Unit 7 ANIMAL FORM AND FUNCTION

Meet the "phage wrangler," Steffanie Strathdee, Professor of Medicine in the Division of Infectious Diseases and Global Public Health at the University of California, San Diego. Born in Canada, she completed her M.Sc. and Ph.D. degrees in epidemiology at the University of Toronto. Since joining the faculty at UC San Diego in 2004, she has focused on HIV research and prevention in the underserved populations of Tijuana, just across the Mexican border. In 2017, extreme personal circumstances prompted a radical shift in her research, as detailed in *The Perfect Predator: A Scientist's Race to Save Her Husband from a Deadly Superbug*, a book co-authored by Dr. Strathdee and her husband. In 2018, Dr. Strathdee became co-director of the newly established Center for Innovative Phage Applications and Therapeutics at UC San Diego.

AN INTERVIEW WITH

Steffanie Strathdee

Tell us about your start in science.

I always had a natural curiosity as a young girl. I did not have an innate ability at science or math, even though I was interested in them. I struggled in math. Even in university, I got D's in calculus. I still don't like math, but I've learned to surround myself with people that do really well in math. I think it's important for students to realize that just because they're not good at everything doesn't mean that they can't pursue their dreams.

How did you become interested in epidemiology?

After both my course instructor and my Masters and Ph.D. advisor passed away from AIDS, I decided I wanted to focus on ending the HIV epidemic. I had started out in the laboratory and realized I was really lousy at tissue culture experiments. So I turned my attention to public health, of which epidemiology is one part. Epidemiology involves studying risk factors and patterns, not just at an individual level, like what people eat and how they behave, but also the social, political, and economic forces that drive those behaviors.

▼ Dr. Steffanie Strathdee's husband, Dr. Tom Patterson, holding an electron micrograph of his superbug (left), and Dr. Strathdee, with an artist's rendition of the bacteriophage that defeated it (right).

What changed your research focus?

My husband became ill with a superbug infection—an infection caused by a bacterium that is resistant to many antibiotics. As an infectious disease epidemiologist, you would think that I would have understood the global crisis we are facing in multidrug-resistant organisms. But it wasn't until it hit me on a personal level that I fully understood the threat.

How did the story of your husband's illness unfold?

My husband and I were in Egypt, and he became very ill. The doctor gave him IV antibiotics and said, "He'll be fine," but he wasn't. It turned out that a gallstone had blocked his bile duct, causing an abscess (cavity) to form, and a superbug moved into that abscess and multiplied. Tom's particular bacterium had 51 different antibiotic-resistance genes. It was winning its battle against the immune system, none of the standard antibiotic treatments were working, and my husband was dying. I did a literature search and found a hundred-year-old, forgotten cure based on bacteriophages. These viruses, called phages for short, attack bacteria, but not human cells. Each phage is specific for a particular bacterium. Phages inject their DNA into bacteria, turning them into phage factories and killing the bacteria in the process. I emailed Tom's doctor, who is a colleague of Tom's and mine, and he thought the idea was worth a shot. So, I had to go out and find people who had phages that were active against Tom's bacterium, and that felt harder than looking for a needle in a haystack. Luckily, labs at the Naval Medical Research Center in Maryland and at Texas A&M University dedicated themselves to the search and found phages that matched. The phages were grown, purified, and injected into Tom's body, a billion phages per dose. Three days later, Tom woke up from his coma.

"This student . . . ended up helping save the life of a total stranger, and it's jump-started a whole new field."

Tell us a bit more about your collaborators.

A Ph.D. student at Texas A&M worked around the clock and found the phages that made up the first infusion. This student was at a really low point in her studies, thinking, "I don't know what I'm going to do with my career, I don't know if what I do really matters." And then she ended up helping save the life of a total stranger, and it's jump-started a whole new field—phage therapy.

What advice do you have for students starting to study biology?

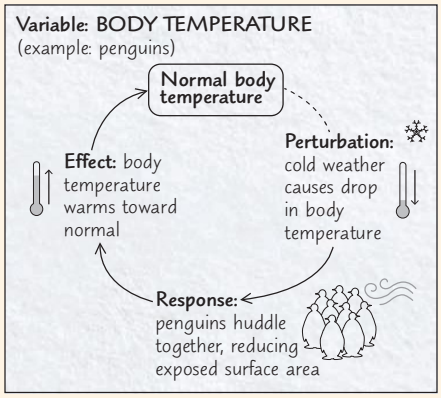
Students should look for mentors with whom they share the same values. For me, that was what really turned my D in calculus and some of the troubles that I had in science into success. I found mentors who were encouraging and helped me identify my strengths. Knowing what your weaknesses and your strengths are is, I think, one of the big components to making a successful career.

40 Basic Principles of Animal Form and Function

KEY CONCEPTS

Study Tip

Draw a diagram: When you encounter an example in the chapter of how an animal maintains a steady internal state, draw a simple circuit diagram (see example—illustrations are optional!). Label the variable being controlled, a perturbation that affects the variable, the response, and its effect in restoring the normal state.



Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 40
- Figure 40.17 Walkthrough: Thermoregulation in Humans

For Instructors to Assign (in Item Library)
- Everyday Biology: How to Keep Your Cool
- Tutorial: Thermoregulation

Figure 40.1 Emperor penguins (*Aptenodytes forsteri*) live in Antarctica, Earth's coldest and windiest continent. In summer, these birds catch fish by diving down 500 meters in water only 2°C above freezing. In winter, the females forage and the males incubate eggs while temperatures drop to –40°C and winds gust to 200 km/hr.

How do animals regulate their internal state even in changing or harsh environments?

Adaptations in **form, function, and behavior** help maintain an animal's internal environment. Adaptations that limit variation in temperature and other internal variables are widespread and diverse. Consider, for example, three adaptations that help an Emperor penguin stay warm:

Form (anatomy): An insulating layer of fat (blubber) reduces heat loss from most of the penguin's body (blue body areas in this thermal image).

Function (physiology): Rapid cycles of muscle contraction and relaxation during shivering produce heat at a cellular level.

Behavior: By packing together in groups of up to several thousand, Emperor penguins greatly reduce their exposure to wind and cold.

CONCEPT 40.1

Animal form and function are correlated at all levels of organization

Over the course of its life, an Emperor penguin 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 survive to produce offspring. Given that all animal species share these and other basic requirements, why does their form, including **anatomy**—biological structure—vary so widely? The answer lies in natural selection and adaptation. Natural selection favors those variations in a population that increase relative fitness (see Concept 23.4). The evolutionary adaptations that enable survival vary among environments and species but frequently result in a close match of form to function, as illustrated for the Emperor penguins in Figure 40.1. Because structure and function are correlated, examining anatomy often provides clues to **physiology**—biological function.

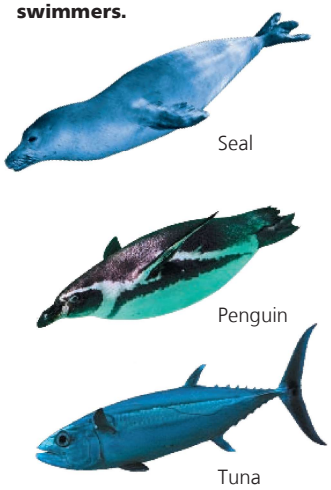
An animal's size and shape are fundamental aspects of form that significantly affect the way the animal interacts with its environment. Although we may refer to size and shape as elements of a "body plan" or "design," this does not imply a process of conscious invention. The body plan of an animal is the result of a pattern of development programmed by the genome, itself the product of millions of years of evolution.

Evolution of Animal Size and Shape

EVOLUTION Many different body plans have arisen during the course of evolution, but these variations fall within certain bounds. Physical laws that govern strength, diffusion, movement, and heat exchange limit the range of animal forms.

As an example of how physical laws constrain evolution, let's consider how some properties of water limit the possible shapes for animals that are fast swimmers. Water is about 1,000 times denser than air and also far more viscous. Therefore, any bump on an animal's body surface that causes drag impedes a swimmer more than it would a runner or flyer. Tuna and other fast ray-finned fishes can swim at speeds up to 80 km/hr (50 miles/hour). Sharks, penguins, dolphins, and seals are also relatively fast swimmers. As illustrated by the three examples in **Figure 40.2**, these animals all have a shape that is fusiform, meaning tapered on both ends. The similar streamlined shape found in these speedy vertebrates is an example of convergent evolution (see Concept 22.3). Natural selection often results in similar adaptations when diverse organisms face the same environmental challenge, such as overcoming drag during swimming.

▼ Figure 40.2 Convergent evolution in fast swimmers.



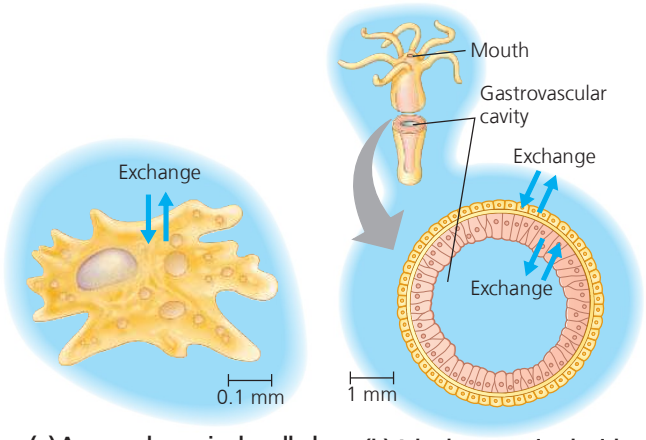
Physical laws also influence animal body plans with regard to maximum size. As body dimensions increase, thicker skeletons are required to maintain adequate support. This limitation affects internal skeletons, such as those of vertebrates, as well as external skeletons, such as those of insects and other arthropods. In addition, as bodies increase in size, the muscles required for locomotion must represent an ever-larger fraction of the total body mass. At some point, mobility becomes limited. By considering the fraction of body mass in leg muscles and the effective force such muscles generate, scientists can estimate maximum speed for a wide range of body plans. In the case of the 6-meter-tall dinosaur *Tyrannosaurus rex*, there is controversy, with some scientists calculating a top running speed as fast as that of an Olympic sprinter—30 km/hr (19 miles/hour), but others inferring that *T. rex* was at best a fast walker.

Exchange with the Environment

Animals must exchange nutrients, waste products, and gases with their environment, and this requirement imposes an additional limitation on body plans. Exchange occurs as substances dissolved in an aqueous solution move across the plasma membrane of each cell. A single-celled organism, such as the amoeba in **Figure 40.3a**, has a sufficient membrane surface area in contact with its environment to carry out all necessary exchange. In contrast, an animal is composed of many cells, each with its own plasma membrane across which exchange must occur. The rate of exchange is proportional to the membrane surface area involved in exchange, whereas the amount of material that must be exchanged is proportional to the total body volume. A multicellular organization therefore works only if every cell has access to a suitable aqueous environment, either inside or outside the animal's body.

Many animals with a simple internal organization have body plans that enable direct exchange between almost all their cells and the external environment. For example, a pond-dwelling hydra has a saclike body plan and a body wall only two cell layers thick **(Figure 40.3b)**. Because its gastrovascular cavity opens to the external environment, both the outer and inner layers of cells are constantly bathed by pond water. Another common body plan that maximizes exposure to the surrounding medium is a flat shape. Consider, for instance, a parasitic tapeworm, which can reach several meters in length (see Figure 33.11). A thin, flat shape places most cells of the worm in direct contact with its particular environment—the nutrient-rich intestinal fluid of a vertebrate host.

▼ Figure 40.3 Direct exchange with the environment.



(a) An amoeba, a single-celled organism

(b) A hydra, an animal with two layers of cells

Our bodies and those of most other animals are composed of compact masses of cells, with an internal organization much more complex than that of a hydra or a tapeworm. For such a body plan, increasing the number of cells decreases the ratio of outer surface area to total volume. As an extreme comparison, the ratio of outer surface area to volume for a whale is hundreds of thousands of times smaller than that for a water flea. Nevertheless, every cell in the whale has access to oxygen, nutrients, and other resources. How is this accomplished?

In whales and most other animals, the evolutionary adaptations that enable sufficient exchange with the environment are specialized surfaces that are extensively branched or folded **(Figure 40.4)**. In almost all cases, these exchange surfaces lie within the body, an arrangement that protects their delicate tissues from abrasion or dehydration and allows for streamlined body contours. The branching or folding greatly increases surface area (see Figure 33.8). In humans, for example, the exchange surfaces for digestion, respiration, and circulation each have an area more than 25 times larger than that of the skin.

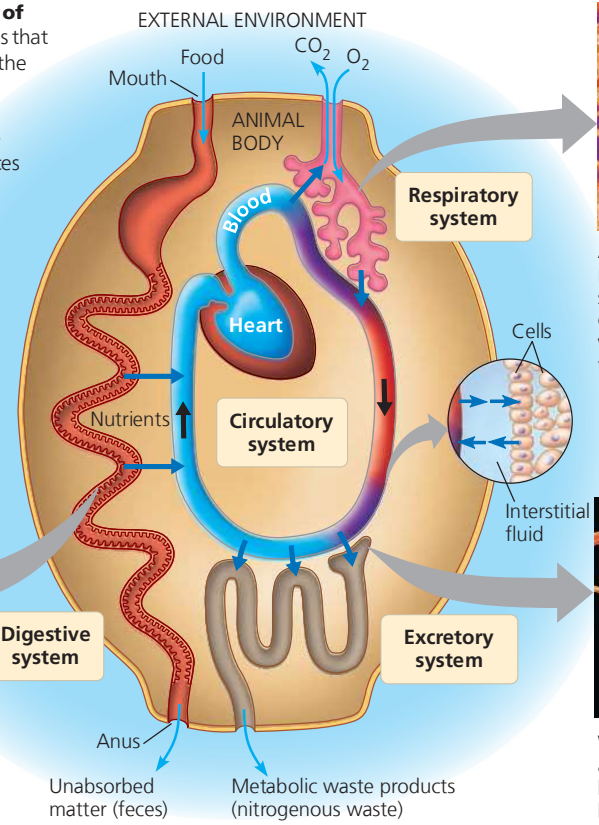
Internal body fluids link exchange surfaces to body cells. The spaces between cells are filled with fluid, known in many animals as **interstitial fluid** (from the Latin for "stand between"). Complex body plans also include a circulatory fluid, such as blood. Exchange between the interstitial fluid and the circulatory fluid enables cells throughout the body to obtain nutrients and get rid of wastes (see Figure 40.4).

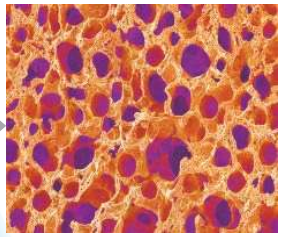
Complex body plans offer numerous benefits. For example, an external skeleton can protect against predators, and sensory organs can provide detailed information on the animal's surroundings. Internal digestive organs can break down

▶ Figure 40.4 Internal exchange surfaces of complex animals. Most animals have surfaces that are specialized for exchanging chemicals with the surroundings. These exchange surfaces are usually internal but are connected to the environment via openings on the body surface (the mouth, for example). The exchange surfaces are finely branched or folded, giving them a very large area. The digestive, respiratory, and excretory systems all have such exchange surfaces. Chemicals exchanged across these surfaces are transported throughout the body via the circulatory system.

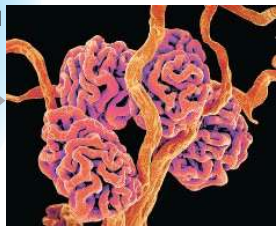
VISUAL SKILLS *Using this diagram, explain how exchange carried out by animals can be described as both internal and external.*

The lining of the small intestine has finger-like projections that expand the surface area for nutrient absorption (SEM).





A microscopic view of the lung reveals that it is much more sponge-like than balloon-like. This construction provides an expansive wet surface for gas exchange with the environment (SEM).



Within the kidney, blood is filtered across the surface of long, narrow blood vessels packed into ball-shaped structures (SEM).

food gradually, controlling the release of stored energy. In addition, specialized filtration systems can adjust the composition of the internal fluid that bathes the animal's body cells. In this way, an animal can maintain a relatively stable internal environment despite the fact that it is living in a changeable external environment. A complex body plan is especially advantageous for animals living on land, where the external environment may be highly variable.

Hierarchical Organization of Body Plans

Cells form a working animal body through their *emergent properties*, which arise from successive levels of structural and functional organization (see Concept 1.1). 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, providing an additional level of organization and coordination, make up an **organ system** (Table 40.1). Thus, for example, the skin is an organ of the integumentary system, which protects against infection and helps regulate body temperature.

Many organs have more than one physiological role. If the roles are distinct enough, 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 but 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. Organ systems include specialized organs made up of specialized tissues and cells. Consider the human digestive system: Each organ has specific roles. In the case of the stomach, one role is to initiate protein breakdown. 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 therefore share many properties.

There are four main types of animal tissues: epithelial, connective, muscle, and nervous. **Figure 40.5** explores the structure and function of each type. In later chapters, we'll discuss how these tissue types contribute to the functions of particular organ systems.

Mastering Biology **Animation: Overview of Animal Tissues**

Table 40.1 Organ Systems in Mammals

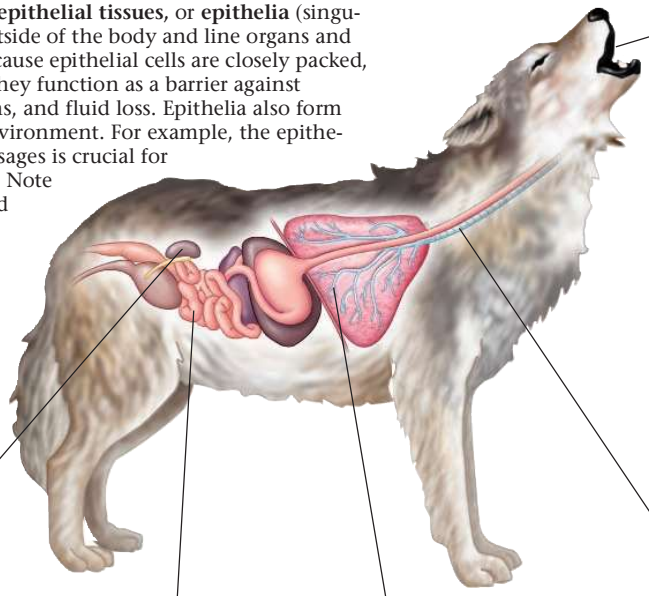
Organ System	Main Components	Main Functions
Digestive	Mouth, pharynx, esophagus, stomach, intestines, liver, pancreas, anus (See Figure 41.8.)	Food processing (ingestion, digestion, absorption, elimination)
Circulatory	Heart, blood vessels, blood (See Figure 42.5.)	Internal distribution of materials
Respiratory	Lungs, trachea, other breathing tubes (See Figure 42.24.)	Gas exchange (uptake of oxygen; disposal of carbon dioxide)
Immune and lymphatic	Bone marrow, lymph nodes, thymus, spleen, lymph vessels (See Figure 43.6.)	Body defense (fighting infections and virally induced cancers)
Excretory	Kidneys, ureters, urinary bladder, urethra (See Figure 44.12.)	Disposal of metabolic wastes; regulation of osmotic balance of blood
Endocrine	Pituitary, thyroid, pancreas, adrenal, and other hormone-secreting glands (See Figure 45.8.)	Coordination of body activities (such as digestion and metabolism)
Reproductive	Ovaries or testes and associated organs (See Figures 46.9 and 46.10.)	Gamete production; promotion of fertilization; support of developing embryo
Nervous	Brain, spinal cord, nerves, sensory organs (See Figure 49.6.)	Coordination of body activities; detection of stimuli and formulation of responses to them
Integumentary	Skin and its derivatives (such as hair, claws, sweat glands) (See Figure 50.5.)	Protection against mechanical injury, infection, dehydration; thermoregulation
Skeletal	Skeleton (bones, tendons, ligaments, cartilage) (See Figure 50.37.)	Body support, protection of internal organs, movement
Muscular	Skeletal muscles (See Figure 50.26.)	Locomotion and other movement

▼ Figure 40.5 Exploring Structure and Function in Animal Tissues

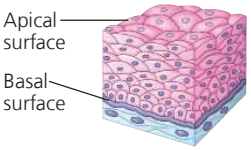
Epithelial Tissue

Occurring as sheets of cells, **epithelial tissues**, or **epithelia** (singular, *epithelium*), cover the outside of the body and line organs and cavities within the body. Because epithelial cells are closely packed, often with tight junctions, they function as a barrier against mechanical injury, pathogens, and fluid loss. Epithelia also form active interfaces with the environment. For example, the epithelium that lines the nasal passages is crucial for olfaction, the sense of smell. Note how different cell shapes and arrangements correlate with distinct functions.

Mastering Biology
Animation: Epithelial Tissue

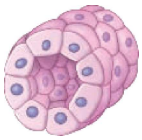


Stratified squamous epithelium



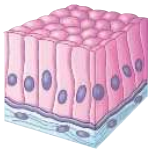
A stratified squamous epithelium is multilayered and regenerates rapidly. New cells formed by division near the basal surface push outward, replacing cells that are sloughed off. This epithelium is commonly found on surfaces subject to abrasion, such as the outer skin and the linings of the mouth, anus, and vagina.

Cuboidal epithelium



A cuboidal epithelium, with dice-shaped cells specialized for secretion, makes up the epithelium of kidney tubules and many glands, including the thyroid gland and salivary glands.

Simple columnar epithelium

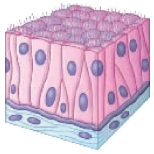


The large, brick-shaped cells of simple columnar epithelia are often found where secretion or active absorption is important. For example, a simple columnar epithelium lines the intestines, secreting digestive juices and absorbing nutrients.

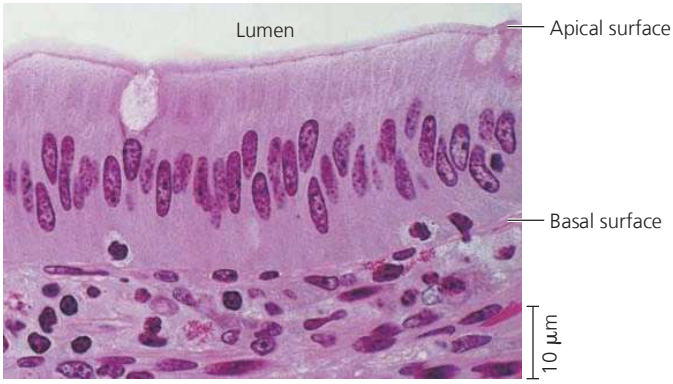
Simple squamous epithelium

The single layer of platelike cells that form a simple squamous epithelium functions in the exchange of material by diffusion. This type of epithelium, which is thin and leaky, lines blood vessels and the air sacs of the lungs, where diffusion of nutrients and gases is essential.

Pseudostratified columnar epithelium



A pseudostratified epithelium consists of a single layer of cells varying in height and the position of their nuclei. In many vertebrates, a pseudostratified epithelium of ciliated cells forms a mucous membrane that lines portions of the respiratory tract. The beating cilia sweep the film of mucus along the surface.



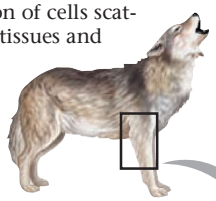
Polarity of epithelia

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. Specialized projections often cover this surface. For example, the apical surface of the epithelium lining the small intestine is covered with microvilli, projections that increase the surface area available for absorbing nutrients. Opposite the apical surface of each epithelium is the *basal* surface.

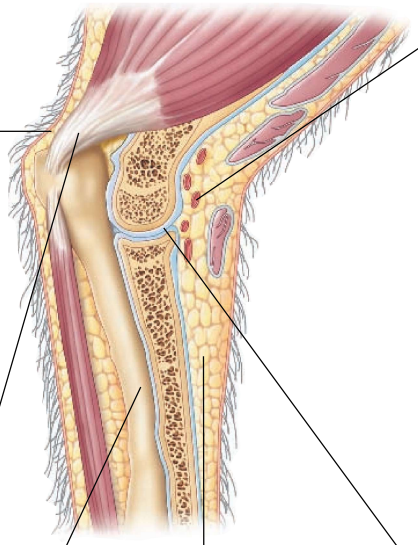
Connective Tissue

Connective tissue, consisting of a sparse population of cells scattered through an extracellular matrix, holds many tissues and organs together and in place. The matrix generally consists 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 any cell debris by phagocytosis.

Connective tissue fibers are of three kinds: *Collagenous fibers* provide strength and flexibility, *reticular fibers* join connective tissue to adjacent tissues, and *elastic fibers* make tissues elastic. If you pinch a fold of tissue on the back of your hand, the collagenous and reticular fibers prevent the skin from being pulled far from the bone, whereas the elastic fibers restore the skin to its original shape when you release your grip. Different mixtures of fibers and foundation form the major types of connective tissue shown below.

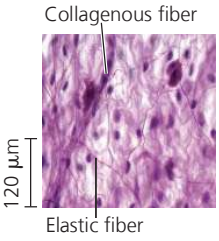


Mastering Biology **Animation: Connective Tissue**



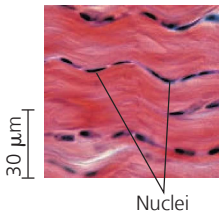
Loose connective tissue

The most widespread connective tissue in the vertebrate body is *loose connective tissue*, which binds epithelia to underlying tissues and holds organs in place. Loose connective tissue gets its name from the loose weave of its fibers, which include all three types. It is found in the skin and throughout the body.



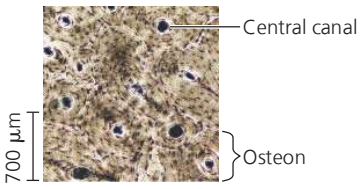
Fibrous connective tissue

Fibrous connective tissue is dense with collagenous fibers. It is found in **tendons**, which attach muscles to bones, and in **ligaments**, which connect bones at joints.



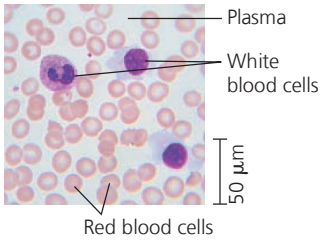
Bone

The skeleton of most vertebrates is made of **bone**, a mineralized connective tissue. Bone-forming cells called *osteoblasts* deposit a matrix of collagen. Calcium, magnesium, and phosphate ions combine into a hard mineral within the matrix. The microscopic structure of hard mammalian bone consists of repeating units called *osteons*. Each osteon has concentric layers of the mineralized matrix, which are deposited around a central canal containing blood vessels and nerves.



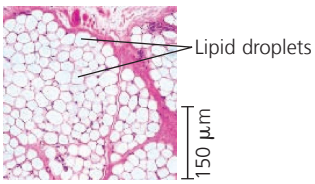
Blood

Blood has a liquid extracellular matrix called plasma, which consists of water, salts, and dissolved proteins. Suspended in plasma are erythrocytes (red blood cells), leukocytes (white blood cells), and cell fragments called platelets. Red cells carry oxygen, white cells function in defense, and platelets aid in blood clotting.



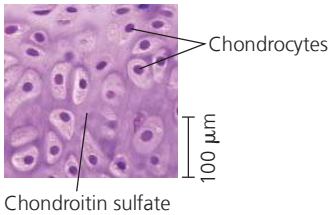
Adipose tissue

Adipose tissue is a specialized loose connective tissue that stores fat in adipose cells distributed throughout its matrix. Adipose tissue pads and insulates the body and stores fuel as fat molecules. Each adipose cell contains a large fat droplet that swells when fat is stored and shrinks when the body uses that fat as fuel.



Cartilage

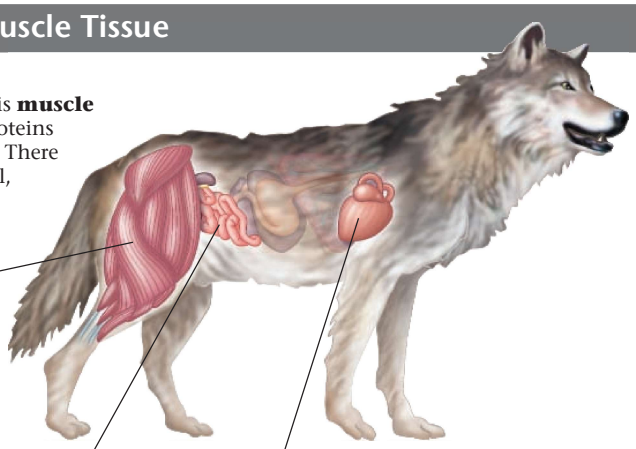
Cartilage contains collagenous fibers embedded in a rubbery protein-carbohydrate complex called chondroitin sulfate. Cells called *chondrocytes* secrete the collagen and chondroitin sulfate, which together make cartilage a strong yet flexible support material. The skeletons of many vertebrate embryos contain cartilage that is replaced by bone as the embryo matures. Cartilage remains in some locations, such as the disks that act as cushions between vertebrae.



Muscle Tissue

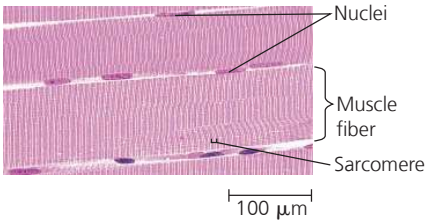
The tissue responsible for nearly all types of body movement is **muscle tissue**. All muscle cells consist of filaments containing the proteins actin and myosin, which together enable muscles to contract. There are three types of muscle tissue in the vertebrate body: skeletal, smooth, and cardiac.

Mastering Biology **Animation: Muscle Tissue**



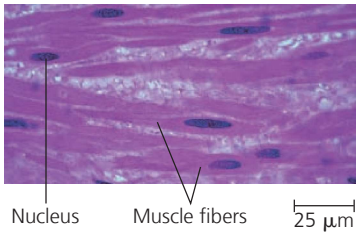
Skeletal muscle

Attached to bones by tendons, **skeletal muscle**, or *striated muscle*, is responsible for voluntary movements. Skeletal muscle consists of bundles of long cells that are called muscle fibers. During development, skeletal muscle fibers form by the fusion of many cells, resulting in multiple nuclei in each muscle fiber. The arrangement of contractile units, or sarcomeres, along the fibers gives the cells a striped (striated) appearance. In adult mammals, building muscle increases the size but not the number of muscle fibers.



