1998 researchers discovered that the adult human brain contains neural stem cells, which divide indefinitely and can give rise to new neurons. More recently, studies with mice have shown that the neural stem cells are astrocytes and that the new neurons they produce play an essential role in learning and memory.

Organization of the Vertebrate Nervous System

In vertebrates, the spinal cord runs lengthwise inside the vertebral column, known as the spine **(Figure 38.4)**. The spinal cord conveys information to and from the brain and generates basic patterns of locomotion. It also acts independently of the brain as part of the simple nerve circuits that produce certain **reflexes**, the body's automatic responses to particular stimuli. For example, the spinal cord controls the reflex that jerks your hand away if you accidently touch a hot pan.

Both the brain and the spinal cord contain gray and white matter. **Gray matter** consists mainly of neuron cell bodies and glia. **White matter** consists of bundled axons, whose myelin sheaths are responsible for the light color of this portion of the CNS. In the spinal cord, white matter makes up the outer layer, where it links the CNS to sensory and motor neurons of the PNS. In the brain, white matter is predominantly located in the interior, where signaling between neurons functions in learning, feeling emotions, processing sensory information, and generating commands.

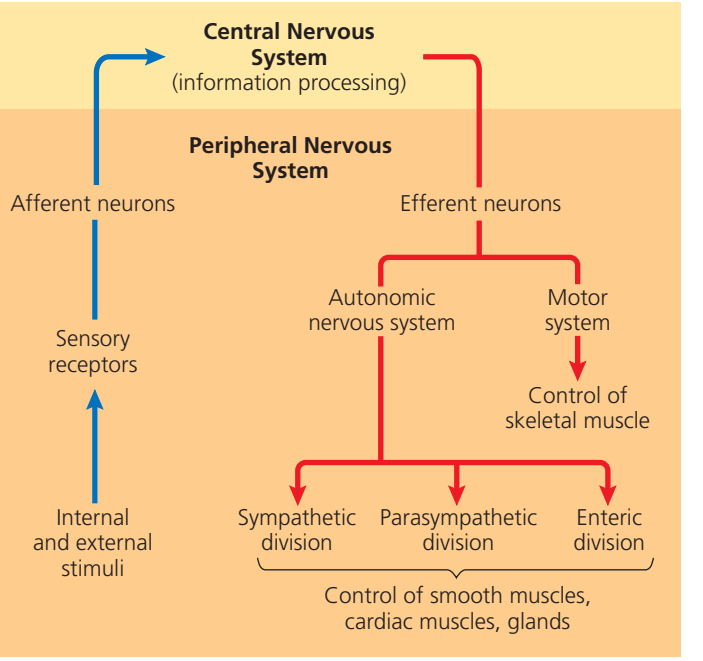
The CNS also contains fluid-filled spaces, called *ventricles* in the brain and the *central canal* in the spinal cord. The fluid inside, called *cerebrospinal fluid*, is formed in the brain by filtering arterial blood. It circulates through the ventricles and central canal and then drains into the veins, supplying the CNS with nutrients and hormones and carrying away wastes.



▲ **Figure 38.4 The vertebrate nervous system.** The central nervous system consists of the brain and spinal cord (yellow). Left-right pairs of cranial nerves, spinal nerves, and ganglia make up most of the peripheral nervous system (dark gold).

The Peripheral Nervous System

The PNS transmits information to and from the CNS and plays a large role in regulating both an animal's movement and its internal environment **(Figure 38.5)**. Sensory information reaches the CNS along PNS neurons designated as *afferent* (from the Latin, meaning "to carry toward"). Following information processing within the CNS, instructions travel



▲ **Figure 38.5 Functional hierarchy of the vertebrate peripheral nervous system.**

to muscles, glands, and endocrine cells along PNS neurons designated as *efferent* (meaning "to carry away"). Most nerves contain both afferent and efferent neurons.

The PNS has two efferent components: the motor system and the autonomic nervous system (see Figure 38.5). The **motor system** consists of neurons that carry signals to skeletal muscles. Motor control can be voluntary, as when you raise your hand to ask a question, or involuntary, as in a reflex. In contrast, regulation of smooth and cardiac muscles by the **autonomic nervous system** is generally involuntary. The three divisions of the autonomic nervous system—enteric, sympathetic, and parasympathetic—together control the organs of the digestive, cardiovascular, excretory, and endocrine systems. For example, networks of neurons that form the **enteric division** of the autonomic nervous system are active in the digestive tract, pancreas, and gallbladder.

The sympathetic and parasympathetic divisions of the autonomic nervous system have largely antagonistic (opposite) functions in regulating organ function. Activation of the **sympathetic division** is responsible for the "fight-or-flight" response, a state of hyperarousal with which we and other animals respond to a threat. In mammals, the heart beats faster, digestion slows or stops, and the adrenal medulla secretes more epinephrine (adrenaline). Activation of the **parasympathetic division** generally causes opposite responses that promote calming and a return to self-maintenance functions ("rest and digest").

As we have seen, each component of the PNS has functions specific to particular locations in the body. We therefore describe the PNS as having regional specialization, a property also apparent in the brain, our next topic.

CONCEPT CHECK 38.1

1. Which division of the autonomic nervous system would likely be activated if a student learned that an exam she had forgotten about would start in 5 minutes? Explain.
2. **WHAT IF?** Suppose a person had an accident that severed a small nerve required to move some of the fingers of the right hand. Would you also expect an effect on sensation from those fingers?

For suggested answers, see Appendix A.

CONCEPT 38.2

The vertebrate brain is regionally specialized

We turn now to the vertebrate brain, a structure that in humans contains 100 billion neurons. How are so many cells organized into circuits and networks that can perform highly sophisticated information processing, storage, and retrieval? To study this question, let's begin with **Figure 38.6**, on the next two pages, which explores the overall architecture of the brain. Use this figure to trace how brain structures arise during embryonic development; as a reference for their size, shape, and location in the adult brain; and as an introduction to their best-understood functions.

In examining brain organization and function, we'll first consider activity cycles and the physiological basis of emotions.

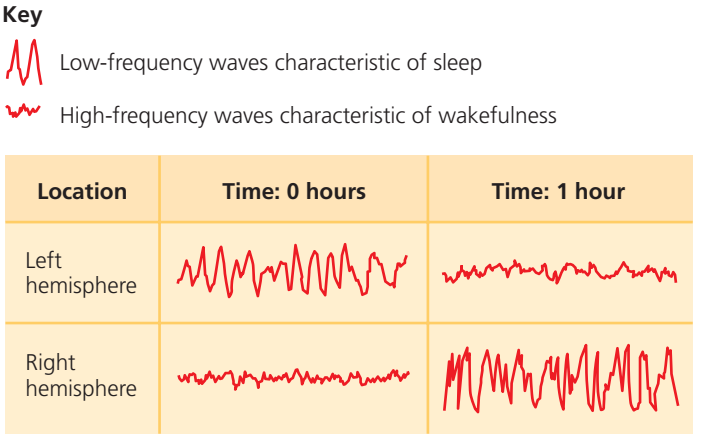
Arousal and Sleep

If you've ever drifted off to sleep while listening to a lecture (or reading a textbook), you know that your attentiveness and mental alertness can change rapidly. Such transitions are regulated by the brainstem and cerebrum, which control arousal and sleep. Arousal is a state of awareness of the external world. Sleep is a state in which external stimuli are received but not consciously perceived.

Contrary to appearances, sleep is an active state, at least for the brain. By placing electrodes at multiple sites on the scalp, researchers can record patterns of electrical activity—brain waves—in an electroencephalogram (EEG). These recordings reveal that brain wave frequencies change as the brain progresses through distinct stages of sleep.

Arousal and sleep are controlled in part by clusters of neurons in the midbrain and pons. These neurons control the timing of sleep periods characterized by rapid eye movements (REM) and by vivid dreams. Sleep is also regulated by the biological clock, discussed later, and by regions of the forebrain that regulate sleep intensity and duration.

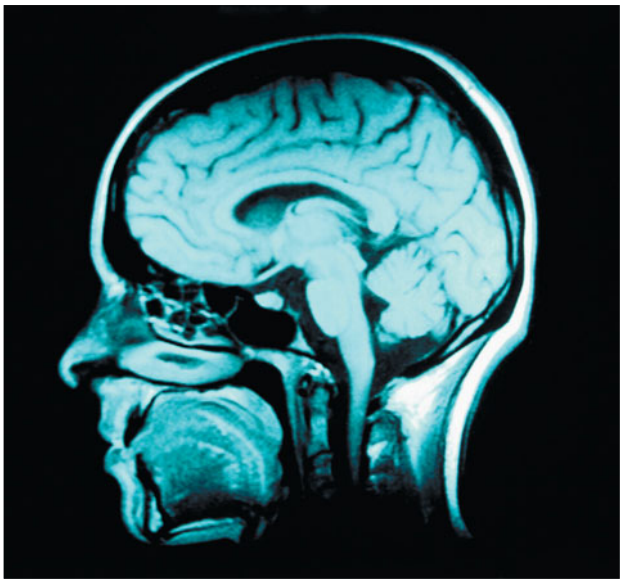
Some animals have evolutionary adaptations that allow for substantial activity during sleep. Bottlenose dolphins, for example, swim while sleeping, rising to the surface to breathe air on a regular basis. How do they manage this feat? As in other mammals, the forebrain of dolphins is divided into two halves, the right and left hemispheres. Noting that dolphins sleep with one eye open and one closed, researchers hypothesized that only one side of the dolphin brain is asleep at a time. EEG recordings from each hemisphere of sleeping dolphins support this hypothesis **(Figure 38.7)**.



▲ **Figure 38.7 Dolphins can be asleep and awake at the same time.** EEG recordings were made separately for the two sides of a dolphin's brain. At each time point, low-frequency activity was recorded in one hemisphere while higher-frequency activity typical of being awake was recorded in the other hemisphere.

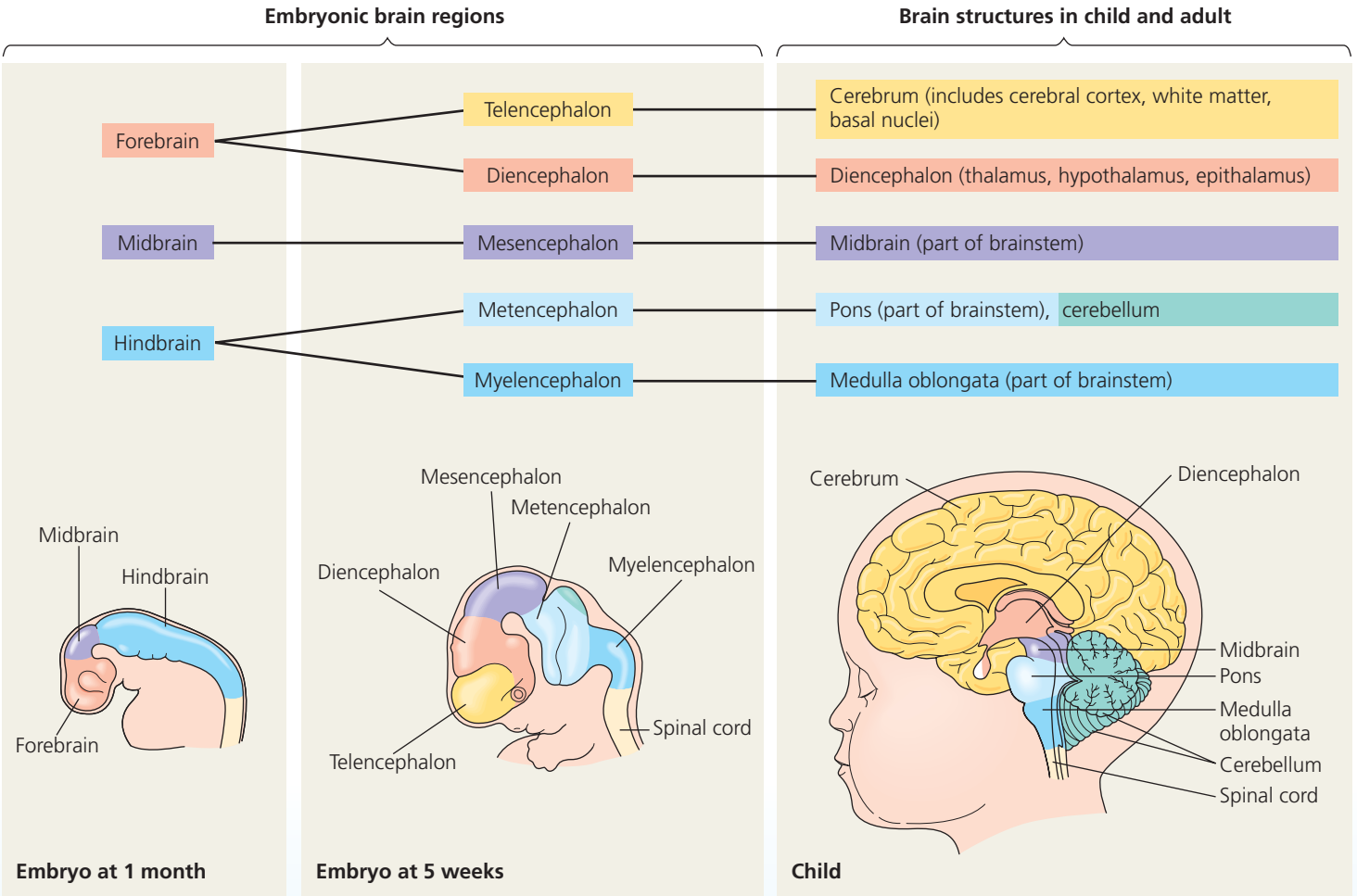
▼ Figure 38.6 Exploring the Organization of the Human Brain

The brain is the most complex organ in the human body. Surrounded by the thick bones of the skull, the brain is divided into a set of distinctive structures, some of which are visible in the magnetic resonance image (MRI) shown at right of an adult's head. The diagram below traces the development of these structures in the embryo. Their major functions are explained on the facing page.



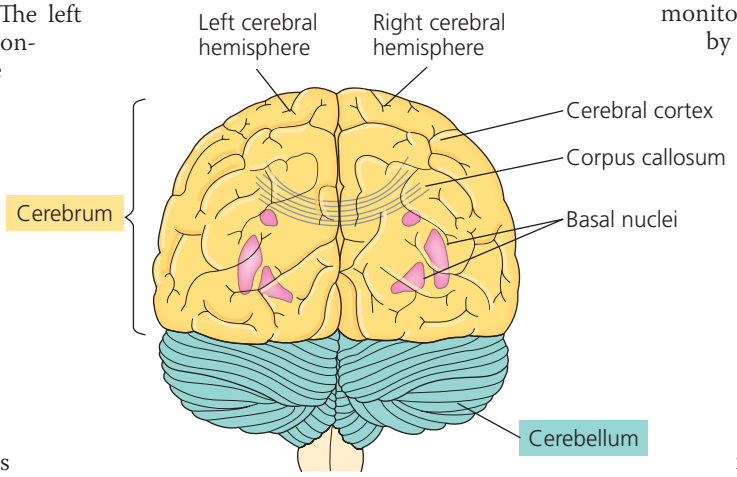
Human Brain Development

As a human embryo develops, the neural tube forms three anterior bulges—the **forebrain**, **midbrain**, and **hindbrain**—that together produce the adult brain. The midbrain and portions of the hindbrain give rise to the **brainstem**, a stalk that joins with the spinal cord at the base of the brain. The rest of the hindbrain gives rise to the **cerebellum**, which lies behind the brainstem. The third anterior bulge, the forebrain, develops into the diencephalon, including the neuroendocrine tissues of the brain, and the telencephalon, which becomes the **cerebrum**. Rapid, expansive growth of the telencephalon during the second and third months causes the outer portion, or cortex, of the cerebrum to extend over and around much of the rest of the brain.



The Cerebrum

The cerebrum controls skeletal muscle contraction and is the center for learning, emotion, memory, and perception. It is divided into right and left **cerebral hemispheres**. The **cerebral cortex** is vital for perception, voluntary movement, and learning. Like the rest of the cerebrum, the cerebral cortex is divided into right and left sides. The left side receives information from, and controls the movement of, the right side of the body, and vice versa. A thick band of axons known as the **corpus callosum** enables the right and left cerebral cortices to communicate. Deep within the white matter, clusters of neurons called *basal nuclei* serve as centers for planning and learning movement sequences. Damage to these sites during fetal development can result in cerebral palsy, a disorder resulting from a disruption in the transmission of motor commands to the muscles.



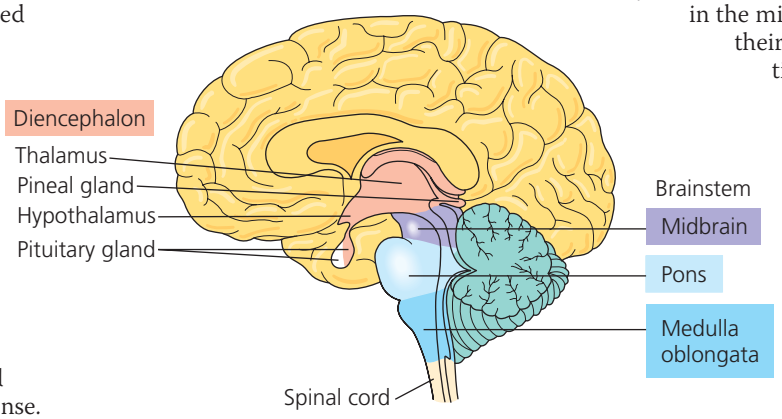
Adult brain viewed from the rear

The Cerebellum

The cerebellum coordinates movement and balance and helps in learning and remembering motor skills. The cerebellum receives sensory information about the positions of the joints and the lengths of the muscles, as well as input from the auditory (hearing) and visual systems. It also monitors motor commands issued by the cerebrum. The cerebellum integrates this information as it carries out coordination and error checking during motor and perceptual functions. Hand-eye coordination is an example of cerebellar control; if the cerebellum is damaged, the eyes can follow a moving object, but they will not stop at the same place as the object. Hand movement toward the object will also be erratic.

The Diencephalon

The diencephalon gives rise to the thalamus, hypothalamus, and epithalamus. The **thalamus** is the main input center for sensory information going to the cerebrum. Incoming information from all the senses is sorted in the thalamus and sent to the appropriate cerebral centers for further processing. The thalamus is formed by two masses, each roughly the size and shape of a walnut. A much smaller structure, the **hypothalamus**, constitutes a control center that includes the body's thermostat as well as the central biological clock. Through its regulation of the pituitary gland, the hypothalamus regulates hunger and thirst, plays a role in sexual and mating behaviors, and initiates the fight-or-flight response. The hypothalamus is also the source of posterior pituitary hormones and of releasing hormones that act on the anterior pituitary. The *epithalamus* includes the pineal gland, the source of melatonin. It also contains one of several clusters of capillaries that generate cerebrospinal fluid from blood.



The Brainstem

The brainstem consists of the midbrain, the **pons**, and the **medulla oblongata** (commonly called the *medulla*). The midbrain receives and integrates several types of sensory information, which it then sends on to specific regions of the forebrain. All sensory axons involved in hearing either terminate in the midbrain or pass through it on their way to the cerebrum. In addition, the midbrain coordinates visual reflexes, such as the peripheral vision reflex: The head turns toward an object approaching from the side without the brain having formed an image of the object.

A major function of the pons and medulla is to transfer information between the PNS and the midbrain and forebrain. The pons and medulla also help coordinate large-scale body movements, such as running and climbing. Most axons that carry instructions about these movements cross from one side of the CNS to the other in the medulla. As a result, the right side of the brain controls much of the movement of the left side of the body, and vice versa. An additional function of the medulla is the control of several automatic, homeostatic functions, including breathing, heart and blood vessel activity, swallowing, vomiting, and digestion. The pons also participates in some of these activities; for example, it regulates the breathing centers in the medulla.

Biological Clock Regulation

Cycles of sleep and wakefulness are an example of a circadian rhythm, a daily cycle of biological activity. Such cycles, which occur in organisms ranging from bacteria to humans, rely on a **biological clock**, a molecular mechanism that directs periodic gene expression and cellular activity. Although biological clocks are typically synchronized to the cycles of light and dark in the environment, they can maintain a roughly 24-hour cycle even in the absence of environmental cues. For example, humans studied in a constant environment exhibit a sleep/wake cycle of 24.2 hours, with very little variation among individuals.

What normally links an animal's biological clock to environmental cycles of light and dark? In mammals, circadian rhythms are coordinated by a group of neurons in the hypothalamus called the **suprachiasmatic nucleus (SCN)**. (Certain clusters of neurons in the CNS are referred to as "nuclei.") In response to sensory information from the eyes, the SCN acts as a pacemaker, synchronizing the biological clock in cells throughout the body to the natural cycles of day length. In the **Scientific Skills Exercise**, you can interpret data from an experiment and propose additional experiments to test the role of the SCN in hamster circadian rhythms.

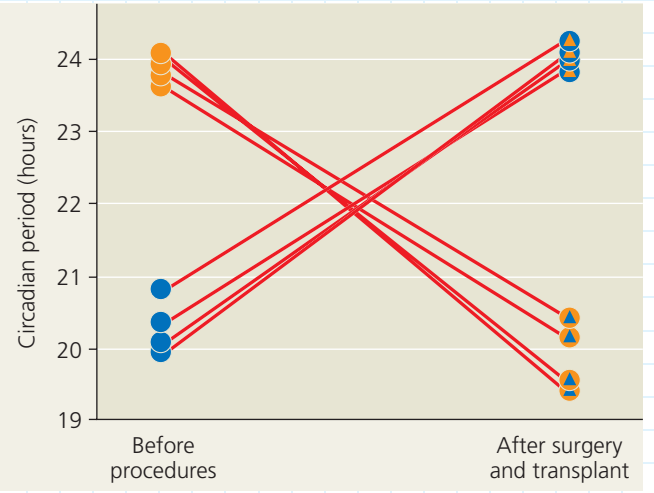
Scientific Skills Exercise

Designing an Experiment Using Genetic Mutants

Does the SCN Control the Circadian Rhythm in Hamsters? By surgically removing the SCN from laboratory mammals, scientists demonstrated that the SCN is required for circadian rhythms. But these studies did not reveal whether circadian rhythms originate in the SCN. To answer this question, researchers performed an SCN transplant experiment on wild-type and mutant hamsters (*Mesocricetus auratus*). Whereas for wild-type hamsters the period between cyclic peaks in activity is 24 hours in the absence of external cues, hamsters homozygous for the τ (tau) mutation have a period lasting only about 20 hours. In this exercise, you will evaluate the design of this experiment and propose additional experiments to gain further insight.

How the Experiment Was Done The researchers surgically removed the SCN from wild-type and τ hamsters. Several weeks later, each of these hamsters received a transplant of an SCN from a hamster of the opposite genotype. The researchers then measured the period length for the transplant recipients.

Data from the Experiment In 80% of the hamsters in which the SCN had been removed, transplanting an SCN from another hamster restored rhythmic activity. For hamsters in which an SCN transplant restored a circadian rhythm, the net effect of the two procedures (SCN removal and replacement) on the circadian cycle is graphed below. Each red line represents the change in the measured period for an individual hamster.

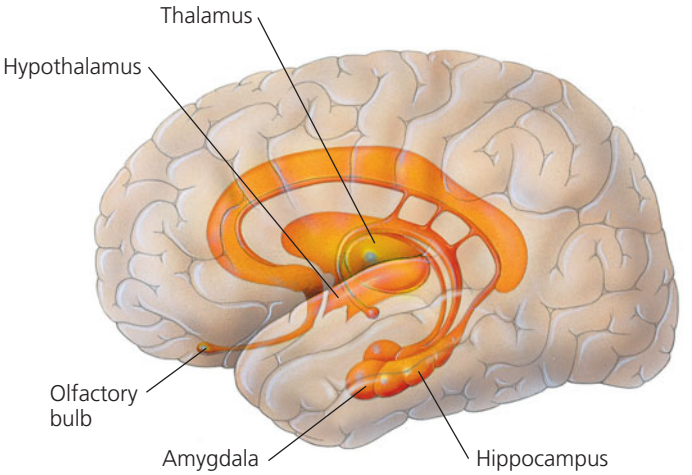


Interpret the Data

1. In a controlled experiment, researchers manipulate one variable at a time. What was the experimental variable in this study? Why did the researchers use more than one hamster for each procedure? What traits of the individual hamsters would likely have been controlled among the treatment groups?
2. For the wild-type hamsters that received τ SCN transplants, what would have been an appropriate control?
3. What general trends does the graph reveal about the period of the circadian rhythm in transplant recipients? Do the trends differ for the wild-type and τ recipients? Based on these data, what can you conclude about the role of the SCN in determining the period length?
4. In 20% of the hamsters, there was no restoration of rhythmic activity following the SCN transplant. What are some possible reasons for this finding? Do you think you can be confident of your conclusion about the role of the SCN based on data from 80% of the hamsters? Explain.
5. Suppose that researchers identified a mutant hamster that lacked rhythmic activity; that is, its circadian cycle had no regular pattern. Propose SCN transplant experiments using such a mutant along with (a) wild-type and (b) τ hamsters. Predict the results of those experiments in light of your conclusion in question 3.

Data from M. R. Ralph et al., Transplanted suprachiasmatic nucleus determines circadian period, *Science* 247:975–978 (1990).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.



▲ **Figure 38.8 The limbic system.**

Emotions

Whereas a single structure in the brain controls the biological clock, generating and experiencing emotions depend on many brain structures, including the amygdala, hippocampus, and parts of the thalamus. As shown in **Figure 38.8**, these structures border the brainstem in mammals and are therefore termed the *limbic system* (from the Latin *limbus*, border).

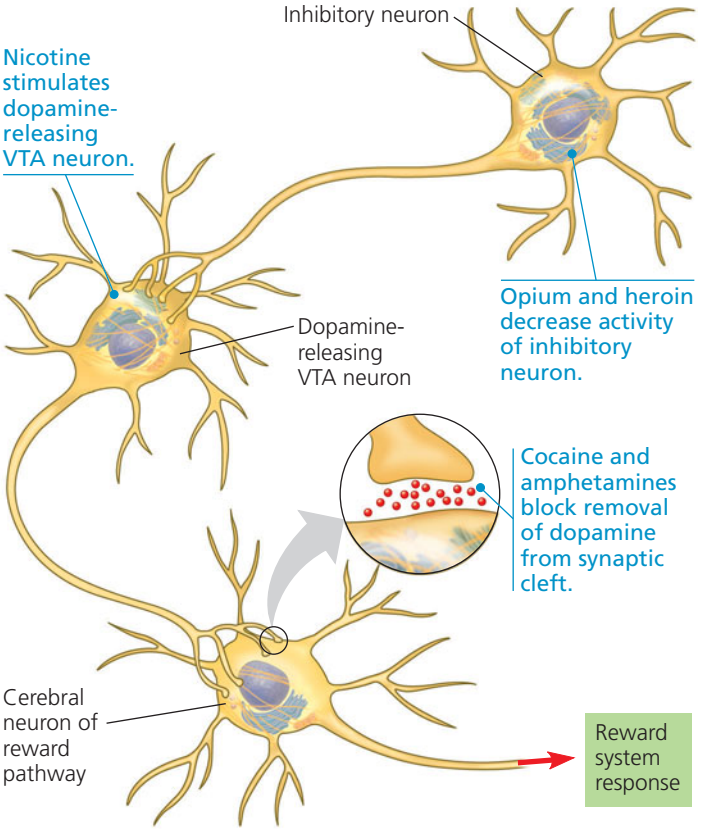
Generating and experiencing emotion often require interactions between different regions of the brain. For example, laughing and crying both involve the limbic system interacting with sensory areas of the forebrain. Similarly, structures in the forebrain attach emotional "feelings" to survival-related functions controlled by the brainstem, including aggression, feeding, and sexuality.

Emotional experiences are sometimes stored as memories that can be recalled by similar circumstances. For example, a situation that causes you to remember a frightening event can trigger a faster heart rate, sweating, and mental state of fear, even if there is currently nothing scary or threatening in your surroundings. The brain structure that is most important for this emotional memory is the amygdala.

The Brain's Reward System and Drug Addiction

Emotions are strongly influenced by a neural circuit in the brain called the reward system. The reward system provides motivation for activities that enhance survival and reproduction, such as eating in response to hunger, drinking when thirsty, and engaging in sexual activity when aroused. Inputs to the reward system are received by neurons in a region near the base of the brain called the *ventral tegmental area (VTA)*. When activated, these neurons release dopamine from their synaptic terminals in specific regions of the cerebrum.

The brain's reward system is dramatically affected by drug addiction, a disorder characterized by compulsive consumption of a drug and loss of control in limiting intake. Addictive drugs, which range from sedatives to stimulants and include



▲ **Figure 38.9 Effects of addictive drugs on the reward system of the mammalian brain.** Addictive drugs alter the transmission of signals in the pathway formed by neurons of the ventral tegmental area (VTA).

MAKE CONNECTIONS *Review depolarization in Concept 37.3. What effect would you expect if you depolarized the neurons in the VTA? Explain.*

alcohol, cocaine, nicotine, and heroin, enhance the activity of the dopamine pathway **(Figure 38.9)**. As addiction develops, there are also long-lasting changes in the reward circuitry. The result is a craving for the drug independent of any pleasure associated with consuming it.