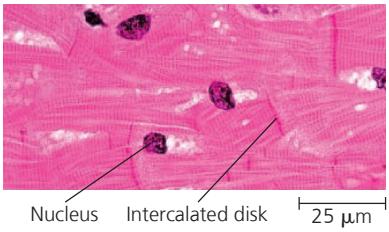
Smooth muscle

Smooth muscle, which lacks striations, is found in the walls of the digestive tract, urinary bladder, arteries, and other internal organs. The cells are spindle-shaped. Smooth muscles are responsible for involuntary body activities, such as churning of the stomach and constriction of arteries.



Cardiac muscle

Cardiac muscle forms the contractile wall of the heart. It is striated like skeletal muscle and has similar contractile properties. Unlike skeletal muscle, however, cardiac muscle has branched fibers that interconnect via intercalated disks, which relay signals from cell to cell and help synchronize heart contraction.



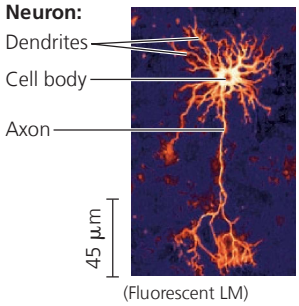
Nervous Tissue

Nervous tissue functions in the receipt, processing, and transmission of information. Nervous tissue contains **neurons**, or nerve cells, which transmit nerve impulses, as well as support cells called **glial cells**, or simply **glia**. In many animals, a concentration of nervous tissue forms a brain, an information-processing center.

Mastering Biology **Animation: Nervous Tissue**

Neurons

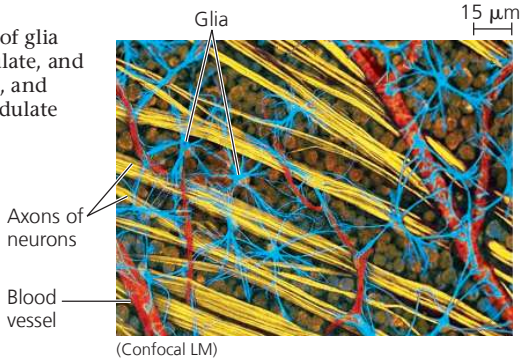
Neurons are the basic units of the nervous system. A neuron receives nerve impulses from other neurons via its cell body and multiple extensions called dendrites. Neurons transmit impulses to neurons, muscles, or other cells via extensions called axons, which are often bundled together into nerves.



(Fluorescent LM)

Glia

The various types of glia help nourish, insulate, and replenish neurons, and in some cases, modulate neuron function.



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Coordination and Control

For an animal's tissues and organ systems to function effectively, they must act in concert with one another. For example, when the wolf shown in Figure 40.5 hunts, blood flow is regulated to bring adequate nutrients and gases to its leg muscles, which in turn are activated by the brain in response to cues detected by the nose. What signals coordinate activity? How do the signals move within the body?

Animals have two major systems for coordinating and controlling responses to stimuli: the endocrine and nervous systems **(Figure 40.6)**. 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 regardless of whether the signal's ultimate target is at the other end of the body or just a few cell diameters away.

The signaling molecules that are broadcast throughout the body by the endocrine system are called **hormones**. It takes 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.

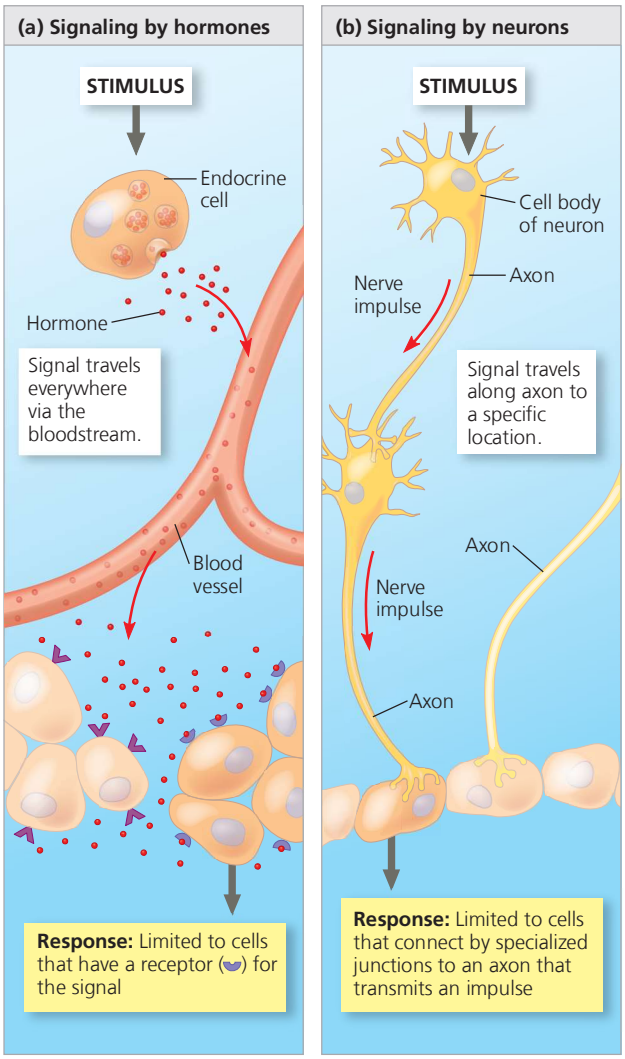
Different hormones cause distinct effects, and only cells that have receptors for a particular hormone respond (Figure 40.6a). Depending on which cells have receptors for that hormone, the hormone may have an effect in just a single location or in sites throughout the body. For example, thyroid-stimulating hormone (TSH) acts solely on cells in the thyroid gland. They in turn release thyroid hormone, which acts on nearly every body tissue to increase oxygen consumption and heat production.

In the nervous system, signals called nerve impulses travel to specific target cells along communication lines consisting mainly of axons (Figure 40.6b). 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.

Nerve impulses can act on other neurons, on muscle cells, and on cells and glands that produce secretions. 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 neurons in the ear that connect to slightly different locations in 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.

▼ Figure 40.6 Signaling in the endocrine and nervous systems.



VISUAL SKILLS *After comparing the two diagrams, explain why a particular nerve impulse signal has only one physical pathway but a particular hormone molecule can have multiple physical pathways.*

Because the two major communication systems of the body differ in signal type, transmission, speed, and duration, it is not surprising that 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, such as reflexes and other rapid movements. Nevertheless, the two systems often work in close coordination. Both help maintain a stable internal environment, our next topic of discussion.

CONCEPT CHECK 40.1

1. What properties do all types of epithelia share?
2. **VISUAL SKILLS** Consider the idealized animal in Figure 40.4. At which sites must oxygen cross a plasma membrane in traveling from the external environment to the cytoplasm of a body cell?
3. **WHAT IF?** Suppose you are standing at the edge of a cliff and suddenly slip, barely managing to keep your balance and avoid falling. As your heart races, you feel a burst of energy, due in part to a surge of blood into dilated (widened) vessels in your muscles and an upward spike in the level of glucose in your blood. Why might you expect that this "fight-or-flight" response requires both the nervous and endocrine systems?

For suggested answers, see Appendix A.

CONCEPT 40.2

Feedback control maintains the internal environment in many animals

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 slurped a steaming bowl of soup. Faced with environmental fluctuations, animals manage their internal environment by either regulating or conforming.

Regulating and Conforming

Compare the two sets of data in **Figure 40.7**. The river otter's body temperature is largely independent of that of the surrounding water, whereas the largemouth bass's body warms or cools when the water temperature changes. We can convey these two trends by labeling the otter a regulator and the bass a conformer with regard to body temperature. An animal is a **regulator** for an environmental variable if it uses internal mechanisms to control internal change in the face of external fluctuation. In contrast, an animal is a **conformer** if it allows its internal condition to change in accordance with external changes in the particular variable.

An animal may allow some internal conditions to conform to the environment but regulate others. For instance, the bass conforms to the temperature of the water in which it lives, but regulates the solute concentration in its blood and interstitial fluid. In addition, conforming need not involve changes in an internal variable: Many marine invertebrates, such as spider crabs (genus *Libinia*), let their internal solute concentration conform to the relatively stable salinity of their ocean environment.

Homeostasis

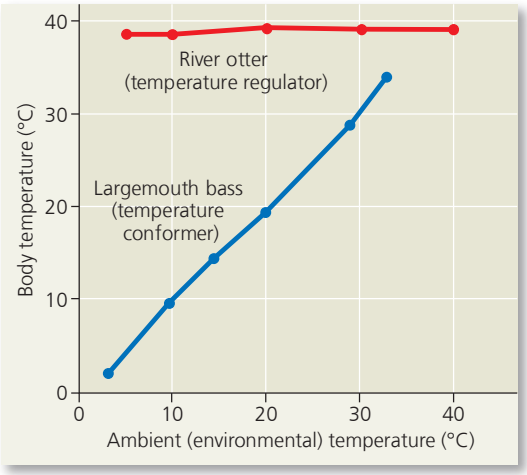
The steady body temperature of a river otter and the stable concentration of solutes in a freshwater bass are examples of **homeostasis**, which means the maintenance of internal balance. In achieving homeostasis, animals maintain a "steady state"—a relatively constant internal environment—even when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

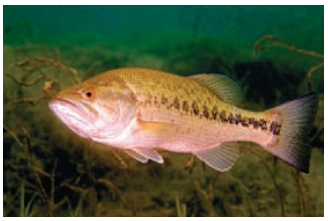
Many animals exhibit homeostasis for a range of physical and chemical properties. For example, humans maintain a fairly constant body temperature of about 37°C (98.6°F), a blood pH within 0.1 pH unit of 7.4, and a blood glucose concentration that is predominantly in the range of 70–110 mg of glucose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

Mechanisms of Homeostasis

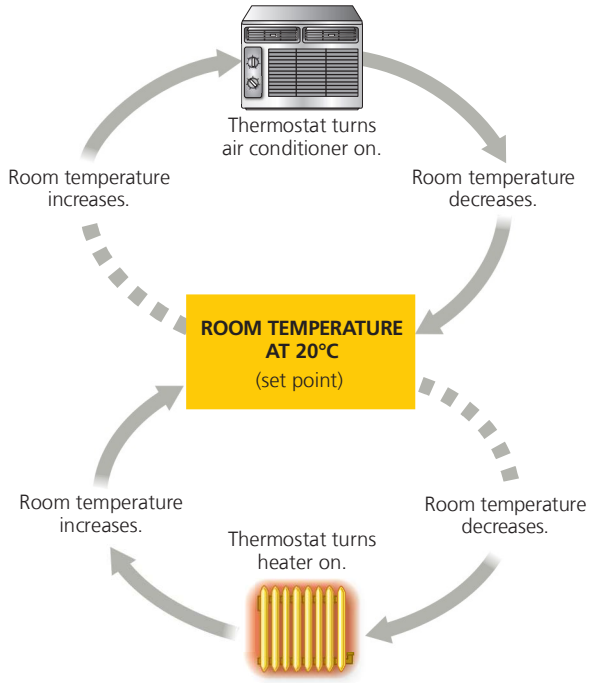
Homeostasis requires a control system. Before exploring homeostasis in animals, let's get a basic picture of how a control system works by considering a nonliving example: the regulation of room temperature. Let's assume you want to keep a room at 20°C (68°F), a comfortable temperature for normal activity. You set a control device—the thermostat—to 20°C. A thermometer in the thermostat monitors the room temperature. If the temperature falls

▼ Figure 40.7 The relationship between body and environmental temperatures in an aquatic temperature regulator and an aquatic temperature conformer. The river otter regulates its body temperature, keeping it stable across a wide range of environmental temperatures. The largemouth bass, meanwhile, allows its internal environment to conform to the water temperature.





▼ Figure 40.8 A nonliving example of temperature regulation: control of room temperature. Regulating room temperature depends on a sensor/control center (a thermostat) that detects temperature change and activates mechanisms that reverse that change.



DRAW IT *Label at least one stimulus, response, and sensor/control center in the above figure.*

below 20°C, the thermostat turns on a radiator, furnace, or other heater **(Figure 40.8)**. When the room exceeds 20°C, the thermostat switches off the heater. If the temperature then drifts below 20°C, the thermostat activates another heating cycle. If the temperature instead rises above 20°C, the thermostat activates a cooling mechanism, such as by turning on an air conditioner.

Like a home heating system, the homeostatic control system in animals maintains a variable, such as body temperature or solute concentration, at or near a particular value, or **set point**. A fluctuation in the variable above or below the set point serves as the **stimulus** detected by a **sensor**. The sensor signals a *control center*, which triggers a **response**, a physiological activity that helps return the variable to the set point. In the home heating example, a drop in temperature below the set point acts as a stimulus, the thermostat serves as the sensor and control center, and the heater produces the response.

Feedback Control in Homeostasis

If you examine the circuit in Figure 40.8, you can see that either response (heating or cooling) reduces the stimulus (the change in temperature) that triggered that response. The circuit thus displays **negative feedback**, a control mechanism that "damps" its stimulus (see Figure 1.10). This type of feedback regulation plays a major role in homeostasis in animals. For example, when you exercise vigorously, you produce heat, which increases your body temperature. Your nervous system detects this increase and triggers sweating. The evaporation of sweat from your skin then cools your body, helping return body temperature to its set point and eliminating the stimulus.

Homeostasis is a dynamic equilibrium, an interplay between external factors that tend to change the internal environment and internal control mechanisms that oppose such changes. Note that physiological responses to stimuli are not instantaneous, just as switching on a furnace does not immediately warm a room. As a result, homeostasis moderates but doesn't eliminate changes in the internal environment. Fluctuation is greater 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 is programmed to produce heat when the room temperature drops to 19°C (66°F) and to stop heating when the temperature reaches 21°C (70°F). Regardless of whether there is a set point or a normal range, homeostasis is enhanced by adaptations that reduce fluctuations, such as insulation in the case of temperature and physiological buffers in the case of pH.

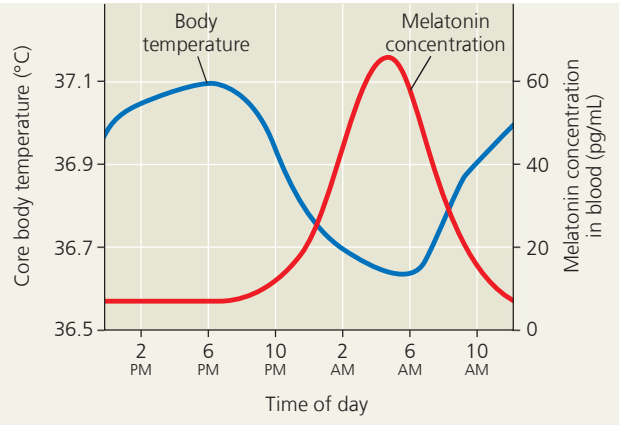
Unlike negative feedback, **positive feedback** is a control mechanism that amplifies the stimulus. In animals, positive-feedback loops do not play a major role in homeostasis, but instead help drive processes to completion. During childbirth, for instance, the pressure of the baby's head against sensors near the opening of the mother's uterus stimulates the uterus to contract. These contractions result in greater pressure against the opening of the uterus, heightening the contractions and thereby causing even greater pressure, ultimately causing the baby to be born.

Alterations in Homeostasis

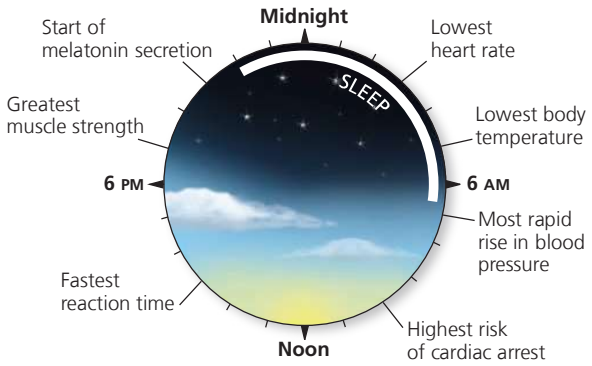
The set points and normal ranges for homeostasis can change under various circumstances. In fact, *regulated changes* in the internal environment are essential to normal body functions. Some regulated changes occur during a particular stage in life, such as the radical shift in hormone balance that occurs during puberty. Other regulated changes are cyclic, such as the variation in hormone levels responsible for a woman's menstrual cycle (see Figure 46.14).

In all animals (and plants), certain cyclic alterations in metabolism reflect a **circadian rhythm**, a set of physiological changes that occur roughly every 24 hours **(Figure 40.9)**. One way to observe this rhythm is to monitor body temperature, which in humans typically undergoes a cyclic rise and fall of more than 0.6°C (1°F) in every 24-hour period. Remarkably, a biological clock maintains this rhythm even when variations in human activity, room temperature, and light levels are minimized (see Figure 40.9a). A circadian rhythm is thus intrinsic to the body, although the biological

▼ Figure 40.9 Human circadian rhythm.



(a) Variation in core body temperature and melatonin concentration in blood. Researchers studied resting but awake volunteers in an isolation chamber with constant temperature and low light. (Melatonin is a hormone secreted by the pineal gland.)



(b) The human circadian clock. Metabolic activities undergo daily cycles in response to the circadian clock. As illustrated for a typical individual who rises early in the morning, eats lunch around noon, and sleeps at night, these cyclic changes occur throughout a 24-hour day.

clock is normally coordinated with the cycle of light and darkness in the environment (see Figure 40.9b). For example, the hormone melatonin is secreted at night, and more is released during the longer nights of winter. External stimuli can reset the biological clock, but the effect is not immediate. That is why flying across several time zones results in jet lag, a mismatch between the circadian rhythm and local environment that persists until the clock fully resets.

Noting the importance of biological clocks to human health and disease, the Nobel Prize Committee awarded the 2017 Nobel Prize in Physiology or Medicine to Americans Jeffrey Hall, Michael Rosbash, and Michael Young, who studied the fruit fly *Drosophila* to map out the molecular mechanisms that underlie circadian rhythms.

▼ Figure 40.10 Acclimatization by mountain climbers in the Himalayas. To lessen the risk of altitude sickness when ascending a high peak, climbers acclimatize by camping partway up the mountain. Spending time at an intermediate altitude allows the circulatory and respiratory systems to become more efficient in capturing and distributing oxygen at a lower concentration.

Homeostasis is sometimes altered by **acclimatization**, an animal's physiological adjustment to changes in its external environment. For instance, when an elk moves up into the mountains from sea level, the lower oxygen concentration in the high mountain air stimulates the animal to breathe more rapidly and deeply. As a result, more CO_2 is lost through exhalation, raising blood pH above its normal range. As the animal acclimatizes over several days, changes in kidney function cause it to excrete urine that is more alkaline, returning blood pH to its normal range. Other mammals, including humans, are also capable of acclimatizing to dramatic altitude changes **(Figure 40.10)**, although health risks remain.

CONCEPT CHECK 40.2

1. **MAKE CONNECTIONS** How does negative feedback in thermoregulation differ from feedback inhibition in an enzyme-catalyzed biosynthetic process (see Figure 8.21)?
2. If you were deciding where to put the thermostat in a house, what factors would govern your decision? How do these factors relate to the fact that many homeostatic control sensors in humans are located in the brain?
3. **MAKE CONNECTIONS** Like animals, cyanobacteria have a circadian rhythm. By analyzing the genes that maintain biological clocks, scientists concluded that the 24-hour rhythms of humans and cyanobacteria reflect convergent evolution (see Concept 26.2). What evidence would have supported this conclusion? Explain.

For suggested answers, see Appendix A.

CONCEPT 40.3

Homeostatic processes for thermoregulation involve form, function, and behavior

In this section, we'll examine the regulation of body temperature as an example of how form and function work together in regulating an animal's internal environment. Later chapters in this unit will discuss other physiological systems involved in maintaining homeostasis.

Thermoregulation is the process by which animals maintain their body temperature within a normal range. Body temperatures outside the 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.

In talking about thermoregulation, we will need to talk about heat. Formally, heat is defined as thermal energy in transfer from one body of matter to another (see Concept 8.1). Here, however, we will use the term heat to refer simply to thermal energy.

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. Some fishes and insect species and a few nonavian reptiles are also mainly endothermic. In contrast, amphibians, many nonavian reptiles and fishes, and most invertebrates are **ectothermic**, meaning that they gain most of their heat from external sources. Endothermy and ectothermy are not mutually exclusive, however. For example, a bird is mainly endothermic but may warm itself in the sun on a cold morning, much as an ectothermic lizard does.

Endotherms can maintain a stable body temperature even in the face of large fluctuations in the environmental temperature. In a cold environment, an endotherm generates enough heat to keep its body substantially warmer than its surroundings **(Figure 40.11a)**. In a hot environment, endothermic vertebrates have mechanisms for cooling their bodies, enabling them to withstand temperatures that are intolerable for most ectotherms.

Many ectotherms adjust their body temperature by behavioral means, such as seeking out shade or basking in the sun **(Figure 40.11b)**. 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. Ectotherms also usually tolerate larger fluctuations in their internal temperature.

Variation in Body Temperature

Animals also differ in whether their body temperature is variable or constant. An animal whose body temperature varies with its environment is called a *poikilotherm* (from the Greek *poikilos*, varied). In contrast, a *homeotherm* has a relatively constant body temperature. For example, the largemouth bass is a poikilotherm, and the river otter is a homeotherm (see Figure 40.7).

From the descriptions of ectotherms and endotherms, it might seem that all ectotherms are poikilothermic and all endotherms are homeothermic. In fact, there is no fixed relationship between the source of heat and the stability of body temperature. Many ectothermic marine fishes and invertebrates inhabit waters with such stable temperatures that their body temperature varies less than that of mammals and other endotherms. Conversely, the body temperature of a few endotherms varies considerably. For example, the body temperature of some bats drops from 40°C to a few degrees above zero when they enter hibernation.

▼ Figure 40.11 Thermoregulation by internal or external sources of heat. Endotherms obtain heat from their internal metabolism, whereas ectotherms rely on heat from their external environment.

(a) King penguins (*Aptenodytes patagonicus*), endotherms

(b) Florida red-bellied turtles (*Pseudemys nelsoni*), ectotherms

It is a common misconception that ectotherms are "cold-blooded" and endotherms are "warm-blooded." Ectotherms do not necessarily have low body temperatures. On the contrary, when sitting in the sun, many ectothermic lizards have higher body temperatures than mammals. Thus, the terms *cold-blooded* and *warm-blooded* are misleading and are avoided in scientific communication.

Balancing Heat Loss and Gain

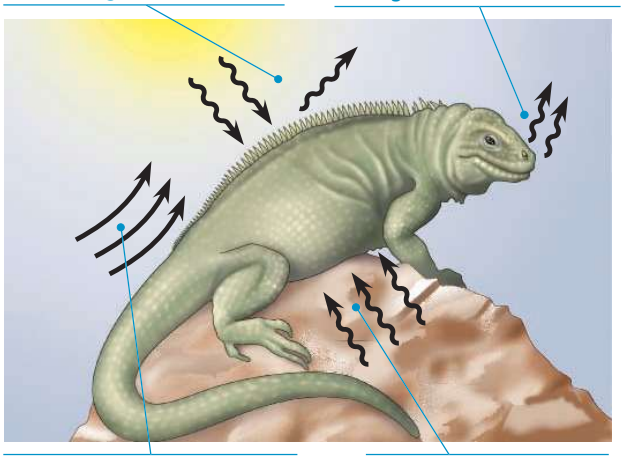
Thermoregulation depends on an animal's ability to control the exchange of heat with its environment. That exchange can occur by any of four processes: radiation, evaporation, convection, and conduction **(Figure 40.12)**. In each, heat is transferred from an object of higher temperature to one of lower temperature.

The essence of thermoregulation is maintaining a rate of heat gain that equals the rate of heat loss. Animals do this through mechanisms that either reduce heat exchange overall or favor heat exchange in a particular direction. In mammals, several of these mechanisms involve the **integumentary system**, the outer covering of the body, consisting of the skin, hair, and nails (claws or hooves in some species).

▼ Figure 40.12 Heat exchange between an organism and its environment.

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 transfer of heat between molecules of objects in contact with each other, as when a lizard sits on a hot rock.

VISUAL SKILLS *If this figure showed a penguin (an endotherm) on an ice floe rather than an iguana (an ectotherm) on a rock, would any of the arrows point in a different direction? Explain.*

Insulation

Insulation, which reduces the flow of heat between an animal's body and its environment, is a major adaptation for thermoregulation in both mammals and birds. Insulation is found both at the body surface—hair and feathers—and beneath—layers of fat formed by adipose tissue. In addition, some animals secrete oily substances that repel water, protecting the insulating capacity of feathers or fur. Birds, for example, secrete oils that they apply to their feathers during preening.

Often, animals can adjust their insulating layers to further regulate body temperature. Most land mammals and birds, for example, react to cold by raising their fur or feathers. This action traps a thicker layer of air, thereby increasing the effectiveness of the insulation. Lacking feathers or fur, humans must rely primarily on fat for insulation. We do, however, get "goose bumps," a vestige of hair raising inherited from our furry ancestors.

Insulation is particularly important for marine mammals, such as whales and walruses. These animals swim in water colder than their body core, and many species spend at least part of the year in nearly freezing polar seas. Furthermore, the transfer of heat to water occurs 50 to 100 times more rapidly than heat transfer to air. Survival under these conditions is made possible by an evolutionary adaptation called blubber, a very thick layer of insulating fat just under the skin. The insulation that blubber provides is so effective that marine mammals can maintain body core temperatures of about 36–38°C (97–100°F) without requiring much more energy from food than land mammals of similar size.

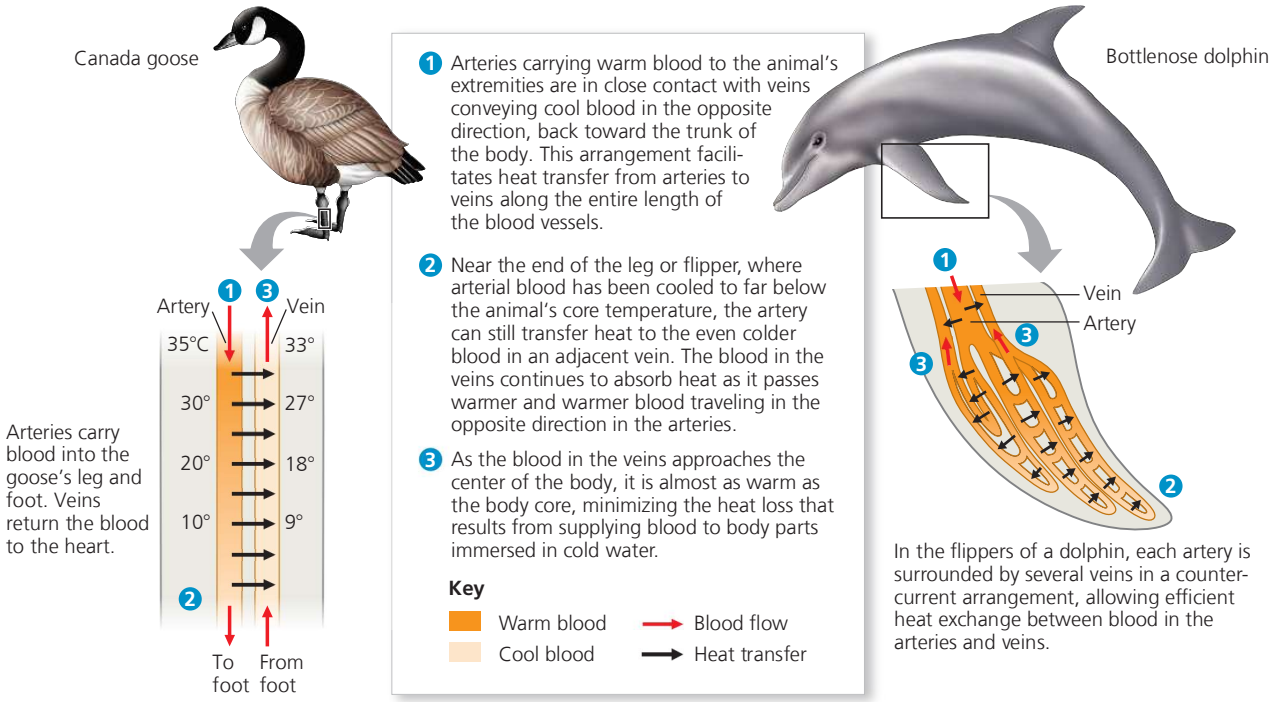
Circulatory Adaptations

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 increases the transfer of body heat to the environment by radiation, conduction, and convection (see Figure 40.12). The reverse process, *vasoconstriction*, reduces blood flow and heat transfer by decreasing the diameter of superficial vessels.

Like endotherms, some ectotherms control heat exchange by regulating blood flow. For example, when the marine

▼ Figure 40.13 Countercurrent heat exchangers. A countercurrent exchange system traps heat in the body core, thus reducing heat loss from the extremities, particularly when they are immersed in cold water or in contact with ice or snow. In essence, heat in the arterial blood emerging from the body core is transferred directly to the returning venous blood instead of being lost to the environment.



iguana of the Galápagos Islands swims in the cold ocean, its superficial blood vessels undergo vasoconstriction. This process routes more blood to the body core, conserving body heat.

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 40.13)**. Because blood flows through the arteries and veins in opposite directions, this arrangement allows heat exchange to be remarkably efficient. As warm blood in the arteries moves outward from the body core, it transfers heat to the colder blood in the veins returning from the extremities. Most importantly, heat is transferred along the entire length of the exchanger, maximizing the rate of heat exchange and minimizing heat loss to the environment.