Laboratory animals have proved especially useful in teaching us how the brain's reward system works and how particular drugs affect its function. Rats, for example, will provide themselves with cocaine, heroin, or amphetamine when given a dispensing system linked to a lever in their cage. Furthermore, they exhibit addictive behavior in such circumstances, continuing to self-administer the drug rather than seek food, even to the point of starvation.

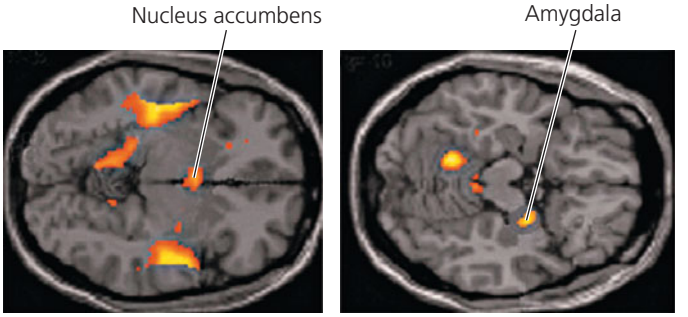
Functional Imaging of the Brain

Functional imaging methods are transforming our understanding of normal and diseased brains. The first widely used technique was positron-emission tomography (PET), in which an injection of radioactive glucose enables a display of metabolic activity. Today, many studies rely on functional magnetic resonance imaging (fMRI). In fMRI, a subject lies with his or her head in

the center of a large, doughnut-shaped magnet. Brain activity in a region is detected by changes in the local oxygen concentration. By scanning the brain while the subject performs a task, such as forming a mental image of a person's face, researchers can correlate particular tasks with activity in specific brain areas.

In one experiment using fMRI, researchers mapped brain activity while subjects listened to music that they described as happy or sad **(Figure 38.10)**. Listening to happy music led to increased activity in the nucleus accumbens, a brain structure important for the perception of pleasure (in fact, the nucleus accumbens is one of the targets of the reward system). In contrast, subjects who heard sad music had increased activity in the amygdala, the focus for emotional memory.

The range of fMRI applications includes monitoring recovery from stroke, mapping abnormalities in migraine headaches, and increasing the effectiveness of brain surgery. This technique has even been used to explore sex-based differences in the CNS, demonstrating, for instance, that cerebral blood flow is higher on average in women than in men.



▲ Figure 38.10 Functional brain imaging in the working brain. Functional magnetic resonance imaging (fMRI) was used to reveal brain activity associated with happy or sad music.

WHAT IF? *In the experiment that produced the images shown above, some regions of the brain were active under all conditions. What function might such regions carry out?*

CONCEPT CHECK 38.2

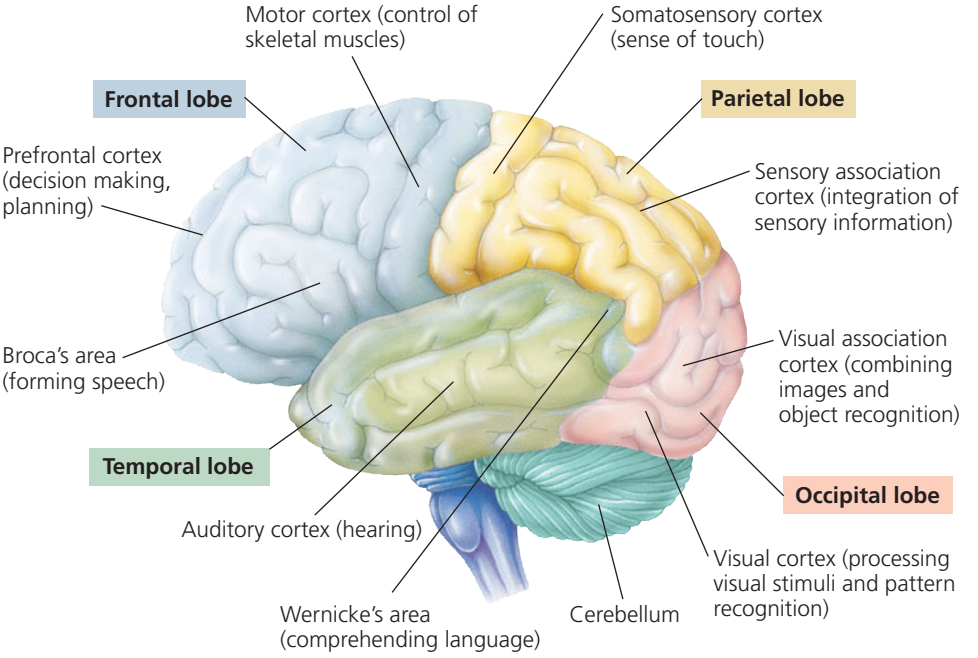
1. When you wave your right hand, what part of your brain initiates the action?
2. People who are inebriated have difficulty touching their nose with their eyes closed. Based on this observation, name one of the brain regions impaired by alcohol.
3. **WHAT IF?** Suppose you examine two groups of individuals with CNS damage. In one group, the damage has resulted in a coma (a prolonged state of unconsciousness). In the other group, it has caused total paralysis (a loss of skeletal muscle function throughout the body). Relative to the position of the midbrain and pons, where is the likely site of damage in each group? Explain.

For suggested answers, see Appendix A.

CONCEPT 38.3

The cerebral cortex controls voluntary movement and cognitive functions

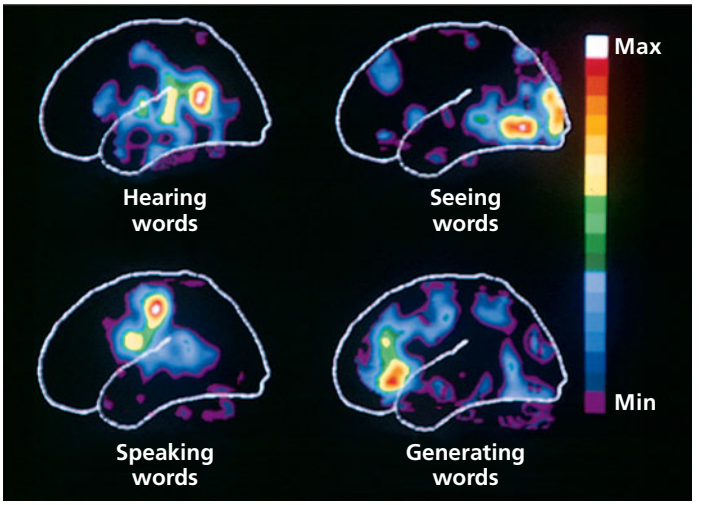
We turn now to the cerebrum, the part of the brain essential for language, cognition, memory, consciousness, and awareness of our surroundings. For the most part, cognitive functions reside in the cerebral cortex, the outer layer of the cerebrum. Within the cortex, sensory areas receive and process sensory information, association areas integrate the information, and motor areas transmit instructions to other parts of the body. In discussing the cortex, neurobiologists often use four regions, or *lobes*, as physical landmarks. As shown in **Figure 38.11**, each side of the cortex has a frontal, temporal, occipital, and parietal lobe (each is named for a nearby bone of the skull).



◀ Figure 38.11 The human cerebral cortex. Each side of the cerebral cortex is divided into four lobes, and each lobe has specialized functions, some of which are listed here. Some areas on the left side of the brain (shown here) have different functions from those on the right side (not shown).

Language and Speech

The mapping of cognitive functions within the cortex began in the 1800s when physicians studied the effects of damage to particular regions of the cortex by injuries, strokes, or tumors. The French physician Pierre Broca conducted postmortem (after



▲ Figure 38.12 Mapping language areas in the cerebral cortex. These PET images show regions with different activity levels in one person's brain during four activities related to speech. Hearing words activates Wernicke's area, speaking words activates Broca's area, seeing words activates the visual cortex, and generating words (without reading them) activates parts of the frontal lobe.

death) examinations of patients who had been able to understand language but unable to speak. He discovered that many had defects in a small region of the left frontal lobe, now known as *Broca's area*. The German physician Karl Wernicke found that damage to a posterior portion of the left temporal lobe, now called *Wernicke's area*, abolished the ability to comprehend speech but not the ability to speak. More recently, PET studies have revealed activity in Broca's area during speech generation and Wernicke's area when speech is heard **(Figure 38.12)**.

Lateralization of Cortical Function

Both Broca's area and Wernicke's area reside in the left cortical hemisphere, reflecting a greater role with regard to language for the left side of the cerebrum than for the right side. The left hemisphere is also more adept at math and logical operations. In contrast, the right hemisphere appears to be dominant in the recognition of faces and patterns, spatial relations, and nonverbal thinking. The establishment of these differences in hemisphere function is called **lateralization**.

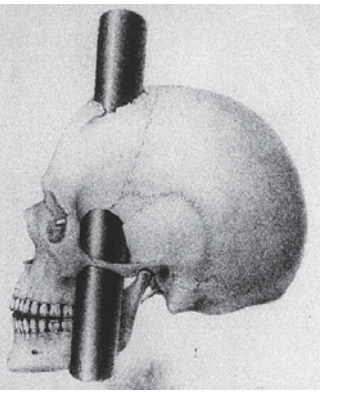
The two cortical hemispheres normally exchange information through the fibers of the corpus callosum (see Figure 38.6). Severing this connection (a treatment of last resort for the most extreme forms of epilepsy, a seizure disorder) results in a "split-brain" effect. In such patients, the two hemispheres function independently. The patients cannot read even a familiar word that appears in their left field of vision: The sensory information that travels from the left field of vision to the right hemisphere cannot reach the language centers in the left hemisphere.

Information Processing

As we will discuss later in this chapter, some sensory input to the cerebral cortex comes from groups of receptors clustered in dedicated sensory organs, such as the eyes and nose. Other sensory input originates in individual receptors in the hands, scalp, and elsewhere in the body. These somatic sensory, or *somatosensory*, receptors (from the Greek *soma*, body) provide information about touch, pain, pressure, temperature, and the position of muscles and limbs.

Most sensory information coming into the cortex is directed via the thalamus to primary sensory areas within the brain lobes. Information received at the primary sensory areas is passed along to nearby association areas, which process particular features in the sensory input. In the occipital lobe, for instance, some groups of neurons in the primary visual area are specifically sensitive to rays of light oriented in a particular direction. Once processed, sensory information passes to the prefrontal cortex, which helps plan actions. The cerebral cortex may then generate motor commands that cause particular behaviors, such as waving a hand.

Frontal Lobe Function



In 1848, a horrific accident pointed to the role of the prefrontal cortex in temperament and decision making. Phineas Gage was the foreman of a railroad construction crew when an explosion drove an iron rod through his head. The rod, which was more than 3 cm in diameter at one end, entered his skull just below his left eye and exited through the top of his head, damaging large portions of his frontal lobe. Gage recovered, but his personality changed dramatically. He became emotionally detached, impatient, and erratic in his behavior.

Support for the hypothesis that Gage's brain injury and his personality change inform us about frontal lobe function comes from the fact that some frontal lobe tumors cause similar symptoms. Intellect and memory seem intact, but decision making is flawed and emotional responses are diminished. In the 20th century, the same problems resulted from frontal lobotomy, a surgical procedure that severs the connection between the prefrontal cortex and the limbic system. Together, these observations provide evidence that the frontal lobes have a substantial influence on what are called "executive functions."

Once a common treatment for severe behavioral disorders, frontal lobotomy is no longer in use. Instead, behavioral disorders are typically treated with medications.

Evolution of Cognition in Vertebrates

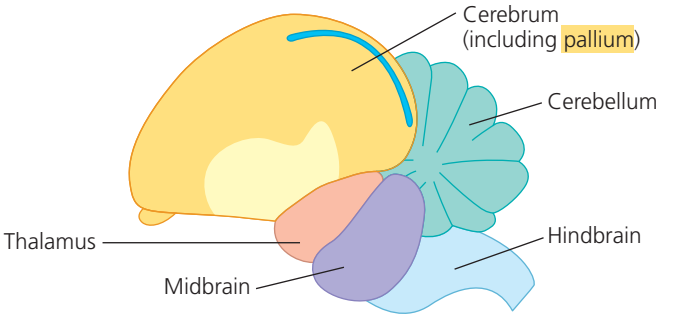
EVOLUTION In nearly all vertebrates, the brain has the same number of divisions. Given this uniform overall structure, what changed during evolution that provided certain species with a capacity for advanced *cognition*, the perception and reasoning that constitute knowledge? One hypothesis is that higher order

reasoning required evolution of a highly convoluted cerebral cortex, such as is found in humans, other primates, and cetaceans (whales, dolphins, and porpoises). Indeed, in humans, the cerebral cortex accounts for about 80% of total brain mass.

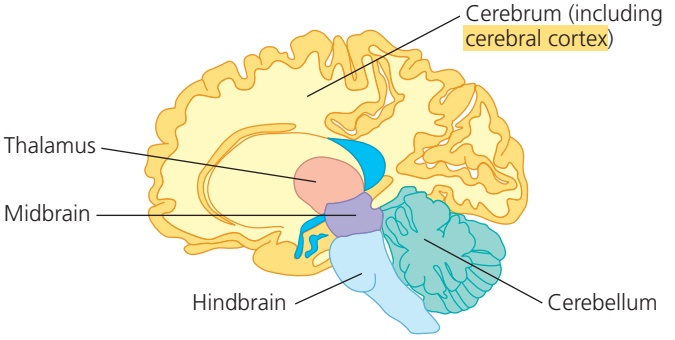
Birds, on the other hand, lack a convoluted cerebral cortex and were long thought to have much lower intellectual capacity than primates and cetaceans. Experiments in recent years, however, have refuted this idea. Western scrub jays (*Aphelocoma californica*) can remember the relative period of time that has passed after they have stored and hid specific food items. Furthermore, African gray parrots (*Psittacus erithacus*) understand numerical and abstract concepts, such as "same," "different," and "none."

The anatomical basis for sophisticated information processing in birds appears to be a nuclear (clustered) organization of neurons within the *pallium*, the top or outer portion of the brain **(Figure 38.13)**. This arrangement is different from that seen in the human cerebral cortex, where six parallel layers of neurons are arranged tangential to the brain surface. Thus, evolution has resulted in two different types of outer brain organization in vertebrates, each of which supports complex and flexible brain function.

How did the bird pallium and human cerebral cortex arise during evolution? The current consensus is that the common ancestor of birds and mammals had a pallium in which neurons were organized into nuclei, as is still found in birds. Early in mammalian evolution, this nuclear organization was transformed into a layered one. However, connectivity was maintained such that, for example, the thalamus relays sensory input relating to sights, sounds, and touch to the pallium in birds and the cerebral cortex in mammals.



(a) Songbird brain



(b) Human brain

▲ Figure 38.13 Comparison of regions for higher cognition in avian and human brains. Although structurally different, the pallium of a songbird brain (top cross section) and the cerebral cortex of the human brain (bottom cross section) play similar roles in higher cognitive activities and make many similar connections with other brain structures.

Sophisticated information processing depends not only on the overall organization of a brain but also on small-scale changes that enable learning and encode memory. We'll turn to these changes in the context of humans in the next section.

Neural Plasticity

Although the overall organization of the CNS is established during embryonic development, the connections between neurons are subject to modification. This capacity for the nervous system to be remodeled, especially in response to its own activity, is called **neural plasticity**.

Much of the reshaping of the nervous system occurs at synapses. When the activity of a synapse coincides with that of other synapses, changes may occur that reinforce that synaptic connection. Conversely, when the activity of a synapse fails to correlate in this way with that of other synapses, the synaptic connection sometimes becomes weaker. In this way, synapses belonging to circuits that link information in useful ways are maintained, whereas those that convey bits of information lacking any context may be lost.

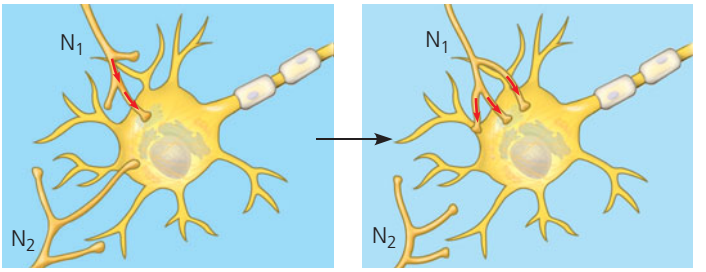
Figure 38.14a illustrates how activity-dependent events can result in either the addition or loss of a synapse. If you think of signals in the nervous system as traffic on a highway, such changes are comparable to adding or removing an entrance ramp. The net effect is to increase signaling between particular pairs of neurons and decrease signaling between other pairs. As shown in **Figure 38.14b**, changes can also strengthen or weaken signaling at a synapse. In our traffic analogy, this would be equivalent to widening or narrowing an entrance ramp.

Research indicates that *autism*, a developmental disorder that first appears early in childhood, involves a disruption of activity-dependent remodeling at synapses. Children with autism display impaired communication and social interaction, as well as stereotyped and repetitive behaviors.

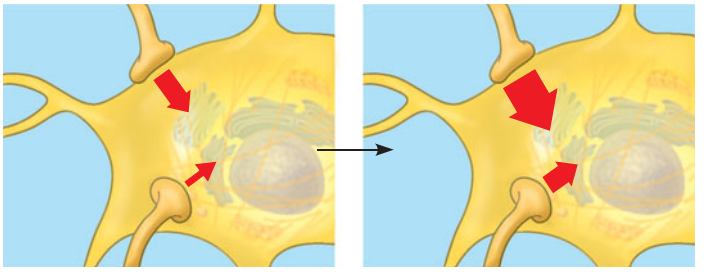
Memory and Learning

Neural plasticity is essential to the formation of memories. We are constantly checking what is happening against what just happened. We hold information for a time in **short-term memory** and then release it if it becomes irrelevant. If we wish to retain knowledge of a name, phone number, or other fact, the mechanisms of **long-term memory** are activated. If we later need to recall the name or number, we fetch it from long-term memory and return it to short-term memory.

Both short-term and long-term memory involve the storage of information in the cerebral cortex. In short-term memory, this information is accessed via temporary links formed in the hippocampus. When information is transferred to long-term memory, the links in the hippocampus are replaced by connections within



(a) Connections between neurons are strengthened or weakened in response to activity. High-level activity at the synapse of the postsynaptic neuron with presynaptic neuron N_1 leads to recruitment of additional axon terminals from that neuron. Lack of activity at the synapse with presynaptic neuron N_2 leads to loss of functional connections with that neuron.



(b) If two synapses on the same postsynaptic cell are often active at the same time, the strength of the postsynaptic response may increase at both synapses.

▲ Figure 38.14 Neural plasticity. Synaptic connections can change over time, depending on the activity level at the synapse.

the cerebral cortex itself. Some of this memory consolidation is thought to occur during sleep. Furthermore, the reactivation of the hippocampus that is required for memory consolidation likely forms the basis for at least some of our dreams.

What evolutionary advantage might be offered by organizing short-term and long-term memories differently? One hypothesis is that the delay in forming connections in the cerebral cortex allows long-term memories to be integrated gradually into the existing store of knowledge and experience, providing a basis for more meaningful associations. Consistent with this hypothesis, the transfer of information from short-term to long-term memory is enhanced by the association of new data with data previously learned and stored in long-term memory. For example, it's easier to learn a new card game if you already have "card sense" from playing other card games.

CONCEPT CHECK 38.3

1. Outline two mechanisms by which information flow between two neurons in adults can increase.
2. How do the functions of Broca's area and Wernicke's area each relate to the activity of the surrounding cortex?
3. **WHAT IF?** If a woman with a severed corpus callosum viewed a photograph of a familiar face, first in her left field of vision and then in her right field, why would she find it difficult to put a name to the face?

For suggested answers, see Appendix A.

CONCEPT 38.4

Sensory receptors transduce stimulus energy and transmit signals to the central nervous system

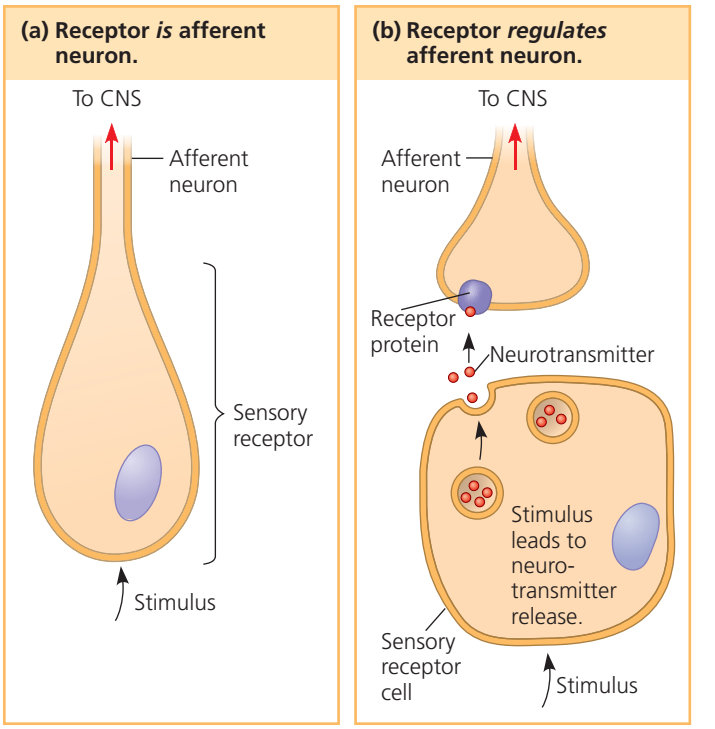
Much brain activity begins with sensory input. A stimulus is detected by a sensory receptor, and the resulting change in membrane potential in turn alters the transmission of action potentials to the CNS. When this information is decoded within the CNS, a sensation results. In this section, we'll examine these steps in more detail.

Sensory Reception and Transduction

A sensory pathway begins with **sensory reception**, the detection of a stimulus by sensory cells. Some sensory cells are themselves specialized neurons, whereas others are non-neuronal cells that regulate neurons **(Figure 38.15)**. Some exist singly; others are collected in sensory organs, such as an eye.

The term **sensory receptor** is used to describe a sensory cell or organ, as well as the subcellular structure that detects stimuli. Many sensory receptors detect stimuli from outside the body, such as heat or chemicals, but there are also receptors for stimuli from within the body, such as blood pressure. Activating a sensory receptor does not necessarily require a large amount of stimulus energy. Most light receptors, for example, can detect a single quantum (photon) of light.

▼ Figure 38.15 Neuronal and non-neuronal sensory receptors.



Although animals use a range of sensory receptors to detect widely varying stimuli, the effect in all cases is to open or close ion channels. Thus, for example, ion channels either open or close when a substance outside the cell binds to a chemical receptor in the plasma membrane. The resulting flow of ions across the membrane changes the membrane potential.

The conversion of a stimulus to a change in the membrane potential of a sensory receptor is called **sensory transduction**, and the change in membrane potential is called a **receptor potential**. Receptor potentials are graded; their magnitude varies with the strength of the stimulus.

Transmission

Sensory information is transmitted as nerve impulses, or action potentials. For many sensory receptors, transducing stimulus energy into a receptor potential initiates action potentials that travel to the CNS.

Neurons that act directly as sensory receptors produce action potentials and have an axon that extends into the CNS (see Figure 38.15). Non-neuronal sensory receptor cells form chemical synapses with sensory (afferent) neurons and typically respond to stimuli by increasing the rate at which the afferent neurons produce action potentials. (One exception is in the vertebrate visual system, discussed in Concept 38.6.)

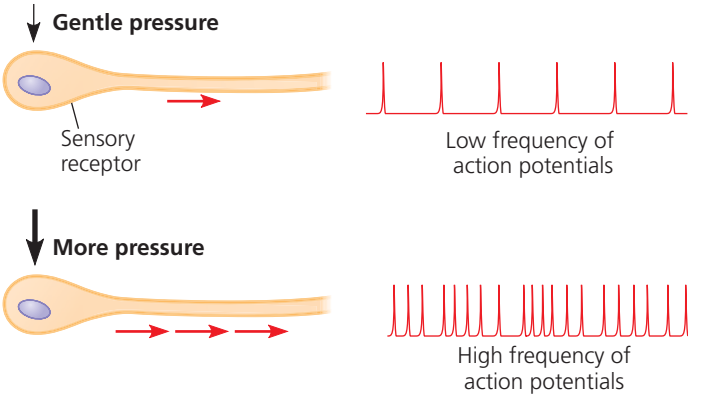
The size of a receptor potential increases with stimulus intensity. If the receptor is a sensory neuron, a larger receptor potential results in more frequent action potentials **(Figure 38.16)**. If the receptor is not a sensory neuron, a larger receptor potential usually causes more neurotransmitter to be released.

Many sensory neurons spontaneously generate action potentials at a low rate. In these neurons, a stimulus does not switch production of action potentials on or off, but it does change *how often* an action potential is produced. In this manner, such neurons convey information about changes in stimulus intensity.

Perception

When action potentials reach the brain via sensory neurons, circuits of neurons process this input, generating the brain's **perception** of the stimuli. Perceptions—such as colors, smells, and sounds—are constructions formed in the brain and do not exist outside it. So, if a tree falls and no animal is present to hear it, is there a sound? The falling tree certainly produces pressure waves in the air, but there is no sound unless an animal senses the waves and its brain perceives them.

An action potential triggered by light striking the eye has the same properties as an action potential triggered by air vibrating in the ear. How, then, do we distinguish sights, sounds, and other stimuli? The answer lies in the connections that link sensory receptors to the brain. Action potentials from sensory receptors travel along neurons that are dedicated to a particular stimulus; these dedicated neurons form synapses with particular neurons in the brain or spinal cord. As a result, the brain distinguishes stimuli such as sight or sound solely by the path along which the action potentials have arrived.



▲ Figure 38.16 Coding of stimulus intensity by a single sensory receptor.

Amplification and Adaptation

The transduction of stimuli by sensory receptors may be modified by amplification and adaptation. **Amplification** is the strengthening of a sensory signal during transduction. The effect can be considerable: For example, an action potential conducted from the eye to the human brain has about 100,000 times as much energy as the few photons of light that triggered it.

Amplification that occurs in sensory receptor cells often requires signal transduction pathways involving second messengers. Because these pathways include enzyme-catalyzed reactions, they amplify signal strength through the formation of many product molecules by a single enzyme molecule. Amplification may also take place in accessory structures of a complex sense organ, as when the pressure associated with sound waves is enhanced by a factor of more than 20 before reaching receptors in the innermost part of the ear.

Upon continued stimulation, many receptors undergo a decrease in responsiveness termed **sensory adaptation** (not to be confused with the evolutionary term *adaptation*). Without sensory adaptation, you would be constantly aware of feeling every beat of your heart and every bit of clothing on your body. Adaptation also enables you to see, hear, and smell changes in the environment that vary widely in stimulus intensity.

Types of Sensory Receptors

We commonly classify sensory receptors based on the kind of stimuli they transduce: mechanoreceptors, electromagnetic receptors, thermoreceptors, pain receptors, and chemoreceptors.

Mechanoreceptors

Mechanoreceptors respond to forms of mechanical energy such as pressure, touch, stretch, motion, and sound. Mechanoreceptors typically consist of ion channels that are linked to structures that extend outside the cell, such as "hairs" (cilia), as well as internal cell structures, such as the cytoskeleton. Bending or stretching of the external structure generates tension that alters the permeability of the ion channels. This change in

ion permeability alters the membrane potential, resulting in a depolarization or hyperpolarization.

Some animals use mechanoreceptors to literally get a feel for their environment. For example, cats as well as many rodents have sensitive mechanoreceptors at the base of their whiskers. Because deflection of different whiskers triggers action potentials that reach different cells in the brain, an animal's whiskers provide detailed information about nearby objects.

Electromagnetic Receptors

Electromagnetic receptors detect various forms of electromagnetic energy, such as light, electricity, and magnetism. For example, snakes have very sensitive receptors that detect the infrared radiation emitted by warm prey **(Figure 38.17a)**. Similarly, the platypus has electroreceptors on its bill that are thought to detect the electric field generated by the muscles of crustaceans and other prey. In a few cases, the animal detecting the stimulus is also its source: Some fishes generate electric currents and then use electroreceptors to locate prey that disturb those currents.

Many animals appear to use Earth's magnetic field lines to orient themselves as they migrate **(Figure 38.17b)**, and the iron-containing mineral magnetite may be responsible for this ability. Magnetite is found in many vertebrates (including salmon, pigeons, sea turtles, and humans), bees, and some molluscs.

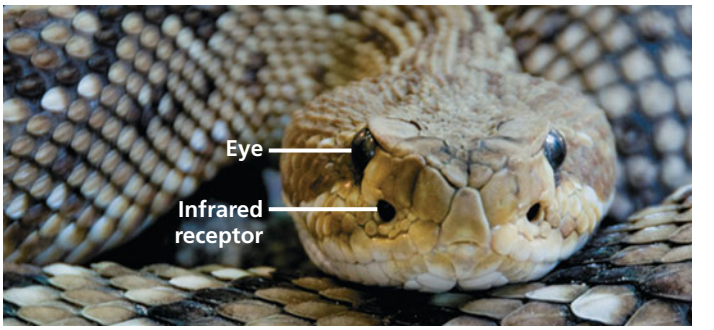
Thermoreceptors

Thermoreceptors detect heat and cold. In humans, thermoreceptors located in the skin and in the anterior hypothalamus send information to the body's thermostat in the posterior hypothalamus. Our understanding of thermoreception has increased recently, thanks to scientists with an appreciation for fiery foods. It turns out that exposing sensory neurons to capsaicin—the molecule that makes jalapeno peppers taste "hot"—triggers calcium ion influx. When scientists identified the receptor protein that binds capsaicin, they made a fascinating discovery: The receptor opens a calcium channel in response not only to capsaicin, but also to high temperatures (42°C or higher). In essence, spicy foods taste "hot" because they activate the same receptors as hot soup and coffee. Similarly, the receptor for temperatures below 28°C is activated by menthol, a plant product that we perceive to have a "cool" flavor.

Pain Receptors

Extreme pressure or temperature, as well as certain chemicals, can damage animal tissues. To detect stimuli that reflect such noxious (or harmful) conditions, animals rely on **nociceptors** (from the Latin *nocere*, to hurt), also called **pain receptors**. By triggering defensive reactions, such as withdrawal from danger, the perception of pain serves an important function.

In humans, certain naked dendrites act as nociceptors by detecting noxious thermal, mechanical, or chemical stimuli. The capsaicin receptor is thus a nociceptor as well as a thermoreceptor. Although nociceptor density is highest in skin, some pain receptors are associated with other organs.



(a) This rattlesnake and other pit vipers have a pair of infrared receptors, one anterior to and just below each eye. These organs are sensitive enough to detect the infrared radiation emitted by a warm mouse a meter away. The snake moves its head from side to side until the radiation is detected equally by the two receptors, indicating that the mouse is straight ahead.

(b) Some migrating animals, such as these beluga whales, apparently sense Earth's magnetic field and use the information, along with other cues, for orientation.

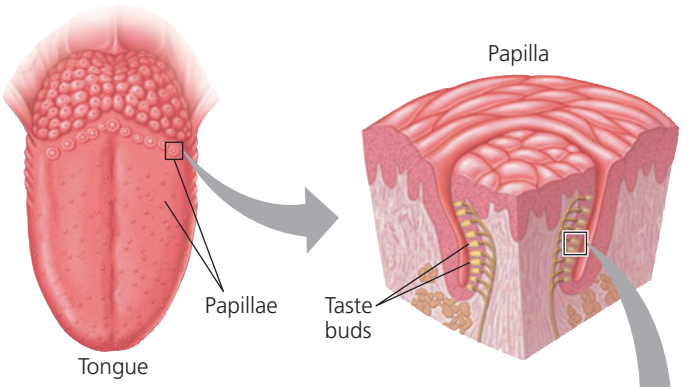
▲ **Figure 38.17 Specialized electromagnetic receptors.**

Chemicals produced in an animal's body sometimes enhance the perception of pain. For example, damaged tissues produce prostaglandins, which act as local regulators of inflammation. Prostaglandins worsen pain by increasing nociceptor sensitivity to noxious stimuli; aspirin and ibuprofen reduce pain by inhibiting the synthesis of prostaglandins.

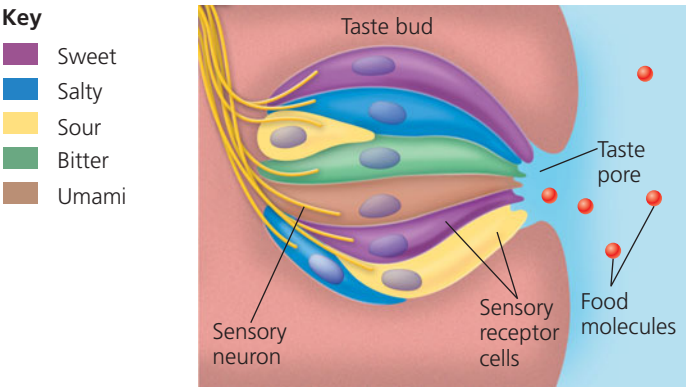
Chemoreceptors

Chemoreceptors can be general, transmitting information about total solute concentration—or specific, responding to individual kinds of molecules. Osmoreceptors in the mammalian brain, for example, detect changes in the solute concentration of the blood and stimulate thirst when osmolarity increases. Most animals also have receptors for specific molecules, including glucose, oxygen, carbon dioxide, and amino acids.

The perceptions of **olfaction** (smell) and **gustation** (taste) both depend on chemoreceptors. In the case of terrestrial animals, smell is the detection of **odorants** that are carried through the air, and taste is the detection of chemicals called **tastants** that are present in a solution. The insect repellent DEET (*N,N*-diethyl-meta-toluamide) works by blocking the chemoreceptor in mosquitoes that detects an odorant produced by humans. Humans can distinguish thousands of different odors, each caused by a structurally distinct odorant. This level of sensory discrimination requires many different odorant receptors. In 2004, Richard Axel and Linda Buck shared a



(a) Small raised structures called papillae cover the tongue surface. The enlarged cross section shows the side walls of a papilla lined with taste buds.



(b) Taste buds in all regions of the tongue contain sensory receptor cells specific for each of the five taste types.

▲ Figure 38.18 Human taste receptors.

Nobel Prize for their discovery of a family of more than 1,000 odorant receptor genes—about 3% of all human genes.

With regard to tastants, humans (and other mammals) recognize just five types: sweet, sour, salty, bitter, and umami. Umami (Japanese for "delicious") is elicited by the amino acid glutamate. Often used as a flavor enhancer, monosodium glutamate (MSG) occurs naturally in foods such as meat and aged cheese, imparting a quality described as savory.

For decades, many researchers assumed that a taste cell could have more than one type of receptor. However, recent experiments have shown that a taste cell in fact has a single receptor type, programming the cell to detect only one of the five tastes **(Figure 38.18)**. Taste receptor cells are organized into **taste buds**, most of which are found in projections called papillae. In contrast to the common misconception, any region of the tongue with taste buds can detect any of the five types of taste.

CONCEPT CHECK 38.4

1. Which one of the five categories of sensory receptors is primarily dedicated to external stimuli?
2. Why can eating "hot" peppers cause a person to sweat?
3. **WHAT IF?** If you stimulated a sensory neuron of an animal electrically, how would the animal perceive that stimulation?

For suggested answers, see Appendix A.

CONCEPT 38.5

The mechanoreceptors responsible for hearing and equilibrium detect moving fluid or settling particles

Hearing and the perception of body equilibrium, or balance, are related in most animals. For both senses, mechanoreceptor cells produce receptor potentials when settling particles or moving fluid causes deflection of cell-surface structures.

Sensing of Gravity and Sound in Invertebrates

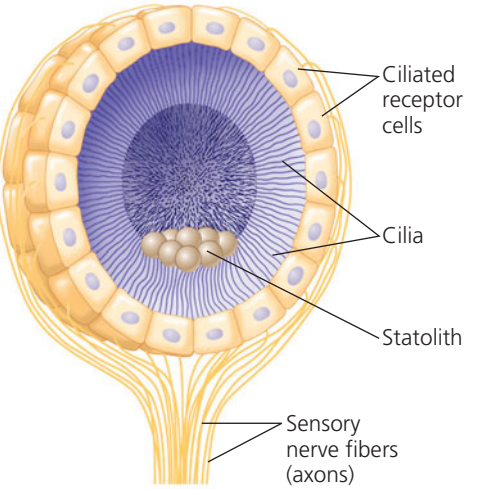
To sense gravity and maintain equilibrium, most invertebrates rely on mechanoreceptors located in organs called **statocysts (Figure 38.19)**. In a typical statocyst, ciliated receptor cells line a chamber that contains one or more *statoliths*, which are grains of sand or other dense granules. When statoliths settle, they stimulate mechanoreceptors at the low point in the chamber. In experiments in which statoliths were replaced with metal shavings, researchers "tricked" crayfish into swimming upside down by using magnets to pull the shavings to the upper end of the statocysts located at the base of their antennae.

Many (perhaps most) insects have body hairs that vibrate in response to sound waves. Hairs of different stiffnesses and lengths vibrate at different frequencies. Many insects also detect sound by means of vibration-sensitive organs, which consist in some species of a tympanic membrane (eardrum) stretched over an internal air chamber. For cockroaches, these organs can provide enough warning for the insect to avoid being crushed by a descending human foot.

Hearing and Equilibrium in Mammals

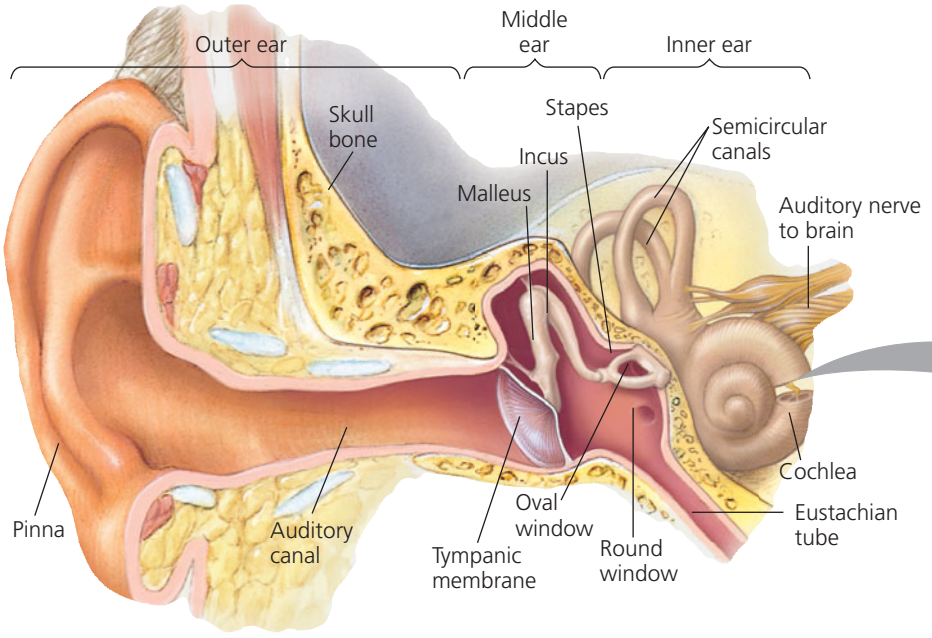
In mammals, as in most other terrestrial vertebrates, the sensory organs for hearing and equilibrium are closely associated. **Figure 38.20** explores the structure and function of these organs in the human ear.

▶ Figure 38.19 The statocyst of an invertebrate. The settling of granules called statoliths to the low point in the chamber bends cilia on receptor cells in that location, providing the brain with information about the orientation of the body with respect to gravity.



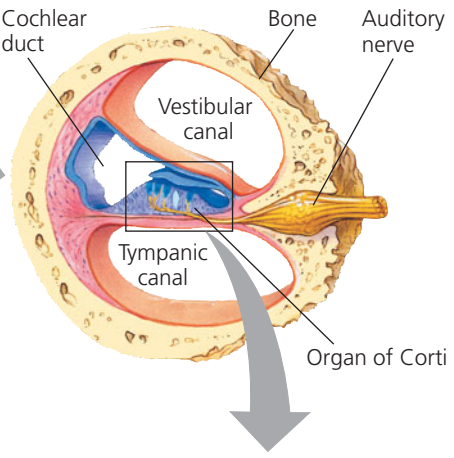
1 Overview of Ear Structure

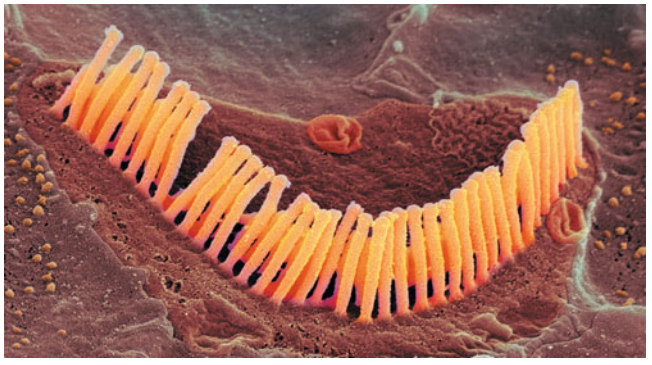
The **outer ear** consists of the external pinna and the auditory canal, which collect sound waves and channel them to the **tympanic membrane** (eardrum), which separates the outer ear from the middle ear. In the **middle ear**, three small bones—the malleus (hammer), incus (anvil), and stapes (stirrup)—transmit vibrations to the **oval window**, which is a membrane beneath the stapes. The middle ear also opens into the **Eustachian tube**, which connects to the pharynx and equalizes pressure between the middle ear and the atmosphere. The **inner ear** consists of fluid-filled chambers, including the **semicircular canals**, which function in equilibrium, and the coiled **cochlea** (from the Latin meaning "snail"), a bony chamber that is involved in hearing.



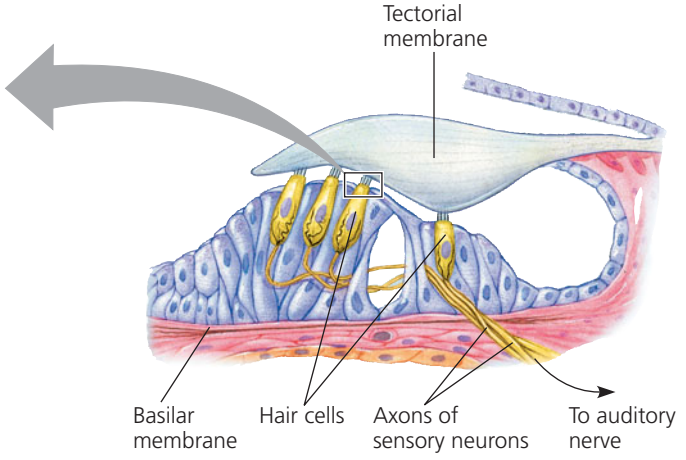
2 The Cochlea

The cochlea has two large canals—an upper vestibular canal and a lower tympanic canal—separated by a smaller cochlear duct. Both canals are filled with fluid.





▲ Bundled hairs projecting from a single mammalian hair cell (SEM). Two shorter rows of hairs lie behind the tall hairs in the foreground.



4 Hair Cell

Projecting from each hair cell is a bundle of rod-shaped "hairs," each containing a core of actin filaments. Vibration of the basilar membrane in response to sound raises and lowers the hair cells, bending the hairs against the surrounding fluid and the tectorial membrane. When the hairs within the bundle are displaced, mechanoreceptors are activated, changing the membrane potential of the hair cell.

3 The Organ of Corti

The floor of the cochlear duct, the basilar membrane, bears the **organ of Corti**, which contains the mechanoreceptors of the ear, hair cells with hairs projecting into the cochlear duct. Many of the hairs are attached to the tectorial membrane, which hangs over the organ of Corti like an awning. Sound waves make the basilar membrane vibrate, which results in bending of the hairs and depolarization of the hair cells.

Hearing

Vibrating objects, such as a plucked guitar string or the vocal cords of a classmate, create pressure waves in the surrounding air. In hearing, the ear transduces this mechanical stimulus (pressure waves) into nerve impulses that the brain perceives as sound. To hear music, speech, or other sounds in our environment, we rely on **hair cells**, sensory receptors with hair-like projections on the cell surface that detect motion. Before the vibration waves reach the hair cells, however, they are amplified and transformed by several accessory structures.

The first steps in hearing involve structures in the ear that convert the vibrations of moving air to pressure waves in fluid. Upon reaching the outer ear, moving air causes the tympanic membrane to vibrate. The three bones of the middle ear transmit the vibrations to the oval window, a membrane on the cochlea's surface. When one of those bones, the stapes, vibrates against the oval window, it creates pressure waves in the fluid (called perilymph) inside the cochlea.

Upon entering the vestibular canal, the pressure waves push down on the cochlear duct and basilar membrane. In response, the basilar membrane and attached hair cells vibrate up and down. The hairs projecting from the moving hair cells are deflected by the fixed tectorial membrane, which lies above (see Figure 38.20). With each vibration, the hairs bend first in one direction and then the other, causing ion channels in the hair cells to open or close **(Figure 38.21)**. The result is a change in auditory nerve sensations that the brain interprets as sound.

Once pressure waves travel through the vestibular canal, they pass around the apex (tip) of the cochlea and dissipate as they strike the **round window**. This damping of sound waves resets the apparatus for the next round of vibrations that arrives.

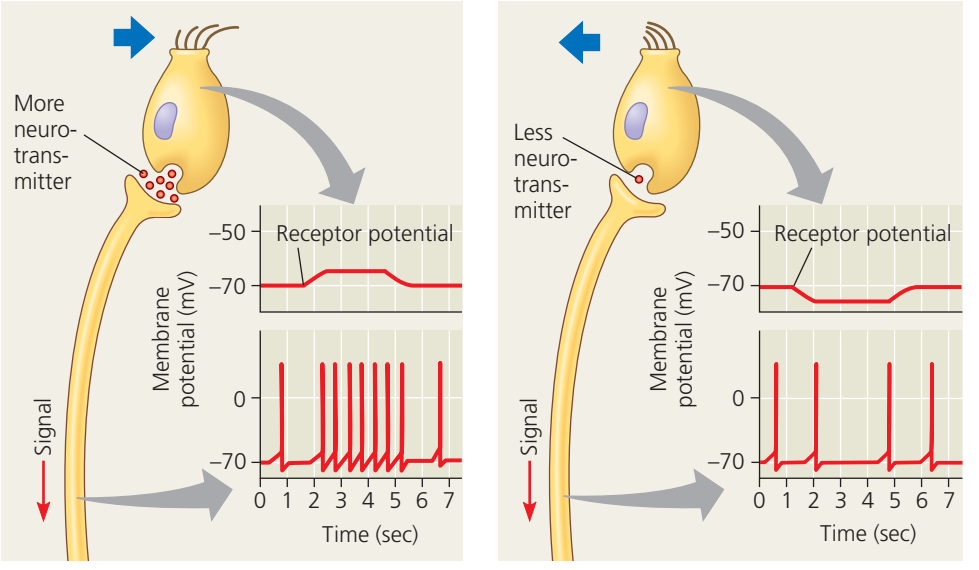
The ear conveys information about two important sound variables: volume and pitch. *Volume* (loudness) is determined by the amplitude, or height, of the sound wave. A large-amplitude wave causes more vigorous vibration of the basilar membrane, greater bending of the hairs on hair cells, and more action potentials in the sensory neurons. *Pitch* is a function of a sound wave's frequency, the number of vibrations per unit time. High-frequency waves produce high-pitched sounds, whereas low-frequency waves produce low-pitched sounds.

The cochlea can distinguish pitch because the basilar membrane is not uniform along its length: It is relatively narrow and stiff at the base of the cochlea near the oval window and wider and more flexible at the apex. Each region of the basilar membrane is tuned to a particular vibration frequency. Signals triggered by sounds are relayed to specific parts of the cerebral cortex according to the region of the basilar membrane in which the signals originated. Consequently, when a particular site in our cortex is stimulated, we perceive sound of a particular pitch.

Equilibrium

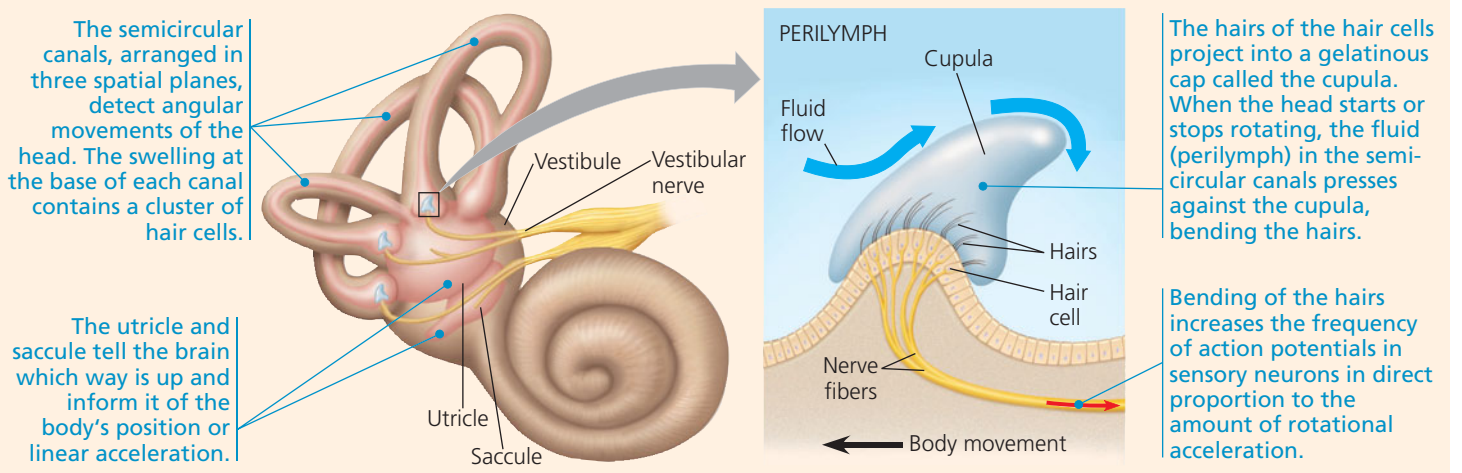
Several organs in the inner ear of humans and most other mammals detect body movement, position, and balance. Situated in a vestibule behind the oval window, the chambers called the **utricle** and **saccule** allow us to perceive position with respect to gravity or linear movement **(Figure 38.22)**. Each chamber contains hair cells that project into a gelatinous material. Embedded in this gel are small calcium carbonate particles called otoliths ("ear stones"). When you tilt your head, the otoliths press on the hairs protruding into the gel. The hair cell receptors transform this deflection into a change in the output of sensory neurons, signaling the brain that your head is at an angle. The otoliths are also responsible for your ability to perceive acceleration, as, for example, when a stationary car in which you are sitting pulls forward.

Three fluid-filled semicircular canals connected to the utricle detect turning of the head and other angular acceleration. Because the three canals are arranged in the three spatial planes, they detect angular motion of the head in any direction. If you spin in place, the fluid in each canal eventually comes to equilibrium and remains in that state until you stop. At that point, the moving fluid encounters a stationary cupula (see Figure 38.22), triggering the false sensation of angular motion that we call dizziness.



(a) Bending of hairs in one direction **(b) Bending of hairs in other direction**

▲ Figure 38.21 Sensory reception by hair cells. Bending of a hair cell bundle in one direction depolarizes the hair cell. This increases neurotransmitter release, resulting in more frequent action potentials in the sensory neuron. Bending in the other direction has the opposite effect.



▲ **Figure 38.22 Organs of equilibrium in the inner ear.**

CONCEPT CHECK 38.5

1. How are otoliths adaptive for burrowing mammals, such as the star-nosed mole?
2. **WHAT IF?** Suppose a series of pressure waves in your cochlea caused a vibration of the basilar membrane that moved gradually from the apex toward the base. How would your brain interpret this stimulus?
3. **WHAT IF?** If the stapes became fused to the other middle ear bones or to the oval window, how would this condition affect hearing? Explain.

For suggested answers, see Appendix A.

Light-Detecting Organs

Most invertebrates have some kind of light-detecting organ. One of the simplest is that of planarians **(Figure 38.23)**. A pair of ocelli (singular, *ocellus*), which are sometimes called eyespots, are located in the head region. Photoreceptors in each ocellus receive light only through an opening where there are no pigmented cells. By comparing the rates of action potentials coming from the two ocelli, the planarian is able to move away from a light source until it reaches a shaded location, where a rock or other object is likely to hide it from predators.

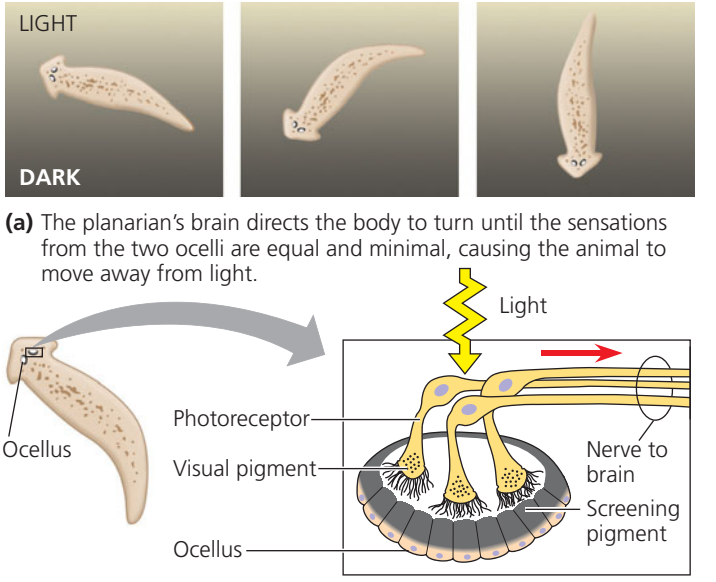
CONCEPT 38.6

The diverse visual receptors of animals depend on light-absorbing pigments

The ability to detect light has a central role in the interaction of nearly all animals with their environment. Although the organs used for vision vary considerably among animals, the underlying mechanism for capturing light is the same, suggesting a common evolutionary origin.

Evolution of Visual Perception

EVOLUTION Light detectors in animals range from simple clusters of cells that detect only the direction and intensity of light to complex organs that form images. These diverse light detectors all contain **photoreceptors**, cells that contain light-absorbing pigment molecules. Furthermore, the genes that specify where and when photoreceptors arise during embryonic development are shared among flatworms, annelids, arthropods, and vertebrates. It is thus very probable that the genetic underpinnings of all photoreceptors were already present in the earliest bilaterian animals.



(a) The planarian's brain directs the body to turn until the sensations from the two ocelli are equal and minimal, causing the animal to move away from light.

(b) Whereas light striking the front of an ocellus excites the photoreceptors, light striking the back is blocked by the screening pigment. In this way, the ocelli indicate the direction of a light source, triggering the light avoidance behavior.

▲ **Figure 38.23 Ocelli and orientation behavior of a planarian.**

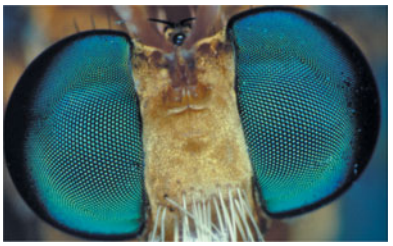
Compound Eyes

Insects and crustaceans have compound eyes, as do some polychaete worms. A **compound eye** consists of anywhere from a few to up to several thousand light detectors called **ommatidia** (the "facets" of the eye), each with its own light-focusing lens **(Figure 38.24)**. Each ommatidium detects light from a small portion of the visual field (the area seen when the eyes point forward). A compound eye is very effective at detecting movement, an important adaptation for flying insects and small animals constantly threatened with predation.

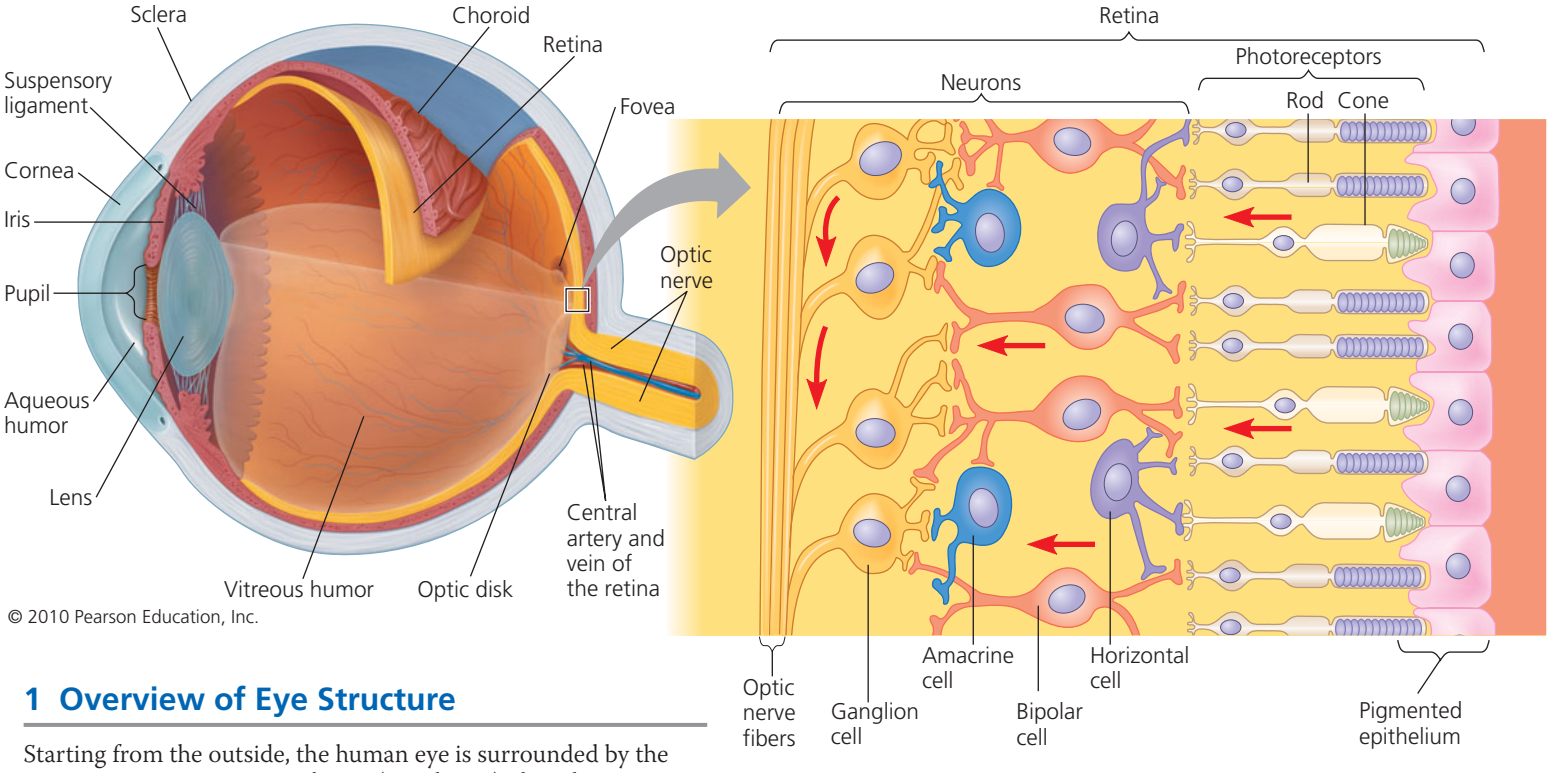
Single-Lens Eyes

Among invertebrates, **single-lens eyes** are found in some jellies and polychaete worms, as well as in spiders and many molluscs. A single-lens eye works somewhat like a camera. The eye of an octopus or squid, for example, has a small opening, the **pupil**, through which light enters. Like a camera's adjustable aperture, the **iris** expands or contracts, changing the diameter of the pupil to let in more light or less light. Behind

▶ Figure 38.24
Compound eyes. The faceted eyes on the head of a fly form a repeating pattern visible in this photomicrograph.