Although most sharks and fishes are temperature conformers, countercurrent heat exchangers are found in some large, powerful swimmers, including great white sharks, bluefin tuna, and swordfish. By keeping the main swimming muscles warm, this adaptation enables vigorous, sustained activity. Similarly, many endothermic insects (bumblebees, honeybees, and some moths) have a countercurrent exchanger that helps maintain a high temperature in their thorax, where flight muscles are located.

Cooling by Evaporative Heat Loss

Many mammals and birds live in places where regulating body temperature requires cooling at some times and warming at others. If environmental temperature is above body temperature, only evaporation can keep body temperature from rising. Water absorbs considerable heat when it evaporates (see Concept 3.2); this heat is carried away from the skin and respiratory surfaces with water vapor.

Some animals exhibit adaptations that greatly facilitate evaporative cooling. A few mammals, including horses and humans, have sweat glands. In many other mammals, as well as in birds, panting is important. Some birds have a pouch richly supplied with blood vessels in the floor of the mouth; fluttering the pouch increases evaporation. Pigeons can use this adaptation to keep their body temperature close to 40°C (104°F) in air temperatures as high as 60°C (140°F), as long as they have sufficient water.

▶ Figure 40.14
Thermoregulatory behavior in a dragonfly. By orienting its body so that the narrow tip of its abdomen faces the sun, the dragonfly minimizes heating by solar radiation.

Behavioral Responses

Ectotherms, and sometimes endotherms, control body temperature through behavioral responses to changes in the environment. When cold, they seek warm places, orienting themselves toward heat sources and expanding the portion of their body surface exposed to the heat source (see Figure 40.11b). When hot, they bathe, move to cool areas, or turn in another direction, minimizing their absorption of heat from the sun. For example, a dragonfly's "obelisk" posture is an adaptation that minimizes the amount of body surface exposed to the sun and thus to heating **(Figure 40.14)**. Although these behaviors are relatively simple, they enable many ectotherms to maintain a nearly constant body temperature.

Social behavior contributes to thermoregulation in both endotherms and ectotherms. Among endotherms, for example, behavior contributes significantly to the winter survival of Emperor penguins (see Figure 40.1). Among ectotherms, honeybees are notable for their use of behavior in achieving homeostasis for temperature. In cold weather, they increase heat production and huddle together, thereby retaining heat. Individuals move between the cooler outer edges of the huddle and the warmer center, thus circulating and distributing the heat. In hot weather, honeybees cool the hive by transporting water to the hive and fanning with their wings, promoting evaporation and convection. Thus, a honeybee colony uses many of the mechanisms of thermoregulation characteristic of individual animals.

Adjusting Metabolic Heat Production

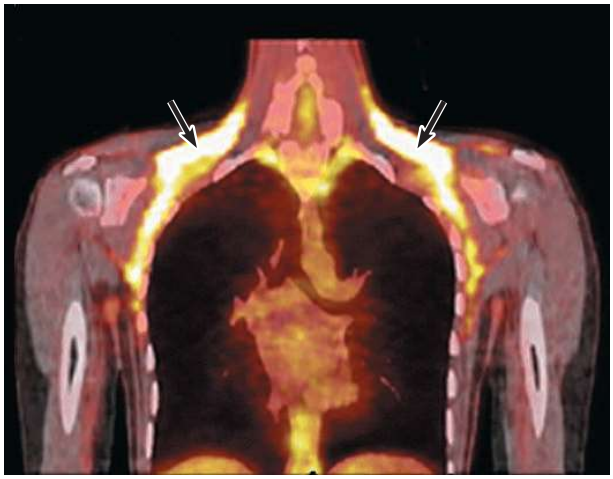
Because endotherms generally maintain a body temperature considerably higher than that of the environment, they must counteract continual heat loss. Endotherms can vary heat production—*thermogenesis*—to match changing rates of heat loss. Thermogenesis is increased by such muscle activity as moving or shivering. For example, shivering helps chickadees, birds with a body mass of only 20 g, remain active and hold their body temperature nearly constant at 40°C (104°F) in environmental temperatures as low as −40°C (−40°F).

Flying insects such as bees and moths can also vary heat production. Many such endothermic insects warm up by shivering before taking off. As they contract their flight muscles in synchrony, only slight wing movements occur, but considerable heat is produced. Chemical reactions, and hence cellular respiration, accelerate in the warmed-up flight "motors," enabling flight even in cold air.

In some mammals, endocrine signals released in response to cold cause mitochondria to increase their metabolic activity and produce heat instead of ATP. This process, called *nonshivering thermogenesis*, takes place throughout the body. Some mammals also have a tissue called *brown fat* in their neck and between their shoulders that is specialized for rapid heat production. (The presence of extra mitochondria is what gives brown fat its characteristic color.) Brown fat is found in the infants of many mammals, representing about 5% of total body weight in human infants. Long known to be present in adult mammals that hibernate, brown fat has also recently been detected in human adults **(Figure 40.15)**. There, the amount has been found to vary, with individuals exposed to a cool environment for a month having increased amounts of brown fat.

Among the nonavian reptiles, endothermy has been observed in some large species in certain circumstances. For example, researchers found that a female Burmese python (*Python molurus bivittatus*) incubating eggs maintained a body temperature roughly 6°C (11°F) above that of the surrounding air. Where did the heat come from? Further studies showed that such pythons, like birds, can raise their body

▼ Figure 40.15 Brown fat activity during cold stress. This PET scan shows metabolically active brown fat deposits (indicated by the arrows) surrounding the neck.

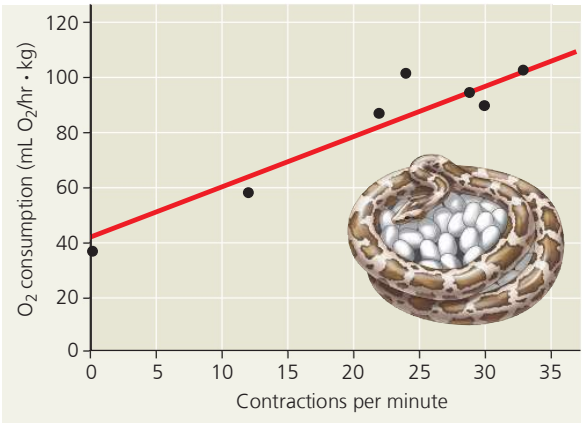


▼ Figure 40.16 Inquiry

How does a Burmese python generate heat while incubating eggs?

Experiment Herndon Dowling and colleagues at the Bronx Zoo in New York observed that when a female Burmese python incubated eggs by wrapping her body around them, she raised her body temperature and frequently contracted the muscles in her coils. To learn if the contractions were elevating her body temperature, they placed the python and her eggs in a chamber. As they varied the chamber's temperature, they monitored the python's muscle contractions as well as her oxygen uptake, a measure of her rate of cellular respiration.

Results The python's oxygen consumption increased when the temperature in the chamber decreased. As shown in the graph, this increase in oxygen consumption paralleled an increase in the rate of muscle contraction.



Conclusion Because oxygen consumption, which generates heat through cellular respiration, was correlated with the rate of muscle contraction, the researchers concluded that the muscle contractions, a form of shivering, were the source of the Burmese python's elevated body temperature.

Data from V. H. Hutchison, H. G. Dowling, and A. Vinegar, Thermoregulation in a brooding female Indian python, *Python molurus bivittatus*, *Science* 151:694–696 (1966).

WHAT IF? *Suppose you varied air temperature and measured oxygen consumption for a female Burmese python without a clutch of eggs. Since she would not show shivering behavior, how would you expect the snake's oxygen consumption to vary with environmental temperature?*

temperature through shivering **(Figure 40.16)**. Whether certain groups of Mesozoic dinosaurs were similarly endothermic is a matter of active debate.

Acclimatization in Thermoregulation

Acclimatization 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.

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 7.5).

Remarkably, some ectotherms can survive subzero temperatures, producing "antifreeze" proteins that prevent ice formation in their cells. In the Arctic and Southern (Antarctic) Oceans, these proteins enable certain fishes to survive in water as cold as −2°C (28°F), a full degree Celsius below the freezing point of body fluids in other species.

Physiological Thermostats and Fever

In humans and other mammals, the sensors responsible for thermoregulation are concentrated in the **hypothalamus**, the brain region that also controls the circadian clock. Within the hypothalamus, a group of nerve cells functions as a thermostat, responding to body temperatures outside the normal range by activating mechanisms that promote heat loss or gain **(Figure 40.17)**.

At body temperatures above the normal range, the hypothalamic thermostat promotes cooling of the body by dilation of vessels in the skin, sweating, or panting. When body temperatures instead drop below the normal range, the thermostat inhibits heat loss mechanisms and activates mechanisms that either save heat, such as constricting vessels in the skin, or generate heat, such as shivering.

In the course of certain bacterial and viral infections, mammals and birds develop *fever*, an elevated body temperature. A variety of experiments have shown that fever reflects an increase in the normal range for the biological thermostat. For example, artificially *raising* the temperature of the hypothalamus in an infected animal *reduces* fever in the rest of the body.

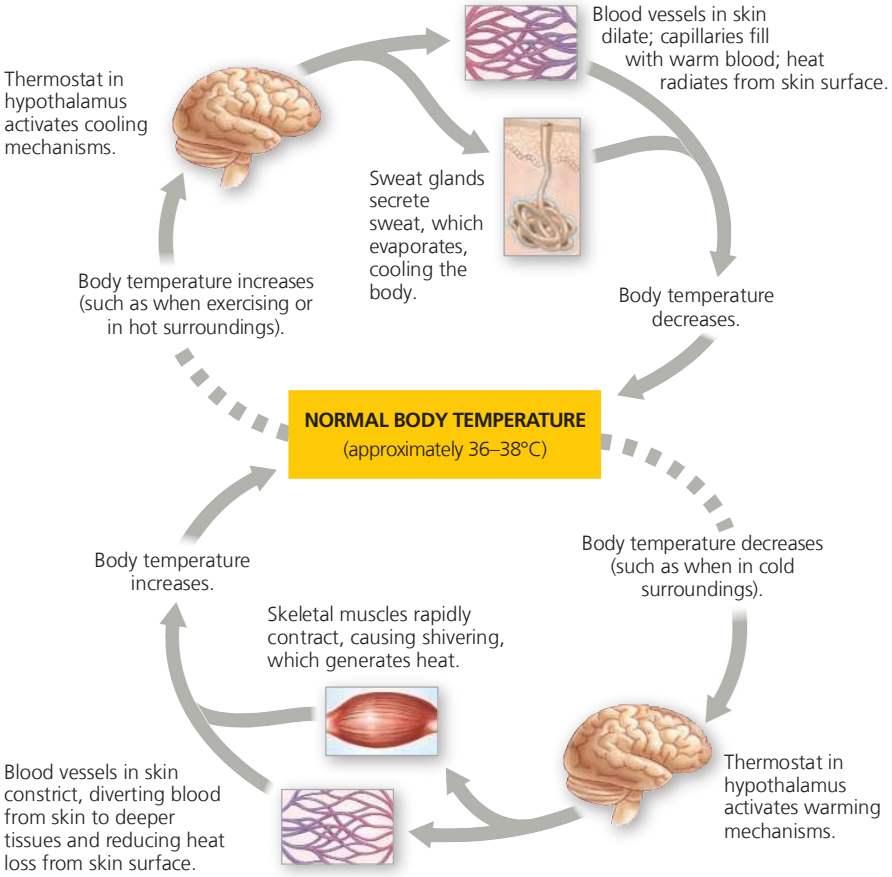
Among certain ectotherms, an increase in body temperature upon infection reflects what is called a behavioral fever. For example, the desert iguana (*Dipsosaurus dorsalis*) responds to infection with certain bacteria by seeking a warmer environment and then maintaining a body temperature that is elevated by 2–4°C (4–7°F). Similar observations in fishes, amphibians, and even cockroaches indicate that fever is common to both endotherms and ectotherms.

Now that we have explored thermoregulation, we'll conclude our introduction to animal form and function by considering the different ways that animals allocate, use, and conserve energy.

▶ Figure 40.17 The thermostatic function of the hypothalamus in human thermoregulation.

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?*

Mastering Biology Figure Walkthrough



CONCEPT CHECK 40.3

1. What mode of heat exchange is involved in "wind chill," when moving air feels colder than still air at the same temperature? Explain.
2. Flowers differ in how much sunlight they absorb. Why might this matter to a hummingbird seeking nectar on a cool morning?
3. **WHAT IF?** Why is shivering likely during the onset of a fever?

For suggested answers, see Appendix A.

CONCEPT 40.4

Energy requirements are related to animal size, activity, and environment

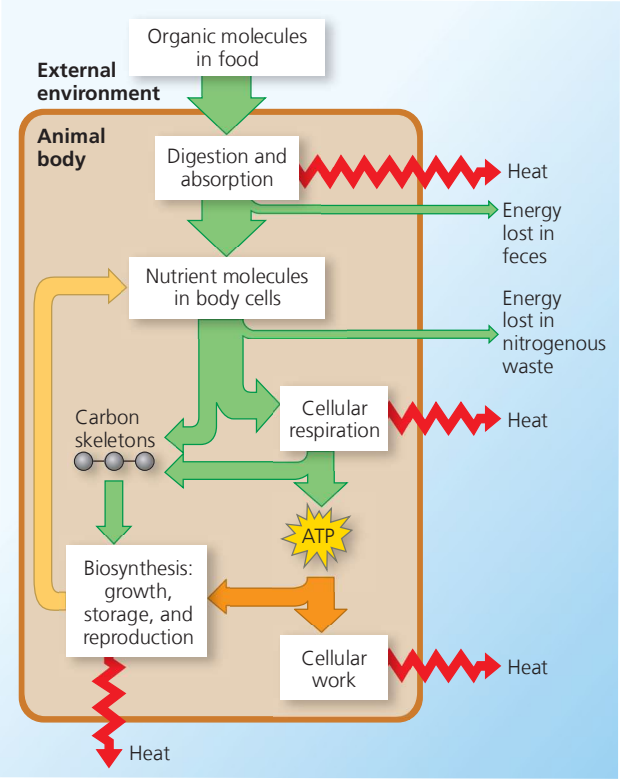
One of the unifying themes of biology, introduced in Concept 1.1, is that life requires energy transfer and transformation. Like other organisms, animals use chemical energy for growth, repair, activity, and reproduction. The overall flow and transformation of energy in an animal—its **bioenergetics**—determines nutritional needs and is related to the animal's size, activity, and environment.

Energy Allocation and Use

Organisms can be classified by how they obtain chemical energy. Most *autotrophs*, such as plants, harness light energy to build energy-rich organic molecules and then use those molecules for fuel. Most *heterotrophs*, such as animals, obtain their chemical energy from food, which contains organic molecules synthesized by other organisms.

Animals use chemical energy harvested from the food they eat to fuel metabolism and activity. Food is digested by enzymatic hydrolysis (see Figure 5.2b), and nutrients are absorbed by body cells. The ATP (adenosine triphosphate) produced by cellular respiration and fermentation powers cellular work, enabling cells, organs, and organ systems to perform the functions that keep an animal alive. Other uses of energy in the form of ATP include biosynthesis, which is needed for

▼ Figure 40.18 Bioenergetics of an animal: an overview.



MAKE CONNECTIONS *Use the idea of energy coupling to explain why heat is produced in the absorption of nutrients, in cellular respiration, and in the synthesis of biopolymers (see Concept 8.3).*

body growth and repair, synthesis of storage material such as fat, and production of gametes. The production and use of ATP generate heat, which the animal eventually gives off to its surroundings **(Figure 40.18)**.

Quantifying Energy Use

How much of the total energy an animal obtains from food does it 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.

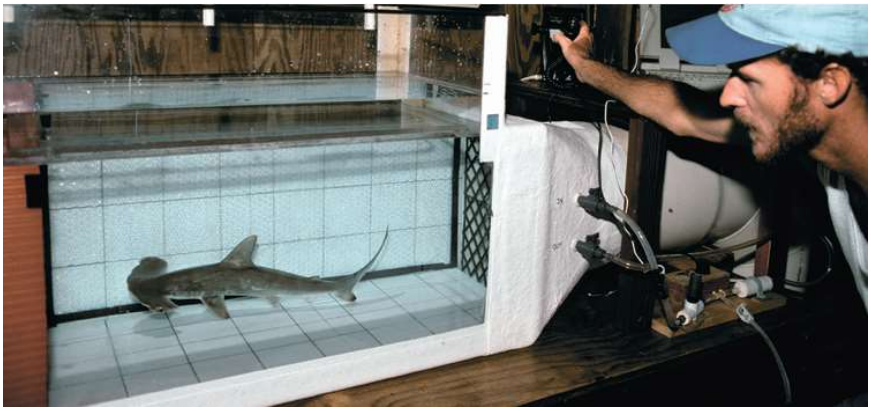
The sum of all the energy an animal uses in a given time interval is called its **metabolic rate**. Energy is measured in joules (J) or in calories (cal) and kilocalories (kcal). A kilocalorie equals 1,000 calories, or 4,184 joules. (The unit Calorie, with a capital C, as used by many nutritionists, is actually a kilocalorie.)

Metabolic rate can be determined in several ways. Because nearly all of the chemical energy used in cellular respiration 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 closed, insulated chamber equipped with a device that records the heat an animal gives off to its environment. Metabolic rate can also be determined from the amount of oxygen consumed or carbon dioxide produced by an animal's cellular respiration **(Figure 40.19)**. To calculate metabolic rate over longer periods, researchers record the rate of food consumption, the energy content of the food (about 4.5–5 kcal per gram of protein or carbohydrate and about 9 kcal per gram of fat), and the chemical energy lost in waste products (feces and urine or other nitrogenous wastes).

Minimum Metabolic Rate and Thermoregulation

Animals must maintain a minimum metabolic rate for basic functions such as cell maintenance, breathing, and circulation. 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 only the minimum generation or shedding of heat. The minimum metabolic rate of ectotherms is 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

▼ Figure 40.19 Measuring the rate of oxygen consumption by a swimming shark. A researcher monitors the decrease in oxygen level over time in the recirculating water of a juvenile hammerhead's tank.



ectotherm at rest at a particular temperature is called its **standard metabolic rate (SMR)**.

Comparisons of minimum metabolic rates reveal the different energy costs of endothermy and ectothermy. The BMR for humans averages 1,600–1,800 kcal per day for adult males and 1,300–1,500 kcal per day for adult females. These BMRs are about equivalent to the rate of energy use by a 75-watt lightbulb. In contrast, the SMR of an American alligator is only about 60 kcal per day at 20°C (68°F). As this represents less than $\frac{1}{20}$ the energy used by a comparably sized adult human, it is clear that ectothermy has a markedly lower energetic requirement than endothermy.

Influences on Metabolic Rate

Metabolic rate is affected by many factors other than an animal being an endotherm or an ectotherm. Some key factors are age, sex, size, activity, temperature, and nutrition. Here we'll examine the effects of size and activity.

Size and Metabolic Rate

Larger animals have more body mass and therefore require more chemical energy. Remarkably, the relationship between overall metabolic rate and body mass is constant across a wide range of sizes and forms, as illustrated for various mammals in **Figure 40.20a**. In fact, for even more varied organisms ranging in size from bacteria to blue whales, metabolic rate remains roughly proportional to body mass to the three-quarter power ($m^{3/4}$). Scientists are still researching the basis of this relationship, which applies to ectotherms as well as endotherms.

The relationship of metabolic rate to size profoundly affects energy consumption by body cells and tissues. As shown in **Figure 40.20b**, the energy it takes to maintain each gram of body mass is inversely related to body size. Each gram of a mouse, for instance, requires about 20 times as many calories as a gram of an elephant, even though the whole elephant uses far more calories than the whole mouse. The smaller animal's higher metabolic rate per gram demands a higher rate of oxygen delivery. To meet this demand, the smaller animal must have a higher breathing rate, blood volume (relative to its size), and heart rate.

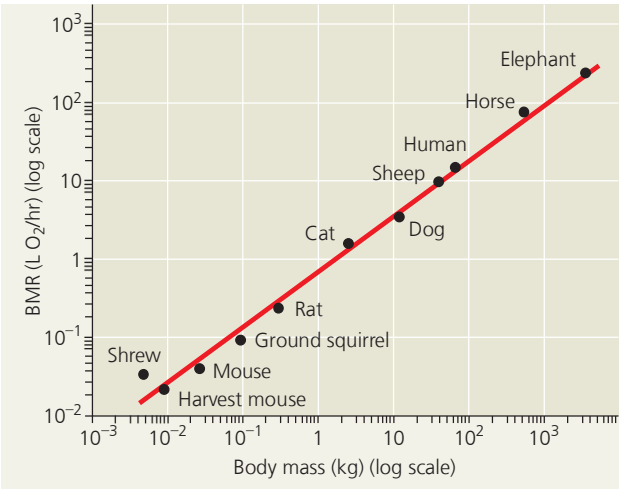
Thinking about body size in bioenergetic terms reveals how trade-offs shape the evolution of body plans. As body size decreases, each gram of tissue increases in energy cost. As body size increases, energy costs per gram of tissue decrease, but an ever-larger fraction of body tissue is required for exchange, support, and locomotion.

Activity and Metabolic Rate

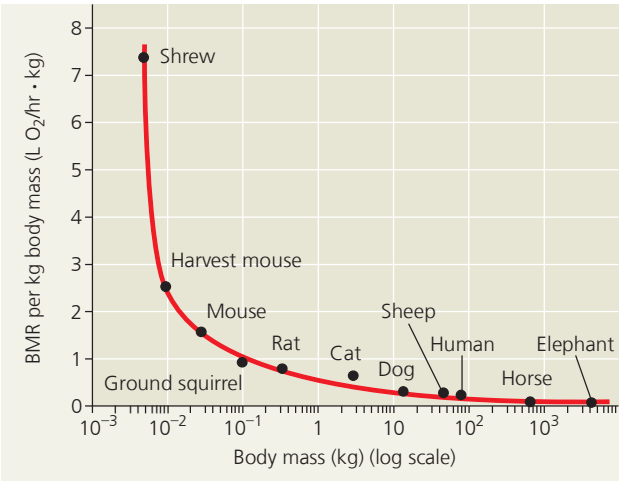
For both ectotherms and endotherms, activity greatly affects metabolic rate. Even a person reading quietly at a desk or an insect twitching its wings consumes energy beyond the BMR or SMR. Maximum metabolic rates (the highest rates of ATP use) occur during peak activity, such as lifting a heavy object, sprinting, or swimming at high speed. 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 two to four times BMR (for endotherms) or SMR (for ectotherms). Humans in most developed countries have an unusually low average daily metabolic rate

▼ Figure 40.20 The relationship of metabolic rate to body size.



(a) Relationship of basal metabolic rate (BMR) to body size for various mammals. From shrew to elephant, size increases 1 millionfold.



(b) Relationship of BMR per kilogram of body mass to body size for the same mammals as in (a).

INTERPRET THE DATA *Based on the graph in (a), one observer suggests that a group of 100 ground squirrels has the same basal metabolic rate as 1 dog. A second observer looking at the graph disagrees. Who is correct and why?*

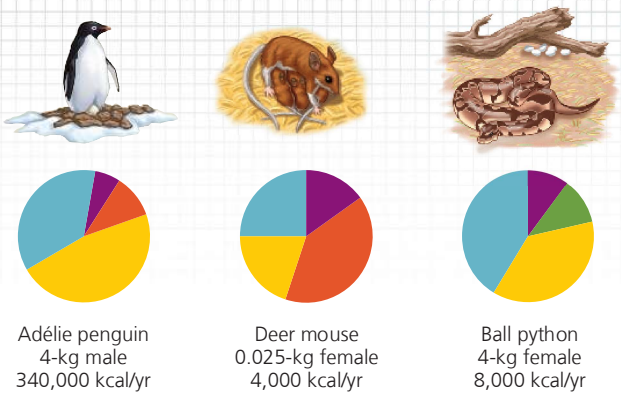
Scientific Skills Exercise

Interpreting Pie Charts

How Do Energy Budgets Differ for Three Terrestrial Vertebrates? To explore bioenergetics in animal bodies, let's consider typical annual energy budgets for three terrestrial vertebrates that vary in size and thermoregulatory strategy: a 4-kg male Adélie penguin, a 25-g (0.025-kg) female deer mouse, and a 4-kg female ball python. The penguin is well-insulated against his Antarctic environment but must expend energy in swimming to catch food, incubating eggs laid by his partner, and bringing food to his chicks. The tiny deer mouse lives in a temperate environment where food may be readily available, but her small size causes rapid loss of body heat. Unlike the penguin and mouse, the python is ectothermic and keeps growing throughout her life. She produces eggs but does not incubate them. In this exercise, we'll compare the energy expenditures of these animals for five important functions: basal (standard) metabolism, reproduction, thermoregulation, activity, and growth.

How the Data Were Obtained Energy budgets were calculated for each of the animals based on measurements from field and laboratory studies.

Data from the Experiments Pie charts are a good way to compare *relative* differences in a set of variables. In the pie charts here, the sizes of the wedges represent the relative annual energy expenditures for the functions shown in the key. The total annual expenditure for each animal is given below its pie chart.



Data from M. A. Chappell et al., Energetics of foraging in breeding Adélie penguins, *Ecology* 74:2450–2461 (1993); M. A. Chappell et al., Voluntary running in deer mice: speed, distance, energy costs, and temperature effects, *Journal of Experimental Biology* 207:3839–3854 (2004); T. M. Ellis and M. A. Chappell, Metabolism, temperature relations, maternal behavior, and reproductive energetics in the ball python (*Python regius*), *Journal of Comparative Physiology B* 157:393–402 (1987).

INTERPRET THE DATA

1. You can estimate the contribution of each wedge in a pie chart by remembering that the entire circle represents 100%, half is 50%, and so on. What percent of the mouse's energy budget goes to basal metabolism? What percent of the penguin's budget is for activity?
2. Without considering the sizes of the wedges, how do the three pie charts differ in which functions they include? Explain these differences.
3. Does the penguin or the mouse expend a greater proportion of its energy budget on thermoregulation? Why?
4. Now look at the *total* annual energy expenditures for each animal. How much more energy does the penguin expend each year compared to the similarly sized python?
5. Which animal expends the most kilocalories per year on thermoregulation?
6. If you monitored energy allocation in the penguin for just a few months instead of an entire year, you might find the growth category to be a significant part of the pie chart. Given that adult penguins don't grow from year to year, how would you explain this finding?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology.**

of about 1.5 times BMR—an indication of a relatively sedentary lifestyle.

The fraction of an animal's energy "budget" that is devoted to activity depends on many factors, including its environment, behavior, size, and thermoregulation. In the **Scientific Skills Exercise**, you'll interpret data on the annual energy budgets of three terrestrial vertebrates.

Torpor and Energy Conservation

Despite their many adaptations for homeostasis, animals may encounter conditions that severely challenge their abilities to balance their heat, energy, and materials budgets. For example, at certain times of the day or year, their surroundings may be extremely hot or cold, or food may be unavailable. A major adaptation that enables animals to save energy in the face of such difficult conditions is **torpor**, a physiological state of decreased activity and metabolism.

Many birds and small mammals exhibit a daily torpor that is well adapted to feeding patterns. For instance, some bats feed at night and go into torpor in daylight. Similarly, chickadees and hummingbirds, which feed during the day, often go into torpor on cold nights.

All endotherms that exhibit daily torpor are relatively small; when active, they have high metabolic rates and thus very high rates of energy consumption. The changes in body temperature, and thus the energy savings, are often considerable: the body temperature of chickadees drops as much as 10°C (18°F) at night, and the core body temperature of a hummingbird can fall 25°C (45°F) or more.

Hibernation is long-term torpor that is an adaptation to winter cold and food scarcity. When a mammal enters hibernation, its body temperature declines as its body's thermostat is turned down **(Figure 40.21)**. Some hibernating mammals cool to as low as 1–2°C (34–36°F), and at least one, the Arctic ground squirrel (*Spermophilus parryii*), can enter a supercooled (unfrozen) state in which its body temperature dips below 0°C (32°F). Periodically, perhaps every two weeks or so, hibernating animals undergo arousal, raising their body temperature and becoming active briefly before resuming hibernation. Metabolic rates during hibernation can be 20 times lower than if the animal attempted to maintain normal body temperatures of 36–38°C (97–100°F). As a result, hibernators such as the ground squirrel can survive through the winter on limited supplies of energy stored in the body tissues or as food cached in a burrow. Similarly, the slow metabolism and inactivity of *estivation*, or summer torpor, enable animals to survive long periods of high temperatures and scarce water.

▼ Figure 40.21 A hazel dormouse (*Muscardinus avellanarius*) hibernating.

What happens to the circadian rhythm in hibernating animals? In the past, researchers reported detecting daily biological rhythms in hibernating animals. However, in some cases the animals were probably in a state of torpor from which they could readily arouse, rather than "deep" hibernation. More recently, a group of researchers in France addressed this question in a different way, examining the machinery of the biological clock rather than the rhythms it controls **(Figure 40.22)**. Working with the European hamster, they found that molecular components of the clock stopped oscillating during hibernation. These findings support the hypothesis that the circadian clock ceases operation during hibernation, at least in this species.

From tissue types to homeostasis, this chapter has focused on the whole animal. We also investigated how animals exchange materials with the environment and how size and activity affect metabolic rate. For much of the rest of this unit, we'll explore how specialized organs and organ systems enable animals to meet the basic challenges of life. In Unit 6, we investigated how plants meet the same challenges. **Figure 40.23**, on the next two pages, highlights some fundamental similarities and differences in the evolutionary adaptations of plants and animals. This figure is thus a review of Unit 6, an introduction to Unit 7, and, most importantly, an illustration of the connections that unify the myriad forms of life.

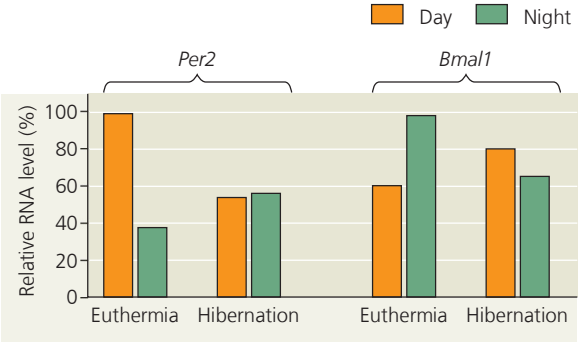
Mastering Biology Interview with George Bartholomew: Exploring connections between animal physiology and the environment

▼ Figure 40.22 Inquiry

What happens to the circadian clock during hibernation?