▼ Figure 38.25 Exploring the Structure of the Human Eye



1 Overview of Eye Structure

Starting from the outside, the human eye is surrounded by the conjunctiva, a mucous membrane (not shown); the sclera, a connective tissue; and the choroid, a thin, pigmented layer. At the front, the sclera forms the transparent *cornea* and the choroid forms the colored *iris*. By changing size, the iris regulates the amount of light entering the pupil, the hole in the center of the iris. Just inside the choroid, the neurons and photoreceptors of the **retina** form the innermost layer of the eyeball. The optic nerve exits the eye at the optic disk.

The **lens**, a transparent disk of protein, divides the eye into two cavities. In front of the lens lies the *aqueous humor*, a clear watery substance. Blockage of ducts that drain this fluid can produce glaucoma, a condition in which increased pressure in the eye damages the optic nerve, causing vision loss. Behind the lens lies the jellylike *vitreous humor* (illustrated here in the lower portion of the eyeball).

2 The Retina

Light (coming from left in the above view) strikes the retina, passing through largely transparent layers of neurons before reaching the rods and cones, two types of photoreceptors that differ in shape and in function. The neurons of the retina then relay visual information captured by the photoreceptors to the optic nerve and brain along the pathways shown with red arrows. Each *bipolar cell* receives information from several rods or cones, and each *ganglion cell* gathers input from several bipolar cells. *Horizontal* and *amacrine cells* integrate information across the retina.

One region of the retina, the optic disk, lacks photoreceptors. As a result, this region forms a "blind spot" where light is not detected.

the pupil, a single lens focuses light on a layer of photoreceptors. Similar to a camera's focusing action, muscles in an invertebrate's single-lens eye move the lens forward or backward, focusing on objects at different distances.

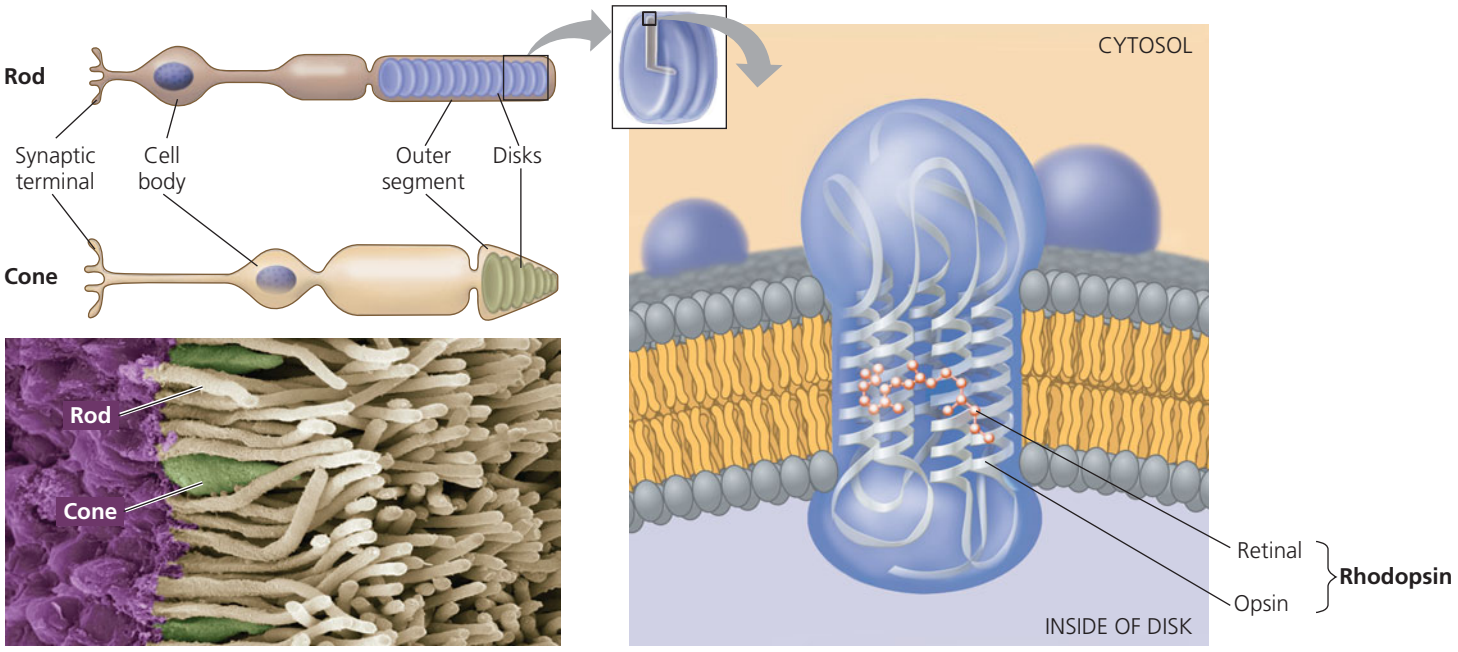
The eyes of all vertebrates have a single lens. In fishes, focusing is as in invertebrates, with the lens moving forward or backward. In other species, including mammals, focusing is achieved by changing the shape of the lens.

The Vertebrate Visual System

The human eye will serve as our model of vision in vertebrates. As described in **Figure 38.25**, vision begins when photons of light enter the eye and strike the rods and cones. Remember, however, that it is actually the brain that "sees." Thus, to understand vision, we must examine how the capture of light by rods and cones changes the production of action potentials and then follow these signals to the visual centers of the brain, where images are perceived.

Sensory Transduction in the Eye

The transduction of visual information to the nervous system begins with the capture of light by the molecule retinal. Retinal can exist as two alternative isomers, forms with the same types and number of atoms but with a different arrangement of chemical bonds. Looking at Figure 38.25, you can see that the *cis* isomer of retinal has a bent shape while the *trans* isomer is straight. When light strikes the eye, the energy of each photon is captured by converting *cis*-retinal to *trans*-retinal.



3 Photoreceptor Cells

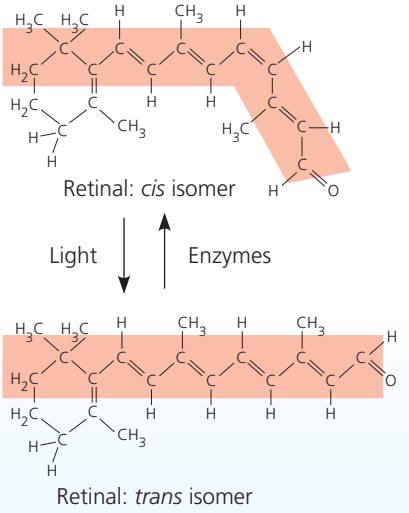
Humans have two main types of photoreceptor cells: rods and cones. Within the outer segment of a rod or cone is a stack of membranous disks in which *visual pigments* are embedded. **Rods** are more sensitive to light but do not distinguish colors; they enable us to see at night, but only in black and white. **Cones** provide color vision, but, being less sensitive, contribute very little to night vision. There are three types of cones. Each has a different sensitivity across the visible spectrum, providing an optimal response to red, green, or blue light.

In the colorized SEM shown above, cones (green), rods (light tan), and adjacent neurons (purple) are visible. The pigmented epithelium, which was removed in this preparation, would be to the right.

4 Visual Pigments

Vertebrate visual pigments consist of a light-absorbing molecule called **retinal** (a derivative of vitamin A) bound to a membrane protein called an **opsin**. Seven α helices of each opsin molecule span the disk membrane. The visual pigment of rods, shown here, is called **rhodopsin**.

Retinal exists as two isomers. Absorption of light shifts one bond in retinal from a *cis* to a *trans* arrangement, converting the molecule from an angled shape to a straight shape. This change in configuration destabilizes and activates the opsin protein to which retinal is bound.



Once retinal captures light, sensory transduction continues as a cascade of events, outlined in **Figure 38.26**. The formation of *trans*-retinal activates rhodopsin, which activates a G protein, which in turn activates an enzyme called phosphodiesterase. The substrate for this enzyme is cyclic GMP, which in the dark binds to sodium ion (Na^+) channels and keeps them open. When phosphodiesterase hydrolyses cyclic GMP, Na^+ channels close, and the cell becomes hyperpolarized.

The signal transduction pathway in photoreceptor cells normally shuts off as enzymes convert retinal back to the *cis* form, returning rhodopsin to its inactive state. In very bright light, however, rhodopsin remains active, and the response in the rods becomes saturated. If the amount of light entering the eyes decreases abruptly, the rods do not regain full responsiveness for several minutes. This is why you are temporarily blinded if you pass quickly from the bright sunshine into a movie theater or other dark environment. (Because light activation changes the color of rhodopsin from purple to yellow, rods in which the light response is saturated are often described as "bleached.")

Processing of Visual Information in the Retina

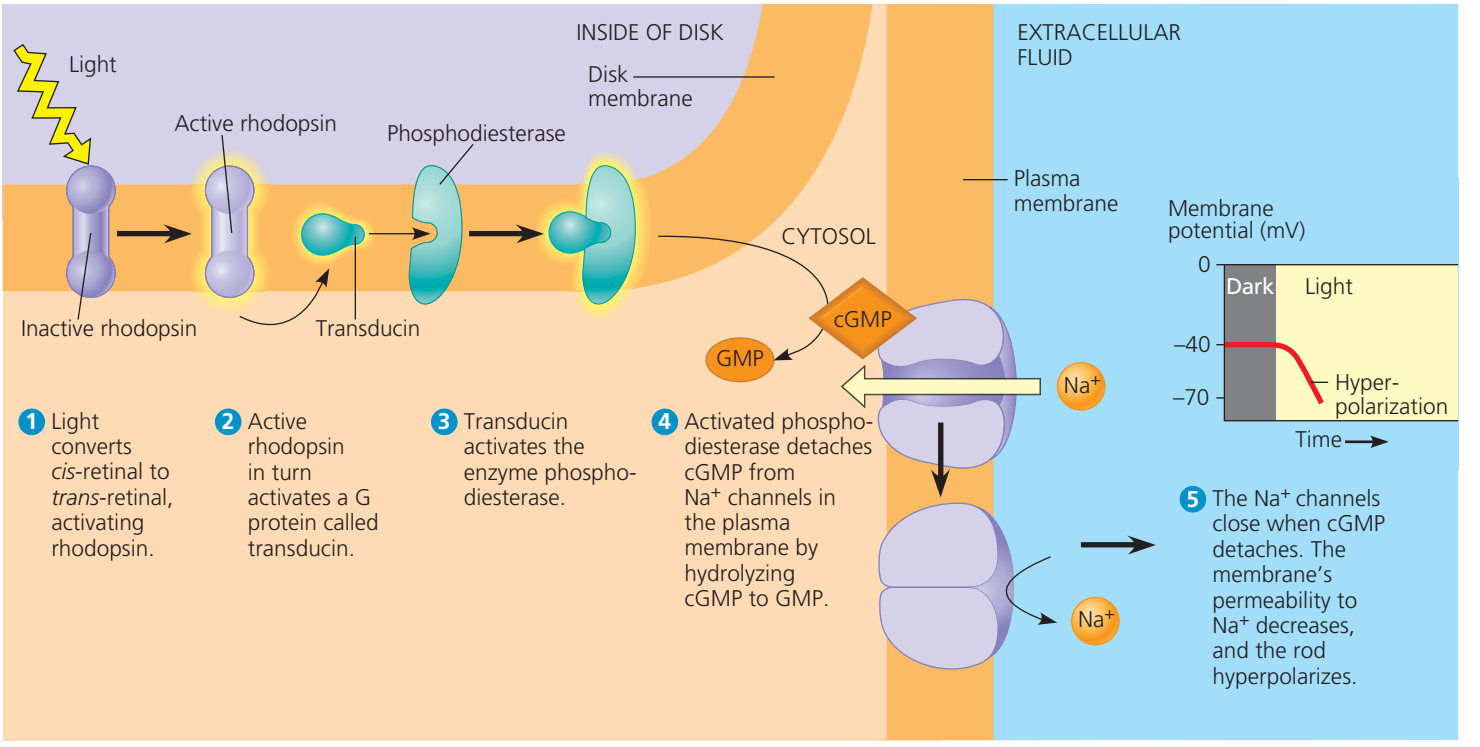
The processing of visual information begins in the retina itself, where both rods and cones form synapses with bipolar cells (see Figure 38.25). In the dark, rods and cones are depolarized and continually release the neurotransmitter glutamate at these synapses. Some bipolar cells depolarize in response to glutamate, whereas others hyperpolarize. When light strikes the rods and cones, they hyperpolarize, shutting off their release of glutamate. In response, the bipolar cells that are depolarized by glutamate hyperpolarize, and those that are hyperpolarized by glutamate depolarize.

Signals from rods and cones can follow several different pathways in the retina. Some information passes directly from photoreceptors to bipolar cells to ganglion cells. In other cases, horizontal cells carry signals from one rod or cone to other photoreceptors and to several bipolar cells. Amacrine cells also contribute to signal processing, distributing information from one bipolar cell to several ganglion cells.

A single ganglion cell receives information from an array of rods and cones, each of which responds to light coming from a particular location. Together, the rods and cones that feed information to one ganglion cell define a *receptive field*—the part of the visual field to which the ganglion cell can respond. The fewer rods or cones that supply a single ganglion cell, the smaller the receptive field is. A smaller receptive field typically results in a sharper image because the information about where light has struck the retina is more precise.

Processing of Visual Information in the Brain

Axons of ganglion cells form the optic nerves that transmit sensations from the eyes to the brain (see Figure 38.25). The two optic nerves meet at the *optic chiasm* near the center of



▲ **Figure 38.26 Production of the receptor potential in a rod cell.** In rods (and cones), the receptor potential triggered by light is a hyperpolarization, not a depolarization.

? *Which steps in the cascade of events shown here provide an opportunity for amplification, the strengthening of the sensory signal?*

the base of the cerebral cortex. Axons in the optic nerves are routed at the optic chiasm such that sensations from the left visual field of both eyes are transmitted to the right side of the brain, and sensations from the right visual field are transmitted to the left side of the brain. (Note that each visual field, whether right or left, involves input from both eyes.)

Researchers estimate that at least 30% of the cerebral cortex, comprising hundreds of millions of neurons in perhaps dozens of integrating centers, takes part in formulating what we actually "see." Determining how these centers integrate such components of our vision as color, motion, depth, shape, and detail is the focus of much exciting research.

Color Vision

Among vertebrates, most fishes, amphibians, and reptiles, including birds, have very good color vision. Humans and other primates also see color well, but are among the minority of mammals with this ability. Many mammals are nocturnal, and having a high proportion of rods in the retina is an adaptation that gives these animals keen night vision. Cats, for instance, are usually most active at night; they have limited color vision and probably see a pastel world during the day.

In humans, the perception of color is based on three types of cones, each with a different visual pigment—red, green, or blue. The three visual pigments, called *photopsins*, are formed from the binding of retinal to three distinct opsin proteins. Slight differences in the opsin proteins cause each photopsin to absorb light optimally at a different wavelength.

Abnormal color vision typically results from mutations in the genes for one or more photopsin proteins. Because the human genes for the red and green pigments are located on the X chromosome, a mutation in one copy of either gene can disrupt color vision in males. For this reason, color blindness is more common in males than in females (5–8% of males, fewer than 1% of females) and nearly always affects perception of red or green. (The human gene for the blue pigment is on chromosome 7.)

The Visual Field

The brain not only processes visual information but also controls what information is captured. One important type of control is focusing, which, as noted earlier, in humans occurs by changing the shape of the lens. When you focus your eyes on a close object, your lenses become almost spherical. When you view a distant object, your lenses are flattened.

Although our peripheral vision allows us to see objects over a nearly 180° range, the distribution of photoreceptors across the eye limits both what we see and how well we see it. Overall, the human retina contains about 125 million rods and about 6 million cones. At the **fovea**, the center of the visual field, there are no rods but a very high density of cones—about 150,000 cones per square millimeter. The ratio of rods to cones increases with distance from the fovea, with the peripheral regions having only rods. In daylight, you achieve your sharpest vision by looking directly at an object, such that light shines on the tightly packed cones in your fovea. At night, looking directly at a dimly lit object is ineffective, since the rods—the more sensitive light receptors—are found outside the fovea. For this reason, you see a dim star best by focusing on a point just to one side of it.

CONCEPT CHECK 38.6

1. Contrast the light-detecting organs of planarians and flies. How is each organ adaptive for the lifestyle of the animal?
2. **WHAT IF?** The human brain receives more action potentials when our eyes are exposed to light even though our photoreceptors release more neurotransmitter in the dark. Propose an explanation.
3. **MAKE CONNECTIONS** Compare the function of retinal in the eye with that of the pigment chlorophyll in a plant photosystem (see Concept 8.2).

For suggested answers, see Appendix A.

38 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 38.1

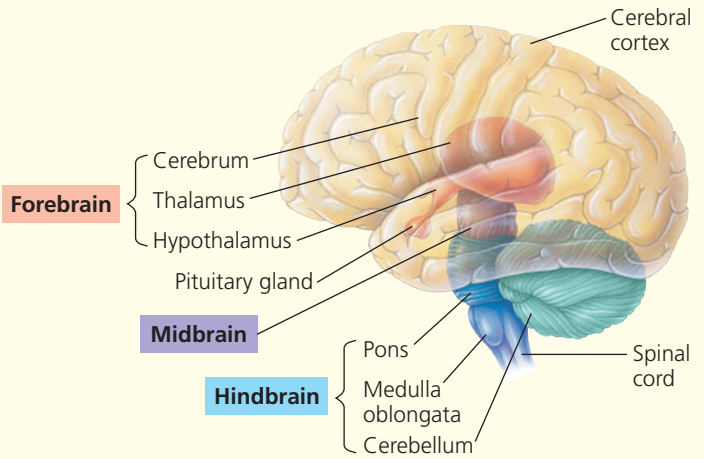
Nervous systems consist of circuits of neurons and supporting cells (pp. 768–771)

- Nervous systems range in complexity from simple **nerve nets** to highly centralized nervous systems. In vertebrates, the **central nervous system (CNS)**, consisting of the brain and the spinal cord, integrates information, while the **nerves** of the **peripheral nervous system (PNS)** transmit sensory and motor signals between the CNS and the rest of the body. The simplest circuits in the vertebrate nervous system control **reflex** responses, in which sensory input is linked to motor output without involvement of the brain. Vertebrate neurons are supported by glia, which nourish, support, and regulate neuron function.
- Afferent neurons carry sensory signals to the CNS. Efferent neurons function in either the **motor system**, which carries signals to skeletal muscles, or the **autonomic nervous system**, which regulates smooth and cardiac muscles. The **sympathetic division** and **parasympathetic division** of the autonomic nervous system have antagonistic effects on a diverse set of target organs, while the **enteric division** controls the activity of many digestive organs.

? *In what ways do different types of glia support the growth and survival of neurons?*

CONCEPT 38.2

The vertebrate brain is regionally specialized (pp. 771–776)



- The cerebrum has two hemispheres, each of which consists of cortical **gray matter** overlying **white matter** and basal nuclei. The basal nuclei are important in planning and learning movements. The **pons** and **medulla oblongata** are relay stations for information traveling between the PNS and the cerebrum. The pons, together with the **brainstem** and parts of the forebrain, also regulate sleep and arousal. The **cerebellum** helps coordinate motor, perceptual, and cognitive functions. The **thalamus** is the main center through which sensory information passes to the **cerebrum**. The **hypothalamus** regulates homeostasis and basic survival behaviors. Within the hypothalamus, the **suprachiasmatic nucleus (SCN)** acts as the pacemaker for circadian rhythms. The **amygdala** plays a key role in recognizing and recalling a number of emotions.

? *What roles do the midbrain, cerebellum, thalamus, and cerebrum play in vision and responses to visual input?*

CONCEPT 38.3

The cerebral cortex controls voluntary movement and cognitive functions (pp. 776–779)

- Each side of the **cerebral cortex** has four lobes that contain primary sensory areas and association areas. Specific types of sensory input enter the primary sensory areas. Association areas integrate information from different sensory areas. Broca's area and Wernicke's area are essential for generating and understanding language. In birds, a brain region called the pallium contains clustered nuclei that carry out functions similar to those performed by the cerebral cortex of mammals.
- Reshaping of the nervous system can involve the loss or addition of synapses or the strengthening or weakening of signaling at synapses. This capacity for remodeling is termed **neural plasticity**. **Short-term memory** relies on temporary links in the hippocampus. In **long-term memory**, these temporary links are replaced by connections within the cerebral cortex.

? *After an accident, a patient has trouble with language and has paralysis on one side of the body. Which side would you expect to be paralyzed? Why?*

CONCEPT 38.4

Sensory receptors transduce stimulus energy and transmit signals to the central nervous system (pp. 779–782)

- The detection of a stimulus precedes **sensory transduction**, the change in the membrane potential of a **sensory receptor** in response to a stimulus. The resulting **receptor potential** controls transmission of action potentials to the CNS, where sensory information is integrated to generate a **perception**. The frequency of action potentials in an axon and the number of axons activated determine stimulus strength. The identity of the axon carrying the signal encodes the nature or quality of the stimulus.
- **Mechanoreceptors** respond to stimuli such as pressure, touch, stretch, motion, and sound. **Electromagnetic receptors** detect different forms of electromagnetic radiation. **Thermoreceptors** signal surface and core temperatures of the body. Pain is detected by a group of **nociceptors** that respond to excess heat, pressure, or specific classes of chemicals. **Chemoreceptors** detect either total solute concentration or specific molecules, as in smell (**olfaction**) and taste (**gustation**). In humans, sensory cells have receptors for more than 1,000 **odorants** and five taste perceptions.

? *To simplify sensory receptor classification, why might it make sense to eliminate nociceptors as a distinct class?*

CONCEPT 38.5

The mechanoreceptors responsible for hearing and equilibrium detect moving fluid or settling particles (pp. 782–785)

- Most invertebrates sense their orientation with respect to gravity by means of **statocysts**. Specialized **hair cells** form the basis for hearing and balance in mammals. In mammals, the **tympanic membrane** (eardrum) transmits sound waves to bones of the middle ear, which transmit the waves through the **oval window** to the fluid in the coiled **cochlea** of the inner ear. Pressure waves in the fluid vibrate the basilar membrane, depolarizing hair cells and triggering action potentials that travel via the auditory nerve to the brain. Receptors in the inner ear function in balance and equilibrium.

? *When a person hears music, how are volume and pitch encoded in signals sent to the brain?*

CONCEPT 38.6

The diverse visual receptors of animals depend on light-absorbing pigments (pp. 785–789)

- Invertebrates have varied light detectors, including simple light-sensitive eyespots, image-forming **compound eyes**, and **single-lens eyes**. In the vertebrate eye, a single **lens** is used to focus light on **photoreceptors** in the **retina**. Both **rods** and **cones** contain a pigment, **retinal**, bonded to a protein (**opsin**). Absorption of light by retinal triggers a signal transduction pathway that hyperpolarizes the photoreceptors, causing them to release less neurotransmitter. Synapses transmit information from photoreceptors to cells that integrate information and convey it to the brain along axons that form the optic nerve.

? *How does the processing of visual information sent to the vertebrate brain differ from that of hearing or olfaction?*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. Patients with damage to Wernicke's area have difficulty
   a. coordinating limb movement.
   b. generating speech.
   c. recognizing faces.
   d. understanding language.
   e. experiencing emotion.
2. The cerebral cortex does *not* play a major role in
   a. short-term memory.
   b. long-term memory.
   c. circadian rhythm.
   d. foot-tapping rhythm.
   e. breath holding.
3. The middle ear converts
   a. air pressure waves to fluid pressure waves.
   b. fluid pressure waves to air pressure waves.
   c. air pressure waves to nerve impulses.
   d. fluid pressure waves to nerve impulses.
   e. pressure waves to hair cell movements.
4. If the following events are arranged in the order in which they occur for an animal hiding in response to seeing a predator, which is the fourth event in the series?
   a. signaling by an afferent PNS neuron
   b. signaling by an efferent PNS neuron
   c. information processing in the CNS
   d. activation of a sensory receptor
   e. activation of a motor system

Level 2: Application/Analysis

5. Injury to just the hypothalamus would most likely disrupt
   a. short-term memory.
   b. coordination during locomotion.
   c. executive functions, such as decision making.
   d. sorting of sensory information.
   e. regulation of body temperature.
6. Which sensory distinction is *not* encoded by a difference in which axon transfers the information to the brain?
   a. white and red
   b. red and green
   c. loud and faint
   d. salty and sweet
   e. spicy and cool

Level 3: Synthesis/Evaluation

7. Although some sharks close their eyes just before they bite, their bites are on target. Researchers have noted that sharks often misdirect their bites at metal objects and that they can find batteries buried under sand. This evidence suggests that sharks keep track of their prey during the split second before they bite in the same way that
   a. a rattlesnake finds a mouse in its burrow.
   b. an insect avoids being stepped on.
   c. a star-nosed mole locates its prey in tunnels.
   d. a platypus locates its prey in a muddy river.
   e. a flatworm avoids light places.
8. **SCIENTIFIC INQUIRY**
   Consider an individual who had been fluent in American Sign Language before suffering an injury to his left cerebral hemisphere. After the injury, he could still understand signs but could not readily generate signs that represented his thoughts. Propose two hypotheses that could explain this finding. How might you distinguish between them?
9. **FOCUS ON EVOLUTION**
   Scientists often use measures of "higher-order thinking" to assess intelligence in other animals. For example, birds are judged to have sophisticated thought processes because they can use tools and make use of abstract concepts. What problems do you see in defining intelligence in these ways?
10. **FOCUS ON ORGANIZATION**
    In a short essay (100–150 words), describe at least three ways in which the structure of the lens of the human eye is well adapted to its function in vision.

For selected answers, see Appendix A.

39 Motor Mechanisms and Behavior

KEY CONCEPTS

39.1 The physical interaction of protein filaments is required for muscle function
39.2 Skeletal systems transform muscle contraction into locomotion
39.3 Discrete sensory inputs can stimulate both simple and complex behaviors
39.4 Learning establishes specific links between experience and behavior
39.5 Selection for individual survival and reproductive success can explain most behaviors
39.6 Inclusive fitness can account for the evolution of behavior, including altruism

OVERVIEW

The How and Why of Animal Activity

Unlike most animals, male fiddler crabs (genus *Uca*) are highly asymmetric. One claw grows to giant proportions, half the mass of the crab's entire body **(Figure 39.1)**. The name *fiddler* comes from the crab's behavior as it feeds on algae from the mudflats where it lives: The smaller front claw moves to and from the mouth in front of the enlarged claw. At times, however, the male waves his large claw in the air. What triggers this behavior? What purpose does it serve?

▼ **Figure 39.1** What prompts a fiddler crab to wave its giant claw?

Claw-waving behavior by a male fiddler crab has two functions. Waving the claw, which can be used as a weapon, helps the crab *repel* other males wandering too close to his burrow. Vigorous claw waving also helps him *attract* females who wander through the crab colony in search of a mate. After the male fiddler crab lures a female to his burrow, he seals her in with mud or sand in preparation for mating.