Experiment To determine whether the 24-hour biological clock continues to run during hibernation, Paul Pévet and colleagues at the University of Louis Pasteur in Strasbourg, France, studied molecular components of the circadian clock in the European hamster (*Cricetus cricetus*). The researchers measured RNA levels for two clock genes—*Per2* and *Bmal1*—during normal activity (euthermia) and during hibernation in constant darkness. The RNA samples were obtained from the suprachiasmatic nuclei (SCN), a pair of structures in the mammalian brain that control circadian rhythms.

Results



Conclusion Hibernation disrupted circadian variation in the hamster's clock gene RNA levels. Further experiments demonstrated that this disruption was not simply due to the dark environment during hibernation, since for nonhibernating animals RNA levels during a darkened daytime were the same as in daylight. The researchers concluded that the biological clock stops running in hibernating European hamsters and, perhaps, in other hibernators as well.

Data from F. G. Revel et al., The circadian clock stops ticking during deep hibernation in the European hamster, *Proceedings of the National Academy of Sciences USA* 104:13816–13820 (2007).

WHAT IF? *Suppose you discovered a new hamster gene and found that the levels of RNA for this gene were constant during hibernation. What could you conclude about the day and night RNA levels for this gene during euthermia?*

CONCEPT CHECK 40.4

1. If a mouse and a small lizard of the same mass (both at rest) were placed in experimental chambers under identical environmental conditions, which animal would consume oxygen at a higher rate? Explain.
2. Which animal must eat a larger proportion of its weight in food each day: a house cat or an African lion caged in a zoo? Explain.
3. **WHAT IF?** Suppose the animals at a zoo were resting comfortably and remained at rest while the nighttime air temperature dropped. If the temperature change were sufficient to cause a change in metabolic rate, what changes would you expect for an alligator and a lion?

For suggested answers, see Appendix A.

▼ Figure 40.23

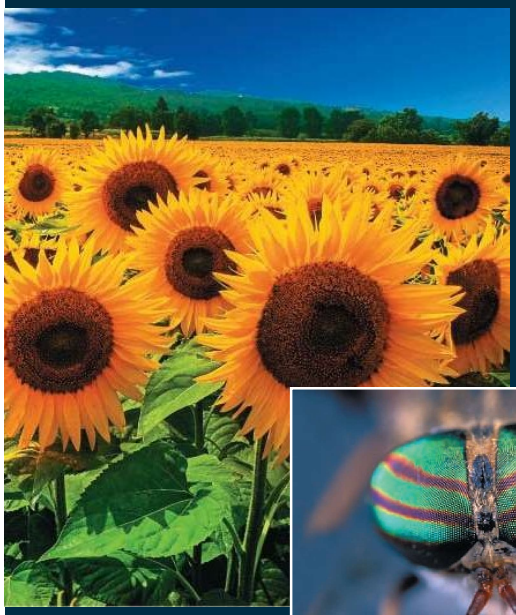
MAKE CONNECTIONS

Life Challenges and Solutions in Plants and Animals

Multicellular organisms face a common set of challenges. Comparing the solutions that have evolved in plants and animals reveals both unity (shared elements) and diversity (distinct features) across these two lineages.

Nutritional Mode

All living things must obtain energy and carbon from the environment to grow, survive, and reproduce. Plants are autotrophs, obtaining their energy through photosynthesis and their carbon from inorganic sources, whereas animals are heterotrophs, obtaining their energy and carbon from food. Evolutionary adaptations in plants and animals support these different nutritional modes. The broad surface of many leaves enhances light capture for photosynthesis. When hunting, a bobcat relies on stealth, speed, and sharp claws. (See Figure 36.2 and Figure 41.16.)



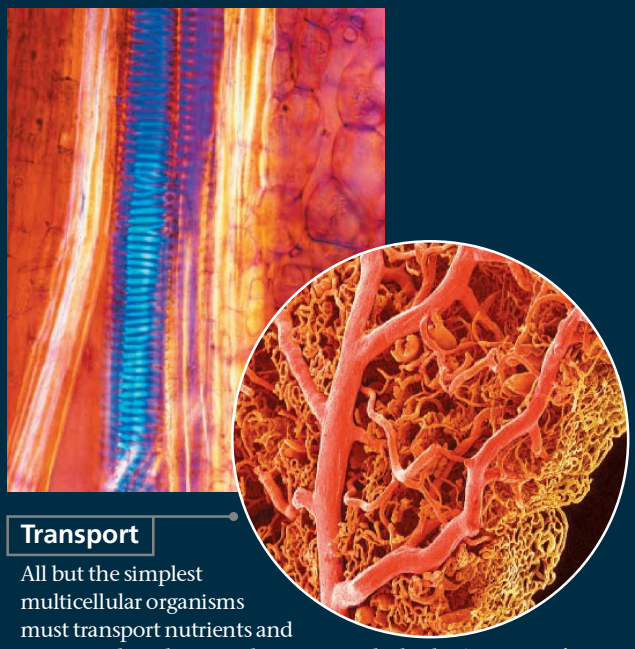
Growth and Regulation

The growth and physiology of both plants and animals are regulated by hormones. In plants, hormones may act in a local area or be transported in the body. They control growth patterns, flowering, fruit development, and more. In animals, hormones circulate throughout the body and act in specific target tissues, controlling homeostatic processes and developmental events such as molting. (See Figure 39.10 and Figure 45.12.)

Environmental Response

All forms of life must detect and respond appropriately to conditions in their environment. Specialized organs sense environmental signals. For example, the floral head of a sunflower and an insect's eyes both contain photoreceptors that detect light. Environmental signals activate specific receptor proteins, triggering signal transduction pathways that initiate cellular responses coordinated by chemical and electrical communication. (See Figure 39.19 and Figure 50.15.)

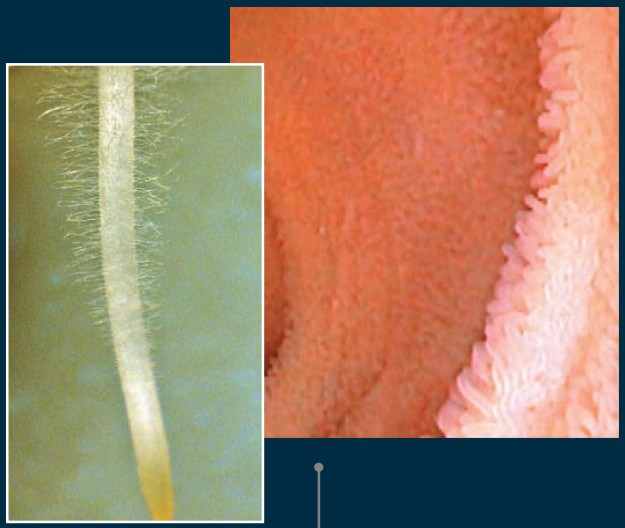
Mastering Biology BioFlix® Animation: Homeostasis: Regulating Blood Sugar



Transport

All but the simplest multicellular organisms must transport nutrients and waste products between locations in the body. A system of tubelike vessels is the common evolutionary solution, while the mechanism of circulation varies. Plants harness solar energy to transport water, minerals, and sugars through specialized tubes (left). In animals, a pump (heart) moves circulatory fluid through vessels (right). (See Figure 35.10 and Figure 42.9.)

Mastering Biology BioFlix® Animation: Water Transport in Plants



Absorption

Organisms need to absorb nutrients. The root hairs of plants (left) and the villi (projections) that line the intestines of vertebrates (right) increase the surface area available for absorption. (See Figure 35.3 and Figure 41.12.)

Reproduction

In sexual reproduction, specialized tissues and structures produce and exchange gametes. Offspring are generally supplied with nutritional stores that facilitate rapid growth and development. For example, seeds have stored food reserves that supply energy to the young seedling, while milk provides sustenance for juvenile mammals. (See Figure 38.8 and Figure 34.40.)

Gas Exchange

The exchange of certain gases with the environment is essential for life. Respiration by plants and animals requires taking up oxygen (O_2) and releasing carbon dioxide (CO_2). In photosynthesis, net exchange occurs in the opposite direction: CO_2 uptake and O_2 release. In both plants and animals, highly convoluted surfaces that increase the area available for gas exchange have evolved, such as the spongy mesophyll of leaves (left) and the alveoli of lungs (right). (See Figure 35.18 and Figure 42.24.)

Mastering Biology BioFlix® Animation: Gas Exchange

MAKE CONNECTIONS

Compare the adaptations that enable plants and animals to respond to the challenges of living in hot and cold environments. See Concept 39.4 and Concept 40.3.

40 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 40.1

Animal form and function are correlated at all levels of organization *(pp. 874–881)*

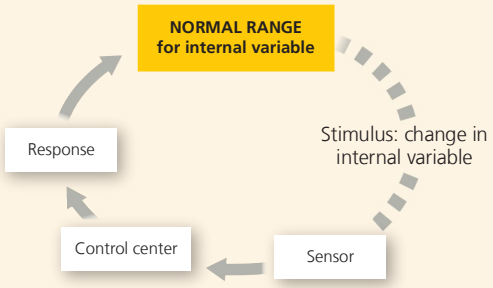
- Physical laws constrain the evolution of an animal's size and shape. These constraints contribute to convergent evolution in animal body forms.
- Each animal cell must have access to an aqueous environment. Simple two-layered sacs and flat shapes maximize exposure to the surrounding medium. More complex body plans have highly folded internal surfaces specialized for exchanging materials.
- 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.
- The **endocrine** and **nervous systems** are the two means of communication between different locations in the body. The endocrine system broadcasts signaling molecules called **hormones** everywhere via the bloodstream, but 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.

? *For a large animal, what challenges would a spherical shape pose for carrying out exchange with the environment?*

CONCEPT 40.2

Feedback control maintains the internal environment in many animals *(pp. 881–883)*

- An animal is a **regulator** if it controls an internal variable and a **conformer** if it allows an internal variable to vary with external changes. **Homeostasis** is the maintenance of a steady state despite internal and external changes.
- Homeostatic mechanisms are usually based on **negative feedback**, in which the **response** reduces the **stimulus**. In contrast, **positive feedback** involves amplification of a stimulus by the response and often brings about a change in state, such as the transition from pregnancy to childbirth.



- Regulated change in the internal environment is essential to normal function. **Circadian rhythms** are daily fluctuations in metabolism and behavior tuned to the cycles of light and dark in the environment. Other environmental changes may trigger **acclimatization**, a temporary shift in the steady state.

? *Is it accurate to define homeostasis as a constant internal environment? Explain.*

CONCEPT 40.3

Homeostatic processes for thermoregulation involve form, function, and behavior *(pp. 884–889)*

- An animal maintains its internal temperature within a tolerable range by **thermoregulation. Endothermic** animals are warmed mostly by heat generated by metabolism. **Ectothermic** animals get most of their heat from external sources. Endothermy requires a greater expenditure of energy. Body temperature may vary with environmental temperature, as in *poikilotherms*, or be relatively constant, as in *homeotherms*.
- In thermoregulation, physiological and behavioral adjustments balance heat gain and loss, which occur through radiation, evaporation, convection, and conduction. Insulation and **countercurrent exchange** reduce heat loss, whereas panting, sweating, and bathing increase evaporation, cooling the body. Many ectotherms and endotherms adjust their rate of heat exchange with their surroundings by vasodilation or vasoconstriction and by behavioral responses.
- Many mammals and birds adjust their amount of body insulation in response to changes in environmental temperature. Ectotherms undergo a variety of changes at the cellular level to acclimatize to shifts in temperature.
- The **hypothalamus** acts as the thermostat in mammalian regulation of body temperature. Fever reflects a resetting of this thermostat to a higher normal range in response to infection.

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

CONCEPT 40.4

Energy requirements are related to animal size, activity, and environment *(pp. 889–895)*

- Animals obtain chemical energy from food, storing it for short-term use in ATP. The total amount of energy used in a unit of time defines an animal's **metabolic rate**.
- Under similar conditions and for animals of the same size, the **basal metabolic rate** of endotherms is substantially higher than the **standard metabolic rate** of ectotherms. Minimum metabolic rate per gram is inversely related to body size among similar animals. Animals allocate energy for basal (or standard) metabolism, activity, homeostasis, growth, and reproduction.
- **Torpor**, a state of decreased activity and metabolism, conserves energy during environmental extremes. Animals may enter torpor according to a circadian rhythm (daily torpor), in winter (**hibernation**), or in summer (estivation).

? *Why do small animals breathe more rapidly than large animals?*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. The body tissue that consists largely of material located outside of cells is
   (A) epithelial tissue.
   (B) connective tissue.
   (C) muscle tissue.
   (D) 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
3. Consider the energy budgets for a human, an elephant, a penguin, a mouse, and a snake. The _____ would have the highest total annual energy expenditure, and the _____ would have the highest energy expenditure per unit mass.
   (A) elephant; mouse
   (B) elephant; human
   (C) mouse; snake
   (D) penguin; mouse

Levels 3-4: Applying/Analyzing

4. Compared with a smaller cell, a larger cell of the same shape has
   (A) less surface area.
   (B) less surface area per unit of volume.
   (C) the same surface-area-to-volume ratio.
   (D) a smaller cytoplasm-to-nucleus ratio.
5. An animal's inputs of energy and materials would exceed its outputs
   (A) if the animal is an endotherm, which must always take in more energy because of its high metabolic rate.
   (B) if it is actively foraging for food.
   (C) if it is growing and increasing its mass.
   (D) never; due to homeostasis, these energy and material budgets always balance.
6. You are studying a large tropical reptile that has a high and relatively stable body temperature. How do you determine whether this animal is an endotherm or an ectotherm?
   (A) You know from its high and stable body temperature that it must be an endotherm.
   (B) You subject this reptile to various temperatures in the lab and find that its body temperature and metabolic rate change with the ambient temperature. You conclude that it is an ectotherm.
   (C) You note that its environment has a high and stable temperature. Because its body temperature matches the environmental temperature, you conclude that it is an ectotherm.
   (D) You measure the metabolic rate of the reptile, and because it is higher than that of a related species that lives in temperate forests, you conclude that this reptile is an endotherm and its relative is an ectotherm.
7. Which of the following animals uses the largest percentage of its energy budget for homeostatic regulation?
   (A) marine jelly (an invertebrate)
   (B) snake in a temperate forest
   (C) desert insect
   (D) desert bird
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.

Levels 5-6: Evaluating/Creating

9. **EVOLUTION CONNECTION** In 1847, the German biologist Christian Bergmann noted that mammals and birds living at higher latitudes (farther from the equator) are on average larger and bulkier than related species found at lower latitudes. Suggest an evolutionary hypothesis to explain this observation.
10. **SCIENTIFIC INQUIRY** Eastern tent caterpillars (*Malacosoma americanum*) live in large groups in silk nests resembling tents, which they build in trees. They are among the first insects to be active in early spring, when daily temperature fluctuates from freezing to very hot. Over the course of a day, they display striking differences in behavior: Early in the morning, they rest in a tightly packed group on the tent's east-facing surface. In midafternoon, they are on its undersurface, each caterpillar hanging by a few of its legs. Propose a hypothesis to explain this behavior. How could you test it?
11. **SCIENCE, TECHNOLOGY, AND SOCIETY** Medical researchers are investigating artificial substitutes for various human tissues. Why might artificial blood or skin be useful? What characteristics would these substitutes need in order to function well in the body? Why do real tissues work better? Why not use the real tissues if they work better? What other artificial tissues might be useful? What problems do you anticipate in developing and applying them?
12. **WRITE ABOUT A THEME: ENERGY AND MATTER** In a short essay (about 100–150 words) focusing on energy transfer and transformation, discuss the advantages and disadvantages of hibernation.
13. **SYNTHESIZE YOUR KNOWLEDGE**

These macaques (*Macaca fuscata*) are partially immersed in a hot spring in a snowy region of Japan. What are some ways that form, function, and behavior contribute to homeostasis for these animals?

For selected answers, see Appendix A.

41 Animal Nutrition

KEY CONCEPTS

41.1 **An animal's diet must supply chemical energy, organic building blocks, and essential nutrients** *p. 899*

41.2 **Food processing involves ingestion, digestion, absorption, and elimination** *p. 902*

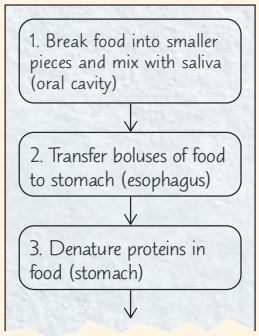
41.3 **Organs specialized for sequential stages of food processing form the mammalian digestive system** *p. 905*

41.4 **Evolutionary adaptations of vertebrate digestive systems correlate with diet** *p. 911*

41.5 **Feedback circuits regulate digestion, energy storage, and appetite** *p. 915*

Study Tip

Make a flowchart: Digestion occurs stepwise in the human alimentary canal. As you study the molecular details, keep track of the overall process by adding to this start of a flowchart listing the overall effect and location of each step.



Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 41
- Figure 41.10 Walkthrough: The Stomach and Its Secretions
- BioFlix® Animation: Homeostasis: Regulating Blood Sugar

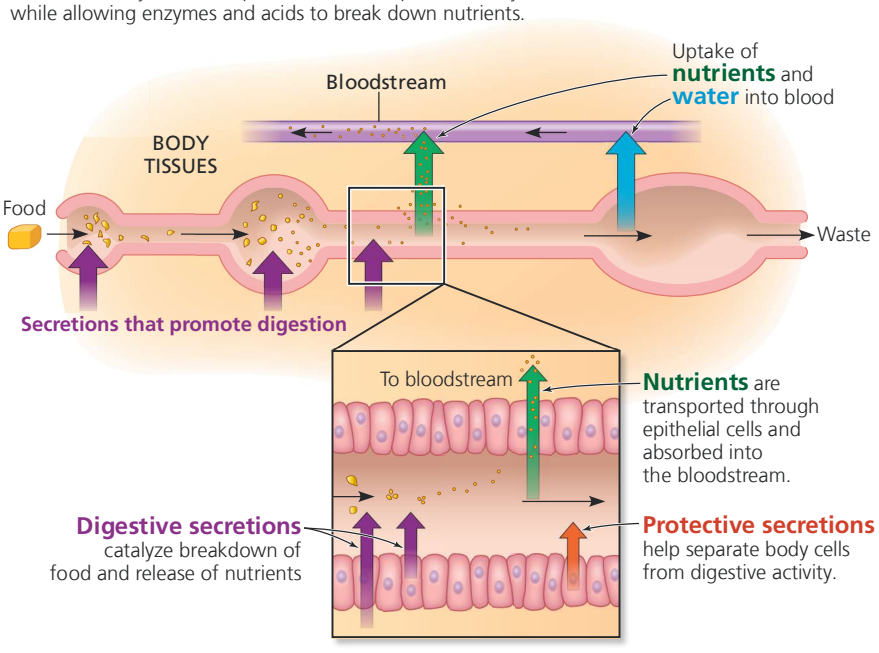
For Instructors to Assign (in Item Library)
- Tutorial: Fat Absorption and Fat Structure
- Tutorial: What Role Do Genes Play in Appetite Regulation?

Ready-to-Go Teaching Module (in Instructor Resources)
- The Human Digestive System

Figure 41.1 For this herring gull, dinnertime has arrived. Once this meal has been taken in, the tissues of the sea star will be taken apart and its nutrients taken up. Paradoxically, the classes of nutrients in the sea star—largely proteins, fats, and carbohydrates—also make up the tissues of the gull.

How can animals extract the nutrients they need from food while not digesting their own tissues?

An animal digests food using **compartmentalized processing** in a tube-like system. Compartmentalization protects body tissues while allowing enzymes and acids to break down nutrients.



CONCEPT 41.1

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

Although dining on sea stars, crabs, and fish is the herring gull's specialty, 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. Overall, an adequate diet must satisfy three needs: chemical energy for cellular processes, organic building blocks for macromolecules, and essential nutrients. The process by which an animal takes in and makes use of food to meet these needs constitutes **nutrition**.

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 (see Concept 8.3). To meet the need for ATP, animals ingest and digest nutrients, including carbohydrates, proteins, and lipids, for use in cellular respiration and energy storage.

In addition to fuel for ATP production, an animal requires raw materials for biosynthesis. To build the complex molecules it needs to grow, maintain itself, and reproduce, an animal's food must provide a source of organic carbon (such as sugar) and a source of organic nitrogen (such as protein).

The third requirement of an animal's diet is to provide **essential nutrients**, substances that an animal requires but cannot assemble from simple organic molecules.

Essential Nutrients

Essential nutrients in the diet include certain amino acids and fatty acids, as well as vitamins and minerals. The key functions of essential nutrients include serving as substrates of enzymes, as coenzymes, and as cofactors in biosynthetic reactions **(Figure 41.2)**.

In general, an animal can obtain all essential amino acids and fatty acids, as well as vitamins and minerals, by feeding on plants or other animals. Needs for particular nutrients vary among species. For instance, some animals (including humans) must get ascorbic acid (vitamin C) from their diet, whereas most animals can synthesize it from other nutrients.

Essential Amino Acids

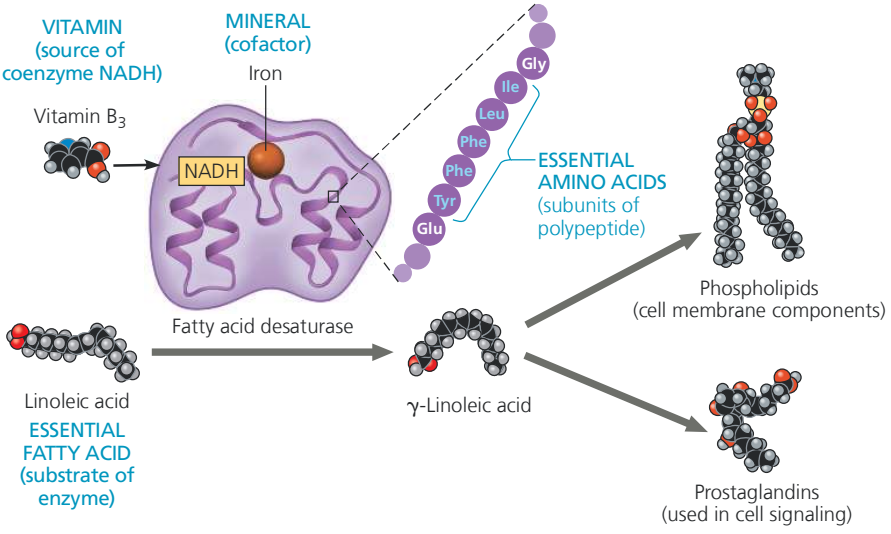
All organisms require a standard set of 20 amino acids to make a complete set of proteins (see Figure 5.14). Plants and microorganisms normally can produce all 20. Most animals have the enzymes to synthesize about half of these amino acids, as long as their diet includes sulfur and organic nitrogen. The remaining amino acids must be obtained from the animal's food in prefabricated form and are therefore called **essential amino acids**. Many animals, including adult humans, require eight amino acids in their diet: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. (Human infants also need a ninth, histidine.)

The proteins in animal products such as meat, eggs, and cheese are "complete," providing all the essential amino acids. 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.

Essential Fatty Acids

Animals require fatty acids to synthesize a variety of cellular components, including membrane phospholipids, signaling molecules, and storage fats. Although animals can synthesize many fatty acids, they lack the enzymes to form the double bonds found in certain required fatty acids. Instead, these molecules must be obtained from the diet and are considered **essential fatty acids**. In mammals, they include linoleic acid (see Figure 41.2). Animals typically obtain ample quantities of essential fatty acids from seeds, grains, and vegetables in their diet.

▼ Figure 41.2 Roles of essential nutrients. This example of a biosynthetic reaction illustrates some common functions for essential nutrients. The conversion of linoleic acid to γ-linoleic acid by the enzyme fatty acid desaturase involves all four classes of essential nutrients, as labeled in blue. Note that almost all enzymes and other proteins in animals contain some essential amino acids, as indicated in the partial sequence shown for fatty acid desaturase.



Vitamins

As Albert Szent-Györgyi, the discoverer of 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).

The 13 vitamins required by humans vary in both chemical properties and function **(Table 41.1)**. Vitamin B_2, for example, is a water-soluble vitamin that is converted in the body to FAD, a coenzyme used in many metabolic processes, including cellular respiration (see Figure 9.12). Vitamin C, which is required for the production of connective tissue, is also water-soluble.

Fat-soluble vitamins include vitamin A, which is incorporated into visual pigments of the eye, and vitamin D, which aids in calcium absorption and bone formation. Our dietary requirement for vitamin D, unlike other vitamins, turns out to be variable. Why? When our skin is exposed to sunlight, our bodies synthesize vitamin D, reducing our dietary need.

For people with imbalanced diets, taking vitamin supplements at recommended daily levels is reasonable. It is far less clear that massive doses of vitamins confer any health benefits or are even safe. Moderate overdoses of water-soluble vitamins are probably harmless because excesses are excreted in urine. However, excesses of fat-soluble vitamins are deposited in body fat, so overconsumption may cause them to accumulate to toxic levels.

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. As shown in **Table 41.2**, minerals have diverse functions in animal physiology. Some are assembled into the structure of proteins; iron, for example, is incorporated into the oxygen carrier hemoglobin as well as some enzymes (see Figure 41.2). Others, such as 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 hormone, which regulates metabolic rate. Vertebrates also require relatively large quantities of calcium and phosphorus for building and maintaining bone.

Ingesting too much of some minerals can cause health problems. For example, excess sodium can contribute to

Table 41.1 Vitamin Requirements of Humans

Vitamin	Major Dietary Sources	Major Functions in the Body	Symptoms of Deficiency
Water-Soluble Vitamins			
B_1 (thiamine)	Pork, legumes, peanuts, whole grains	Coenzyme used in removing CO_2 from organic compounds	Beriberi (tingling, poor coordination, reduced heart function)
B_2 (riboflavin)	Dairy products, meats, enriched grains, vegetables	Component of coenzymes FAD and FMN	Skin lesions, such as cracks at corners of mouth
B_3 (niacin)	Nuts, meats, grains	Component of coenzymes NAD^+ and $NADP^+$	Skin and gastrointestinal lesions, delusions, confusion
B_5 (pantothenic acid)	Meats, dairy products, whole grains, fruits, vegetables	Component of coenzyme A	Fatigue, numbness, tingling of hands and feet
B_6 (pyridoxine)	Meats, vegetables, whole grains	Coenzyme used in amino acid metabolism	Irritability, convulsions, muscular twitching, anemia
B_7 (biotin)	Legumes, other vegetables, meats	Coenzyme in synthesis of fat, glycogen, and amino acids	Scaly skin inflammation, neuromuscular disorders
B_9 (folic acid)	Green vegetables, oranges, nuts, legumes, whole grains	Coenzyme in nucleic acid and amino acid metabolism	Anemia, neural tube malformation in fetus
B_{12} (cobalamin)	Meats, eggs, dairy products	Production of nucleic acids and red blood cells	Anemia, numbness, loss of balance
C (ascorbic acid)	Citrus fruits, broccoli, tomatoes	Used in collagen synthesis; antioxidant	Scurvy (degeneration of skin and teeth), delayed wound healing
Fat-Soluble Vitamins			
A (retinol)	Dark green and orange vegetables and fruits, dairy products	Component of visual pigments; maintenance of epithelial tissues	Blindness, skin disorders, impaired immunity
D	Dairy products, egg yolk	Aids in absorption and use of calcium and phosphorus	Rickets (bone deformities) in children, bone softening in adults
E (tocopherol)	Vegetable oils, nuts, seeds	Antioxidant; helps prevent damage to cell membranes	Nervous system degeneration
K (phylloquinone)	Green vegetables, tea; also made by colon bacteria	Important in blood clotting	Defective blood clotting

Table 41.2 Mineral Requirements of Humans*

	Mineral	Major Dietary Sources	Major Functions in the Body	Symptoms of Deficiency
More than 200 mg per day required	Calcium (Ca)	Dairy products, dark green vegetables, legumes	Bone and tooth formation, blood clotting, nerve and muscle function	Impaired growth, loss of bone mass
	Phosphorus (P)	Dairy products, meats, grains	Bone and tooth formation, acid-base balance, nucleotide synthesis	Weakness, loss of minerals from bone, calcium loss
	Sulfur (S)	Proteins from many sources	Component of certain amino acids	Impaired growth, fatigue, swelling
	Potassium (K)	Meats, dairy products, many fruits and vegetables, grains	Acid-base balance, water balance, nerve function	Muscular weakness, paralysis, nausea, heart failure
	Chlorine (Cl)	Table salt	Acid-base balance, formation of gastric juice, nerve function, osmotic balance	Muscle cramps, reduced appetite
	Sodium (Na)	Table salt	Acid-base balance, water balance, nerve function	Muscle cramps, reduced appetite
	Magnesium (Mg)	Whole grains, green leafy vegetables	Enzyme cofactor; ATP bioenergetics	Nervous system disturbances
Iron (Fe)		Meats, eggs, legumes, whole grains, green leafy vegetables	Component of hemoglobin and of electron carriers; enzyme cofactor	Iron-deficiency anemia, weakness, impaired immunity
Fluorine (F)		Drinking water, tea, seafood	Maintenance of tooth structure	Higher frequency of tooth decay
Iodine (I)		Seafood, iodized salt	Component of thyroid hormones	Goiter (enlarged thyroid gland)

*Additional minerals required in trace amounts include cobalt (Co), copper (Cu), manganese (Mn), molybdenum (Mo), selenium (Se), and zinc (Zn). All of these minerals, as well as those in the table, can be harmful in excess.

high blood pressure. This is a particular problem in the United States, where the typical person consumes enough salt (sodium chloride) to provide about 20 times the required amount of sodium. Processed foods often contain large amounts of sodium chloride, even if they do not taste salty.