Animal behaviors, whether solitary or social, fixed or variable, are based on physiological systems and processes. An individual **behavior** is an action carried out by muscles under control of the nervous system. Examples include an animal using its throat muscles to produce a song, releasing a scent to mark its territory, or simply waving a claw. Behavior is an essential part of acquiring nutrients and finding a partner for sexual reproduction. Behavior also contributes to homeostasis, as when honeybees huddle to conserve heat. In short, all of physiology contributes to behavior, and behavior influences all of physiology.

Many behaviors, especially those involved in recognition and communication, rely on specialized body structures or form. For instance, the enormous claw of a male fiddler crab enables recognition by rival males and by potential mates. Similarly, having eyes on stalks high above his head enables the male crab to identify other crabs from far away. As these examples illustrate, the process of natural selection that shapes behaviors also influences the evolution of animal anatomy.

In this chapter, we'll begin by considering the structure and function of muscles and skeletons, as well as mechanisms of animal movement. These topics will lead us naturally to the questions of how behavior is controlled, how it develops during an animal's life, and how it is influenced by genes and the environment. Finally, we'll investigate the ways in which behavior evolves over many generations. Moving our study from an animal's inner workings to its interactions with the outside world will set the stage for exploring ecology (the focus of Unit Seven).

CONCEPT 39.1

The physical interaction of protein filaments is required for muscle function

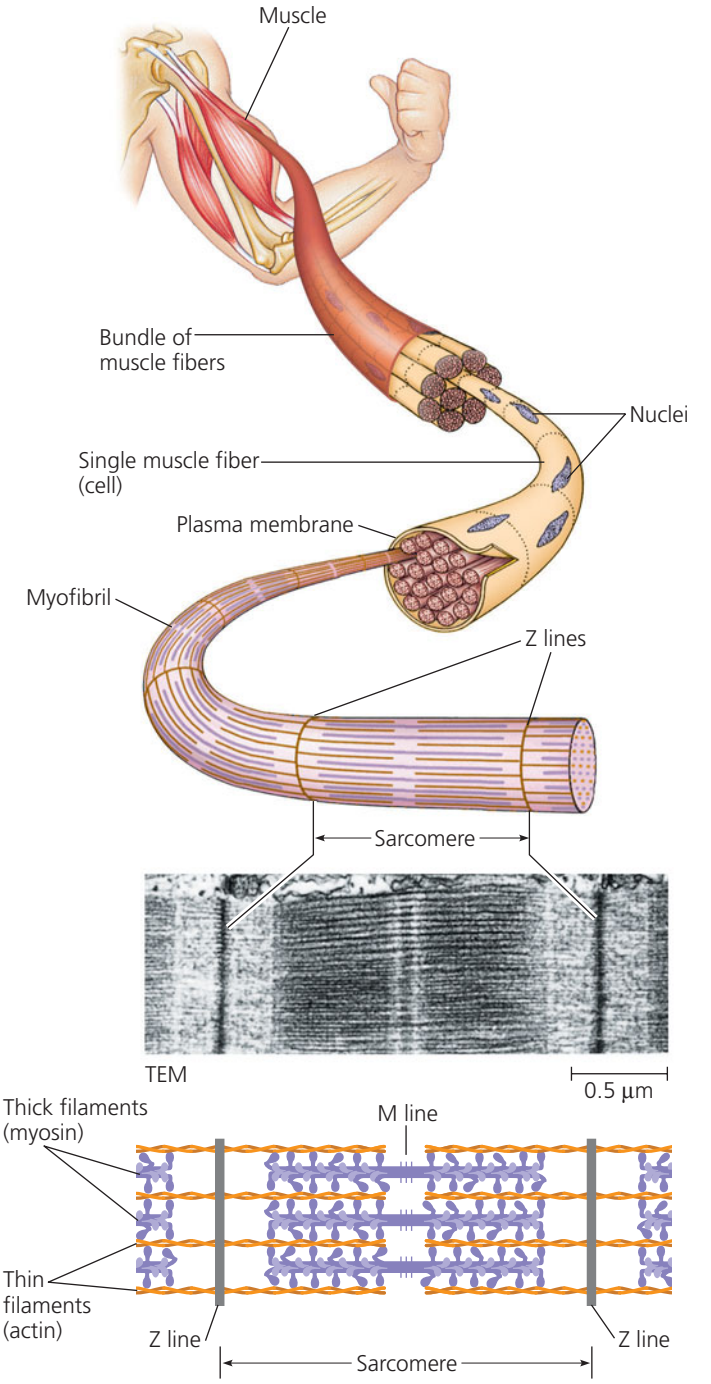
The touch-guided foraging of a star-nosed mole, the upside-down swimming of a crayfish with manipulated statocysts, and the light-avoiding maneuvers of planarians are examples of specific behaviors triggered by sensory inputs to the nervous system (see Chapter 38). Underlying these diverse behaviors are common fundamental mechanisms—feeding, swimming, and crawling all require muscle activity in response to nervous system input.

Muscle cell contraction relies on the interaction between protein structures called thin and thick filaments. The major component of **thin filaments** is the globular protein actin. In thin filaments, two strands of polymerized actin are coiled around one another; similar actin structures called microfilaments function in cell motility (see Concept 4.6). **Thick filaments** are staggered arrays of myosin molecules. Muscle contraction is the product of filament movement powered by chemical energy; muscle relaxation is a passive process. To understand how filaments contribute to muscle contraction, we'll begin with the skeletal muscle of vertebrates.

Vertebrate Skeletal Muscle

Vertebrate **skeletal muscle**, which moves individual bones and the whole body, is made up of a hierarchy of smaller and smaller units **(Figure 39.2)**. Most skeletal muscles consist of a bundle of long fibers running parallel to the length of the muscle. Each fiber is a single cell that contains multiple nuclei, reflecting its formation by the fusion of many embryonic cells. Inside the fiber lies a longitudinal bundle of **myofibrils**, which contain the thin and thick filaments.

The myofibrils in muscle fibers are made up of repeating sections called **sarcomeres**, which are the basic contractile units of skeletal muscle. The borders of the sarcomeres line up in adjacent myofibrils, forming a pattern of light and dark bands (striations) visible with a light microscope. Therefore, skeletal muscle is also sometimes called *striated muscle*. As shown in Figure 39.2, thin filaments attach at the ends of the sarcomeres (Z lines), while thick filaments are anchored in the middle (M line). In a muscle fiber at rest, thick and thin filaments partially overlap. Near the edge of the sarcomere there are only thin filaments, whereas the zone in the center contains only thick filaments. This arrangement is the key to how the sarcomere, and hence the whole muscle, contracts.

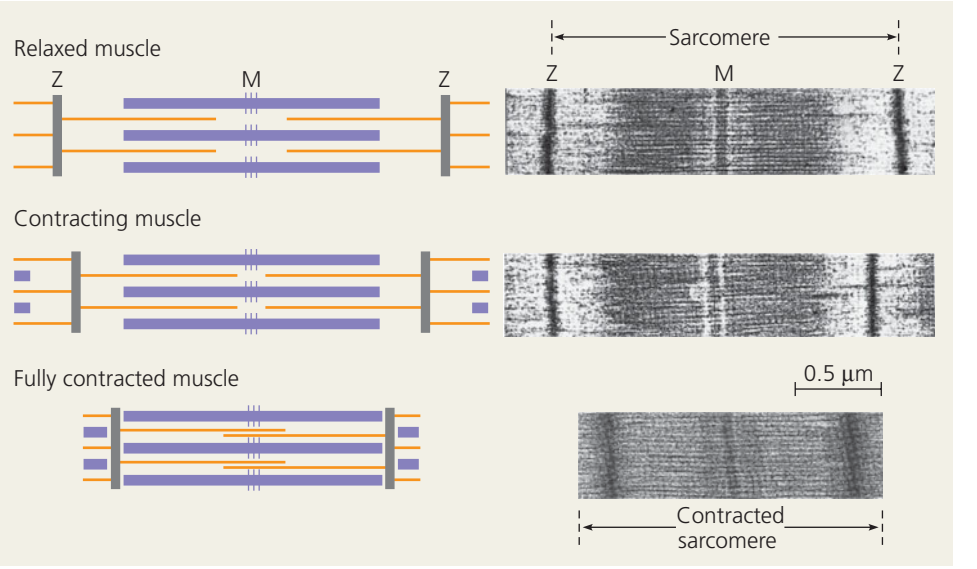


▲ **Figure 39.2 The structure of skeletal muscle.**

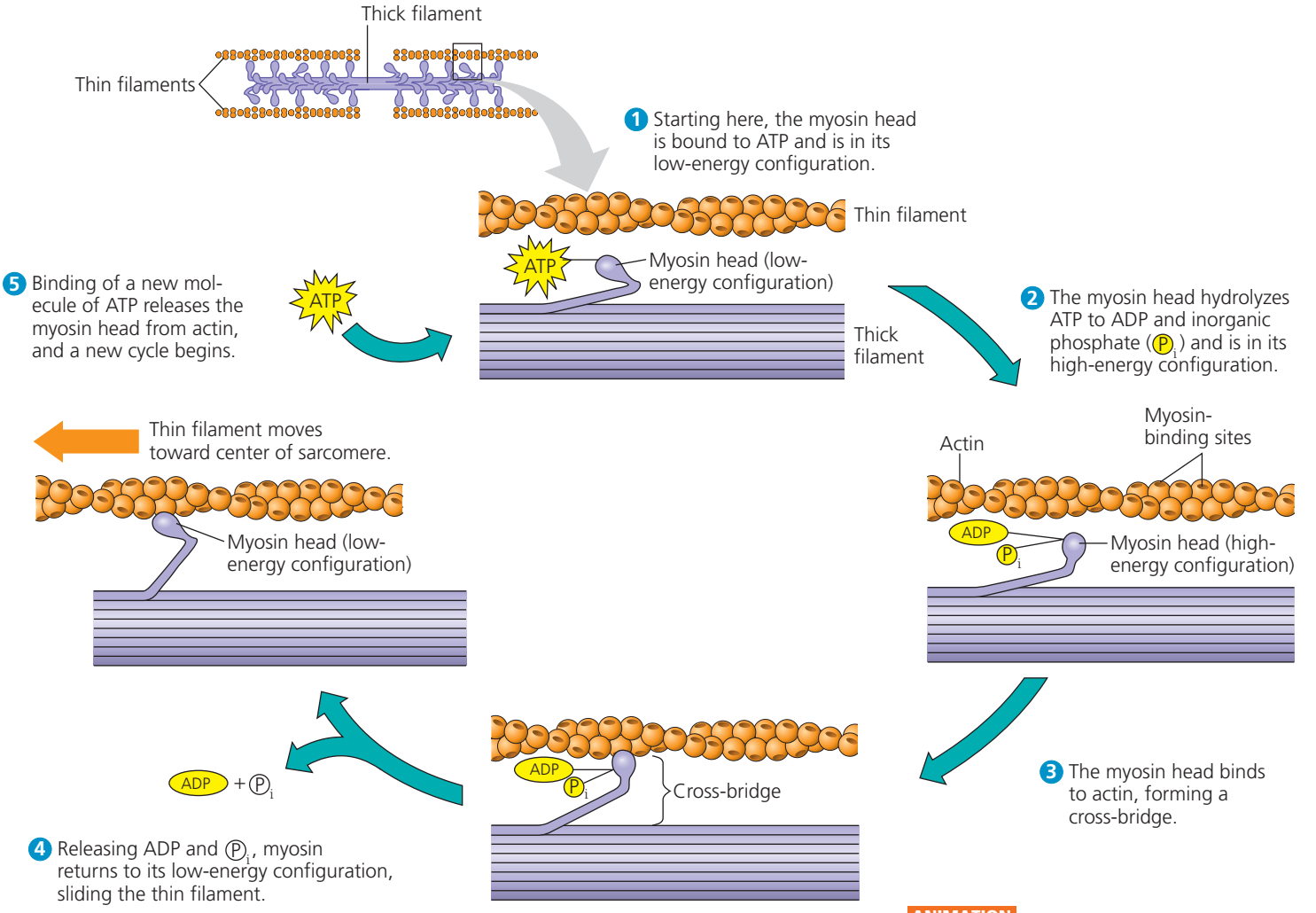
The Sliding-Filament Mechanism of Muscle Contraction

A contracting muscle shortens, but the filaments that bring about contraction stay the same length. To explain this apparent paradox, we'll focus first on a single sarcomere. As shown in **Figure 39.3**, the filaments slide past each other, much like the segments of a telescoping support pole. According to the widely accepted **sliding-filament model**, the thin and thick filaments interact and actually ratchet past each other, powered by myosin molecules.

Figure 39.4 illustrates the cycles of change in the myosin molecule that form the basis for the longitudinal sliding of the thick and thin filaments.

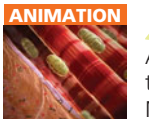


▲ **Figure 39.3 The sliding-filament model of muscle contraction.** The drawings on the left show that the lengths of the thick (myosin) filaments (purple) and thin (actin) filaments (orange) remain the same as a muscle fiber contracts.



▲ **Figure 39.4 Myosin-actin interactions underlying muscle fiber contraction.**

? *When ATP binds, what prevents the filaments from sliding back into their original positions?*



BioFlix Visit the Study Area in **MasteringBiology** for the BioFlix® 3-D Animation on Muscle Contraction.

Each myosin molecule has a long "tail" and a globular "head." The tail adheres to the tails of other myosin molecules, binding together the thick filament. The head, which extends to the side, can bind ATP. Hydrolysis of this ATP converts myosin to a high-energy form that binds to actin, forming a cross-bridge. The myosin head then returns to its low-energy form as it pulls the thin filament toward the center of the sarcomere. When a new molecule of ATP binds to the head, the cross-bridge is broken.

Muscle contraction requires repeated cycles of binding and release. In each cycle, the myosin head freed from a cross-bridge cleaves the newly bound ATP and binds to actin farther along the thin filament. A thick filament contains approximately 350 myosin heads, each of which forms and re-forms about five cross-bridges per second, driving the thick and thin filaments past each other.

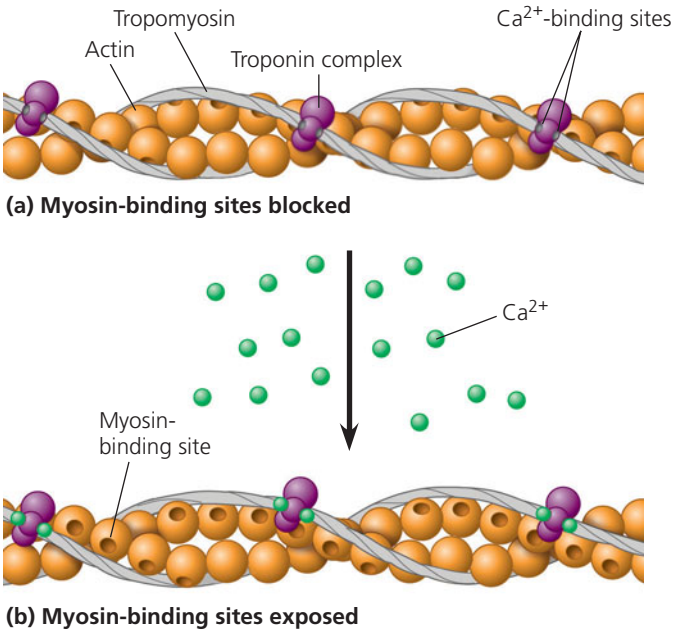
A typical muscle fiber at rest contains only enough ATP for a few contractions. To power repetitive contractions, the muscle cell relies on two other storage compounds: creatine phosphate and glycogen. Transferring a phosphate group from creatine phosphate to ADP in an enzyme-catalyzed reaction synthesizes additional ATP. In this way, the resting supply of creatine phosphate can sustain contractions for about 15 seconds. ATP stores are also replenished when glycogen is broken down to glucose, which can be used to generate ATP by either aerobic respiration or glycolysis (see Chapter 7). Using a typical muscle fiber's glycogen store, glycolysis can support about 1 minute of sustained contraction, whereas aerobic respiration can power contractions for nearly an hour.

The Role of Calcium and Regulatory Proteins

Calcium ions (Ca^{2+}) and proteins bound to actin play crucial roles in muscle contraction and relaxation. **Tropomyosin**, a regulatory protein, and the **troponin complex**, a set of additional regulatory proteins, are bound to the actin strands of thin filaments. In a muscle fiber at rest, tropomyosin covers the myosin-binding sites along the thin filament, preventing actin and myosin from interacting **(Figure 39.5a)**. When Ca^{2+} accumulates in the cytosol, it binds to the troponin complex, causing tropomyosin bound along the actin strands to shift position and expose the myosin-binding sites on the thin filament **(Figure 39.5b)**. Thus, when the Ca^{2+} concentration rises in the cytosol, the thin and thick filaments slide past each other, and the muscle fiber contracts. When the Ca^{2+} concentration falls, the binding sites are covered, and contraction stops.

Motor neurons cause muscle contraction by triggering the release of Ca^{2+} into the cytosol of muscle cells with which they form synapses. This regulation of Ca^{2+} concentration is a multistep process involving a network of membranes and compartments within the muscle cell. As you read the following description, refer to the overview and diagram in **Figure 39.6**.

When an action potential arrives at the synaptic terminal of a motor neuron, it causes the neurotransmitter acetylcholine



▲ Figure 39.5 The role of regulatory proteins and calcium in muscle fiber contraction. Each thin filament consists of two strands of actin, tropomyosin, and the troponin complex.

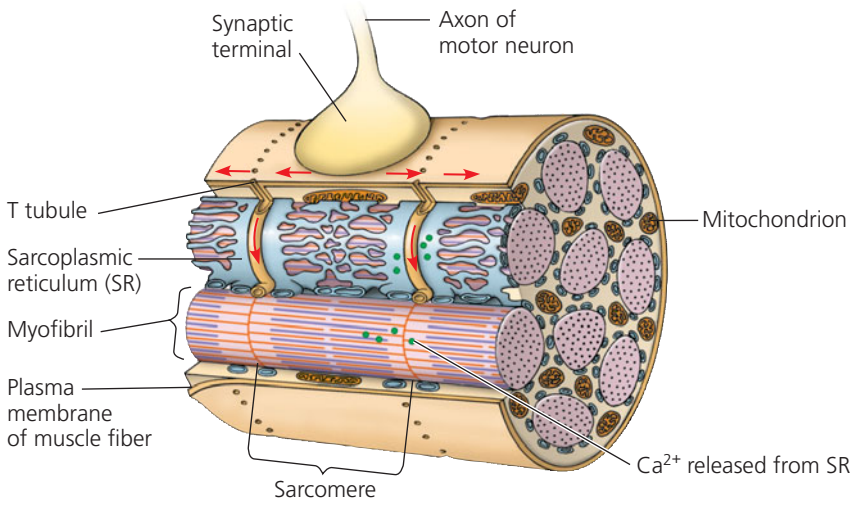
to be released. Binding of acetylcholine to receptors on the muscle fiber leads to a depolarization, triggering an action potential. Within the muscle fiber, the action potential spreads deep into the interior, following infoldings of the plasma membrane called **transverse (T) tubules**. These make close contact with the **sarcoplasmic reticulum (SR)**, a specialized endoplasmic reticulum. As the action potential spreads along the T tubules, it triggers changes in the SR, opening Ca^{2+} channels. Calcium ions stored in the interior of the SR flow through open channels into the cytosol and bind to the troponin complex, initiating muscle fiber contraction.

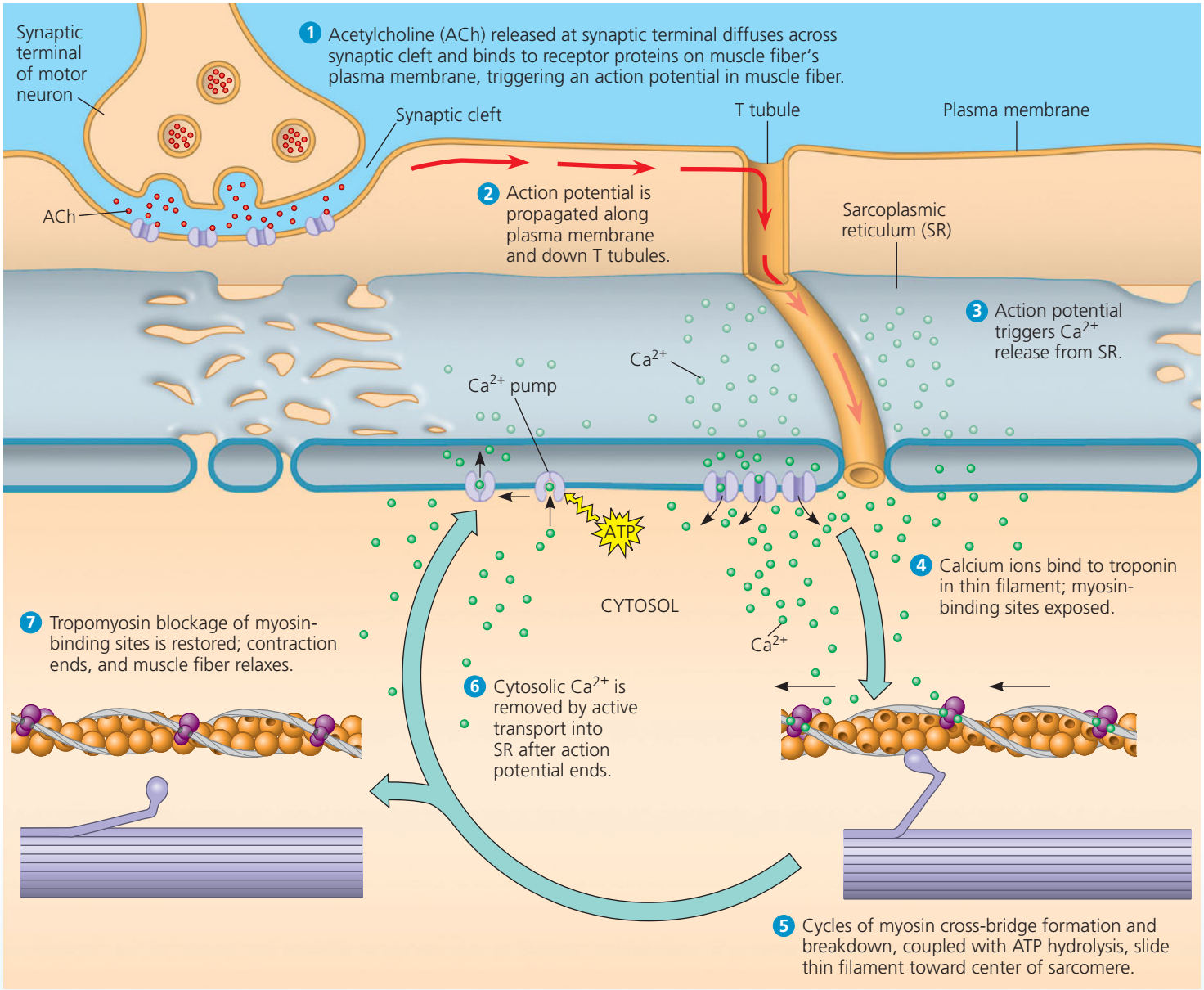
When motor neuron input stops, the filaments slide back to their starting position. Relaxation begins as transport proteins in the SR pump Ca^{2+} in from the cytosol. When the Ca^{2+} concentration in the cytosol drops to a low level, the regulatory proteins bound to the thin filament shift back to their starting position, once again blocking the myosin-binding sites. At the same time, the Ca^{2+} pumped from the cytosol accumulates in the SR, providing the stores needed to respond to the next action potential.

There are several human diseases that cause paralysis by interfering with motor neurons' ability to excite skeletal muscle fibers. In amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease), motor neurons in the spinal cord and brainstem degenerate, and muscle fibers atrophy. ALS is progressive and usually fatal within five years after symptoms appear. In myasthenia gravis, an autoimmune disease, a person produces antibodies to the acetylcholine receptors of skeletal muscle. As the immune system attacks these receptors, transmission between motor neurons and

▼ Figure 39.6 Exploring the Regulation of Skeletal Muscle Contraction

The electrical, chemical, and molecular events regulating skeletal muscle contraction are shown in a cutaway view of a muscle cell and in the enlarged diagram below. Action potentials (red arrows) triggered by the motor neuron sweep across the muscle fiber and into it along the transverse (T) tubules, initiating the movements of calcium (green dots) that regulate muscle activity.



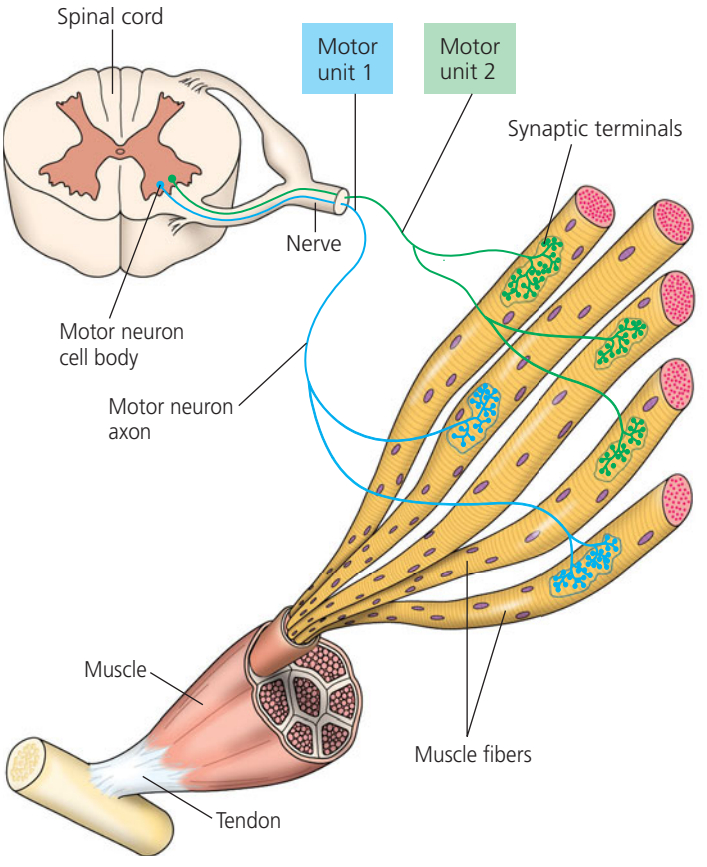


muscle fibers declines. Myasthenia gravis can generally be controlled with drugs that inhibit acetylcholinesterase or suppress the immune system.

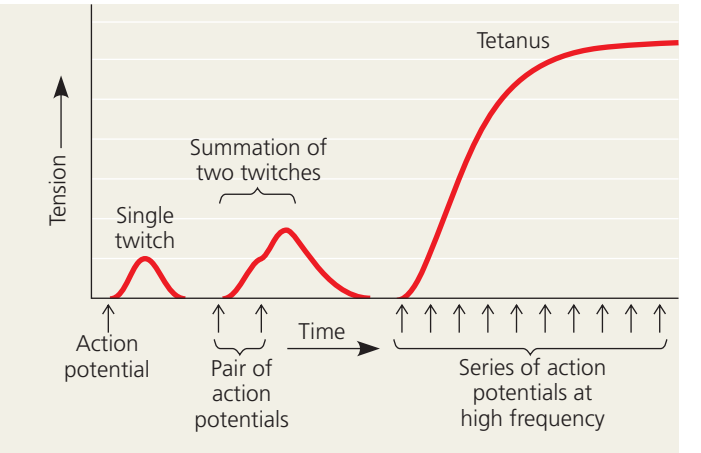
Nervous Control of Muscle Tension

Whereas an individual skeletal muscle fiber's contraction is a brief all-or-none twitch, contraction of a whole muscle, such as the biceps in your upper arm, is graded—you can voluntarily alter the extent and strength of its contraction. There are two basic mechanisms by which the nervous system produces graded contractions of whole muscles: (1) by varying the number of muscle fibers that contract and (2) by varying the rate at which muscle fibers are stimulated. Let's consider each mechanism in turn.

In vertebrates, each motor neuron may synapse with many muscle fibers, although each fiber is controlled by only one motor neuron. A **motor unit** consists of a single motor neuron and all the muscle fibers it controls **(Figure 39.7)**. When a motor neuron produces an action potential, all the muscle fibers in its motor unit contract as a group. The strength of the resulting contraction depends on how many muscle fibers the motor neuron controls. In the whole muscle, there may be hundreds of motor units.



▲ Figure 39.7 Motor units in a vertebrate skeletal muscle. Each muscle fiber (cell) forms synapses with only one motor neuron, but each motor neuron typically synapses with many muscle fibers. A motor neuron and all the muscle fibers it controls constitute a motor unit.



▲ Figure 39.8 Summation of twitches. This graph illustrates how the number of action potentials in a short period of time influences the tension developed in a muscle fiber.

? *How could the nervous system cause a skeletal muscle to produce the most forceful contraction it is capable of?*

The force (tension) developed by a muscle progressively increases as more and more of the motor neurons controlling the muscle are activated, a process called *recruitment* of motor neurons. Depending on the number of motor neurons your brain recruits and the size of their motor units, you can lift a fork or something much heavier, like your biology textbook. Some muscles, especially those that hold up the body and maintain posture, are almost always partially contracted. In such muscles, the nervous system may alternate which motor units are activated, reducing the length of time any one set of fibers is contracted.

The nervous system regulates muscle contraction not only by controlling which motor units are activated, but also by varying the rate of muscle fiber stimulation. A single action potential produces a twitch lasting about 100 msec or less. If a second action potential arrives before the muscle fiber has completely relaxed, the two twitches add together, resulting in greater tension **(Figure 39.8)**. Further summation occurs as the rate of stimulation increases. When the rate is so high that the muscle fiber cannot relax at all between stimuli, the twitches fuse into one smooth, sustained contraction called **tetanus**. (Although this smooth, sustained contraction is part of normal muscle function, tetanus is also the name of a disease of uncontrolled muscle contraction caused by a bacterial toxin.)

Types of Skeletal Muscle Fibers

Our discussion to this point has focused on the general properties of vertebrate skeletal muscles. There are, however, several distinct types of skeletal muscle fibers, each of which is adapted to a particular set of functions. Scientists typically classify these varied fiber types both by the source of ATP used to power their activity and by the speed of their contraction **(Table 39.1)**.

Table 39.1 Types of Skeletal Muscle Fibers

	Slow Oxidative	Fast Oxidative	Fast Glycolytic
Contraction speed	Slow	Fast	Fast
Major ATP source	Aerobic respiration	Aerobic respiration	Glycolysis
Rate of fatigue	Slow	Intermediate	Fast
Mitochondria	Many	Many	Few
Myoglobin content	High (red muscle)	High (red muscle)	Low (white muscle)

Oxidative and Glycolytic Fibers Fibers that rely mostly on aerobic respiration are called oxidative fibers. Such fibers are specialized in ways that enable them to make use of a steady energy supply: They have many mitochondria, a rich blood supply, and a large amount of an oxygen-storing protein called **myoglobin**. A brownish red pigment, myoglobin binds oxygen more tightly than does hemoglobin, enabling oxidative fibers to extract oxygen from the blood efficiently. In contrast, glycolytic fibers have a larger diameter and less myoglobin. Also, glycolytic fibers use glycolysis as their primary source of ATP and fatigue more readily than oxidative fibers. These different fiber types are readily apparent in the muscle of poultry and fish: The dark meat is made up of oxidative fibers rich in myoglobin, and the light meat is composed of glycolytic fibers.

Fast-Twitch and Slow-Twitch Fibers Muscle fibers vary in the speed with which they contract: **Fast-twitch fibers** develop tension two to three times faster than **slow-twitch fibers**. Fast fibers enable brief, rapid, powerful contractions. Slow fibers, often found in muscles that maintain posture, can sustain long contractions. A slow fiber has less sarcoplasmic reticulum and pumps Ca^{2+} more slowly than a fast fiber. Because Ca^{2+} remains in the cytosol longer, a muscle twitch in a slow fiber lasts about five times as long as one in a fast fiber.

The difference in contraction speed between slow-twitch and fast-twitch fibers mainly reflects the rate at which their myosin heads hydrolyze ATP. However, there isn't a one-to-one relationship between contraction speed and ATP source. Whereas all slow-twitch fibers are oxidative, fast-twitch fibers can be either glycolytic or oxidative (see Table 39.1).

Most human skeletal muscles contain both fast- and slow-twitch fibers, although the muscles of the eye and hand are exclusively fast-twitch. In a muscle that has a mixture of fast and slow fibers, the relative proportions of each are genetically determined. However, if such a muscle is used repeatedly for activities requiring high endurance, some fast glycolytic fibers can develop into fast oxidative fibers. Because fast oxidative fibers fatigue more slowly than fast glycolytic fibers, the result will be a muscle that is more resistant to fatigue.

▲ **Figure 39.9 Specialization of skeletal muscle.** The male toadfish (*Opsanus tau*) uses superfast muscles surrounding its swim bladder to produce its mating call.

The skeletal muscles of some vertebrates twitch at rates far faster than any human muscle. For example, superfast muscles produce a dove's coo and a rattlesnake's rattle. The fastest such muscles, however, surround the gas-filled swim bladder of the male toadfish **(Figure 39.9)**. In producing its characteristic "boat whistle" mating call, the toadfish can contract and relax these muscles more than 200 times per second.

Other Types of Muscle

Although all muscles share the same fundamental mechanism of contraction—actin and myosin filaments sliding past each other—animals have more than one type of muscle. Vertebrates, for example, have cardiac muscle and smooth muscle in addition to skeletal muscle.

Vertebrate **cardiac muscle** is found in only one part of the body: the heart. Like skeletal muscle, cardiac muscle is striated. Whereas skeletal muscle fibers do not produce action potentials unless stimulated by a motor neuron, cardiac muscle cells have ion channels in their plasma membrane that cause rhythmic depolarizations, triggering action potentials without input from the nervous system. Action potentials of cardiac muscle cells last up to 20 times longer than those of skeletal muscle fibers.

Plasma membranes of adjacent cardiac muscle cells interlock at specialized regions called **intercalated disks**, where gap junctions provide direct electrical coupling between the cells (see Figure 4.27). Thus, the action potential generated by specialized cells in one part of the heart spreads to all other cardiac muscle cells, causing the whole heart to contract. A long refractory period prevents summation and tetanus.

Smooth muscle in vertebrates is found mainly in the walls of hollow organs, such as blood vessels and organs of the digestive tract. Smooth muscle cells lack striations because their filaments are not regularly arrayed. Instead, the thick

filaments are scattered throughout the cytoplasm, and the thin filaments are attached to structures called dense bodies, some of which are tethered to the plasma membrane. Some smooth muscle cells contract only when stimulated by neurons of the autonomic nervous system. Others are electrically coupled to one another and can generate action potentials without input from neurons. Smooth muscles contract and relax more slowly than striated muscles.

Although Ca^{2+} regulates smooth muscle contraction, the mechanism for regulation is different from that in skeletal and cardiac muscle. Smooth muscle cells have no troponin complex or T tubules, and their sarcoplasmic reticulum is not well developed. During an action potential, Ca^{2+} enters the cytosol mainly through the plasma membrane. Calcium ions cause contraction by binding to the protein calmodulin, which activates an enzyme that phosphorylates the myosin head, enabling cross-bridge activity.

Invertebrates have muscle cells similar to vertebrate skeletal and smooth muscle cells, and arthropod skeletal muscles are nearly identical to those of vertebrates. However, because the flight muscles of insects are capable of independent, rhythmic contraction, the wings of some insects can actually beat faster than action potentials can arrive from the central nervous system. Another interesting evolutionary adaptation has been discovered in the muscles that hold a clam's shell closed. The thick filaments in these muscles contain a protein called paramyosin that enables the muscles to remain contracted for as long as a month with only a low rate of energy consumption.

CONCEPT CHECK 39.1

1. Contrast the role of Ca^{2+} in the contraction of a skeletal muscle fiber and a smooth muscle cell.
2. **WHAT IF?** Why are the muscles of an animal that has recently died likely to be stiff?
3. **MAKE CONNECTIONS** How does the activity of tropomyosin and troponin in muscle contraction compare with the activity of a competitive inhibitor in enzyme action? (See Figure 6.17.)

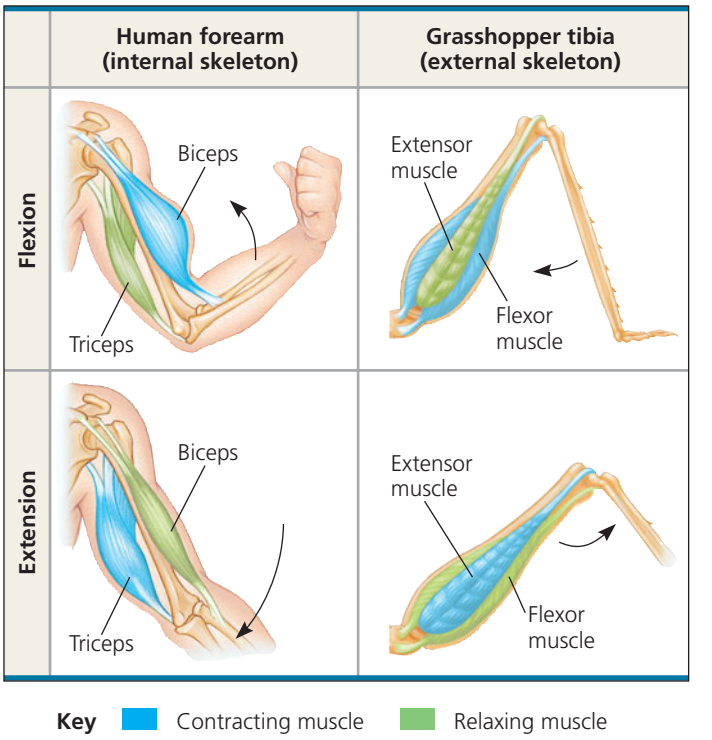
For suggested answers, see Appendix A.

CONCEPT 39.2

Skeletal systems transform muscle contraction into locomotion

Converting muscle contraction to movement requires a skeleton—a rigid structure to which muscles can attach. An animal changes its shape or location by contracting muscles that connect two parts of its skeleton.

Because muscles exert force only during contraction, moving a body part back and forth typically requires two muscles attached to the same section of the skeleton. We can see such an arrangement of muscles in the upper portion of a human arm or grasshopper leg **(Figure 39.10)**. Although we call such



▲ Figure 39.10 The interaction of muscles and skeletons in movement. Back-and-forth movement of a body part is generally accomplished by antagonistic muscles. This arrangement works with either an internal skeleton, as in mammals, or an external skeleton, as in insects.

muscles an antagonistic pair, their function is actually cooperative, coordinated by the nervous system. For example, when you extend your arm, motor neurons trigger your triceps muscle to contract while the absence of neuronal input allows your biceps to relax.

Vital for movement, the skeletons of animals also function in support and protection. Most land animals would collapse if they had no skeleton to support their mass. Even an aquatic animal would be formless without a framework to maintain its shape. In many animals, a hard skeleton also protects soft tissues. For example, the vertebrate skull protects the brain, and the ribs of terrestrial vertebrates form a cage around the heart, lungs, and other internal organs.

Types of Skeletal Systems

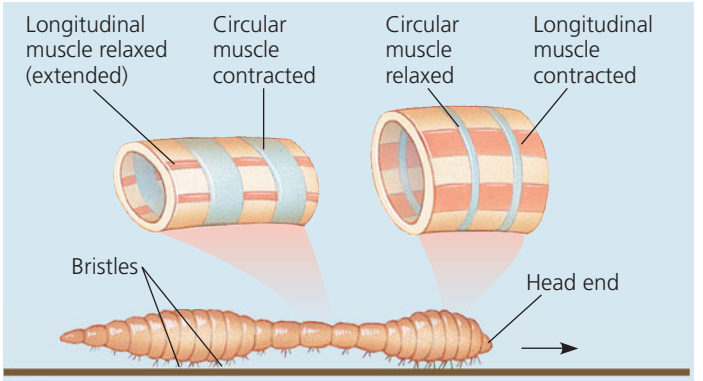
Although we tend to think of skeletons only as interconnected sets of bones, skeletons come in many different forms. Hardened support structures can be external (as in exoskeletons), internal (as in endoskeletons), or even absent (as in fluid-based, or hydrostatic, skeletons).

Hydrostatic Skeletons

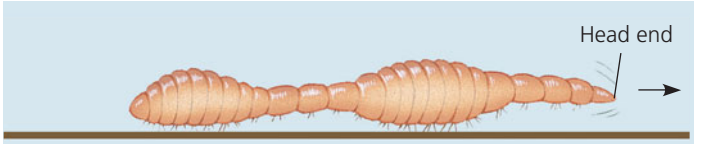
A **hydrostatic skeleton** consists of fluid held under pressure in a closed body compartment. This is the main type of skeleton in most cnidarians, flatworms, nematodes (roundworms), and annelids (segmented worms). These animals control their form and movement by using muscles to change the shape

of fluid-filled compartments. For example, a hydra (a cnidarian) elongates its body by closing its mouth and constricting its central gastrovascular cavity. Because water cannot be compressed very much, decreasing the diameter of the cavity forces the cavity to become longer.

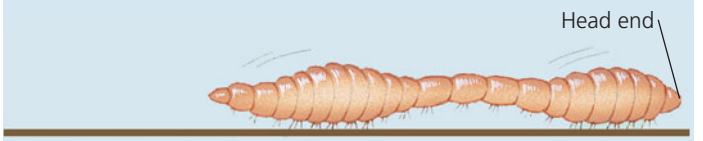
Worms use hydrostatic skeletons in diverse ways to move through their environment. In planarians and other flatworms, muscles in the body wall exert localized forces against the interstitial fluid. In nematodes, longitudinal muscles contracting around the fluid-filled body cavity move the animal forward by wavelike motions called undulations. In earthworms and many other annelids, circular and longitudinal muscles act together to change the shape of individual fluid-filled segments, which are divided by septa. These shape changes bring about **peristalsis**, a movement produced by rhythmic waves of muscle contractions passing from front to back **(Figure 39.11)**.



1 At the moment depicted, body segments at the earthworm's head end and just in front of the rear end are short and thick (longitudinal muscles contracted; circular muscles relaxed) and are anchored to the ground by bristles. The other segments are thin and elongated (circular muscles contracted; longitudinal muscles relaxed).



2 The head has moved forward because circular muscles in the head segments have contracted. Segments behind the head and at the rear are now thick and anchored, thus preventing the worm from slipping backward.



3 The head segments are thick again and anchored in their new positions. The rear segments have released their hold on the ground and have been pulled forward.

▲ **Figure 39.11 Crawling by peristalsis.** Contraction of the longitudinal muscles thickens and shortens the earthworm; contraction of the circular muscles constricts and elongates it.

Hydrostatic skeletons are well suited for life in aquatic environments. On land, they provide support for crawling and burrowing and may cushion internal organs. However, a hydrostatic skeleton cannot support walking or running, in which an animal's body is held off the ground.

Exoskeletons

The clamshell you find on a beach once served as an **exoskeleton**, a hard encasement deposited on an animal's surface. The shells of clams and most other molluscs are made of calcium carbonate secreted by the mantle, a sheetlike extension of the body wall. Clams and other bivalves close their hinged shell using muscles attached to the inside of this exoskeleton. As the animal grows, it enlarges its shell by adding to the outer edge.

Insects and other arthropods have a jointed *cuticle,* a coat secreted by the epidermis. About 30–50% of the cuticle consists of **chitin**, a polysaccharide similar to cellulose. Fibrils of chitin are embedded in a protein matrix, forming a composite material that is strong and flexible. Except in body parts that must be flexible, such as leg joints, the cuticle may be hardened by cross-linking the matrix proteins. Muscles attach to knobs and plates of the cuticle that extend into the interior of the body. With each growth spurt, an arthropod must shed its exoskeleton (molt) and produce a larger one.

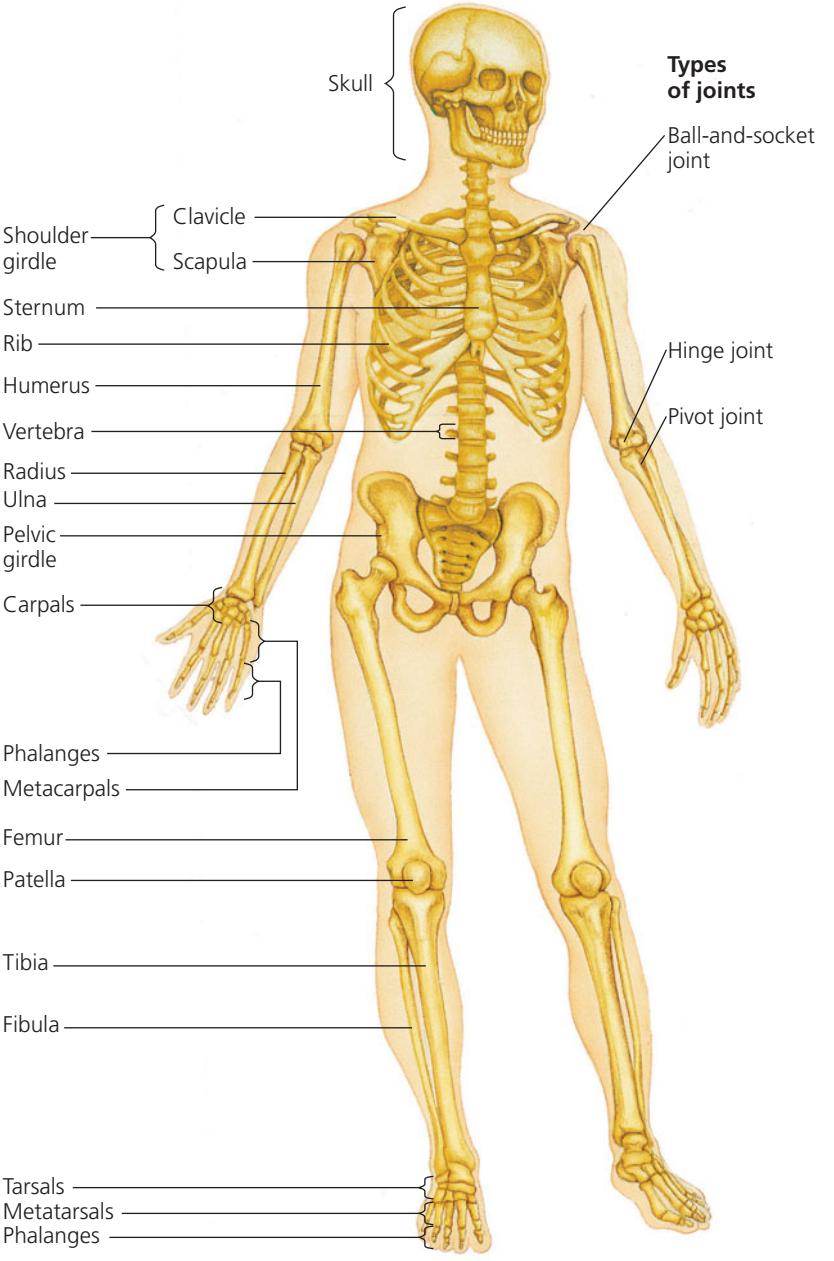
Endoskeletons

Animals ranging from sponges to mammals have a hardened internal skeleton, or **endoskeleton**, buried within their soft tissues. In sponges, the endoskeleton often consists of hard needlelike structures of inorganic material (see Figure 27.3). Echinoderms' bodies are reinforced by ossicles, hard plates composed of magnesium carbonate and calcium carbonate crystals. While the ossicles of sea urchins are tightly bound, those of sea stars are more loosely linked, allowing a sea star to change the shape of its arms.

Chordates have an endoskeleton consisting of cartilage, bone, or some combination of these materials. The human skeleton is built from more than 200 bones **(Figure 39.12)**. Some are fused together; others are connected at joints by ligaments that allow freedom of movement in a manner determined by the joint architecture **(Figure 39.13)**.

Size and Scale of Skeletons

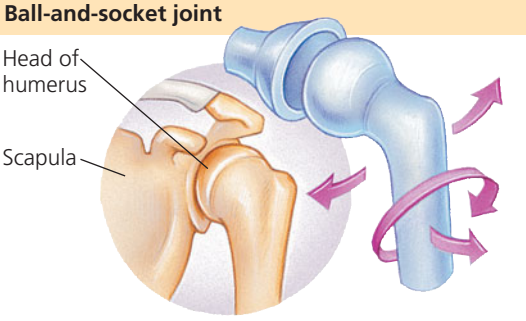
An exoskeleton needs to cover and protect an animal's body, but what determines how thick an endoskeleton must be? Consider a mouse. Its weight is proportional to its volume, a *cubic* measurement (roughly height times width times length). However, the strength of a bone, such as that in the mouse's leg, is proportional to cross-sectional area (and thus the *square* of the radius). We can predict that if we scaled up a mouse to the size of an elephant, the legs of the giant mouse would be too thin to support its weight. Indeed, large animals do have very different body proportions from those of small animals.



▲ **Figure 39.12** **Bones and joints of the human skeleton.**

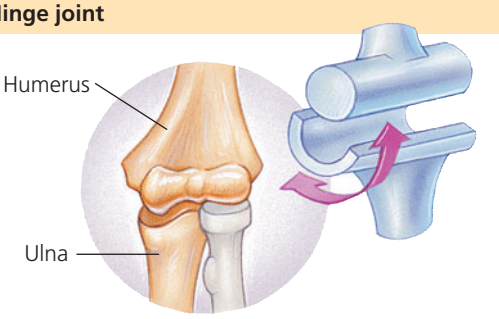
▼ **Figure 39.13** **Types of joints.**

Ball-and-socket joint



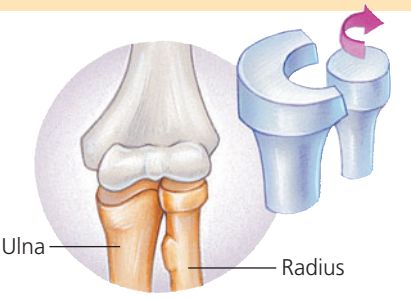
Ball-and-socket joints are found where the humerus contacts the shoulder girdle and where the femur contacts the pelvic girdle. These joints enable the arms and legs to rotate and move in several planes.

Hinge joint



Hinge joints, such as between the humerus and the head of the ulna, restrict movement to a single plane.

Pivot joint



Pivot joints enable rotating the forearm at the elbow and turning the head from side to side.

Based on physical principles, we might also predict that the size of an animal's leg bones should be directly proportional to the strain imposed by its body weight. However, it turns out that body posture—the position of the legs relative to the main body—is more important than leg size, at least in mammals and birds. Muscles and tendons (connective tissue that joins muscle to bone) hold the legs of large mammals relatively straight and positioned under the body and actually bear most of the load.

Types of Locomotion

For most animals, activities such as obtaining food, avoiding danger, and finding a mate involve **locomotion**—active travel from place to place. To move, an animal must expend energy to overcome two forces: friction and gravity. As you will see next, the amount of energy required to oppose friction or gravity is often reduced by an animal body plan adapted for movement in a particular environment.

Flying

Active flight (in contrast to gliding downward from a tree) has evolved in only a few animal groups: insects, reptiles (including birds), and, among the mammals, bats. One group of flying reptiles, the pterosaurs, died out millions of years ago, leaving birds and bats as the only flying vertebrates.

Gravity poses a major problem for a flying animal because its wings must develop enough lift to overcome gravity's downward force. The key to flight is wing shape. All wings are airfoils—structures whose shape alters air currents in a way that helps animals or airplanes stay aloft. As for the body to which the wings attach, a sleek, fusiform (torpedo-like) shape helps reduce drag.

Flying animals are relatively light, with body masses ranging from less than a gram for some insects to about 20 kg for the largest flying birds. Many flying animals have structural adaptations that contribute to low body mass. Birds, for example, have no urinary bladder or teeth and have relatively large bones with air-filled regions that help lessen the bird's mass.

Locomotion on Land

On land, an animal must be able to support itself and move against gravity, but air poses relatively little resistance, at least at moderate speeds. When an animal walks, runs, or hops, its leg muscles expend energy both to propel it and to keep it from falling down. With each step, the leg muscles must overcome inertia by accelerating a leg from a standing start. Thus, on land, powerful muscles and strong skeletal support are more important than a streamlined shape.

Diverse adaptations for traveling on land have evolved in various vertebrates. For example, kangaroos have large, powerful muscles in their hind legs, suitable for hopping **(Figure 39.14)**. As a kangaroo lands after each leap, tendons in its hind legs momentarily store energy. The farther the animal hops, the more energy its tendons store. Like the energy in a compressed spring, the energy stored in the tendons is available for the next jump, reducing the total amount of energy the animal must expend to travel. Human legs also retain some energy during walking or running, although a considerably smaller share than the legs of a kangaroo.

▲ **Figure 39.14 Energy-efficient locomotion on land.** Members of the kangaroo family travel from place to place mainly by leaping on their large hind legs. Kinetic energy momentarily stored in tendons after each leap provides a boost for the next leap. In fact, a large kangaroo hopping at 30 km/hr uses no more energy per minute than it does at 6 km/hr. The large tail helps balance the kangaroo when it leaps as well as when it sits.

Balance is another prerequisite for walking, running, or hopping. A kangaroo's large tail helps balance its body during leaps and forms a stable tripod with its hind legs when it moves slowly. Similarly, a cat, dog, or horse keeps three feet on the ground when walking. Bipedal animals, such as humans and birds, keep part of at least one foot on the ground when walking. At running speeds, momentum more than foot contact keeps the body upright, enabling all the feet to be off the ground briefly.

Crawling poses a very different situation. Because much of its body is in contact with the ground, a crawling animal must exert considerable effort to overcome friction. You have read how earthworms crawl by peristalsis. Many snakes crawl by undulating their entire body from side to side. Assisted by large, movable scales on its underside, a snake's body pushes against the ground, propelling the animal forward. In contrast, boa constrictors and pythons creep straight forward, driven by muscles that lift belly scales off the ground, tilt the scales forward, and then push them backward against the ground.

Swimming

Because most animals are reasonably buoyant in water, overcoming gravity is less of a problem for swimming than for movement on land or through the air. However, water is a much denser and more viscous medium than air, and thus drag (friction) is a major problem for aquatic animals. A fusiform (torpedo-like) shape is a common adaptation of fast swimmers, such as tuna.

Although most animal phyla include species that swim, swimming occurs in diverse ways. For instance, many insects and four-legged vertebrates use their legs as oars to push against the water. Squids, scallops, and some cnidarians are jet-propelled, taking in water and squirting it out in bursts. Sharks and bony fishes swim by moving their body and tail from side to side, while whales and dolphins move by undulating their body and tail up and down.

All these forms of locomotion place different energetic demands on animals. In the **Scientific Skills Exercise**, you can interpret a graph that compares the relative energy costs of flying, running, and swimming.

CONCEPT CHECK 39.2

1. In what way are septa an important feature of the earthworm skeleton?
2. Contrast swimming and flying in terms of the main problems they pose and the adaptations that allow animals to overcome those problems.
3. **WHAT IF?** When using your arms to lower yourself into a chair, you bend your arms without using your biceps. Explain how this is possible. (*Hint*: Think about gravity as an antagonistic force.)

For suggested answers, see Appendix A.

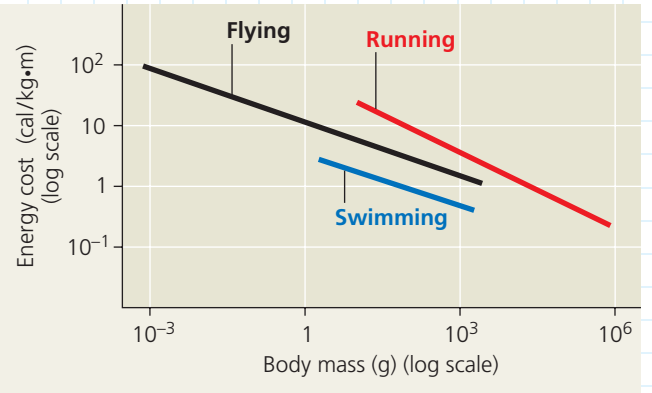
Scientific Skills Exercise

Interpreting a Graph with Log Scales

What Are the Energy Costs of Locomotion? In the 1960s, animal physiologist Knut Schmidt-Nielsen, at Duke University, wondered whether general principles govern the energy costs of different forms of locomotion among diverse animal species. To answer this question, he drew on his own experiments as well as those of other researchers. In this exercise, you will analyze the combined results of these studies and evaluate the rationale for plotting the experimental data on a graph with logarithmic scales.

How the Experiments Were Done Researchers measured the rate of oxygen consumption or carbon dioxide production in animals that ran on treadmills, flew in wind tunnels, or swam in water flumes. From these measurements, Schmidt-Nielsen calculated the amount of energy each animal used to transport a given amount of body mass over a given distance (in calories per kilogram per meter).

Data from the Experiments Schmidt-Nielsen plotted the cost of running, flying, and swimming versus body mass on a single graph with logarithmic (log) scales for the axes. He then drew a best-fit straight line through the data points for each form of locomotion. (On the graph below, only the best-fit lines are shown.)



Interpret the Data

1. The body masses of the animals used in these experiments ranged from about 0.001 g to 1,000,000 g, and their rates of energy use ranged from about 0.1 cal/kg•m to 100 cal/kg•m. If you were to plot these data on a graph with linear instead of log scales for the axes, how would you draw the axes so that all of the data would be visible? What is the advantage of using log scales for plotting data with a wide range of values? (For additional information about graphs, see the Scientific Skills Review in Appendix F and in the Study Area in MasteringBiology.)
2. Based on the graph, how much greater is the energy cost of flying for an animal that weighs 10^{-3} g than for an animal that weighs 1 g? For any given form of locomotion, which travels more efficiently, a larger animal or a smaller animal?
3. The slopes of the flying and swimming lines are very similar. Based on your answer to question 2, if the energy cost of a 2-g swimming animal is 1.2 cal/kg•m, what is the estimated energy cost of a 2-kg swimming animal?
4. Considering animals with a body mass of about 100 g, rank the three forms of locomotion from highest energy cost to lowest energy cost. Were these the results you expected, based on your own experience? What could explain the energy cost of running compared with that of flying or swimming?
5. Schmidt-Nielson calculated the swimming cost for a mallard duck and found that it was nearly 20 times as high as the swimming cost for a salmon of the same body mass. What could explain the greater swimming efficiency of salmon?