Variation in Diet

Despite many shared nutritional needs, animals have diverse diets. **Herbivores**, such as cattle, sea slugs, and caterpillars, dine mainly on plants or algae. **Carnivores**, such as sea otters, hawks, and spiders, mostly eat other animals. Rats and other **omnivores** (from the Latin *omnis*, 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. However, most animals are opportunistic feeders, broadening their diet when their usual foods aren't available. For example, deer are herbivores, but occasionally eat insects, worms, or bird eggs. Similarly, herring gulls eat marine invertebrates, insects, and small fishes, but also human refuse. Note that microorganisms are an unavoidable "supplement" in every animal's diet.

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 affects one out of four children worldwide, impairing health and often survival.

Deficiencies in Essential Nutrients

Insufficient intake of essential nutrients can cause deformities, disease, and even death. For example, deer and other herbivores can develop fragile bones if the plants they consume grew in phosphorus-deficient soil. In such environments, some grazing animals obtain missing nutrients by consuming concentrated sources of salt or other minerals **(Figure 41.3)**. Similarly, some birds supplement their diet with snail shells, and certain tortoises obtain minerals from stones they ingest.

Like other animals, humans sometimes have diets lacking in essential nutrients. A diet with insufficient amounts of one or more essential amino acids causes protein deficiency, the most common type of malnutrition among humans. In children, protein deficiency may arise if their diet shifts entirely from breast milk to foods that contain relatively little protein, such as rice. Such children, if they survive infancy, often have impaired physical and mental development.

► Figure 41.3 Obtaining essential nutrients from an unusual source. A juvenile chamois (*Rupicapra rupicapra*), an herbivore, licks salts from exposed rocks in its alpine habitat. This behavior is common among herbivores that live where soils and plants provide insufficient amounts of minerals.

Undernourishment

As mentioned earlier, malnutrition can also be caused by a diet that fails to provide enough chemical energy. In this situation, the body first uses up stored carbohydrates and fat. It then begins breaking down its own proteins for fuel: Muscles shrink, 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.

Inadequate nourishment in humans is most common when drought, war, or other crisis severely disrupts the food supply. In sub-Saharan Africa, where the AIDS epidemic has crippled both rural and urban communities, approximately 200 million children and adults cannot obtain enough food.

Sometimes undernourishment occurs within well-fed human populations as a result of eating disorders. For example, anorexia nervosa involves weight loss to a level that is unhealthy for the individual's age and height and may be related to a distorted body image.

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 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 (see Concept 47.2). The English scientist Richard Smithells thought that malnutrition among these women might be responsible. As described in **Figure 41.4**, he found that vitamin supplementation greatly reduced the risk of neural tube defects. In other studies, he obtained evidence that folic acid (vitamin B_9) was the specific vitamin responsible, a finding confirmed by other researchers. Based on this evidence, the United States in 1998 began to require that folic acid be added to enriched grain products used to make bread, cereals, and other foods. Follow-up studies have documented the effectiveness of this program in reducing the frequency of neural tube defects. Thus, at a time when microsurgery and sophisticated diagnostic imaging dominate the headlines, a simple dietary change such as folic acid supplementation may be among the greatest contributors to human health.

▼ Figure 41.4 Inquiry

Can diet influence the frequency of neural tube defects?

Experiment Richard Smithells, of the University of Leeds, in England, examined the effect of vitamin supplementation on the risk of neural tube defects. Women who had had one or more babies with such a condition were put into two study groups. The experimental group consisted of those who were planning a pregnancy and began taking a multivitamin at least four weeks before attempting conception. The control group, who were not given vitamins, included women who declined them and women who were already pregnant. The numbers of neural tube defects resulting from the pregnancies were recorded for each group.

Results

Group	Number of Infants/Fetuses Studied	Infants/Fetuses with a Neural Tube Defect
Vitamin supplements (experimental group)	141	1
No vitamin supplements (control group)	204	12

Data from R. W. Smithells et al., Possible prevention of neural-tube defects by periconceptional vitamin supplementation, *Lancet* 315:339–340 (1980).

Conclusion This controlled study provided evidence that vitamin supplementation protects against neural tube defects, at least after the first pregnancy. Follow-up trials demonstrated that folic acid alone provided an equivalent protective effect.

INTERPRET THE DATA *After folic acid supplementation became standard in the United States, the frequency of neural tube defects dropped to an average of just one in 5,000 live births. Propose two explanations of why the observed frequency was much higher in the experimental group of the Smithells study.*

INQUIRY IN ACTION Read and analyze the original paper in *Inquiry in Action: Interpreting Scientific Papers.*

CONCEPT CHECK 41.1

1. An animal requires 20 amino acids to make proteins. Why aren't all 20 essential to animal diets?
2. **MAKE CONNECTIONS** Considering how enzymes function (see Concept 8.4), explain why vitamins are required in very small amounts.
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.

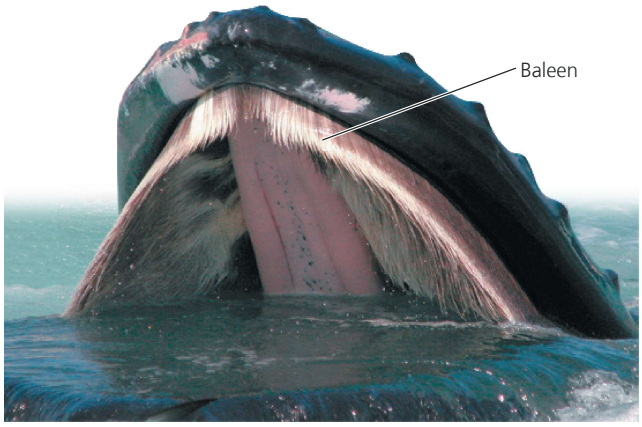
CONCEPT 41.2

Food processing involves ingestion, digestion, absorption, and elimination

Whatever their diet, animals need to process food. We can divide food processing into ingestion, digestion, absorption, and elimination. The first stage— **ingestion**—is the act of eating or feeding. As shown in **Figure 41.5**, four quite different categories describe the feeding mechanisms of most animal species.

▼ Figure 41.5 Exploring Four Main Feeding Mechanisms of Animals

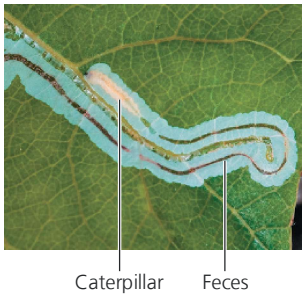
Filter Feeding



Many aquatic animals are **filter feeders**, which strain small organisms or food particles from the surrounding medium. The humpback whale, shown above, is one example. Attached to the whale's upper jaw are comblike plates called baleen, which remove small invertebrates and fish from enormous volumes of water and sometimes mud. Filter feeding in water is a type of suspension feeding, which also includes removing suspended food particles from the surrounding medium by capture or trapping mechanisms.

Substrate Feeding

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. Other substrate feeders include maggots (fly larvae), which burrow into animal carcasses.



Fluid Feeding

Fluid feeders suck nutrient-rich fluid from a living host. This tsetse fly has pierced the skin of its human host with hollow, needlelike mouthparts and is consuming a blood meal. 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 Feeding

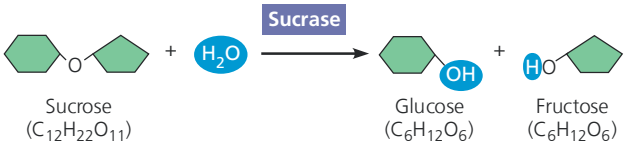
Most animals, including humans, are **bulk feeders**, which eat relatively large pieces of food. Their adaptations include tentacles, pincers, claws, venomous fangs, jaws, and teeth that kill their prey or tear off pieces of meat or vegetation. In this amazing scene, a rock python is beginning to ingest 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.

During **digestion**, the second stage of food processing, food is broken down into molecules small enough for the body to absorb. Both mechanical and chemical processes are typically required. Mechanical digestion, such as chewing or grinding, breaks food into smaller pieces, increasing surface area. The food particles then undergo chemical digestion, which cleaves large molecules into smaller components.

Chemical digestion is necessary because animals cannot directly use the proteins, carbohydrates, nucleic acids, fats, and phospholipids in food. These molecules are too large to pass through cell membranes and also are not all identical to those the animal needs for its particular tissues and functions. But when large molecules in food are broken down into their smaller components, the animal can use these products of digestion to assemble the large molecules it needs. For example, although the humpback whale and the tsetse fly in Figure 41.5 have very different diets, both break down proteins in their food to the same 20 amino acids from which they assemble all of the specific proteins in their bodies.

Enzyme-catalyzed synthesis of a fat or macromolecule links together smaller components, releasing a molecule of water for each new covalent bond formed. Chemical breakdown by digestive enzymes reverses this process, breaking bonds through the addition of water. This splitting process is called *enzymatic hydrolysis*. Polysaccharides and disaccharides are split into simple sugars, as shown here for sucrose and the enzyme sucrase:

▼ Enzymatic hydrolysis of a disaccharide



Similarly, proteins are broken down into small peptides and 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. In many animals, bacteria living in the digestive system carry out some chemical digestion.

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**, in which undigested material passes out of the digestive system, completes the process.

Digestive Compartments

You have just read 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 that allows animals to avoid self-digestion is the processing of food within specialized intracellular or extracellular compartments.

Intracellular Digestion

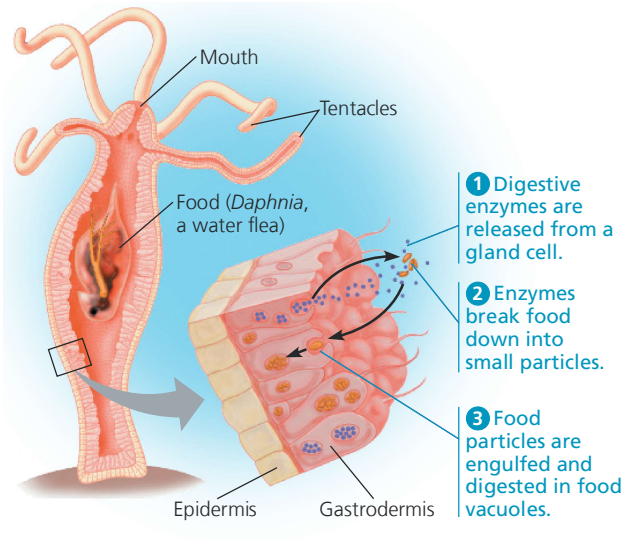
Food vacuoles—cellular organelles in which hydrolytic enzymes break down food—are the simplest digestive compartments. The hydrolysis of food inside vacuoles, called intracellular digestion, begins after a cell engulfs solid food by phagocytosis or liquid food by pinocytosis (see Figure 7.21). Newly formed food vacuoles fuse with lysosomes, organelles containing hydrolytic enzymes. This fusion of organelles brings food in contact with these enzymes, allowing digestion to occur safely within a compartment enclosed by a protective membrane. A few animals, such as sponges, digest all their food in this way (see Figure 33.4).

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.

Animals with relatively simple body plans typically 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). Small freshwater cnidarians called hydras provide a good example **(Figure 41.6)**. The

▼ Figure 41.6 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.

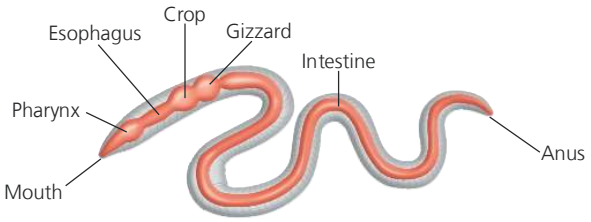


DRAW IT *Draw and label a simple diagram showing the pathway that nutrients follow from when food enters the hydra's mouth to when nutrients reach a cell on the outside of the tip of one of its tentacles.*

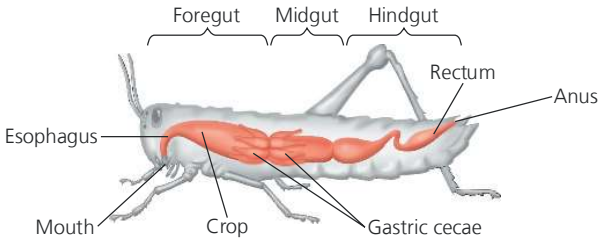
Mastering Biology Video: *Hydra* Eating *Daphnia*

hydra—a carnivore—uses its tentacles to stuff captured prey through its mouth into its gastrovascular cavity. Specialized gland cells of the hydra's gastrodermis, the tissue layer that lines the cavity, then secrete digestive enzymes that break the soft tissues of the prey into tiny pieces. Other cells of the gastrodermis engulf these food particles, and most of the hydrolysis of macromolecules occurs intracellularly. 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 (see Figure 33.9).

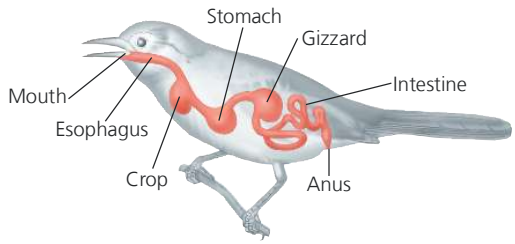
▼ Figure 41.7 Variation in alimentary canals. These examples illustrate how the organization and structure of compartments for digestion, storage, and absorption differ among animals.



(a) Earthworm. The muscular pharynx of an earthworm sucks food in through the mouth. Food passes through the esophagus and is stored and moistened in the crop. Mechanical digestion occurs in the muscular gizzard, which pulverizes food with the aid of small bits of sand and gravel. Further digestion and absorption occur in the intestine before wastes are eliminated through the anus.



(b) Grasshopper. A grasshopper has several digestive chambers grouped into three main regions: 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 (singular, *ceca*) extend from the beginning of 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.

Rather than a gastrovascular cavity, animals with complex body plans have a digestive tube with two openings, a mouth and an anus **(Figure 41.7)**. Such a tube is called a *complete digestive tract* or, more commonly, an **alimentary canal**. Food moves along the alimentary canal in a single direction, encountering a series of specialized compartments that carry out stepwise digestion and nutrient absorption. 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.

Because most animals have an alimentary canal, we'll use the complete digestive system of mammals in the next section to illustrate the general principles of food processing.

CONCEPT CHECK 41.2

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 engine? (You don't have to know about auto mechanics.)

For suggested answers, see Appendix A.

CONCEPT 41.3

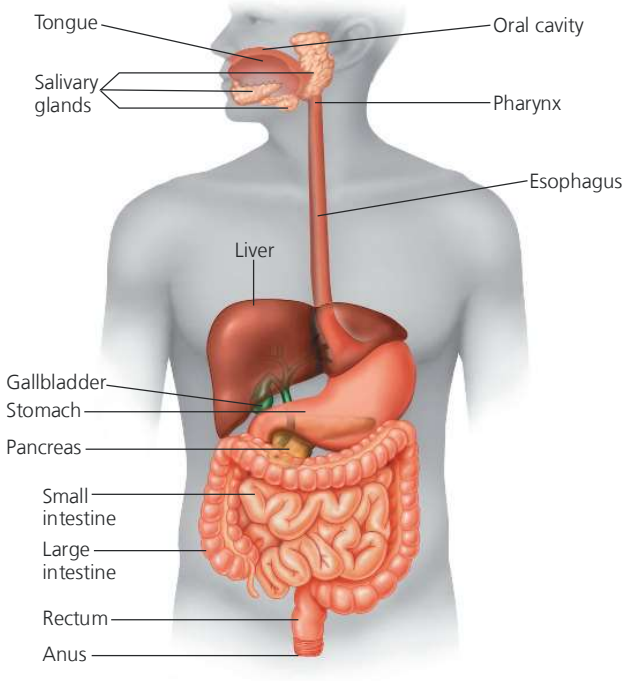
Organs specialized for sequential stages of food processing form the mammalian digestive system

In mammals, a number of accessory glands support food processing by secreting digestive juices through ducts into the alimentary canal. There are three pairs of salivary glands, as well as three individual glands: the pancreas, the liver, and the gallbladder. To explore the coordinated function of the accessory glands and alimentary canal, we'll consider the steps in food processing as a meal travels along the canal in a human.

The Oral Cavity, Pharynx, and Esophagus

As soon as food enters your mouth, or **oral cavity**, food processing begins **(Figure 41.8)**. Teeth with specialized shapes cut, mash, and grind, breaking the food into smaller pieces. This mechanical breakdown not only increases the surface area available for chemical breakdown but also facilitates swallowing. Meanwhile, the anticipation or arrival of food in the oral cavity triggers the release of saliva by the **salivary glands**.

▼ Figure 41.8 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 is stored for 2–6 hours during the first stages of processing. Complete digestion and nutrient absorption occur in the small intestine over a period of 5–6 hours. Processing is completed in the large intestine, and undigested material is expelled through the anus as feces.



Mastering Biology **Animation: Overview of the Human Digestive System**

Saliva is a complex mixture of materials with a number of vital functions. One major component is **mucus**, a viscous mixture of water, salts, cells, and slippery glycoproteins (carbohydrate-protein complexes). Mucus lubricates food for easier swallowing, protects the gums against abrasion, and facilitates taste and smell. Saliva also contains buffers, which help prevent tooth decay by neutralizing acid, and antimicrobial agents (such as lysozyme; see Figure 5.16), which protect against bacteria that enter the mouth with food.

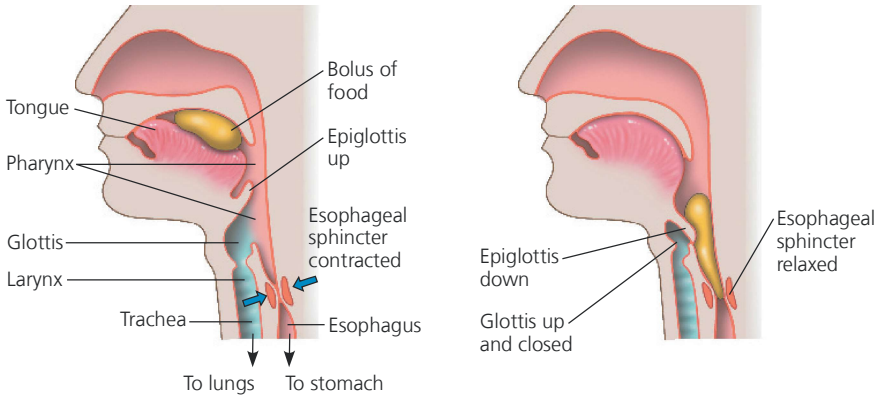
Scientists have long been puzzled by the fact that saliva contains a large amount of the enzyme **amylase**, which breaks down starch (a glucose polymer from plants) and glycogen (a glucose polymer from animals). Most chemical digestion occurs not in the mouth but in the small intestine, where amylase is also present. Why, then, does saliva contain so much amylase? A current hypothesis is that amylase in saliva releases food particles that are stuck to the teeth, thereby reducing the nutrients available to microorganisms living in the mouth.

The tongue also has important roles in food processing. Much as a doorman screens and assists people entering a fancy hotel, the tongue aids digestive processes by evaluating ingested material, distinguishing which foods should be processed further and then enabling their passage. (See Concept 50.4 for a discussion of the sense of taste.) Once chewing begins, tongue movements manipulate the mixture of saliva and food, helping shape it into a ball called a *bolus* **(Figure 41.9)**. During swallowing, the tongue provides further assistance, pushing the bolus to the back of the oral cavity and into the pharynx.

Each bolus of food is received by the **pharynx**, or throat region, which leads to two passageways: the esophagus and the trachea. The **esophagus** is a muscular tube that connects to the stomach; the trachea (windpipe) leads to the lungs. Swallowing must therefore be carefully choreographed to keep food and liquids from entering the trachea and causing 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, a series of back slaps, or a forced upward thrust of the diaphragm (the Heimlich maneuver).

Within the esophagus, food is pushed along by **peristalsis**, alternating waves of smooth muscle contraction and relaxation. Upon reaching

▼ Figure 41.9 Intersection of the human airway and digestive tract. In humans, the pharynx connects to the trachea and the esophagus. **(a)** At most times, a contracted sphincter seals off the esophagus while the trachea remains open. **(b)** When a food bolus arrives at the pharynx, the swallowing reflex is triggered. Movement of the larynx, the upper part of the airway, tips a flap of tissue called the epiglottis down, preventing food from entering the trachea. At the same time, the esophageal sphincter relaxes, allowing the bolus to pass into the esophagus. The trachea then reopens, and peristaltic contractions of the esophagus move the bolus to the stomach.



(a) Trachea open **(b) Esophagus open**

VISUAL SKILLS *If you laugh while drinking water, the liquid may be ejected from your nostrils. Use this diagram to explain why this happens, taking into account that laughing involves exhaling.*

the end of the esophagus, the bolus encounters a **sphincter**, a ringlike valve of muscle **(Figure 41.10)**. Acting like a drawstring, the sphincter regulates passage of the ingested food into the next compartment, the stomach.

Digestion in the Stomach

The **stomach**, which is located just below the diaphragm, has two major roles in digestion. The first is storage. With a very elastic wall and accordion-like folds, the stomach can stretch to accommodate about 2 L of food and fluid. The second major function is to process food into a liquid suspension. The stomach secretes a digestive fluid called **gastric juice** and mixes it with the food through a churning action. This mixture of ingested food and gastric juice is called **chyme**.

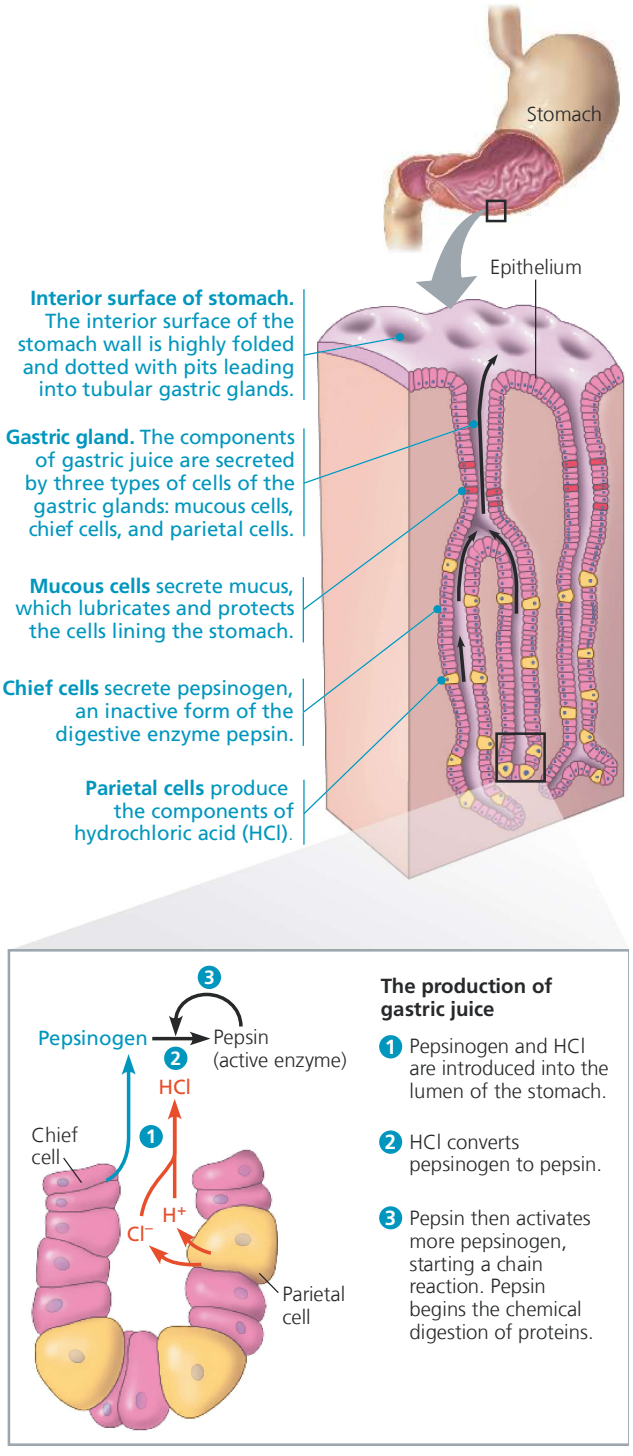
Chemical Digestion in the Stomach

Two components of gastric juice help liquefy food in the stomach. First, hydrochloric acid (HCl) disrupts the extracellular matrix that binds cells together in meat and plant material. 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 then attacked by the second component of gastric juice—a **protease**, or protein-digesting enzyme, called **pepsin**. Unlike most enzymes, pepsin is adapted to work best in a very acidic environment. By breaking peptide bonds, it cleaves proteins into smaller polypeptides and further exposes the contents of ingested tissues.

Two types of cells in the gastric glands of the stomach produce the components of gastric juice (see Figure 41.10). *Parietal cells* use an ATP-driven pump to expel hydrogen ions into the lumen. At the same time, chloride ions diffuse into the lumen through specific membrane channels of the parietal cells. It is therefore only within the lumen that hydrogen and chloride ions combine to form HCl. Meanwhile, *chief cells* release pepsin into the lumen in an inactive form called **pepsinogen**. HCl converts pepsinogen to active pepsin by clipping off a small portion of the molecule and exposing its active site. Through these processes, both HCl and pepsin form in the lumen (cavity) of the stomach, not within the cells of the gastric glands. As a result, the parietal and chief cells produce gastric juice but are not digested from within by its components.

After hydrochloric acid converts a small amount of pepsinogen to pepsin, pepsin itself helps activate the remaining pepsinogen. Pepsin, like HCl, can clip pepsinogen to expose the enzyme's active site. This generates more pepsin, which activates more pepsinogen. This series of events is an example of positive feedback (see Concept 40.2).

▼ Figure 41.10 The stomach and its secretions.



Mastering Biology Figure Walkthrough

Why don't HCl and pepsin eat through the lining of the stomach? For one thing, mucus secreted by cells in gastric glands protects against self-digestion (see Figure 41.10).

In addition, cell division adds a new epithelial layer every three days on average, replacing cells before the lining is fully eroded by digestive juices.

Stomach Dynamics

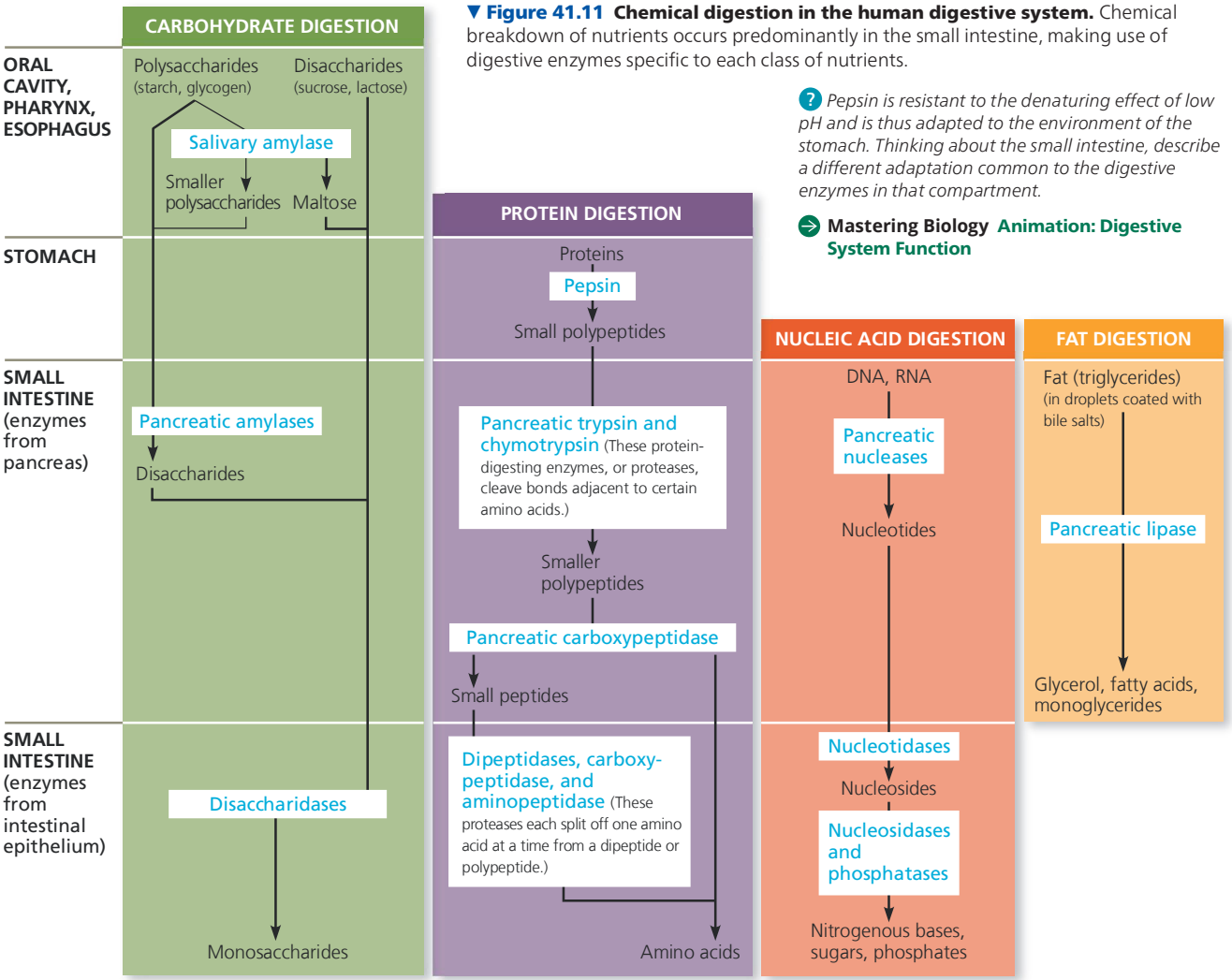
The breakdown of food by gastric juices is enhanced by muscular activity of the stomach. The coordinated series of muscle contractions and relaxations that we call "churning" mixes the stomach contents about every 20 seconds. Churning facilitates the action of HCl and pepsin by bringing all of the food into contact with the gastric juices secreted by the lining of the stomach. As a result, what began as a recently swallowed meal becomes the acidic, nutrient-rich broth known as chyme.

Contractions of stomach muscles also help move material through the alimentary canal. In particular, 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 to enter at a time.

Occasionally, the sphincter at the top of the stomach allows a movement, or flux, of chyme from the stomach back into the lower end of the esophagus. The painful irritation of the esophagus that results from this process of acid reflux is commonly called "heartburn."

Digestion in the Small Intestine

Although there is some chemical digestion in the oral cavity and stomach, most enzymatic hydrolysis of macromolecules from food occurs in the small intestine **(Figure 41.11)**. This organ's name refers to its small diameter compared to the large intestine, not to its length. The **small intestine** is in



▼ Figure 41.11 Chemical digestion in the human digestive system. Chemical breakdown of nutrients occurs predominantly in the small intestine, making use of digestive enzymes specific to each class of nutrients.

? *Pepsin is resistant to the denaturing effect of low pH and is thus adapted to the environment of the stomach. Thinking about the small intestine, describe a different adaptation common to the digestive enzymes in that compartment.*

Mastering Biology Animation: Digestive System Function

fact the alimentary canal's longest compartment—over 6 m (20 feet) long in humans. The first 25 cm (10 inches) 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. As you will read in Concept 41.5, hormones released by the stomach and duodenum control the digestive secretions into the alimentary canal.

The arrival of chyme in the duodenum triggers release of the hormone secretin, which stimulates the **pancreas** to secrete bicarbonate. Bicarbonate neutralizes the acidity of chyme and acts as a buffer for chemical digestion in the small intestine. The pancreas also secretes numerous digestive enzymes into the small intestine. These include the proteases trypsin and chymotrypsin, which are produced in inactive forms. In a chain reaction similar to that for pepsinogen, they are activated when safely located in the lumen of the duodenum.

The epithelial lining of the duodenum is the source of additional digestive enzymes. Some are secreted into the lumen of the duodenum, whereas others are bound to the surface of epithelial cells. Together with the enzymes from the pancreas, they complete most digestion in the duodenum.

Fats present a particular challenge for digestion. Insoluble in water, they form large globules that cannot be attacked efficiently by digestive enzymes. In humans and other vertebrates, fat digestion is facilitated by bile salts, which act as emulsifiers (detergents) that break apart fat and lipid globules. Bile salts are a major component of **bile**, a secretion of the **liver** that is stored and concentrated in the **gallbladder**.

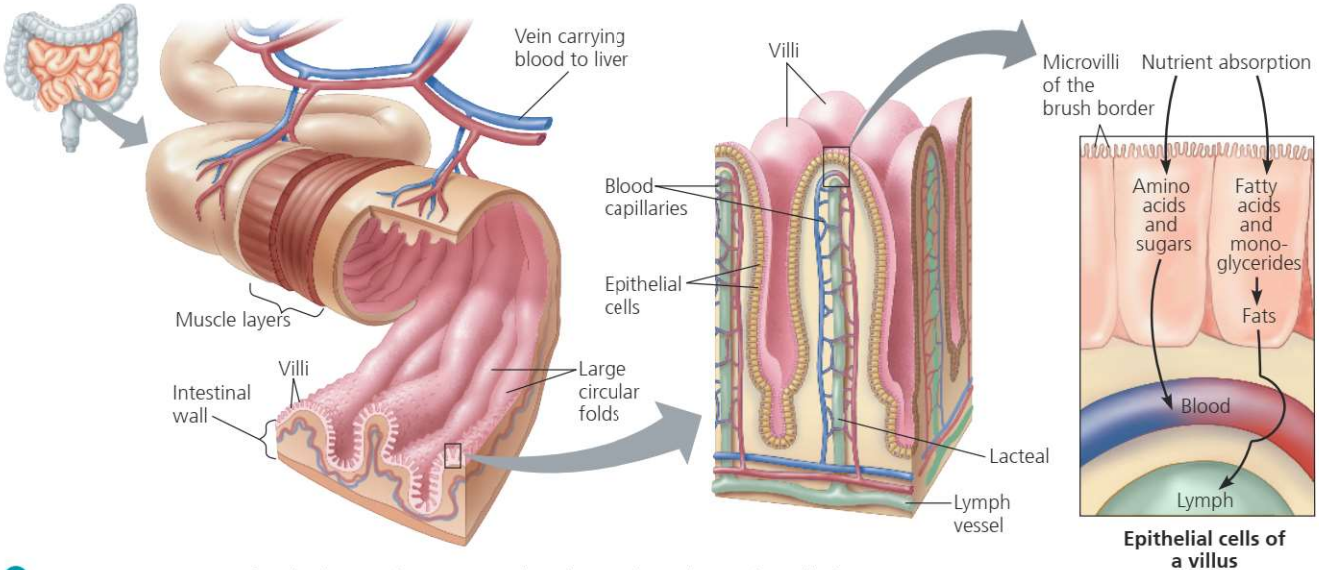
Bile production is metabolically linked to another vital liver function: the destruction of red blood cells that are no longer fully functional. Pigments released during red blood cell disassembly are incorporated into bile pigments, which are eliminated from the body with the feces. In some liver and blood disorders, bile pigments accumulate in the skin, resulting in a yellowing called jaundice.

Absorption in the Small Intestine

With digestion largely complete, the contents of the duodenum move by peristalsis into the *jejunum* and *ileum*, the remaining regions of the small intestine. There, nutrient absorption occurs across the lining of the intestine **(Figure 41.12)**. Large folds in the lining encircle the intestine and are studded with finger-shaped projections called **villi** (singular, *villus*). Within the villi, each epithelial cell has many microscopic projections, or **microvilli**, that face the intestinal lumen. These epithelial microvilli have a brush-like appearance that is reflected in the name *brush border*. Together, the folds, villi, and microvilli 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 (see Figure 33.9 for more discussion and examples of maximizing surface area in diverse organisms).

Depending on the nutrient, transport across the epithelial cells can be passive or active (see Concepts 7.3 and 7.4). The sugar fructose, for example, moves by facilitated diffusion down its concentration gradient from the lumen of the small

▼ Figure 41.12 Nutrient absorption in the small intestine. Water-soluble nutrients, such as amino acids and sugars, enter the bloodstream, whereas fats are transported to the lymphatic system.



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

Mastering Biology **BioFlix® Animation: Nutrient Transport Across Membranes**

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, enter the epithelial cells of the villus by being pumped against concentration gradients. This active transport allows much more absorption of those nutrients than would be possible with passive diffusion alone.

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 converts many organic nutrients to different forms for use elsewhere, blood leaving 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 they can circulate broadly. The liver is the primary site for detoxifying many organic molecules foreign to the body, such as drugs, and certain metabolic waste products.

Although many nutrients leave the small intestine through the bloodstream and pass through the liver for processing, some products of fat (triglyceride, also known as triacylglycerol) digestion take a different path **(Figure 41.13)**. Hydrolysis of a fat by lipase in the small intestine 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 globules called **chylomicrons**.

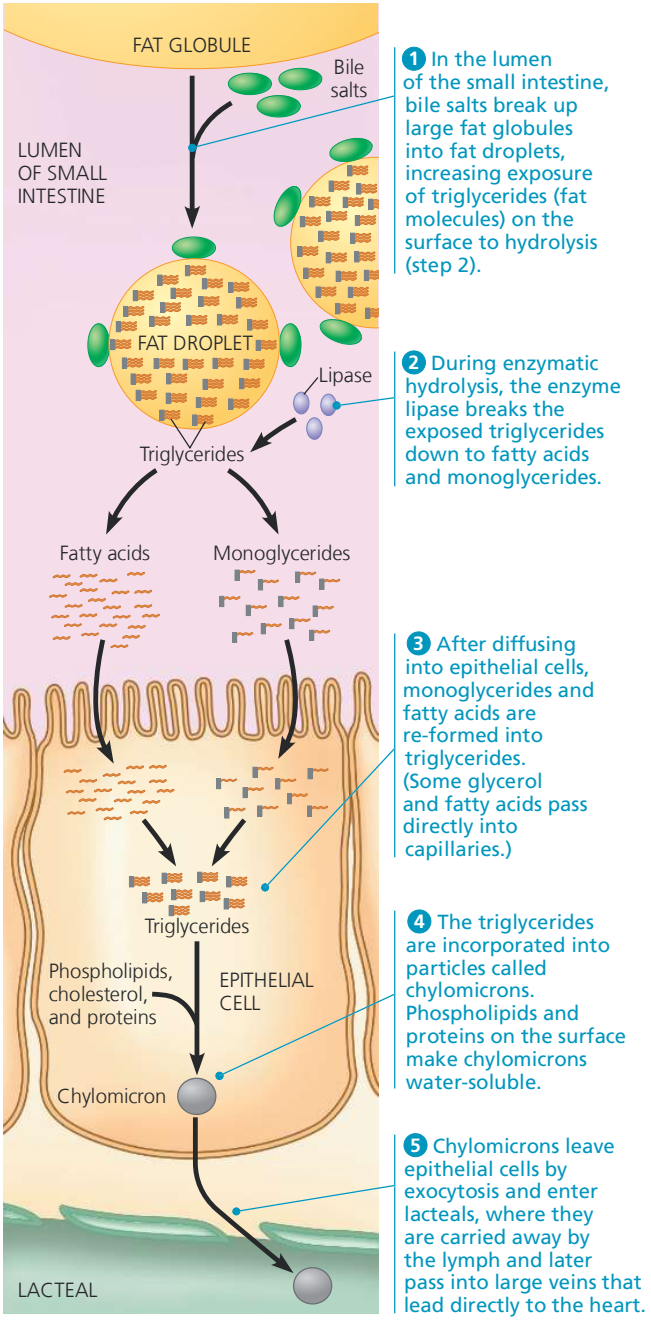
In exiting the small intestine, chylomicrons first enter a **lacteal**, a vessel at the core of each villus. Lacteals are part of the vertebrate lymphatic system, which is a network of vessels filled with a clear fluid called lymph. Starting at the lacteals, lymph containing the chylomicrons passes into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

In addition to absorbing nutrients, the small intestine recovers water and ions. Each day a person consumes about 2 L of water and secretes another 7 L in digestive juices into the alimentary canal. Typically all but 0.1 L of the water is reabsorbed, mostly in the small intestine. 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 small intestine.

Processing 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 41.14)**.

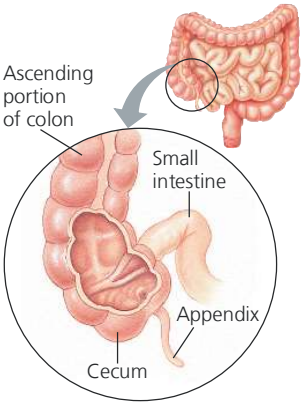
▼ Figure 41.13 Digestion and absorption of fats. Fats, which are insoluble in water, are broken down in the lumen of the small intestine, reassembled in epithelial cells, and then transported in water-soluble globules called chylomicrons. The chylomicrons enter the lymph via narrow vessels called lacteals and are later transferred to the blood in large veins leading to the liver and heart.



VISUAL SKILLS *Arrows at two locations in this figure indicate movement of materials between the epithelial cell and its surroundings. Identify and circle these arrows. At either of these locations, do the movements represented require an input of energy? Explain.*

Mastering Biology HHMI Animation: The Fate of Fat

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**. In animals that eat large amounts of plant material, the cecum has an important role in fermenting ingested material. In humans, the cecum is small and has an **appendix**, a finger-shaped extension that acts as a reservoir for symbiotic microorganisms, which are discussed in Concept 41.4.



▲ Figure 41.14 Junction of the small and large intestines.

The colon completes the recovery of water that began in the small intestine. What remain are the **feces**, the wastes of the digestive system, which 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. The undigested material in feces includes cellulose fiber. Although it provides no caloric value (energy) to humans, it helps move food along the alimentary canal.

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.

The community of bacteria living on unabsorbed organic material in the human colon contributes about one-third of the dry weight of feces. 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.

The terminal portion of the large intestine is the **rectum**, where the feces are stored before elimination. Two sphincters separate the rectum and the anus; the inner one is involuntary and the outer one is 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.

Having followed a meal through the alimentary canal, we'll look next at some adaptations of this general digestive plan in different animals.

CONCEPT CHECK 41.3

1. Explain why a proton pump inhibitor, such as the drug Prilosec, can relieve the symptoms of acid reflux.
2. The acids in bile salts have both lipid-soluble (hydrophobic) and water-soluble (hydrophilic) surfaces. How is such an organization beneficial for the role of bile salts in digestion?
3. **WHAT IF?** Predict what would happen if you mixed gastric juice with crushed food in a test tube.

For suggested answers, see Appendix A.

CONCEPT 41.4

Evolutionary adaptations of vertebrate digestive systems correlate with diet

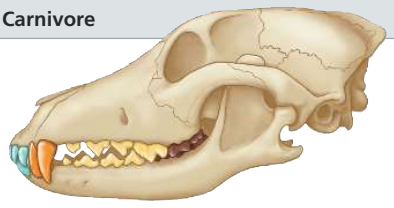
EVOLUTION The digestive systems of vertebrates are varied, with many adaptations linked to an animal's diet. To highlight how form fits function, we'll examine a few of them.

Dental Adaptations

Dentition, an animal's assortment of teeth, is one example of structural variation reflecting diet **(Figure 41.15)**. The

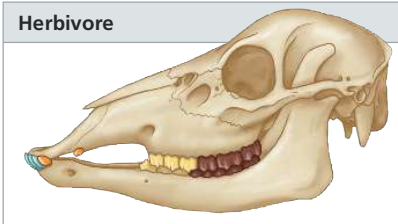
▼ Figure 41.15 Dentition and diet.

Carnivore



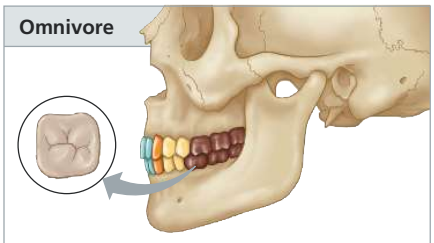
Carnivores, such as members of the dog and cat families, generally have large, pointed incisors and canines that can be used to kill prey and rip or cut away pieces of flesh. The jagged premolars and molars crush and shred food.

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 that mammals have been so successful. For example, a sea otter uses its sharp canine teeth to tear apart prey such as crabs and its slightly rounded molars to crush their shells. Nonmammalian vertebrates generally have less specialized dentition, but there are interesting exceptions. 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.

Stomach and Intestinal Adaptations

Evolutionary adaptations to differences in diet are sometimes apparent as variations in the dimensions of digestive organs. 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. An expandable stomach enables a rock python to ingest a whole gazelle (see Figure 41.5) and a 200-kg African lion to consume 40 kg of meat in one meal!

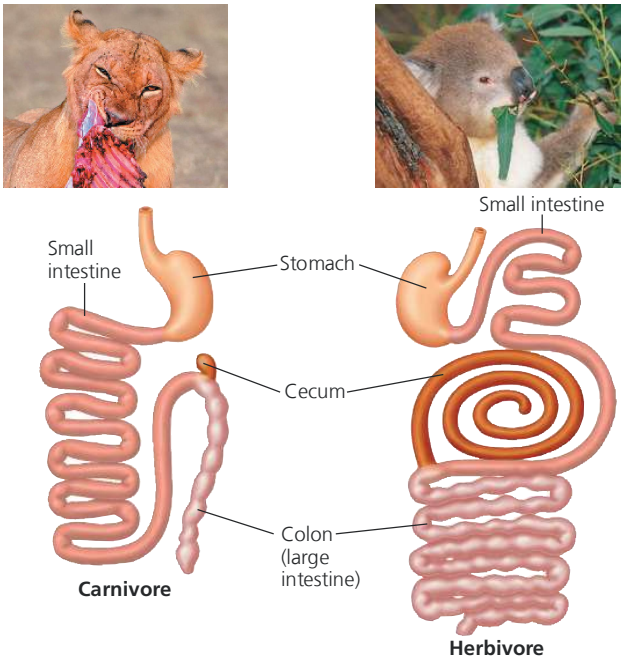
Adaptation is also apparent in the length of the digestive system in different vertebrates. In general, herbivores and omnivores have longer alimentary canals relative to their body size than do carnivores. Plant matter is more difficult to digest than meat because it contains cell walls. A longer digestive tract furnishes more time for digestion and more surface area for nutrient absorption. As an example, consider the lion and koala in **Figure 41.16**. The koala has much longer intestines, relative to its size, enhancing the processing of fibrous, protein-poor eucalyptus leaves from which it obtains nearly all of its nutrients and water.

Mutualistic Adaptations

An estimated 10–100 trillion bacteria live in the human digestive system. The coexistence of humans and many intestinal bacteria is an example of mutualism, an interaction between two species that benefits both of them (see Concept 54.1). For example, some intestinal bacteria produce vitamins, such as vitamin K, biotin, and folic acid, which are absorbed into the blood, supplementing our dietary intake. Intestinal bacteria also regulate the development of the intestinal epithelium and the function of the innate immune system. The bacteria in turn receive a steady supply of nutrients and a stable host environment.

Recently, we have greatly expanded our knowledge of the **microbiome**, the collection of microorganisms living in and on the body, along with their genetic material. To study the microbiome, scientists are using a DNA sequencing approach based on the polymerase chain reaction (PCR, see Figure 20.8). To date they have found more than 400 bacterial species in the human digestive tract, a far greater number than had been identified through approaches relying on laboratory culture and characterization. Furthermore, researchers have found significant differences in the microbiome associated with diet, disease, and age **(Figure 41.17)**.

▼ Figure 41.16 The alimentary canals of a carnivore (lion) and herbivore (koala). The relatively short digestive tract of the lion 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 further digest the shredded leaves, releasing nutrients that the koala can absorb.

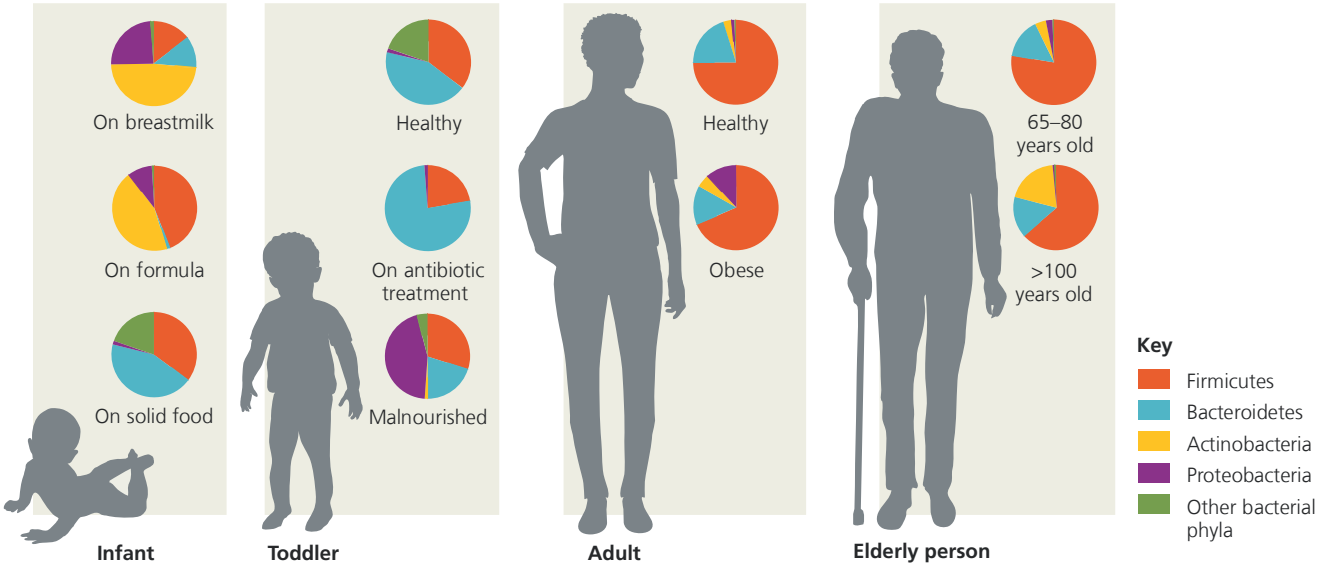


One example of the power of microbiome studies comes from research on gastric ulcers, a disease that damages the stomach lining. Experiments demonstrating that ulcers are caused by infection with the acid-tolerant bacterium *Helicobacter pylori* and can be cured with antibiotics earned Australian researchers Barry Marshall and Robin Warren a Nobel Prize in 2005.

Recently, scientists analyzed the microbiome in samples from human stomachs to learn how *H. pylori* infection leads to ulcers. Their findings were dramatic: *H. pylori* infection led to the near-complete elimination of all bacterial species commonly found in the stomach **(Figure 41.18)**.

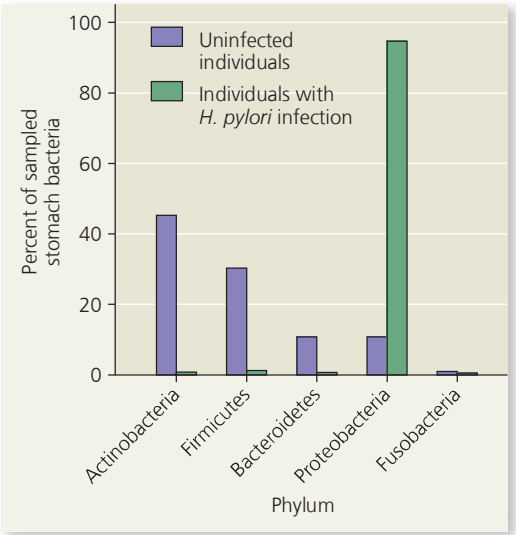
Studies on the microbiome have already led to therapies for intestinal infections by antibiotic-resistant pathogens, a major public health problem. One such therapy is fecal microbial transplantation, in which the microbiome of a healthy individual is introduced into the patient's intestine. This approach has been used for untreatable diarrhea caused

▼ Figure 41.17 Variation in human gut microbiome at different life stages. By copying and sequencing bacterial DNA in samples obtained from intestinal tracts of humans of different ages, researchers characterized the bacterial community that makes up the human gut and how it changes with age.



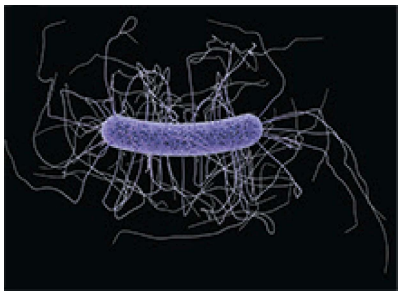
INTERPRET THE DATA *Using data displayed in Figures 41.17 and 41.18, compare the relative abundance of Actinobacteria in the microbiome of a healthy adult's intestinal tract to that in a healthy stomach. Suggest a possible explanation for why the microbiome composition in the two organs is different even though the intestine and stomach are directly connected.*

▼ Figure 41.18 The stomach microbiome and stomach health. In samples from individuals infected with *Helicobacter pylori*, more than 95% of the sequences were from that species, which belongs to the phylum Proteobacteria. The stomach microbiome in uninfected individuals was much more diverse.



by the bacterium *Clostridium difficile* **(Figure 41.19)**. Such infections are most common after antibiotic treatment has killed off the resident microbiome. Clinical trials have shown the fecal transplantation approach to be effective, although there is a real risk of secondary infection.

▶ Figure 41.19 ***Clostridium difficile.***

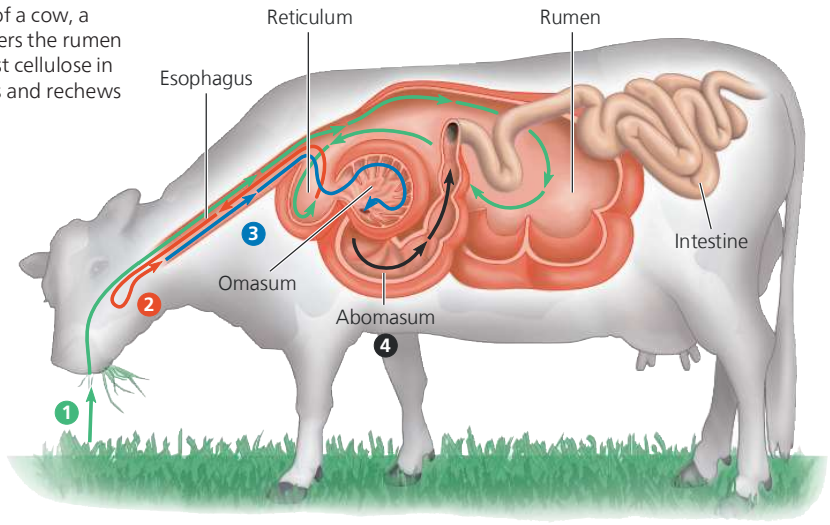


Another treatment against antibiotic-resistant pathogens makes use of bacteriophages, viruses that infect bacteria but not human cells (see Concept 19.1). In 2017, bacteriophages engineered to kill a multidrug-resistant bacterial pathogen, *Acinetobacter baumannii*, were successfully used to restore health to a severely affected patient.

Mastering Biology Interview with Steffanie Strathdee: Harnessing phages to fight deadly infections (see the interview before Chapter 40)

Mutualistic Adaptations in Herbivores

Mutualistic relationships with microorganisms are also very important in herbivores. Herbivores get much of the chemical energy they need from the cellulose of plant cell walls, but, like other animals, herbivores do not produce enzymes that hydrolyze cellulose. Instead, many vertebrates (as well



▶ **Figure 41.20 Ruminant digestion.** The stomach of a cow, a ruminant, has four chambers. 1 Chewed food first enters the rumen and reticulum, where mutualistic microorganisms digest cellulose in the plant material. 2 Periodically, the cow regurgitates and rechews "cud" from the reticulum, further breaking down fibers and thereby enhancing microbial action. 3 The reswallowed cud passes to the omasum, where some water is removed. 4 It then passes 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.

as termites, whose wooden diets consist largely of cellulose) host large populations of mutualistic bacteria and protists in fermentation chambers in their alimentary canals. These symbiotic 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 essential nutrients, such as vitamins and amino acids.

In horses, koalas, and elephants, symbiotic microorganisms are housed in a large cecum. In contrast, the hoatzin, an herbivorous bird found in South American rain forests, hosts microorganisms in a large, muscular crop (an esophageal pouch; see Figure 41.7). Hard ridges in the wall of the crop grind plant leaves into small fragments, and the microorganisms break down cellulose.

In rabbits and some rodents, mutualistic bacteria live in the large intestine as well as the 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*, the cud-chewing animals that include deer, sheep, and cattle **(Figure 41.20)**.

Although we have focused our discussion on vertebrates, adaptations related to digestion are also widespread among other animals. Some of the most remarkable examples are the over 3-meter-long giant tubeworms **(Figure 41.21)** that live at pressures as high as 260 atmospheres around deep-sea hydrothermal vents (see Figure 52.16). These worms have no mouth or digestive system. Instead, they obtain all of their energy and nutrients from mutualistic bacteria that live within their bodies. The bacteria carry out chemoautotrophy (see Concept 27.3) using the carbon dioxide, oxygen, hydrogen sulfide, and nitrate available at the vents. Thus, for invertebrates and vertebrates alike, the evolution of mutualistic relationships with symbiotic microorganisms is an adaptation that expands the sources of nutrition available to animals.

▼ **Figure 41.21 Giant tubeworm, an animal without a digestive system.**

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

CONCEPT CHECK 41.4

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?** People who have lactose intolerance 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 that contains 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 41.5

Feedback circuits regulate digestion, energy storage, and appetite

To complete our consideration of animal nutrition, we'll explore the ways that obtaining and using nutrients are matched to an animal's circumstances and need for energy.

Regulation of Digestion

Many animals face long gaps between meals. Under such circumstances, there is no need for their digestive systems to be active continuously. Instead, processing is activated stepwise. As food reaches each new compartment, it triggers the secretion of digestive juices for the next stage of processing. Muscular contractions then move the contents 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. These events, as well as peristalsis in the small and large intestines, are regulated by the *enteric nervous system*, a network of neurons dedicated to the digestive organs.

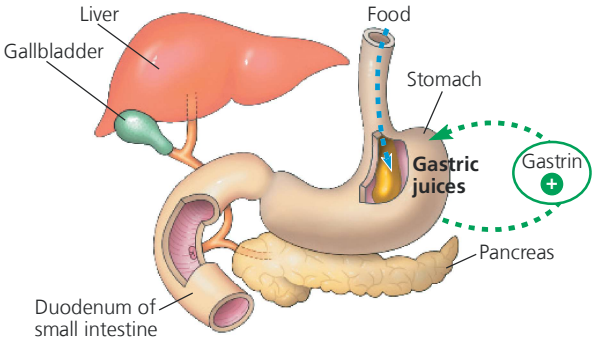
The endocrine system also plays a critical role in controlling digestion. As described in **Figure 41.22**, a series of hormones released by the stomach and duodenum help ensure that digestive secretions are present only when needed. Like all hormones, they are transported through the bloodstream. This is true even for the hormone gastrin, which is secreted by the stomach and targets that same organ.

Regulation of Energy Storage

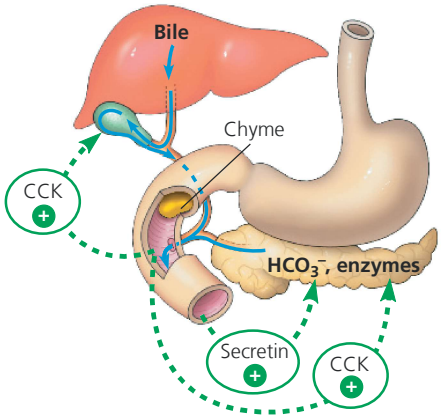
When an animal takes in more energy-rich molecules than it needs for metabolism and activity, it stores the excess energy (see Concept 40.4). In humans, liver and muscle cells serve as the primary sites for energy storage. In these cells, excess energy from the diet is stored in glycogen, a polysaccharide made up of many glucose units (see Figure 5.6b). Once glycogen depots are full, any additional excess energy is usually stored in fat in adipose cells.