Data from K. Schmidt-Nielsen, Locomotion: Energy cost of swimming, flying, and running, *Science* 177:222–228 (1972).

MB A version of this Scientific Skills Exercise can be assigned in MasteringBiology.

CONCEPT 39.3

Discrete sensory inputs can stimulate both simple and complex behaviors

So far we have been discussing the mechanics of animal behaviors—how the animal body produces the movements that make up a particular behavior. In the rest of the chapter, we'll take a broader look at the function of animal behaviors as well as their evolution.

What approach do biologists use to determine how behaviors arise and what functions they serve? The Dutch scientist Niko Tinbergen, a pioneer in the study of animal behavior, suggested that understanding any behavior requires answering four questions, which can be summarized as follows:

1. What stimulus elicits the behavior, and what physiological mechanisms mediate the response?
2. How does the animal's experience during growth and development influence the response?
3. How does the behavior aid survival and reproduction?
4. What is the behavior's evolutionary history?

Tinbergen's first two questions ask about *proximate causation*: "how" a behavior occurs or is modified. The last two questions ask about *ultimate causation*: "why" a behavior occurs in the context of natural selection.

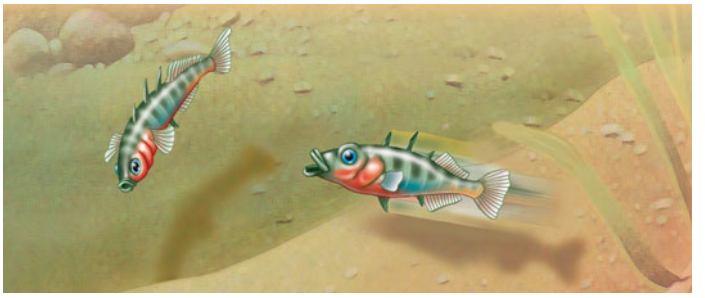
The idea of ultimate causation is central to **behavioral ecology**, the study of the ecological and evolutionary basis for animal behavior. As we explore this vibrant area of modern biological research, we'll also review studies on proximate causation by Tinbergen and two other early researchers—Karl von Frisch and Konrad Lorenz—that earned the three scientists a Nobel Prize in 1973.

In addressing Tinbergen's first question, the nature of the stimuli that trigger behavior, we'll begin with behavioral responses to well-defined stimuli, starting with an example from Tinbergen's own experiments.

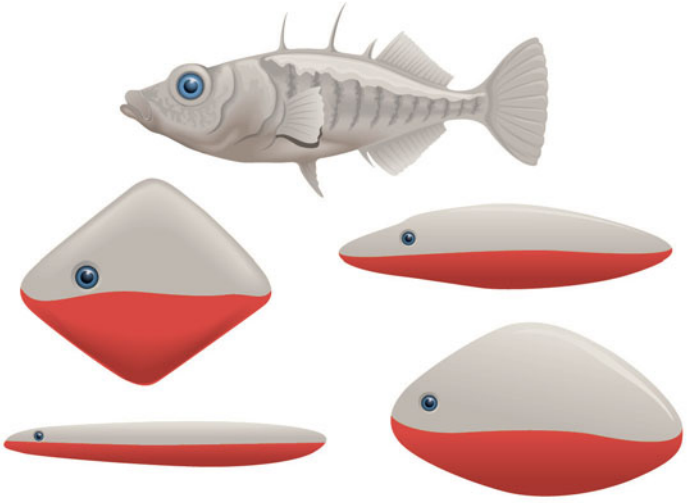
Fixed Action Patterns

As part of his research, Tinbergen kept fish tanks containing three-spined sticklebacks (*Gasterosteus aculeatus*). Male sticklebacks, which have red bellies, attack other males that invade their nesting territories. Tinbergen noticed that his male sticklebacks also behaved aggressively when a red truck passed within view of their tank. Inspired by this chance observation, he carried out experiments showing that the red color of an intruder's underside is what provokes the attack behavior. A male stickleback will not attack a fish lacking red coloration (note that female sticklebacks never have red bellies), but will attack even unrealistic models if they contain areas of red color **(Figure 39.15)**.

The territorial response of male sticklebacks is an example of a **fixed action pattern**, a sequence of unlearned acts directly linked to a simple stimulus. Fixed action patterns are essentially unchangeable and, once initiated, usually carried to completion. The trigger for the behavior is an external cue called a **sign stimulus**, such as a red object prompting the male stickleback's aggressive behavior.



(a) A male stickleback fish attacks other male sticklebacks that invade its nesting territory. The red belly of the intruding male (left) acts as the sign stimulus that releases the aggressive behavior.



(b) The realistic model at the top, without a red underside, produces no aggressive response in a male three-spined stickleback. The other models, with red undersides, produce strong responses.

▲ Figure 39.15 Sign stimuli in a classic fixed action pattern.

? *Suggest an explanation for why this behavior evolved (its ultimate causation).*

Migration

Environmental stimuli not only trigger behaviors but also provide cues that animals use to carry out those behaviors. For example, a wide variety of birds, fishes, and other animals use environmental cues to guide **migration**—a regular, long-distance change in location. In the course of migration, many animals pass through environments they have not previously encountered. How, then, do they find their way in these foreign settings?

Some migrating animals track their position relative to the sun, even though the sun's position relative to Earth changes throughout the day. Animals can adjust for these changes by means of a *circadian clock*, an internal mechanism that maintains a 24-hour activity rhythm or cycle. For example, experiments have shown that migrating birds orient differently relative to the sun at distinct times of the day.

Although the sun as well as stars can provide clues for navigation, these landmarks can be obscured by clouds. How do migrating animals overcome this problem? A simple experiment with homing pigeons provides one answer. On an overcast day, placing a small magnet on the head of a homing pigeon prevents it from returning efficiently to its roost. Researchers concluded that pigeons sense their position relative to Earth's magnetic field and can thereby navigate without solar or celestial cues.

Behavioral Rhythms

Although the circadian clock plays a small but significant role in navigation by some migrating species, it has a major role in the daily activity of all animals. The clock is responsible for a circadian rhythm, a daily cycle of rest and activity (see Concept 38.2). The clock is normally synchronized with the light and dark cycles of the environment but can maintain rhythmic activity even under constant environmental conditions, such as during hibernation.

Some behaviors, such as migration and reproduction, reflect biological rhythms with a longer cycle, or period, than the circadian rhythm. Behavioral rhythms linked to the yearly cycle of seasons are called *circannual rhythms*. Although migration and reproduction typically correlate with food availability, these behaviors are not a direct response to changes in food intake. Instead, circannual rhythms, like circadian rhythms, are influenced by the periods of daylight and darkness in the environment. For example, studies with several bird species have shown that an artificial environment with extended daylight can induce out-of-season migratory behavior.

Not all biological rhythms are linked to the light and dark cycles in the environment. Consider, for instance, the fiddler crab shown in Figure 39.1. The male's claw-waving courtship behavior is linked not to day length but to the timing of the new and full moon. Why? Fiddler crabs begin their lives as plankton, settling in the mudflats after several larval stages. By courting at the time of the new or full moon, crabs link their

reproduction to the times of greatest tidal movement. The tides disperse larvae to deeper waters, where they complete early development in relative safety.

Animal Signals and Communication

Claw waving by fiddler crabs during courtship is an example of one animal (the male crab) generating the stimulus that guides the behavior of another animal (the female crab). A stimulus transmitted from one animal to another is called a **signal**. Signal transmission and reception constitute animal **communication**, an essential element of interactions between individuals.

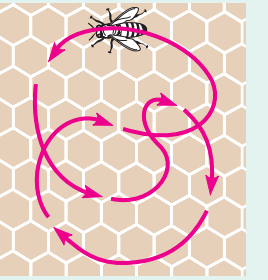
Forms of Animal Communication

Let's consider the courtship behavior of the fruit fly, *Drosophila melanogaster*, as an introduction to the four common modes of animal communication: visual, chemical, tactile, and auditory.

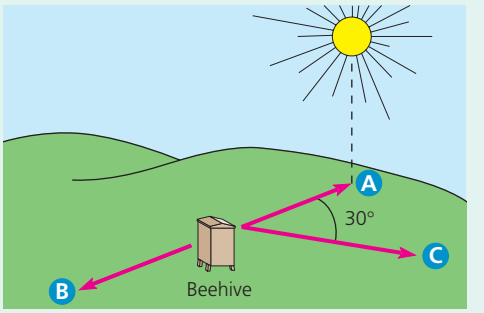
Fruit fly courtship constitutes an example of a *stimulus-response chain*, in which the response to each stimulus is itself the stimulus for the next behavior. In the first step, a male sees a female of the same species and orients his body toward hers. He also uses his olfactory system to detect chemicals released into the air by the female. The male then approaches and touches the female with a foreleg. This touching, or tactile communication, alerts the female to the male's presence. In the third stage of courtship, the male extends and vibrates his wing, producing a specific courtship song. This auditory communication informs the female whether the male is of the same species. Only if all of these forms of communication are successful will the female allow the male to attempt copulation.

The information content of animal communication varies considerably. One of the most remarkable examples is the symbolic language of the European honeybee (*Apis mellifera*), discovered in the early 1900s by Austrian researcher Karl von Frisch. Using glass-walled observation hives, he and his students spent several decades observing honeybees. Methodical recordings of bee movements enabled von Frisch to decipher a "dance language" that returning foragers use to inform other bees about the distance and direction of travel to food sources **(Figure 39.16)**. When the other bees then exit the hive, they fly almost directly to the area indicated by the returning foragers.

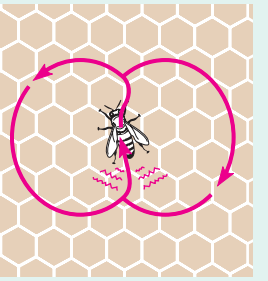
(a) Worker bees cluster around a bee that recently returned from a foraging trip.



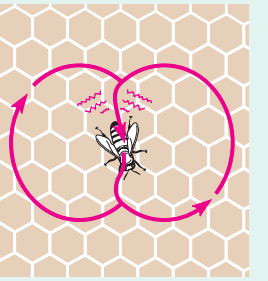
(b) The round dance indicates that food is near.



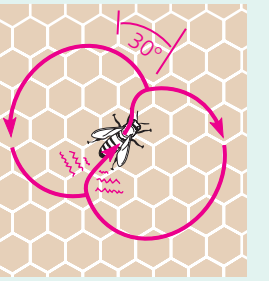
(c) The waggle dance, performed when food is distant, resembles a figure eight (below). Distance is indicated by the number of abdominal waggles performed in the straight-run part of the dance. Direction is indicated by the angle (in relation to the vertical surface of the hive) of the straight run.



Location A: Food source is in same direction as sun.



Location B: Food source is in direction opposite sun.



Location C: Food source is 30° to right of sun.

▲ **Figure 39.16 Honeybee dance language.** Honeybees returning to the hive communicate the location of food sources through the symbolic language of a dance.

Pheromones

Animals that communicate through odors or tastes emit chemical substances called **pheromones**. Pheromones are especially common among mammals and insects and often relate to reproductive behavior. For example, pheromones are the basis for the chemical communication in fruit fly courtship. Pheromones are not limited to short-distance signaling, however. Male silkworm moths have receptors that can detect the pheromone from a female moth from several kilometers away.

In a honeybee colony, pheromones produced by the queen and her daughters, the workers, maintain the hive's complex social order. One pheromone (once called the queen

substance) has a particularly wide range of effects. It attracts workers to the queen, inhibits development of ovaries in workers, and attracts males (drones) to the queen during her mating flights out of the hive.

Pheromones can also serve as alarm signals. For example, when a minnow is injured, a substance released from the fish's skin disperses in the water, causing nearby minnows to become more vigilant and seek safety near the lake bottom.

As we have seen, the forms of animal communication used to convey information are quite diverse. In general, the form of communication that evolves is closely related to an animal's lifestyle and environment. For example, most terrestrial mammals are nocturnal, which makes visual displays relatively ineffective. Instead, these species use olfactory and auditory signals, which work as well in the dark as in the light. In contrast, most birds are diurnal (active mainly in daytime) and communicate primarily by visual and auditory signals. Humans are also diurnal and, like birds, use primarily visual and auditory communication. We can thus appreciate the songs and bright colors used by birds to communicate but miss many chemical cues on which other mammals base their behavior.

So far in this chapter, we have explored the types of stimuli that elicit behaviors—the first part of Tinbergen's first question. The second part of that question—the physiological mechanisms that mediate responses—involve the nervous, muscular, and skeletal systems: Stimuli activate sensory receptors, triggering signals that are processed in the central nervous system and result in motor outputs that constitute behavior. Thus, we are ready to focus on Tinbergen's second question—how experience influences behavior.

CONCEPT CHECK 39.3

1. If an egg rolls out of the nest, a mother graylag goose will retrieve it by nudging it with her beak and head. If researchers remove the egg or substitute a ball during this process, the goose continues to bob her beak and head while she moves back to the nest. Explain how and why this behavior occurs.
2. **MAKE CONNECTIONS** How is the lunar-linked rhythm of fiddler crab courtship similar in mechanism and function to the seasonal timing of plant flowering? (See Concept 31.2.)

For suggested answers, see Appendix A.

CONCEPT 39.4

Learning establishes specific links between experience and behavior

For some behaviors—such as a fixed action pattern, a courtship stimulus-response chain, and pheromone signaling—nearly all individuals in a population behave the same. Behavior that is developmentally fixed in this way is known as **innate behavior**. Other behaviors, however, vary with experience and thus differ between individuals.

Experience and Behavior

Tinbergen's second question asks how an animal's experiences during growth and development influence the response to stimuli. One informative approach to this question is a **cross-fostering study**, in which the young of one species are placed in the care of adults from another species. The extent to which the offspring's behavior changes in such a situation provides a measure of how the social and physical environment influences behavior.

Certain mouse species have behaviors well suited for cross-fostering studies. For example, male California mice (*Peromyscus californicus*) are highly aggressive toward other mice and provide extensive parental care. In contrast, male white-footed mice (*Peromyscus leucopus*) are less aggressive and engage in little parental care. When the pups of each species were placed in the nests of the other species, the cross-fostering altered some behaviors of both species **(Table 39.2)**. For instance, male California mice raised by white-footed mice were less aggressive toward intruders. Thus, experience during development can strongly influence aggressive behavior in these rodents.

One of the most important findings of the cross-fostering experiments with mice was that the influence of experience on behavior can be passed on to progeny: When the cross-fostered California mice became parents, they spent less time retrieving offspring who wandered off than did California mice raised by their own species. Thus, experience during development can modify physiology in a way that alters parental behavior, extending the influence of environment to a subsequent generation.

The influence of genetics and environment on human behavior can be explored by a **twin study**, in which researchers compare the behavior of identical twins raised apart with the behavior of those raised in the same household. Twin studies have been instrumental in studying human behavioral disorders, including schizophrenia, anxiety disorders, and alcoholism.

Learning

One powerful way that an animal's environment can influence its behavior is through **learning**, the modification of behavior based on specific experiences. The capacity for learning

Table 39.2 Influence of Cross-Fostering on Male Mice*

Species	Aggression Toward an Intruder	Aggression in Neutral Situation	Paternal Behavior
California mice fostered by white-footed mice	Reduced	No difference	Reduced
White-footed mice fostered by California mice	No difference	Increased	No difference

*Comparisons are with mice raised by parents of their own species.

depends on nervous system organization established during development following instructions encoded in the genome. Learning itself involves the formation of memories by specific changes in neuronal connectivity (see Concept 38.3). Therefore, the essential challenge for research into learning is not to decide between nature (genes) and nurture (environment), but rather to explore the contributions of *both* nature and nurture in shaping learning and, more generally, behavior.

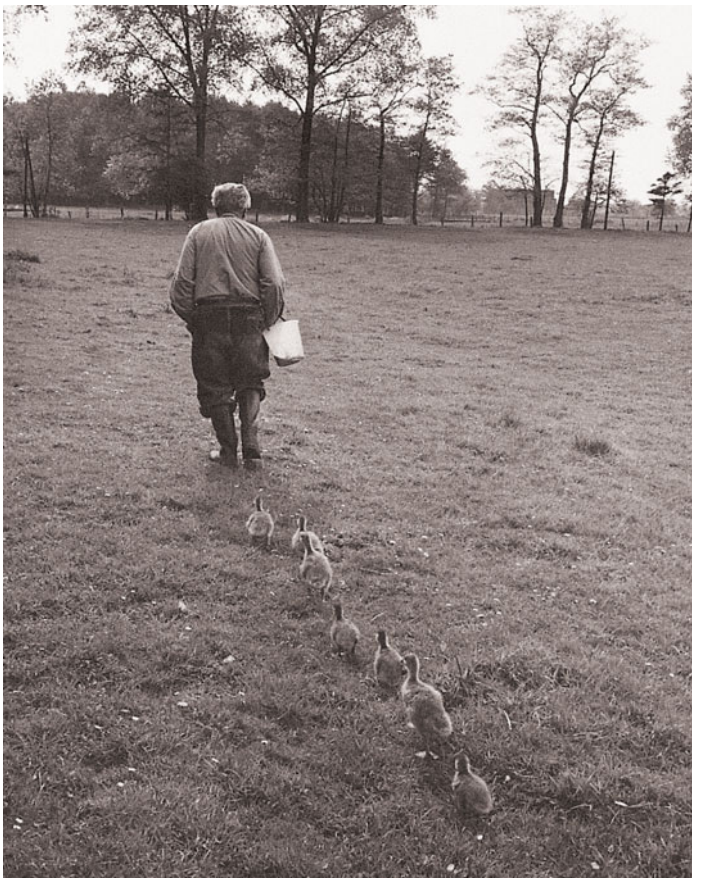
Imprinting

For some offspring, recognizing and being recognized by a parent is essential for survival. In the young, this learning often takes the form of **imprinting**, the establishment of a long-lasting behavioral response to a particular individual. Imprinting can take place only during a specific time in development, called the **sensitive period**. Among gulls, for instance, the sensitive period for a parent to bond with its young lasts one to two days. During the sensitive period, the young imprint on their parent and learn basic behaviors, while the parent learns to recognize its offspring. If bonding does not occur, the parent will not care for the offspring, leading to the death of the offspring and a decrease in the reproductive success of the parent.

How do the young know on whom—or what—to imprint? Experiments with many species of waterfowl indicate that young birds have no innate recognition of "mother." Rather, they identify with the first object they encounter that has certain key characteristics. In the 1930s, the Austrian researcher Konrad Lorenz showed that the principal *imprinting stimulus* in greylag geese (*Anser anser*) is a nearby object that is moving away from the young. When incubator-hatched goslings spent their first few hours with Lorenz rather than with a goose, they imprinted on him and steadfastly followed him from then on **(Figure 39.17a)**. Furthermore, they showed no recognition of their biological mother.

Imprinting has become an important component of efforts to save endangered species, such as the whooping crane (*Grus americana*). Scientists tried raising whooping cranes in captivity by using sandhill cranes (*Grus canadensis*) as foster parents. However, because the whooping cranes imprinted on their foster parents, none formed a *pair-bond* (strong attachment) with a whooping crane mate. To avoid such problems, captive breeding programs now isolate young cranes, exposing them to the sights and sounds of members of their own species.

Scientists have made further use of imprinting to teach cranes born in captivity to migrate along safe routes. Young whooping cranes are imprinted on humans in "crane suits" and then are allowed to follow these "parents" as they fly ultralight aircraft along selected migration routes **(Figure 39.17b)**. Importantly, these cranes still pair-bond with other whooping cranes, indicating that the crane costumes have the features required to direct "normal" imprinting.



(a) These young greylag geese imprinted on ethologist Konrad Lorenz.

(b) A pilot wearing a crane suit and flying an ultralight plane acts as a surrogate parent to direct the migration of whooping cranes.

▲ Figure 39.17 Imprinting. Imprinting can be altered to **(a)** investigate animal behavior or **(b)** direct animal behavior.

? *Suppose the geese following Lorenz were bred to each other. How might their imprinting on Lorenz affect their offspring? Explain.*

Spatial Learning and Cognitive Maps

Every natural environment has spatial variation, as in locations of nest sites, hazards, food, and prospective mates. Therefore, an organism's fitness may be enhanced by the capacity for **spatial learning**, the establishment of a memory that reflects the environment's spatial structure.

The idea of spatial learning intrigued Tinbergen while he was a graduate student in the Netherlands. At that time, he was studying the female digger wasp (*Philanthus triangulum*), which nests in small burrows dug into sand dunes. When a wasp leaves her nest to go hunting, she hides the entrance to the burrow from potential intruders by covering it with sand. When she returns, however, she flies directly to her hidden nest, despite the presence of hundreds of other burrows in the area. How does she accomplish this feat? Tinbergen hypothesized that a wasp locates her nest by learning its position relative to visible landmarks. To test his hypothesis, he carried out an experiment in the wasps' natural habitat **(Figure 39.18)**. By manipulating objects around nest entrances, he demonstrated that digger wasps engage in spatial learning.

In some animals, spatial learning involves the formation of a **cognitive map**, a representation in the nervous system of the spatial relationships between objects in an animal's surroundings. One striking example is found in the Clark's nutcracker (*Nucifraga columbiana*), a relative of ravens, crows, and jays. In the fall, nutcrackers hide pine seeds for retrieval during the winter. By experimentally varying the distance between landmarks in the birds' environment, researchers discovered that birds used the halfway point between landmarks, rather than a fixed distance, to find their hidden food stores.

Associative Learning

Learning often involves making associations between experiences. Consider, for example, a blue jay (*Cyanocitta cristata*) that ingests a brightly colored monarch butterfly (*Danaus plexippus*). Substances that the monarch accumulates from milkweed plants cause the blue jay to vomit almost immediately **(Figure 39.19)**. Following such experiences, blue jays avoid attacking monarchs and similar-looking butterflies. The ability to associate one environmental feature (such as a color) with another (such as a foul taste) is called **associative learning**.

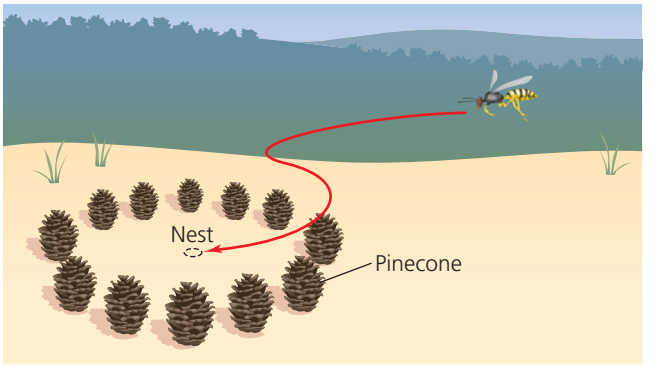
Studies reveal that animals can learn to link many pairs of features of their environment, but not all. For example, pigeons can learn to associate danger with a sound but not with a color. However, they can learn to associate a color with food. What does this mean? The development and organization of the pigeon's nervous system apparently restrict the associations that can be formed. Moreover, such restrictions are not limited to birds. Rats, for example, can learn to avoid illness-inducing foods on the basis of smells, but not on the basis of sights or sounds.

If we consider how behavior evolves, the fact that some animals can't learn to make particular associations appears logical. The associations an animal can readily form typically reflect relationships likely to occur in nature. Conversely, associations that can't be formed are those unlikely to be of selective advantage in a native environment. In the case of a rat's diet in the wild, for example, a harmful food is far more likely to have a certain odor than to be associated with a particular sound.

▼ Figure 39.18 Inquiry

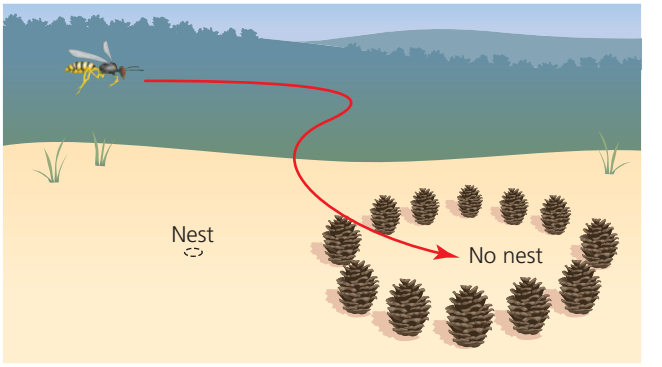
Does a digger wasp use landmarks to find her nest?

Experiment A female digger wasp covers the entrance to her underground nest while foraging long distances for food, but she can return later to the exact location and uncover her hidden nest. Niko Tinbergen hypothesized that the female, before flying off, learns visual landmarks that mark her nest location. To test this hypothesis, he first marked one nest with a ring of pinecones while the wasp was in the nest. After leaving the nest to forage, the wasp returned to the nest successfully.



Two days later, after the wasp had again left, Tinbergen shifted the ring of pinecones away from the nest. Then he waited to observe the wasp's behavior.

Results When the wasp returned, she flew to the center of the pinecone circle instead of to the nearby nest. Repeating the experiment with many wasps, Tinbergen obtained the same results.



Conclusion The experiment supported the hypothesis that digger wasps use visual landmarks to keep track of their nests.

Source N. Tinbergen, *The Study of Instinct*, Clarendon Press, Oxford (1951).

WHAT IF? *Suppose the digger wasp had returned to her original nest site, despite the pinecones having been moved. What alternative hypotheses might you propose regarding how the wasp finds her nest and why the pinecones didn't misdirect the wasp?*

Cognition and Problem Solving

The most complex forms of learning involve **cognition**—the process of knowing that involves awareness, reasoning, recollection, and judgment. Many animals, including insects, appear to exhibit cognition in controlled laboratory studies. For

▲ **Figure 39.19 Associative learning.** Having eaten and vomited a monarch butterfly, a blue jay has probably learned to avoid this species.

example, an experiment using Y-shaped mazes demonstrated that honeybees can distinguish between "same" and "different."

The information-processing ability of a nervous system can also be revealed in **problem solving**, the cognitive activity of devising a method to proceed from one state to another in the face of obstacles. For example, if a chimpanzee is placed in a room with several boxes on the floor and a banana hung high out of reach, the chimp can assess the situation and stack the boxes, enabling it to reach the food. Such problem-solving behavior is highly developed in some mammals, especially primates and dolphins. Notable examples have also been observed in some bird species. In one study, ravens were confronted with food hanging from a branch by a string. After failing to grab the food in flight, one raven flew to the branch and alternately pulled up and stepped on the string until the food was within reach. A number of other ravens eventually arrived at similar solutions. Nevertheless, some ravens failed to solve the problem, indicating that problem-solving success in this species, as in others, varies with individual experience and abilities.

Many animals learn to solve problems by observing the behavior of other individuals. Young wild chimpanzees, for example, learn how to crack open oil palm nuts with two stones by copying experienced chimpanzees. This type of learning through observing others is called **social learning**. Social learning forms the roots of **culture**, which can be defined as a system of information transfer through social learning or teaching that influences the behavior of individuals in a population. Cultural transfer of information can alter behavioral phenotypes and thereby influence the fitness of individuals.

CONCEPT CHECK 39.4

1. How might associative learning explain why different species of stinging insects have similar colors?
2. **WHAT IF?** How might you position and manipulate objects in a lab to test whether an animal can use a cognitive map to remember the location of food?
3. **MAKE CONNECTIONS** How could a learned behavior contribute to speciation? (See Concept 22.1.)

For suggested answers, see Appendix A.

CONCEPT 39.5

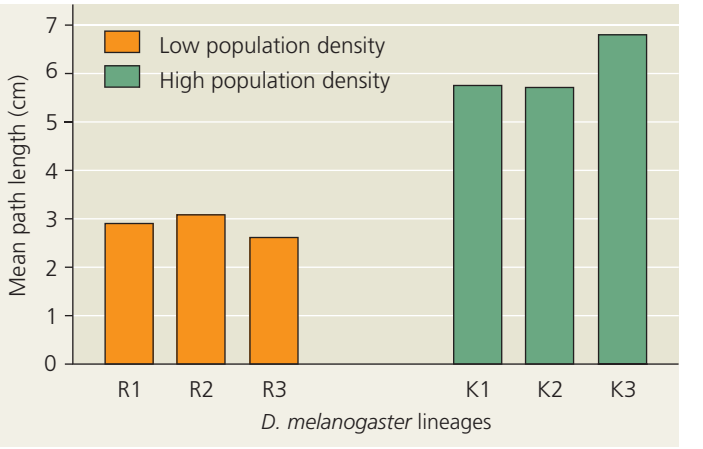
Selection for individual survival and reproductive success can explain most behaviors

We turn now to Tinbergen's third question—how behavior enhances survival and reproduction in a population. We'll begin by examining an activity essential for success in both endeavors: gathering food. Food-obtaining behavior, or **foraging**, includes not only eating but also any activities an animal uses to search for, recognize, and capture food items.

Evolution of Foraging Behavior

EVOLUTION The fruit fly allows us to examine one way foraging behavior might have evolved. Variation in a gene called *forager* (*for*) dictates how far *Drosophila* larvae travel when foraging. On average, larvae carrying the for^R ("Rover") allele travel nearly twice as far while foraging as larvae with the for^s ("sitter") allele.