At times 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.

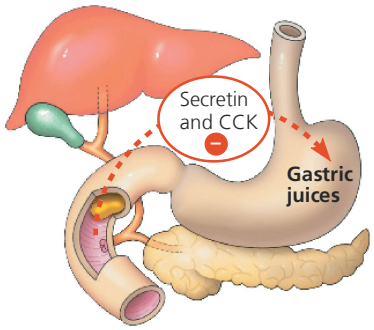
▼ Figure 41.22 Hormonal control of digestion.



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 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 inhibit peristalsis. This slows the movement of chyme and allows the more time-consuming digestion of fats to take place in the small intestine.

Key + Stimulation − Inhibition

Glucose Homeostasis

The synthesis and breakdown of glycogen are central not only to energy storage, but also to maintaining metabolic balance through glucose homeostasis. In humans, the normal range for the concentration of glucose in the blood is 70–110 mg/100 mL. Because glucose is a major fuel for cellular respiration and a key source of carbon skeletons for biosynthesis, maintaining blood glucose concentrations near this normal range is essential.

Glucose homeostasis relies predominantly on the antagonistic (opposing) effects of two hormones, insulin and glucagon **(Figure 41.23)**. When the blood glucose level rises above the normal range, the secretion of **insulin** triggers the uptake of glucose from the blood into body cells, decreasing the blood glucose concentration. When the blood glucose level drops below the normal range, the secretion of **glucagon** promotes the release of glucose into the blood from energy stores, such as liver glycogen, increasing the blood glucose concentration.

The liver is a key site of action for insulin and glucagon. After a carbohydrate-rich meal, for example, insulin secretion promotes biosynthesis of glycogen from glucose that enters the liver in the hepatic portal vein. Between meals, when blood in the hepatic portal vein has a much lower glucose concentration, glucagon stimulates the liver to break down glycogen, convert amino acids and glycerol to glucose, and release glucose into the blood. Together, these opposing effects of insulin and glucagon ensure that blood exiting the liver has a glucose concentration in the normal range at nearly all times.

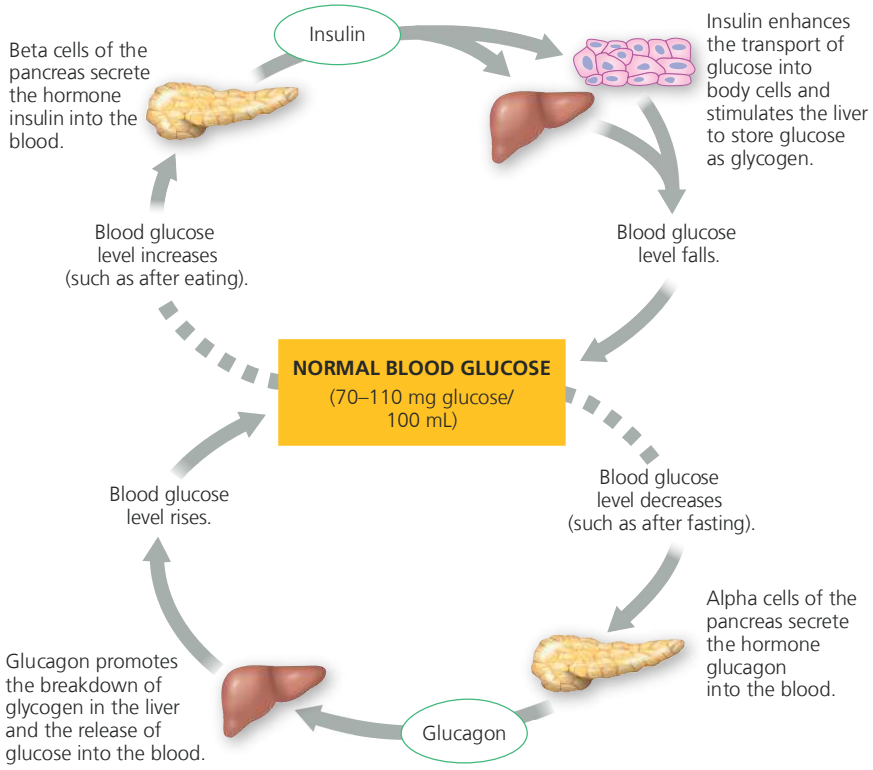
Insulin also acts on nearly all body cells to stimulate glucose uptake from blood. A major exception is brain cells, which can take up glucose whether or not insulin is present. This evolutionary adaptation ensures that the brain almost always has access to circulating fuel, even if supplies are low.

Glucagon and insulin are both produced in the pancreas. Clusters of endocrine cells called pancreatic islets are scattered throughout this organ. Each islet has *alpha cells*, which make glucagon, and *beta cells*, which make insulin. Like other hormones, insulin and glucagon enter the interstitial fluid and then the circulatory system.

Overall, hormone-secreting cells make up only 1–2% of the mass of the pancreas. Other cells in the pancreas produce and secrete bicarbonate ions and the digestive enzymes active in the small intestine (see Figure 41.11). These secretions are released into small ducts that empty into the pancreatic duct, which leads to the small intestine. Thus, the pancreas has functions in both the endocrine and digestive systems.

Diabetes Mellitus

In discussing the role of insulin and glucagon in glucose homeostasis, we have focused exclusively on a healthy metabolic state. However, 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 of these disorders is diabetes mellitus.



▶ Figure 41.23 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 do these regulatory circuits reflect (see Concept 40.2)?*

Mastering Biology **BioFlix® Animation: Homeostasis: Regulating Blood Sugar • Animation: Pancreatic Hormones Regulate Blood Glucose Level**

The disease **diabetes mellitus** is caused by a deficiency of insulin or a decreased response to insulin in target tissues. The blood glucose level rises, 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. The presence of excess sugar in both urine and blood is the basis for the name *diabetes mellitus* (from the Greek *diabainein*, to pass through, and *meli*, honey).

There are two main types of diabetes mellitus: type 1 and type 2. Each is marked by high blood glucose levels, but with very different causes.

Type 1 Diabetes Also called insulin-dependent diabetes, *type 1 diabetes* is an autoimmune disorder in which the immune system destroys the beta cells of the pancreas. Type 1 diabetes, which usually appears during childhood, destroys the person's ability to produce insulin. Treatment consists of insulin injections, typically given multiple times daily. In the past, insulin was extracted from animal pancreases, but now human insulin can be readily obtained at reasonable cost from genetically engineered bacteria (see Figure 20.4). Stem cell research may someday provide a cure for type 1 diabetes by generating replacement beta cells that restore insulin production by the pancreas.

Type 2 Diabetes Non-insulin-dependent diabetes, or *type 2 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 the blood glucose level remains elevated. Although heredity can play a role in type 2 diabetes, excess body weight and lack of exercise significantly increase the risk of developing this disorder. This form of diabetes generally appears after age 40, but even children can develop the disease, particularly if they are overweight and sedentary. More than 90% of people with diabetes have type 2. Many can control their blood glucose levels with regular exercise and a healthy diet; some require medications. Nevertheless, type 2 diabetes is the seventh most common cause of death in the United States and a growing public health problem worldwide.

The resistance to insulin signaling in type 2 diabetes is sometimes due to a genetic defect in the insulin receptor or the insulin response pathway. In many cases, however, events in target cells suppress activity of an otherwise functional response pathway. One source of this suppression appears to be inflammatory signals generated by the innate immune system (see Concept 43.1). How obesity and inactivity relate to this suppression is being studied in both humans and laboratory animals.

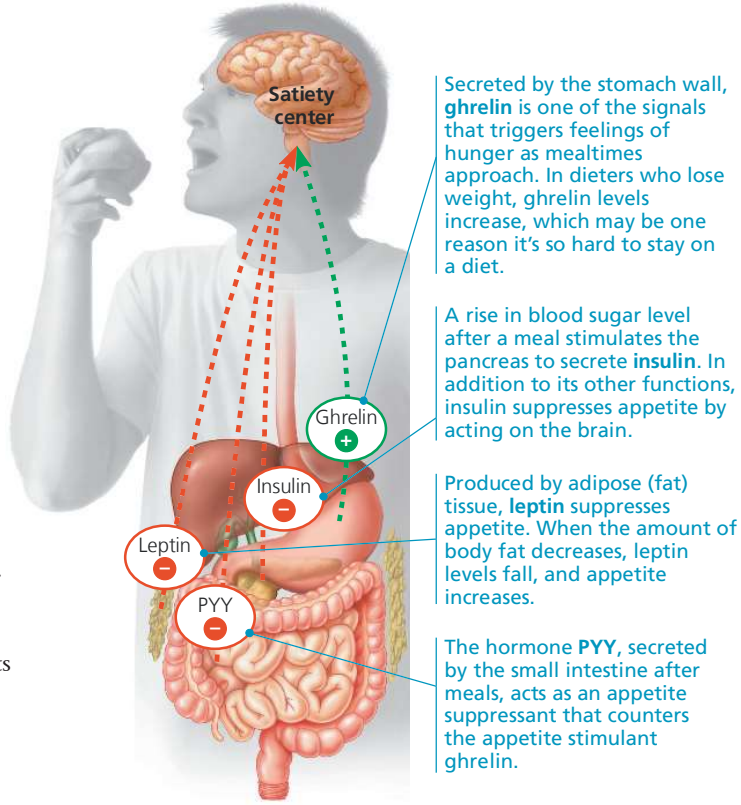
Mastering Biology BioFlix® Animation: Diabetes

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 result in heart attacks and strokes. It is estimated that obesity is a factor in 300,000 deaths per year in the United States alone.

Researchers have discovered several homeostatic mechanisms that operate as feedback circuits controlling the storage and metabolism of fat. A network of neurons relays and integrates information from the digestive system to regulate secretion of hormones that regulate long-term and short-term appetite. The target for these hormones is a "satiety center" in the brain **(Figure 41.24)**. For example, *ghrelin*, a hormone secreted by the

▼ Figure 41.24 A few of the appetite-regulating hormones. Secreted by various organs and tissues, the hormones reach the brain via the bloodstream. These signals act on a region of the brain that in turn controls the "satiety center," which generates the nervous impulses that make us feel either hungry or satiated ("full"). The hormone ghrelin is an appetite stimulant; the other three hormones shown here are appetite suppressants.



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.

▶ 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 mice of various genotypes (the "subjects") 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)			Average Change in Body Mass of Subject (g)
	Subject	Paired with	
(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.

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

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), pairing (c), and pairing (d). Explain how each pairing contributed to the experimental design.
2. Compare the results observed for pairing (a) and 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 these results differ from those for pairing (b). Suggest a hypothesis to explain this difference. How could you test your hypothesis using the kinds of mice in this study?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology.**

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.

Obtaining food, digesting it, and absorbing nutrients are part of the larger story of how animals fuel their activities. Provisioning the body also involves circulating nutrients, and using nutrients for metabolism requires exchanging respiratory gases with the environment. These processes and the adaptations that facilitate such distribution and exchange are the focus of Chapter 42.

CONCEPT CHECK 41.5

1. Explain how people can become obese even if their intake of dietary fat is relatively low compared with carbohydrate intake.
2. **WHAT IF?** Suppose you were studying two groups of people who are obese and have genetic abnormalities in the leptin pathway. In one group, the leptin levels are abnormally high; in the other group, they are abnormally low. How would each group's leptin levels change if they ate a low-calorie diet for an extended period? Explain.
3. **WHAT IF?** An insulinoma is a cancerous mass of pancreatic beta cells that secrete insulin but do not respond to feedback mechanisms. How you would expect an insulinoma to affect blood glucose levels and liver activity?

For suggested answers, see Appendix A.

41 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 41.1

An animal's diet must supply chemical energy, organic building blocks, and essential nutrients *(pp. 899–902)*

- 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 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.
- Malnutrition results from an inadequate intake of essential nutrients or a deficiency in sources of chemical energy. Studies of disease at the population level help researchers determine human dietary requirements.

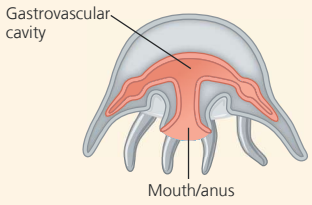
? *How can an enzyme cofactor needed for an essential process be an essential nutrient for only some animals?*

CONCEPT 41.2

Food processing involves ingestion, digestion, absorption, and elimination *(pp. 902–905)*

- Animals differ in the ways they obtain and ingest food. Many animals are **bulk feeders**, eating large pieces of food. Other strategies include **filter feeding, substrate feeding**, and **fluid feeding**.
- Compartmentalization is necessary to avoid self-digestion. In intracellular digestion, food particles are engulfed by phagocytosis 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**.

Gastrovascular cavity (jelly)

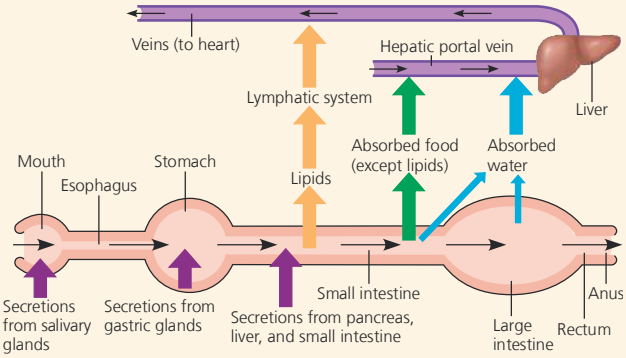


Alimentary canal (earthworm)

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

CONCEPT 41.3

Organs specialized for sequential stages of food processing form the mammalian digestive system *(pp. 905–911)*



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

CONCEPT 41.4

Evolutionary adaptations of vertebrate digestive systems correlate with diet *(pp. 911–914)*

- Vertebrate digestive systems display many evolutionary adaptations associated with diet. For example, the assortment of teeth (dentition) generally correlates with diet. Also, many herbivores have fermentation chambers where mutualistic microorganisms digest cellulose. 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 primate ancestors were not strict vegetarians?*

CONCEPT 41.5

Feedback circuits regulate digestion, energy storage, and appetite *(pp. 915–918)*

- Nutrition is regulated at multiple levels. Food intake triggers nervous and hormonal responses that cause secretion of digestive juices and promote movement of ingested material through the canal. The hormones **insulin** and **glucagon** control the synthesis and breakdown of glycogen, thereby regulating glucose availability.
- 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 cause 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

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. Fat digestion yields fatty acids and glycerol. Protein digestion yields amino acids. Both digestive processes
   (A) occur inside cells in most animals.
   (B) add a water molecule to break bonds.
   (C) require a low pH resulting from HCl production.
   (D) consume ATP.
2. The mammalian trachea and esophagus both connect to the
   (A) pharynx.
   (B) stomach.
   (C) large intestine.
   (D) rectum.
3. In which organ does almost all enzymatic digestion of food occur?
   (A) stomach
   (B) small intestine
   (C) large intestine
   (D) pancreas
4. In which digestive system organ does nearly all nutrient absorption occur?
   (A) stomach
   (B) small intestine
   (C) large intestine
   (D) pancreas

Levels 3-4: Applying/Analyzing

5. If you put the following events in the order they occur in the human digestive system, which would be the third event in the series?
   (A) Cells in gastric pits secrete protons.
   (B) Pepsin activates pepsinogen.
   (C) HCl activates pepsinogen.
   (D) Partially digested food enters the small intestine.
6. After surgical removal of the gallbladder, a person might need to limit his or her dietary intake of
   (A) starch. (C) sugar.
   (B) protein. (D) fat.
7. 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 in the liver
   (D) fat in adipose tissue

Levels 5-6: Evaluating/Creating

8. **DRAW IT** Create a flowchart to summarize the events that occur after partially digested food leaves the stomach in a human. Use the following terms: bicarbonate secretion, circulation, decrease in acidity, increase in acidity, secretin secretion, signal detection. Next to each term, indicate the compartment(s) involved. You may use terms more than once.
9. **EVOLUTION CONNECTION** Lizards and snakes cannot breathe while chewing food because the connection between their external nostrils and their esophagus is in the mouth. In contrast, mammals can continue breathing through the nostrils while chewing food in the mouth. However, choking sometimes occurs when the paths of air and food cross each other. Thinking about the high oxygen demand of active endotherms, explain how the concept of descent with modification explains this "imperfect" anatomy of some amniotes (see Figure 34.2 to review vertebrate phylogeny).
10. **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 individuals 15 to 50 years old, men are ten times as likely as women to suffer from iron overload. Taking into account this range of ages, propose a hypothesis that explains this difference.
11. **WRITE ABOUT A THEME: ORGANIZATION** Hair is largely made up of the protein keratin. In a short essay (100–150 words), explain why a shampoo containing protein cannot replace the protein in damaged hair.
12. **SYNTHESIZE YOUR KNOWLEDGE**

Owls, which have a varied diet, periodically cough up pellets composed of indigestible material, such as bones, feathers, and fur. (a) Compare this aspect of the owl's digestive process to those of the hydra, the rabbit, and the cow. (b) In which digestive compartment do you predict owl pellets form (see Figure 41.7c)? Explain.

For selected answers, see Appendix A.

Explore Scientific Papers with Science in the Classroom AAAS
How does the microbiome affect the nervous system?
Go to "You Are What You Eat... At Least, Your Brain Is" at www.scienceintheclassroom.org.
Instructors: Questions can be assigned in Mastering Biology.

42 Circulation and Gas Exchange

KEY CONCEPTS

Study Tip

Draw and annotate a diagram: Sketch a simplified double circulation system like the idealized one on this page. Label where each of the following is highest: blood pressure, CO_2 concentration, O_2 concentration, and total cross-sectional area of the blood vessels. Note that the left side of your diagram represents the right side of the heart in the body, and remember "**R**e**V**i**T**a**L**ize" to help remind you of the path of blood from the **R**ight **V**entricle **t**o the **L**ungs.

Go to Mastering Biology

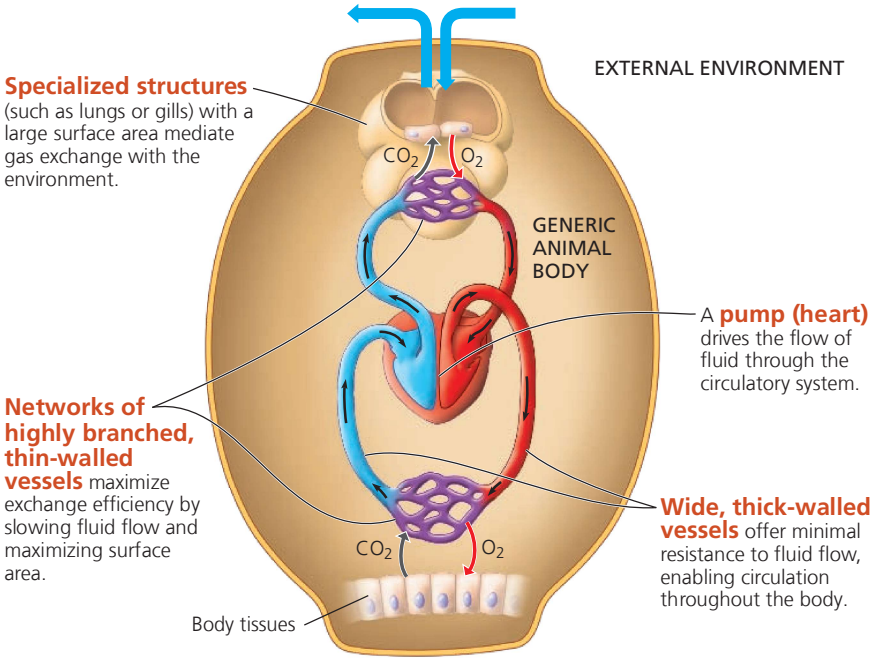
For Students (in the eText and Study Area)
- Get Ready for Chapter 42
- Figure 42.10 Walkthrough: Interrelationship of Blood Vessel Area, Velocity, and Pressure
- Figure 42.22 Walkthrough: Structure and Function of Fish Gills
- BioFlix® Animation: Gas Exchange in the Human Body

For Instructors to Assign (in the Item Library)
- Animation: Gills Are Adapted for Gas Exchange in Aquatic Environments

Ready-to-Go Teaching Module (in Instructor Resources)
- Cardiac Cycle and Heart Function

Figure 42.1 This animal may look like a creature from a science fiction film, but it's actually an axolotl, a salamander native to shallow ponds in central Mexico. The feathery red appendages jutting out from its head are gills. External gills, although uncommon in other adult animals, help axolotls carry out a process common to all organisms: the exchange of substances between body cells and the environment.

How are structure and function related in the exchange and circulation of oxygen and carbon dioxide?



CONCEPT 42.1

Circulatory systems link exchange surfaces with cells throughout the body

The molecular trade that an animal carries out with its environment must ultimately involve every cell in the body. Required resources, such as nutrients and oxygen (O_2), enter the cytoplasm by crossing the plasma membrane. Waste products, such as carbon dioxide, (CO_2), exit the cell by crossing the same membrane.

Small molecules in and around cells, including O_2 and CO_2, undergo **diffusion**, which is random thermal motion (see Concept 7.3). When there is a difference in the concentration of a gas or other substance, such as between a cell and its immediate surroundings, diffusion can result in net movement.

Unicellular organisms exchange materials directly with the external environment via diffusion across the plasma membrane. For most multicellular organisms, however, direct exchange between every cell and the environment is not possible. Furthermore, net movement by diffusion 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.

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 permit efficient exchange for all of an animal's cells.

One adaptation for efficient exchange is a simple body plan that places many or all cells in direct contact with the environment. Each cell can thus exchange materials directly with the surrounding medium. Such an arrangement is characteristic of certain invertebrates, including cnidarians and flatworms. Animals that lack a simple body plan display an alternative adaptation for efficient exchange: a circulatory system. Such systems move fluid between each cell's immediate surroundings and the body tissues. As a result, exchange with the environment and exchange with body tissues both occur over very short distances.

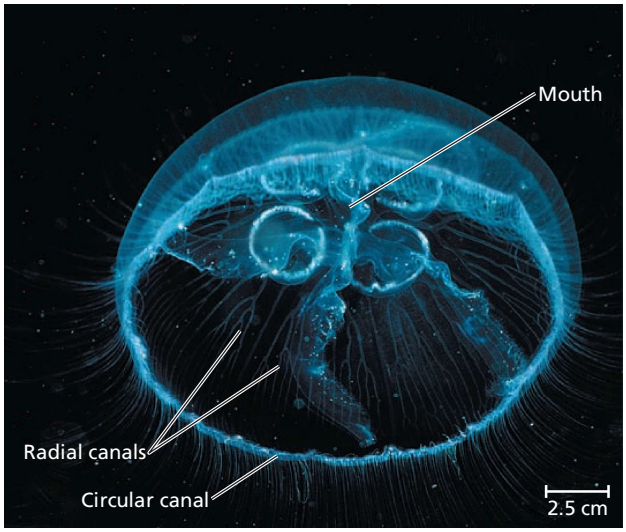
In most animals, the circulatory system is functionally linked to the exchange of gases with the environment and with body cells. For this reason, we'll discuss systems for circulation and gas exchange together in this chapter. By considering examples of these systems from a range of species, we'll explore their common elements as well as their extensive variation.

Gastrovascular Cavities

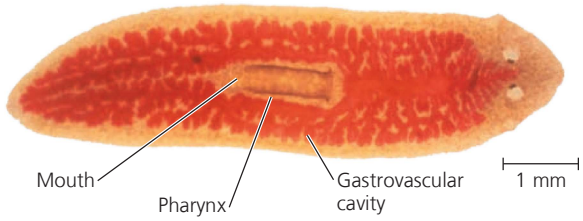
Let's begin by looking at some animals whose body shapes put many of their cells into contact with their environment, enabling them to live without a distinct circulatory system. In hydras, jellies, and other cnidarians, a central **gastrovascular cavity** functions in the distribution of substances throughout the body, as well as in digestion (see Figure 41.6). An opening at one end connects the cavity to the surrounding water. In a hydra, thin branches of the gastrovascular cavity extend into the animal's tentacles. In jellies and some other cnidarians, the gastrovascular cavity has a much more elaborate branching pattern **(Figure 42.2a)**.

In animals with a gastrovascular cavity, fluid bathes both the inner and outer tissue layers, facilitating exchange of gases and cellular waste. Only the cells lining the cavity have direct access to nutrients released by digestion. However, because the body wall is a mere two cells thick, nutrients only need to diffuse a short distance to reach the cells of the outer tissue layer.

▼ Figure 42.2 Diversity of gastrovascular cavities.



(a) The moon jelly *Aurelia*, a cnidarian. The jelly is viewed here from its underside (oral surface). The mouth leads to an elaborate gastrovascular cavity that consists of radial canals leading to and from a circular canal. Ciliated cells lining the canals circulate fluid within the cavity.



(b) The planarian *Dugesia*, a flatworm. The mouth and pharynx on the ventral side lead to the highly branched gastrovascular cavity, stained dark red in this specimen (LM).

WHAT IF? *Suppose a gastrovascular cavity were open at two ends, with fluid entering one end and leaving the other. How would this affect the cavity's functions in gas exchange and digestion?*

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 42.2b)**. A flat body optimizes exchange by increasing surface area and minimizing diffusion distances.

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 circulatory fluid's hydrostatic pressure, which is the pressure the fluid exerts on surrounding vessels. The fluid then flows through the vessels and back to the heart.

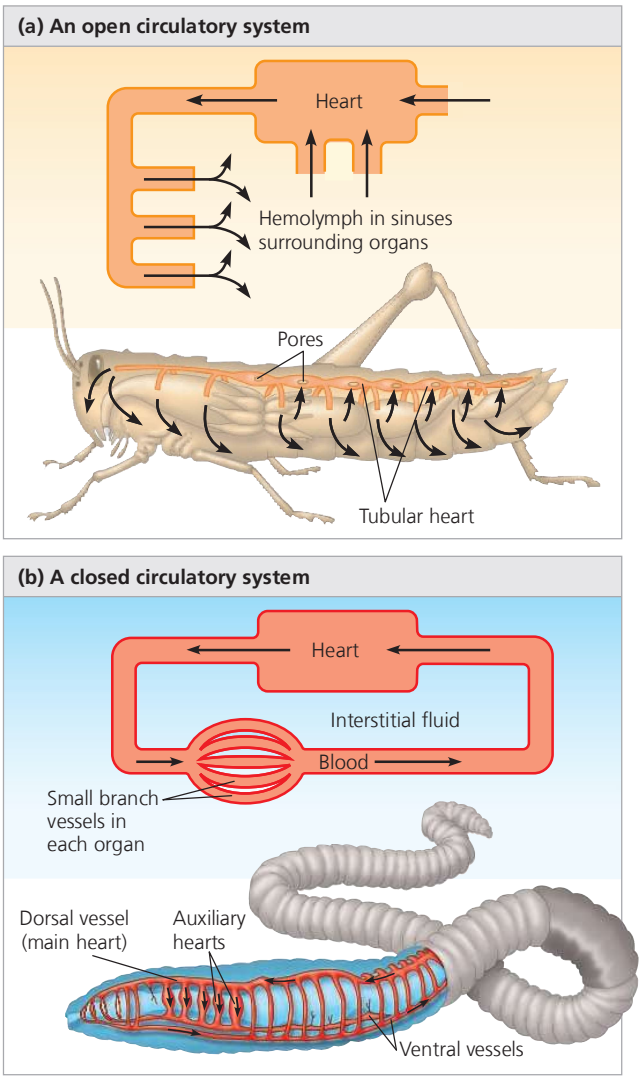
By transporting fluid throughout the body, the circulatory system functionally connects the aqueous environment of the body cells to the organs that exchange gases, absorb nutrients, and dispose of wastes. In mammals, for example, O_2 from inhaled air diffuses across only two layers of cells in the lungs before reaching the blood. The circulatory system then carries the oxygen-rich blood to all parts of the body. As the blood passes throughout the body tissues in tiny blood vessels, O_2 in the blood diffuses only a short distance before entering the fluid that directly bathes the cells.

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, such as grasshoppers, and some molluscs, including clams, have open circulatory systems. Contraction of the heart pumps the hemolymph through the circulatory vessels into interconnected sinuses, spaces surrounding the organs **(Figure 42.3a)**. Within the sinuses, the hemolymph and body cells exchange gases and other chemicals. Relaxation of the heart 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. The open circulatory system of larger crustaceans, such as lobsters and crabs, includes a more extensive system of vessels, as well as an accessory pump.

In a **closed circulatory system**, a circulatory fluid called **blood** is confined to vessels and is distinct from the interstitial fluid **(Figure 42.3b)**. One or more hearts pump blood into large vessels that branch into smaller ones, which infiltrate the tissues and organs. Chemical exchange occurs between the blood and the interstitial fluid, as well as between the interstitial fluid and body cells. Annelids (including earthworms), cephalopods (including squids and octopuses), and all vertebrates have closed circulatory systems.

The fact that both open and closed circulatory systems are widespread among animals suggests that each system offers evolutionary advantages. The lower hydrostatic pressures typically associated with open circulatory systems allow them to use less energy than closed systems. In some invertebrates, open circulatory systems serve additional functions. For example, spiders use the hydrostatic pressure of their open circulatory system to extend their legs. The benefits of closed circulatory systems include blood pressure high enough to enable the effective delivery of O_2 and nutrients in larger and more active animals. Among 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. We'll now examine closed circulatory systems in more detail, focusing on vertebrates.

▼ Figure 42.3 Open and closed circulatory systems.



Organization of Vertebrate Circulatory Systems

The term **cardiovascular system** is often used to describe the heart and blood vessels in vertebrates. 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 capillaries, called **capillary beds**, infiltrate tissues, passing within a few cell diameters of every cell in the body. Across the thin walls of capillaries, dissolved gases and other chemicals are exchanged by 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.