Both the for^R and for^s alleles are present in natural populations. What circumstances might favor one or the other allele? The answer became apparent in experiments that maintained flies at either low or high population densities for many generations. Larvae in populations kept at a low density foraged over shorter distances than those in populations kept at high density **(Figure 39.20)**. Furthermore, the for^s allele increased in frequency in the low-density populations, whereas the for^R allele increased in frequency in the high-density group. These changes make sense. At a low population density, short-distance foraging yields sufficient food, while long-distance foraging would result in unnecessary energy expenditure. Under crowded conditions, long-distance foraging could



▲ **Figure 39.20 Evolution of foraging behavior by laboratory populations of *Drosophila melanogaster*.** After 74 generations of living at low population density, *D. melanogaster* larvae (populations R1–R3) followed foraging paths significantly shorter than those of *D. melanogaster* larvae that had lived at high density (populations K1–K3).

enable larvae to move beyond areas depleted of food. Thus, an interpretable evolutionary change in behavior occurred in the course of the experiment.

Mating Behavior and Mate Choice

Just as foraging is crucial for individual survival, mating behavior and mate choice play a major role in determining reproductive success. These behaviors include seeking or attracting mates, choosing among potential mates, competing for mates, and caring for offspring.

Mating Systems and Sexual Dimorphism

Although we tend to think of mating simply as the union of a male and a female, species vary greatly with regard to *mating systems,* the length and number of relationships between males and females. In some species, there are no strong pair-bonds. In others, mates form a relationship of some duration that is **monogamous** (one male mating with one female) or **polygamous** (an individual of one sex mating with several of the other). Polygamous relationships involve either *polygyny*, a single male and multiple females, or *polyandry*, a single female and multiple males.

The extent to which males and females differ in appearance, a characteristic known as *sexual dimorphism*, typically varies with the type of mating system **(Figure 39.21)**. Among monogamous species, males and females often look very similar. In contrast, among polygamous species, the sex that attracts multiple mating partners is typically showier and larger than the opposite sex. We'll discuss the evolutionary basis of these differences shortly.

Mating Systems and Parental Care

The needs of the young are an important factor constraining the evolution of mating systems. Most newly hatched birds, for instance, cannot care for themselves. Rather, they require a large, continuous food supply, a need that is difficult for a single parent to meet. In such cases, a male that stays with and helps a single mate may ultimately have more viable offspring than if it went off to seek additional mates. This may explain why many birds are monogamous. In contrast, for birds with young that can feed and care for themselves almost immediately after hatching, the males derive less benefit from staying with their partner. Males of these species, such as pheasants and quail, can maximize their reproductive success by seeking other mates, and polygyny is relatively common in such birds. In the case of mammals, the lactating female is often the only food source for the young; males usually play no role in raising the young. In mammalian species where males protect the females and young, such as lions, a male or small group of males typically cares for a harem of many females.

Another factor influencing mating behavior and parental care is *certainty of paternity*. Young born to or eggs laid by a female definitely contain that female's genes. However, even

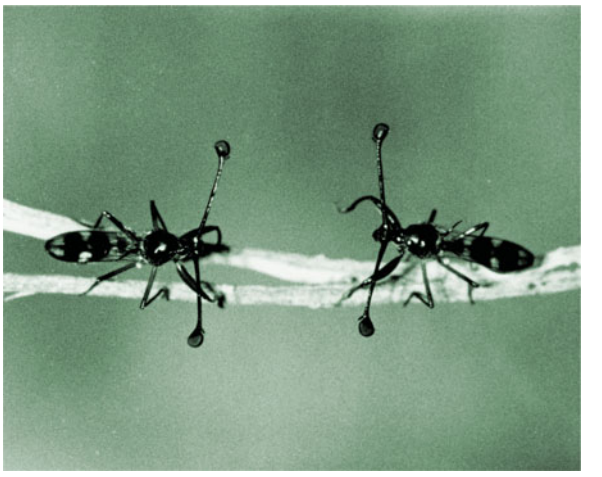
(a) In monogamous species, such as these western gulls, males and females are difficult to distinguish using external characteristics only.

(b) Among polygynous species, such as elk, the male (right) is often highly ornamented.

(c) In polyandrous species, such as these red-necked phalaropes, females (right) are generally more ornamented than males.

▲ Figure 39.21 Relationship between mating system and male and female forms.

▲ **Figure 39.22 Paternal care by a male jawfish.** The male jawfish, which lives in tropical marine environments, holds the eggs it has fertilized in its mouth, keeping them aerated and protecting them from egg predators until the young hatch.



▲ **Figure 39.23 Male stalk-eyed flies.** Male eye span plays a role in mate selection by females and, as shown here, in ritualized contests between males. In such contests, two males face off, with the male whose eye span is smaller very often retreating without any combat taking place.

within a normally monogamous relationship, a male other than the female's usual mate may have fathered that female's offspring.

The certainty of paternity is relatively low in most species with internal fertilization because the acts of mating and birth (or mating and egg laying) are separated over time. This could explain why exclusively male parental care is rare in bird and mammal species. However, the males of many species with internal fertilization engage in behaviors that appear to increase their certainty of paternity. These behaviors include guarding females, removing any sperm from the female reproductive tract before copulation, and introducing large quantities of sperm that displace the sperm of other males.

Certainty of paternity is high when egg laying and mating occur together, as in external fertilization. This may explain why parental care in aquatic invertebrates, fishes, and amphibians, when it occurs at all, is at least as likely to be by males as by females (**Figure 39.22**). Among fishes and amphibians, parental care occurs in less than 10% of species with internal fertilization but in more than half of species with external fertilization.

It is important to note that certainty of paternity does not mean that animals are aware of those factors when they behave a certain way. Parental behavior correlated with certainty of paternity exists because it has been reinforced over generations by natural selection. Nevertheless, the relationship between certainty of paternity and male parental care remains an area of active research.

Sexual Selection and Mate Choice

Sexual dimorphism results from sexual selection, a form of natural selection in which differences in reproductive success among individuals are a consequence of differences in mating success (see Chapter 21). Sexual selection can take the form of *intersexual selection*, in which members of one sex choose mates on the basis of characteristics of the other sex, such as courtship songs, or *intrasexual selection*, which involves competition between members of one sex for mates.

Mate preferences of females may play a central role in the evolution of male behavior and anatomy through intersexual selection. Consider, for example, the courtship behavior of stalk-eyed flies. The eyes of these insects are at the tips of stalks, which are longer in males than in females **(Figure 39.23)**. During courtship, a male approaches the female headfirst. Researchers have shown that females are more likely to mate with males that have relatively long eyestalks. Why would females favor this seemingly arbitrary trait? Ornaments such as long eyestalks in these flies or bright coloration in birds correlate in general with health and vitality (see Concept 21.4). A female whose mate choice is a healthy male is likely to produce more offspring that survive to reproduce.

Our consideration of stalk-eyed flies illustrates how female choice can select for one best type of male. This insect also shows how male competition for mates can reinforce the tendency for reduced variation among males. The length of the eyestalks of the male flies in Figure 39.23 is an important factor in conflict between males. This competition takes the form of an *agonistic behavior*, an often-ritualized contest that determines which competitor gains access to a resource, such as a mate.

CONCEPT CHECK 39.5

1. Why does the mode of fertilization correlate with the presence or absence of male parental care?
2. **MAKE CONNECTIONS** Balancing selection can maintain variation at a locus (see Concept 21.4). Based on the foraging experiments described in this chapter, devise a simple hypothesis to explain the presence of both for^R and for^S alleles in natural fly populations.

For suggested answers, see Appendix A.

CONCEPT 39.6

Inclusive fitness can account for the evolution of behavior, including altruism

EVOLUTION We now come to the focus of Tinbergen's fourth question—the evolutionary history of behaviors. First we'll look at the genetic control of a behavior. Next, we'll examine the genetic variation underlying the evolution of particular behaviors. Finally, we'll see how expanding the definition of fitness beyond individual survival can help explain "selfless" behavior.

Genetic Basis of Behavior

Although variation in multiple genes can bring about distinct behaviors, variation in a single locus is sometimes sufficient to bring about dramatic differences in behavior. One striking example is the behavior of two closely related species of voles, which are small, mouse-like rodents. Male meadow voles (*Microtus pennsylvanicus*) are solitary and do not form lasting relationships with mates. Following mating, they pay little attention to their pups. In contrast, male prairie voles (*Microtus ochrogaster*) form a pair-bond with a single female after they mate **(Figure 39.24)**. Male prairie voles hover over their young pups, licking them and carrying them, while acting aggressively toward intruders.

The peptide neurotransmitter vasopressin is critical for the partnering and parental behavior of male voles. Released during mating, vasopressin binds to a specific receptor in the central nervous system. When male prairie voles are given a drug that inhibits the brain receptor for vasopressin, they fail to form pair-bonds after mating.

The vasopressin receptor gene is highly expressed in the brains of prairie voles but not meadow voles. Testing the hypothesis that vasopressin receptor levels in the brain regulate postmating behavior, researchers inserted the vasopressin receptor gene from prairie voles into meadow voles. The male meadow voles carrying this gene not only developed brains with higher levels of the vasopressin receptor, but also showed many of the same mating behaviors as male prairie voles, such as pair-bonding. Thus, although many genes influence pair-bonding and parenting among voles, a change in vasopressin receptor levels is sufficient to alter the development of these behaviors.

▶ Figure 39.24 A pair of prairie voles (*Microtus ochrogaster*) huddling. Male North American prairie voles associate closely with their mates, as shown here, and contribute substantially to the care of young.

Genetic Variation and the Evolution of Behavior

Behavioral differences between closely related species, such as meadow and prairie voles, are common. Significant differences in behavior can also be found *within* a species. When behavioral variation between populations of a species corresponds to variation in environmental conditions, it may be evidence of past evolution.

Case Study: *Variation in Prey Selection*

An example of genetically based behavioral variation within a species involves prey selection by the western garter snake (*Thamnophis elegans*). The natural diet of this species differs widely across its range in California. Coastal populations feed predominantly on banana slugs (*Ariolimax californicus*) **(Figure 39.25)**. Inland populations feed on frogs, leeches, and fish, but not banana slugs. In fact, banana slugs are rare or absent in the inland habitats.

▲ Figure 39.25 Western garter snake from a coastal habitat eating a banana slug. Experiments indicate that the preference of these snakes for banana slugs may be influenced mainly by genetics rather than by environment.

When researchers offered banana slugs to snakes from each wild population, most coastal snakes readily ate them, whereas inland snakes tended to refuse. To what extent does genetic variation contribute to a fondness for banana slugs? To answer this question, researchers collected pregnant snakes from each wild population and housed them in separate cages in the laboratory. While still very young, the offspring were offered a small piece of banana slug on each of ten days. More than 60% of the young snakes from coastal mothers ate banana slugs on eight or more of the ten days. In contrast, fewer than 20% of the young snakes from inland mothers ate a piece of banana slug even once. Banana slugs thus appear to be a genetically acquired taste.

How did a genetically determined difference in feeding preference come to match the snakes' habitats so well? It turns out that the coastal and inland populations also vary with respect to their ability to recognize and respond to odor molecules produced by banana slugs. Researchers hypothesize that when inland snakes colonized coastal habitats more than 10,000 years ago, some of them could recognize banana slugs by scent. Because these snakes took advantage of this food source, they had higher fitness than snakes in the population that ignored the slugs. Over hundreds or thousands of generations, the capacity to recognize the slugs as prey increased in frequency in the coastal population. The marked variation in behavior observed today between the coastal and inland populations may be evidence of this past evolutionary change.

Altruism

We typically assume that behaviors are selfish; that is, they benefit the individual at the expense of others, especially competitors. For example, superior foraging ability by one individual may leave less food for others. The problem comes, however, with "unselfish" behaviors. How can such behaviors arise through natural selection? To answer this question, let's look more closely at some examples of unselfish behavior and consider how they might arise.

In discussing selflessness, we will use the term **altruism** to describe a behavior that reduces an animal's individual fitness but increases the fitness of other individuals in the population. Consider, for example, the Belding's ground squirrel, which lives in the western United States and is vulnerable to predators such as coyotes and hawks. A squirrel that sees a predator approach often gives a high-pitched alarm call that alerts unaware individuals to retreat to their burrows. Note that for the squirrel that warns others, the conspicuous alarm behavior increases the risk of being killed because it brings attention to the caller's location.

Altruism is also observed in naked mole rats (*Heterocephalus glaber*), highly social rodents that live underground in southern and northeastern Africa. The naked mole rat, which is almost hairless and nearly blind, lives in colonies of 75 or more individuals **(Figure 39.26)**. Each colony has only one reproducing female, the queen, who mates with one to three males, called kings. The rest of the colony consists of nonreproductive females and males who at times sacrifice themselves to protect the queen or kings from snakes or other predators. How can such behavior be maintained by evolution if it does not enhance the survival and reproductive success of the self-sacrificing individuals?

▲ Figure 39.26 Naked mole rats, a species of colonial mammal that exhibits altruistic behavior. Pictured here is a queen nursing offspring while surrounded by other members of the colony.

Inclusive Fitness

The selection for altruistic behavior is most readily apparent in the case of parents sacrificing for their offspring. When parents sacrifice their own well-being to produce and aid offspring, this actually increases the fitness of the parents because it maximizes their genetic representation in the population. However, individuals sometimes help others who are not their offspring.

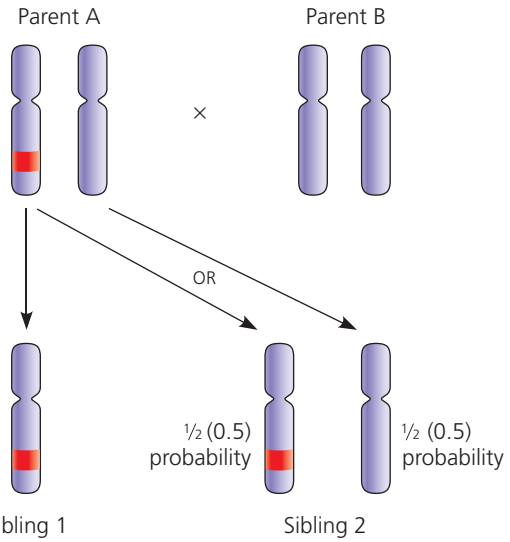
Biologist William Hamilton proposed that an animal could increase its genetic representation in the next generation by helping close relatives other than its own offspring. Like parents and offspring, full siblings have half their genes in common. Therefore, selection might also favor helping siblings or helping one's parents produce more siblings. This idea led to Hamilton's idea of **inclusive fitness**, the total effect an individual has on proliferating its genes by producing its own offspring *and* by providing aid that enables other close relatives to produce offspring.

Hamilton's Rule and Kin Selection

According to Hamilton, the three key variables in an act of altruism are the benefit to the recipient, the cost to the altruist, and the coefficient of relatedness. The benefit, *B*, is the average number of *extra* offspring that the recipient of an altruistic act produces. The cost, *C*, is how many *fewer* offspring the altruist produces. The **coefficient of relatedness**, *r*, equals the fraction of genes that, on average, are shared. Natural selection favors altruism when the benefit to the recipient multiplied by the coefficient of relatedness exceeds the cost to the altruist—in other words, when rB C. This statement is called **Hamilton's rule**.

To better understand Hamilton's rule, let's apply it to a human population in which the average individual has two children. We'll imagine that a young man is close to drowning in

heavy surf, and his sister risks her life to swim out and pull her sibling to safety. If the young man had drowned, his reproductive output would have been zero; but now, if we use the average, he can father two children. The benefit to the man is thus two offspring ($B = 2$). What cost is incurred by his sister? Let's say that she has a 25% chance of drowning in attempting the rescue. The cost of the altruistic act to the sister is then 0.25 times 2, the number of offspring she would be expected to have if she had stayed on shore ($C = 0.25 \times 2 = 0.5$). Finally, we note that a brother and sister share half their genes on average ($r = 0.5$). One way to see this is in terms of the segregation of homologous chromosomes that occurs during meiosis of gametes **(Figure 39.27)**. Plugging in the values, we find that $rB = 0.5 \times 2 = 1$, whereas $C = 0.5$. Because rB is greater than C, Hamilton's rule is satisfied; thus, natural selection would favor this altruistic act.



▲ Figure 39.27 The coefficient of relatedness between siblings. The red band indicates a particular allele (version of a gene) present on one chromosome, but not its homolog, in parent A. Sibling 1 has inherited the allele from parent A. There is a probability of ½ that sibling 2 will also inherit this allele from parent A. Any allele present on one chromosome of either parent will behave similarly. The coefficient of relatedness between the two siblings is thus ½, or 0.5.

Averaging over many individuals and generations, any particular gene in a sister faced with the situation described will be passed on to more offspring if she risks the rescue than if she does not. Among the genes propagated in this way may be some that contribute to altruistic behavior. Natural selection that thus favors altruism by enhancing the reproductive success of relatives is called **kin selection**.

Kin selection weakens with hereditary distance. Consequently, natural selection would not favor rescuing a cousin unless the surf were less treacherous. Along these lines, the geneticist J. B. S. Haldane joked that he would not lay down his life for one brother, but would do so for two brothers or eight cousins.

CONCEPT CHECK 39.6

1. Explain why geographic variation in garter snake prey choice might indicate that the behavior evolved by natural selection.
2. **WHAT IF?** The coefficient of relatedness of an individual to a full (nontwin) sibling or to either parent is the same: 0.5. Is this also true in the cases of polyandry and polygyny?
3. **WHAT IF?** Suppose you applied Hamilton's logic to a situation in which one individual is past reproductive age. Could there still be a selection for an altruistic act? Explain.

For suggested answers, see Appendix A.

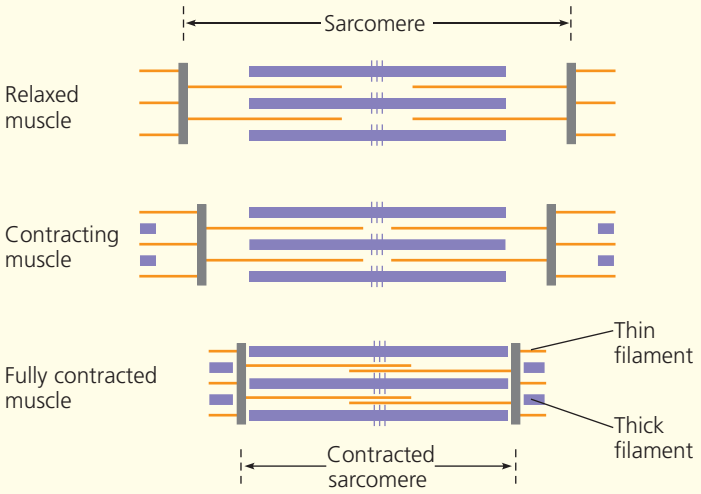
39 Chapter Review

SUMMARY OF KEY CONCEPTS

CONCEPT 39.1

The physical interaction of protein filaments is required for muscle function (pp. 793–799)

- The muscle cells (fibers) of vertebrate **skeletal muscle** contain **myofibrils** composed of **thin filaments** of (mostly) actin and **thick filaments** of myosin. These filaments are organized into repeating units called **sarcomeres**. Myosin heads, energized by the hydrolysis of ATP, bind to the thin filaments, forming cross-bridges, and then release upon binding ATP anew. As this cycle repeats, the thick and thin filaments slide past each other, contracting the muscle fiber.



- Motor neurons release acetylcholine, triggering action potentials in muscle fibers that stimulate Ca^{2+} release from the **sarcoplasmic reticulum**. When the Ca^{2+} binds the **troponin complex**, **tropomyosin** moves, exposing the myosin-binding sites on actin and thus initiating cross-bridge formation. A **motor unit** consists of a motor neuron and the muscle fibers it controls. A twitch results from a single action potential. Skeletal muscle fibers can be **slow-** or **fast-twitch** and oxidative or glycolytic.
- **Cardiac muscle**, found in the heart, consists of striated cells that are electrically connected by **intercalated disks** and that can generate action potentials without input from neurons. In **smooth muscles**, contractions may be initiated by the muscles themselves or by stimulation from neurons in the autonomic nervous system.

? *Describe the differences between oxidative and glycolytic muscle fibers.*

CONCEPT 39.2

Skeletal systems transform muscle contraction into locomotion (pp. 799–803)

- Skeletal muscles, often in antagonistic pairs, contract and pull against the skeleton. Skeletons may be **hydrostatic** and maintained by fluid pressure, as in worms; hardened into **exoskeletons**, as in insects; or internal **endoskeletons**, as in vertebrates.
- Each form of **locomotion**—swimming, movement on land, or flying—presents a particular challenge. For example, swimmers need to overcome friction but face less of a challenge from gravity than do animals that move on land or fly.

? *Explain how microscopic and macroscopic anchoring of muscle filaments enables you to bend your elbow.*

CONCEPT 39.3

Discrete sensory inputs can stimulate both simple and complex behaviors (pp. 803–806)

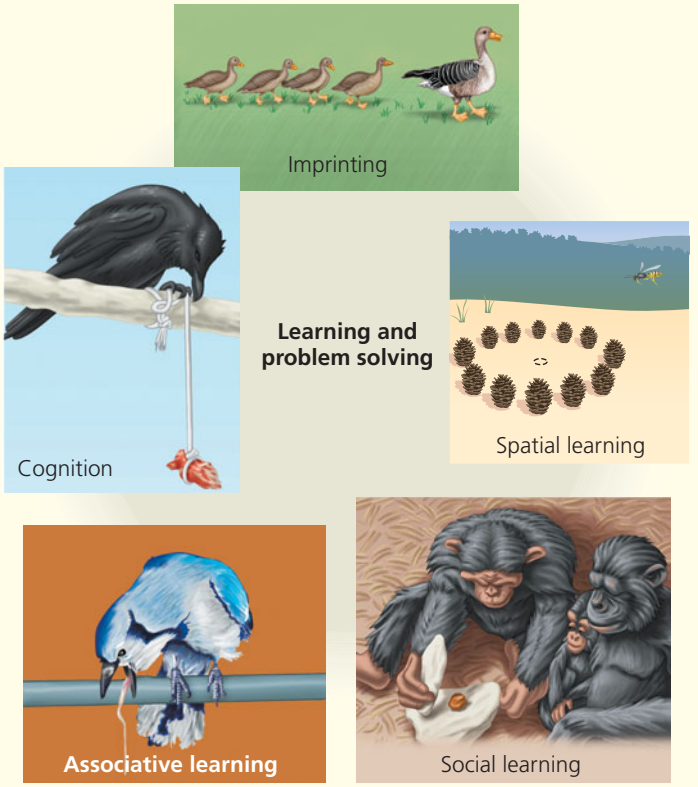
- **Behavior** is the sum of responses to external and internal stimuli. In behavioral studies, proximate, or "how," questions focus on the stimuli that trigger a behavior and on genetic, physiological, and anatomical mechanisms underlying a behavioral act. Ultimate, or "why," questions address evolutionary significance.
- A **fixed action pattern** is a largely invariant behavior triggered by a simple cue known as a **sign stimulus**. Migratory movements involve navigation, which can be based on orientation relative to the sun, the stars, or Earth's magnetic field. Animal behavior is often synchronized to the circadian cycle of light and dark in the environment or to cues that cycle over the seasons.
- The transmission and reception of **signals** constitute animal **communication**. Animals use visual, auditory, chemical, and tactile signals. Chemical substances called **pheromones** transmit information between members of a species in behaviors ranging from foraging to courtship.

? *How is migration based on circannual rhythms poorly suited for adaptation to global climate change?*

CONCEPT 39.4

Learning establishes specific links between experience and behavior (pp. 806–809)

- **Cross-fostering studies** can be used to measure the influence of social environment and experience on behavior.
- **Learning**, the modification of behavior based on experience, can take many forms:



? *Pigeons can learn to associate color with a food but not with danger. How might this observation be explained in terms of the selective forces acting during evolution?*

CONCEPT 39.5

Selection for individual survival and reproductive success can explain most behaviors (pp. 809–811)

- Controlled experiments in the laboratory can give rise to interpretable evolutionary changes in behavior.
- Sexual dimorphism correlates with the type of mating relationship between males and females. These include **monogamous** and **polygamous** mating systems. Variations in mating system and mode of fertilization affect certainty of paternity, which has a significant influence on mating behavior and parental care.

? *In some spider species, the female eats the male immediately after copulation. How might you explain this behavior from an evolutionary perspective?*

CONCEPT 39.6

Inclusive fitness can account for the evolution of behavior, including altruism (pp. 812–814)

- Research on voles has revealed that variation in a single gene can determine differences in complex behaviors involved in both mating and parenting.
- When behavioral variation within a species corresponds to variation in environmental conditions, it may be evidence of past evolution.
- **Altruism** can be explained by the concept of **inclusive fitness**, the total effect an individual has on proliferating its genes by producing its own offspring *and* by providing aid that enables close

relatives to produce offspring. **Kin selection** favors altruistic behavior by enhancing the reproductive success of relatives.

? *If an animal were unable to distinguish close from distant relatives, would the concept of inclusive fitness still be applicable? Explain.*

TEST YOUR UNDERSTANDING

Level 1: Knowledge/Comprehension

1. During the contraction of a vertebrate skeletal muscle fiber, calcium ions
   - **a.** break cross-bridges by acting as a cofactor in the hydrolysis of ATP.
   - **b.** bind with troponin, changing its shape so that the myosin-binding sites on actin are exposed.
   - **c.** transmit action potentials from the motor neuron to the muscle fiber.
   - **d.** spread action potentials through the T tubules.
   - **e.** re-establish the polarization of the plasma membrane following an action potential.
2. Which of the following is true of innate behaviors?
   - **a.** Their expression is only weakly influenced by genes.
   - **b.** They occur with or without environmental stimuli.
   - **c.** They are limited to invertebrate animals.
   - **d.** They are expressed in most individuals in a population.
   - **e.** They occur in invertebrates and some vertebrates but not mammals.
3. According to Hamilton's rule,
   - **a.** natural selection does not favor altruistic behavior that causes the death of the altruist.
   - **b.** natural selection favors altruistic acts when the resulting benefit to the recipient, corrected for relatedness, exceeds the cost to the altruist.
   - **c.** natural selection is more likely to favor altruistic behavior that benefits an offspring than altruistic behavior that benefits a sibling.
   - **d.** the effects of kin selection are larger than the effects of direct natural selection on individuals.
   - **e.** altruism is always reciprocal.
4. The binding of calcium to the troponin complex
   - **a.** activates myosin kinase, causing phosphorylation of myosin heads.
   - **b.** disrupts cross-bridges, allowing filaments to slide past each other.
   - **c.** allows tropomyosin to bind actin.
   - **d.** opens ion channels, allowing sodium to rush into the muscle cells.
   - **e.** causes tropomyosin to shift position, exposing myosin bind sites on actin.

Level 2: Application/Analysis

5. Curare, a substance that blocks the acetylcholine receptors on skeletal muscle, will cause
   - **a.** rapid muscle twitches.
   - **b.** sustained muscle contraction (tetanus).
   - **c.** muscle relaxation.
   - **d.** specific disruption of blood pressure and digestive functions.
   - **e.** no effect in the absence of acetylcholinesterase.
6. Although many chimpanzees live in environments containing oil palm nuts, members of only a few populations use stones to crack open the nuts. The likely explanation is that
   - **a.** the behavioral difference is caused by genetic differences between populations.
   - **b.** members of different populations have different nutritional requirements.
   - **c.** the cultural tradition of using stones to crack nuts has arisen in only some populations.
   - **d.** members of different populations differ in learning ability.
   - **e.** members of different populations differ in manual dexterity.
7. Which of the following is *not* required for a behavioral trait to evolve by natural selection?
   - **a.** In each individual, the form of the behavior is determined entirely by genes.
   - **b.** The behavior varies among individuals.
   - **c.** An individual's reproductive success depends in part on how the behavior is performed.
   - **d.** Some component of the behavior is genetically inherited.
   - **e.** An individual's genotype influences its behavioral phenotype.

Level 3: Synthesis/Evaluation

8. **SCIENTIFIC INQUIRY**
   From your knowledge of the cellular mechanism of muscle contraction, propose a hypothesis to explain how paramyosin enables clamshell muscles to remain contracted for long periods. How would you test your hypothesis experimentally?
9. **SCIENTIFIC INQUIRY**
   Scientists studying scrub jays found that "helpers" often assist mated pairs of birds in raising their young. The helpers lack territories and mates of their own. Instead, they help the territory owners gather food for their offspring. Propose a hypothesis to explain what advantage there might be for the helpers to engage in this behavior instead of seeking their own territories and mates. How would you test your hypothesis? If it is correct, what results would you expect your tests to yield?
10. **FOCUS ON EVOLUTION**
    We often explain our behavior in terms of subjective feelings, motives, or reasons, but evolutionary explanations are based on reproductive fitness. What is the relationship between the two kinds of explanation? For instance, is a human explanation for behavior, such as "falling in love," incompatible with an evolutionary explanation?
11. **FOCUS ON INFORMATION**
    Learning is defined as a change in behavior based on experience. In a short essay (100–150 words), describe the role of heritable information in the acquisition of learning, using some examples from imprinting and associative learning.

For selected answers, see Appendix A.