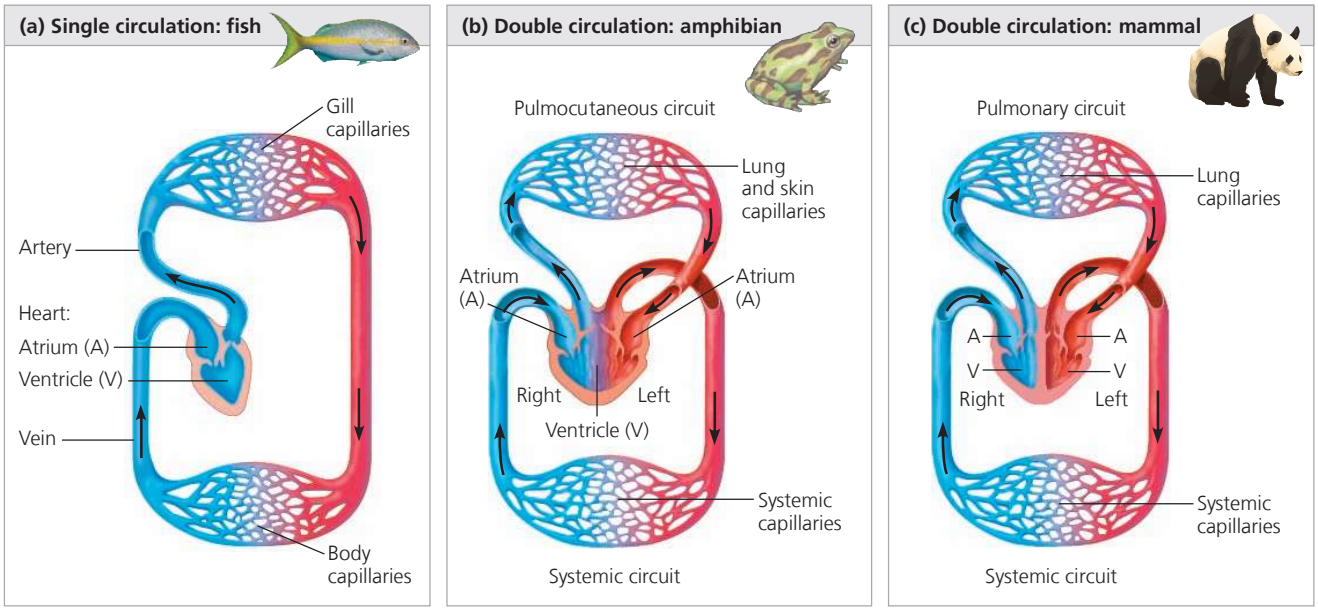
Note that arteries and veins are distinguished by the *direction* in which they carry blood, not by the O_2 content or other characteristics of the blood they contain. Arteries carry blood *away* from the heart toward capillaries, and veins return blood *toward* the heart from capillaries. The only exceptions are the portal veins, which carry blood between pairs of capillary beds. The hepatic portal vein, for example, carries blood from capillary beds in the digestive system to capillary beds in the liver.

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 groups of vertebrates, as we'll discuss next. These important differences reflect the close fit of form to function that arises from natural selection.

Single Circulation

In sharks, rays, and bony fishes, blood travels through the body and returns to its starting point in a single circuit (loop), an arrangement called **single circulation** **(Figure 42.4a)**. These animals have a heart that consists of two chambers: an atrium and a ventricle. Blood entering the heart collects in the atrium before transfer to the ventricle. Contraction of the ventricle pumps blood to a capillary bed in 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. Following

▼ Figure 42.4 Examples of vertebrate circulatory system organization.



(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.)

gas exchange in the capillary beds, blood enters veins and returns to the heart.

In single circulation, blood that leaves the heart passes through two capillary beds before returning to the heart. When blood flows through a capillary bed, blood pressure drops substantially, for reasons we'll explain later in the chapter. The blood pressure drop in the gills limits the rate 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 of blood flow, an arrangement called **double circulation** (Figure 42.4b 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.

In one circuit, the right side of the heart pumps 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. In most vertebrates, including reptiles and mammals, this is called the *pulmonary circuit* (from the Latin *pulmo*, lung) because gas exchange takes place in the lungs. For many amphibians, it is called the *pulmocutaneous circuit* because gas exchange takes place in capillaries in both the lungs and the skin.

The other circuit, called the *systemic circuit*, begins with the left side of the heart pumping oxygen-enriched blood from the gas exchange tissues 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 circuit.

Double circulation provides a vigorous flow of blood to the brain, muscles, and other organs because the heart repressurizes the blood 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. By contrast, in single circulation the 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 either without gas exchange or by relying on another gas exchange tissue, typically the skin. A variety of adaptations found among intermittent breathers enable their circulatory systems 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 42.4b). 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 pulmocutaneous circuit. When a frog is underwater, it takes advantage of the incomplete division of the ventricle, largely shutting off 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 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 rest of 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, which for the most part breathe continuously, differs from double circulation in other vertebrates. As shown for a panda in Figure 42.4c, 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 varying blood flow throughout the body in parallel.

How has natural selection shaped the double circulation of birds and mammals? As endotherms, they use about ten times as much energy as equal-sized ectotherms (see Concept 40.4). 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-scale traffic of substances is made possible by the separate and independently powered systemic and pulmonary circuits and by large hearts. A powerful four-chambered heart arose independently in the distinct ancestors of birds and mammals and thus reflects convergent evolution (see Concept 22.3).

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 42.1

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.

CONCEPT 42.2

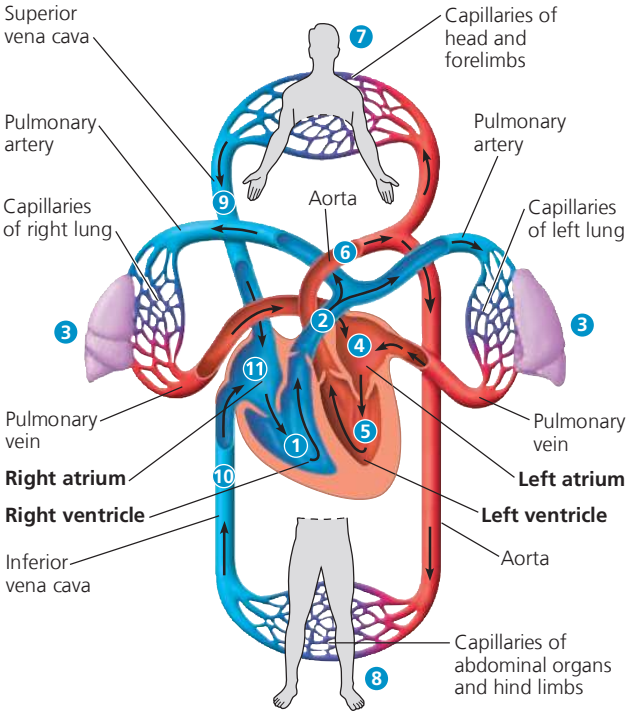
Coordinated cycles of heart contraction drive double circulation in mammals

The timely delivery of O_2 to the body's 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 must consider how the parts of the system are arranged and how each of these parts 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 labeled structures in **Figure 42.5**.) 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. Branches further along the aorta 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 capillary beds, 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.

▼ Figure 42.5 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 contract almost in unison and pump the same volume of blood. However, the total volume of blood in the systemic circuit is much greater than that in the pulmonary circuit.



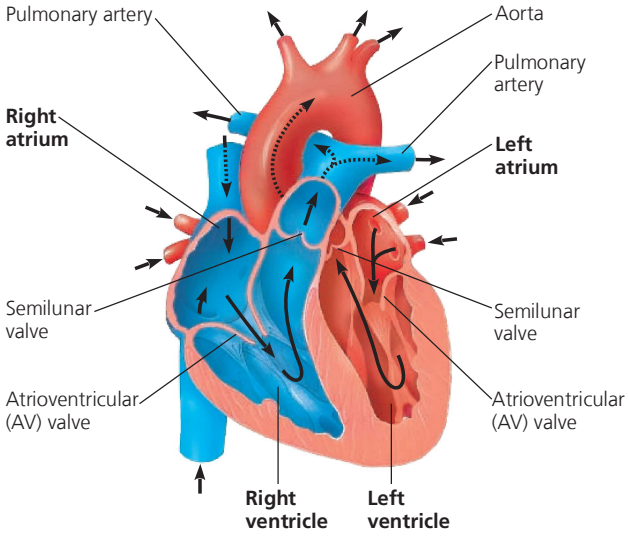
VISUAL SKILLS *If you trace the path of a molecule of carbon dioxide that starts in an arteriole in the right thumb and leaves the body in exhaled air, what is the minimum number of capillary beds the molecule encounters? Explain.*

Mastering Biology **Animation: The Human Heart and Circulation**

The Mammalian Heart: *A Closer Look*

Using the human heart as an example, let's now take a closer look at how the mammalian heart works **(Figure 42.6)**. Located behind the sternum (breastbone), the human heart is about the size of a clenched fist and consists mostly of cardiac muscle (see Figure 40.5). 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. Much of the blood that enters the atria flows into the ventricles while all four heart chambers are relaxed. The remainder is transferred by contraction of the atria before the ventricles

▼ Figure 42.6 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.



Mastering Biology **Animation: Structure of the Human Heart**

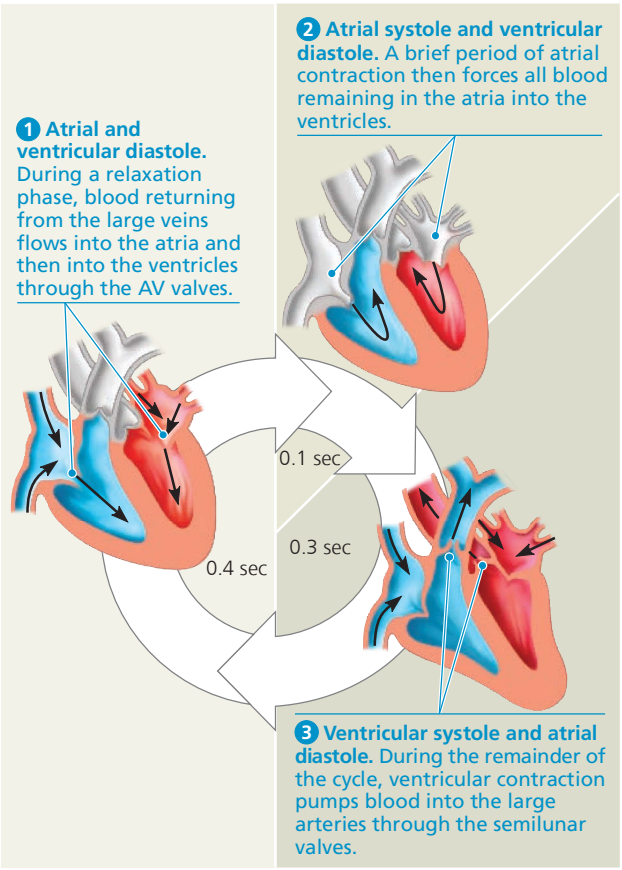
begin to contract. Compared with the atria, the ventricles have thicker walls and contract much more forcefully—especially the left ventricle, which pumps blood throughout the body via the systemic circuit. Although the left ventricle contracts with greater force than the right ventricle, it pumps the 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**. The contraction phase of the cycle is called **systole**, and the relaxation phase is called **diastole (Figure 42.7)**.

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 typical 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, the increased demand for O_2 is met by an increase in cardiac output that can be as much as fivefold.

Four valves in the heart prevent backflow and keep blood moving in the correct direction (see Figures 42.6 and 42.7). 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

▼ Figure 42.7 The cardiac cycle. For an adult human at rest with a heart rate of about 72 beats per minute, one complete cardiac cycle takes about 0.8 second. 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.



and ventricle. The AV valves are anchored by strong fibers that prevent them from turning inside out during ventricular systole. 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 the two exits of the heart: where the pulmonary artery leaves the right ventricle and where the aorta leaves the left 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 pulmonary artery and aorta 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 as a result of infection (for instance, from rheumatic fever, an inflammation caused by infection with certain bacteria). 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.

Maintaining the Heart's Rhythmic Beat

In vertebrates, the heartbeat originates in the heart itself. Some cardiac muscle cells are autorhythmic, meaning they can contract and relax repeatedly without any signal from the nervous system. In fact, these rhythmic contractions continue in tissue removed from the heart and placed in a dish in the laboratory! Given that each of these cells has its own intrinsic contraction rhythm, how are their contractions coordinated in the intact heart? The answer lies in a group of autorhythmic cells located in the wall of the right atrium, near where the superior vena cava enters the heart. This cluster of cells, called the **sinoatrial (SA) node**, acts as a *pacemaker*, setting the rate and timing at which all cardiac muscle cells contract. (In contrast, some arthropods have pacemakers located in the nervous system, outside the heart.)

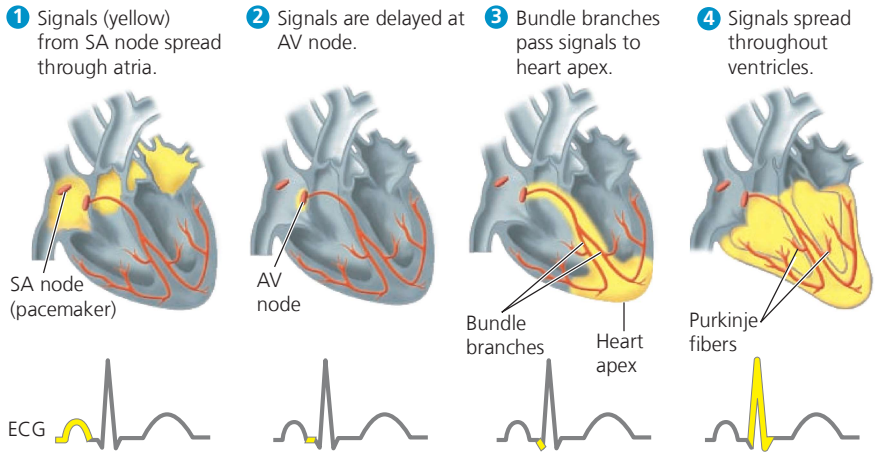
The SA node produces electrical impulses much like those produced by nerve cells. Because cardiac muscle cells are electrically coupled through gap junctions (see Figure 6.30), impulses from the SA node spread rapidly within heart tissue. These impulses generate currents that can be measured when they reach the skin via body fluids. In an **electrocardiogram** (**ECG** or **EKG**, from the German spelling), electrodes placed on the skin record the currents, thus measuring electrical activity of the heart. The graph of current against time has a shape that represents the stages in the cardiac cycle **(Figure 42.8)**.

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 by specialized structures called bundle branches and Purkinje fibers.

Physiological cues alter heart tempo by regulating the pacemaker function of the SA node. Two portions of the nervous system, the sympathetic and parasympathetic divisions, are largely responsible for this regulation. They function like the accelerator and brake in a car. For example, when you stand up and start walking, the sympathetic division 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 parasympathetic division slows down your pacemaker, decreasing your heart rate and thus conserving energy. Hormones secreted into the blood also influence the pacemaker. For instance, epinephrine, the "fight-or-flight" hormone secreted by the adrenal glands, speeds up the pacemaker. A third type of input that affects the pacemaker is body temperature. An increase of only 1°C raises the heart rate by about 10 beats per minute. This is the reason your heart beats faster when you have a fever.

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.

▼ Figure 42.8 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 these signals (yellow) during the cardiac cycle; specialized muscle cells involved in controlling of the rhythm are indicated in orange. Under each step, the corresponding portion of an electrocardiogram (ECG) is highlighted (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?*

CONCEPT CHECK 42.2

1. Explain why blood has a higher O_2 concentration in the pulmonary veins 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 atria to the ventricles?
3. **WHAT IF?** Suppose that after you exercise regularly for several months, your resting heart rate decreases, but your cardiac output at rest is unchanged. Based on these observations, what other change in the function of your heart at rest likely occurred?

For suggested answers, see Appendix A.

CONCEPT 42.3

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

To deliver oxygen and nutrients and remove wastes throughout the body, the vertebrate circulatory system relies on blood vessels that exhibit a close match of structure and function.

Blood Vessel Structure and Function

All blood vessels contain a central lumen (cavity) lined with an **endothelium**, a single layer of flattened epithelial cells. Like the polished surface of a copper pipe, the smooth endothelial layer minimizes resistance to fluid flow. Surrounding the endothelium are tissue layers that differ among capillaries, arteries, and veins, reflecting distinct adaptations to the particular functions of these vessels **(Figure 42.9)**.

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

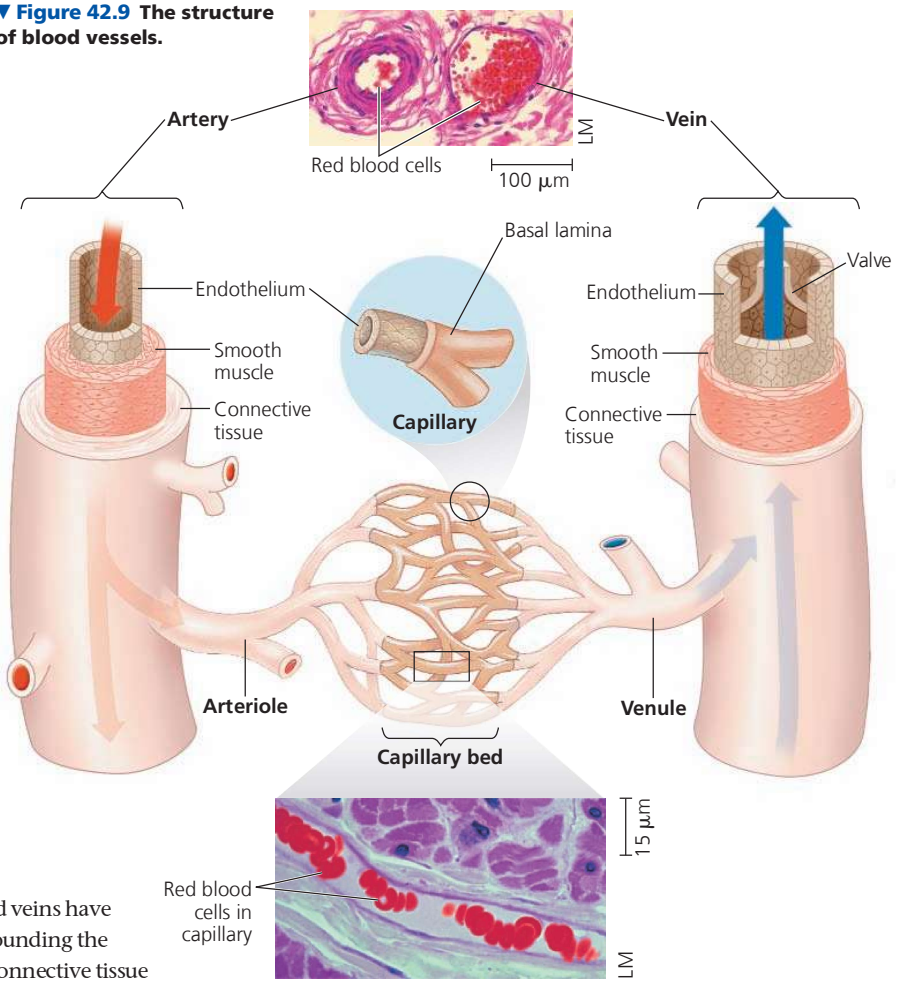
In contrast to capillaries, both arteries and veins have walls that consist of two layers of tissue surrounding the endothelium. The outer layer is formed by connective tissue that contains elastic fibers, which allow the vessel to stretch and recoil, and collagen, which provides strength. The layer next to the endothelium contains smooth muscle and more elastic fibers.

Arterial walls are thick, strong, and elastic. They can thus accommodate blood pumped at high pressure by the heart, bulging outward as blood enters and recoiling as the heart relaxes between contractions. As we'll discuss shortly, this behavior of arterial walls has an essential role in maintaining blood pressure and flow to capillaries.

The smooth muscles in the walls of arteries and arterioles help regulate the path of blood flow. Signals from the nervous system and circulating hormones act on the smooth muscle of these vessels, causing dilation or constriction that modulates blood flow to different parts of the body.

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.

▼ Figure 42.9 The structure of blood vessels.

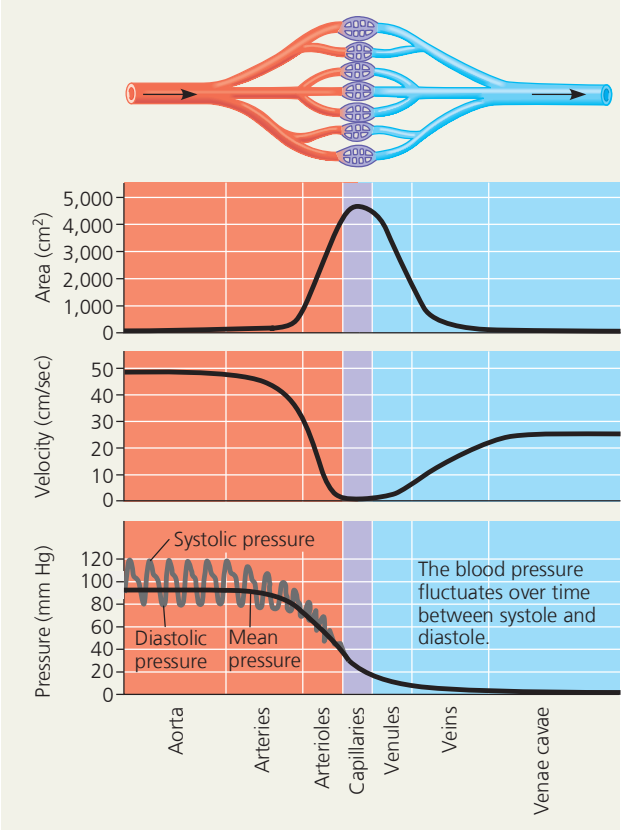


We consider next how blood vessel diameter, vessel number, and blood pressure influence the speed at which blood flows in different locations within the body.

Blood Flow Velocity

To understand how blood vessel diameter influences blood flow, consider how water flows through a thick-walled hose connected to a faucet. When the faucet is turned on, water flows at the same velocity at each point along the hose. What happens when a narrow nozzle is attached to the end of the hose? 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, exiting the nozzle at high velocity.

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 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 capillary beds than in the arteries or any other part of the circulatory system **(Figure 42.10)**. This enormous increase in cross-sectional area results in 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 and *total* cross-sectional areas decreases.



▲ Figure 42.10 The interrelationship of cross-sectional area of blood vessels, blood flow velocity, and blood pressure. As a result of an increase in total cross-sectional area, blood flow velocity decreases markedly in the arterioles and is lowest in the capillaries. Blood pressure, the main force driving blood from the heart to the capillaries, is highest in the aorta and other arteries.

Mastering Biology Figure Walkthrough

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 a force in all directions. The part of the force directed lengthwise in an artery causes the blood to flow away from the heart, the site of highest pressure. The part of the force exerted sideways stretches the wall of the artery. 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, this resistance has dissipated much of the pressure generated by the pumping heart (see Figure 42.10).

Changes in Blood Pressure During the Cardiac Cycle

Arterial blood pressure is highest when the heart contracts during ventricular systole. The pressure at this time is called **systolic pressure** (see Figure 42.10). Each ventricular contraction causes a spike in blood pressure that stretches the walls of the arteries. You can feel this **pulse**—the rhythmic bulging of the artery walls with each heartbeat—by placing the tips of your fingers on the inside of the opposite wrist. 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 to a wider diameter from the rise in pressure.

During diastole, the elastic walls of the arteries snap back. As a consequence, there is a lower but still substantial 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 42.10), blood continuously flows into arterioles and capillaries.

Regulation of Blood Pressure

Homeostatic mechanisms regulate arterial blood pressure by altering the diameter of arterioles. If the smooth muscles

in arteriole walls contract, the arterioles narrow, a process called **vasoconstriction**. Vasoconstriction 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 opposing activities provide homeostatic regulation of blood pressure.

Vasoconstriction and vasodilation are often coupled to changes in cardiac output that also affect blood pressure. This coordination of regulatory mechanisms maintains adequate blood flow as the body's demands on the circulatory system change. During heavy exercise, for example, the arterioles in working muscles dilate, causing a greater flow of oxygen-rich blood to the muscles. By itself, this increased flow to the muscles would cause a drop in blood pressure (and therefore blood flow) in the body as a whole. However, cardiac output increases at the same time, maintaining blood pressure and supporting the necessary increase in blood flow.

Mastering Biology **Interview with Masashi Yanagisawa: Discovering the key inducer of vasoconstriction**

Blood Pressure and Gravity

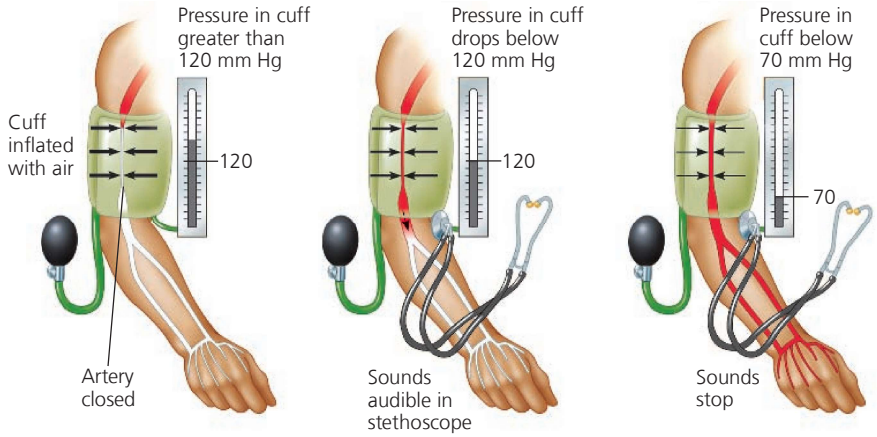
Blood pressure is generally measured for an artery in the arm at the same height as the heart **(Figure 42.11)**. For a healthy 20-year-old human at rest, arterial blood pressure in the systemic circuit is typically about 120 millimeters of mercury (mm Hg) at systole and 70 mm Hg at diastole, expressed as 120/70. (Arterial blood pressure in the pulmonary circuit is six to ten times lower.)

Gravity 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. This relationship of blood pressure and gravity is the key to understanding fainting. The fainting response is triggered when the nervous system detects that the blood pressure in your brain is below the level needed to provide adequate blood flow. 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.

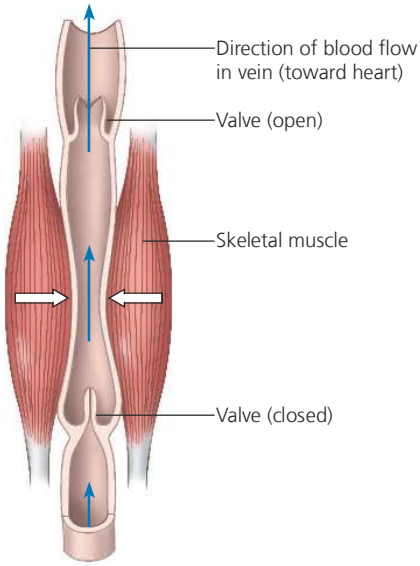
For animals with very long necks, the blood pressure required to overcome gravity is particularly high. A giraffe, for example, requires a systolic pressure of more than 250 mm Hg near the heart to get blood to its head. When a giraffe lowers its head to drink, one-way valves and sinuses, along with feedback mechanisms that reduce cardiac output, reduce blood pressure in the head, preventing brain damage. A dinosaur with a neck nearly 10 m long would have required even greater systolic pressure—nearly 760 mm Hg—to pump blood to its brain when its head was fully raised. However, calculations based on anatomy and inferred metabolic rate suggest that dinosaurs did not have a heart powerful enough to generate such high pressure. Based on this evidence as well as studies of neck bone structure, some biologists have concluded that the long-necked dinosaurs fed close to the ground rather than on high foliage.

Gravity is also a consideration for blood flow in veins, especially those in the legs. When you stand or sit, gravity draws blood downward to your feet and impedes its upward return to the heart. Because blood pressure in veins is relatively low, valves inside the veins have an important function in maintaining the unidirectional flow of blood within these vessels. The return of blood to the heart is further enhanced by rhythmic contractions of smooth muscles in the walls of

▼ Figure 42.11 Measurement of blood pressure. Blood pressure is recorded as two numbers separated by a slash. The first number is the systolic pressure; the second is the diastolic pressure.



1. A sphygmomanometer, an inflatable cuff attached to a pressure gauge, measures blood pressure in an artery. The cuff is inflated until the pressure closes the artery, so that no blood flows past the cuff. When this occurs, the pressure exerted by the cuff exceeds the pressure in the artery.
2. The cuff is allowed to deflate gradually. When the pressure exerted by the cuff falls just below that in the artery, blood pulses into the forearm, generating sounds that can be heard with the stethoscope. The pressure measured at this point is the systolic pressure (120 mm Hg in this example).
3. The cuff is allowed to deflate further, just until the blood flows freely through the artery and the sounds below the cuff disappear. The pressure at this point is the diastolic pressure (70 mm Hg in this example).



▶ Figure 42.12 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.

venules and veins and by the contraction of skeletal muscles during exercise **(Figure 42.12)**.

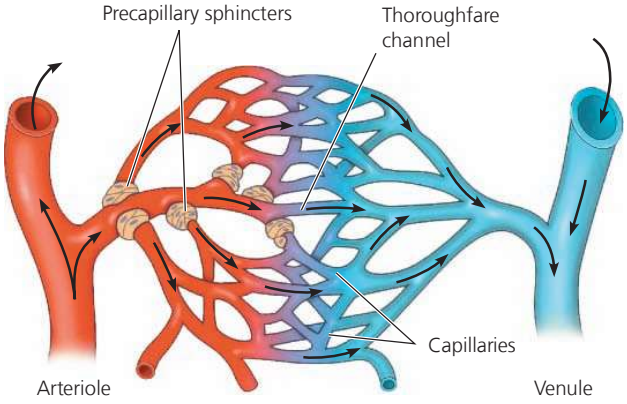
In rare instances, runners and other athletes can suffer heart failure if they stop vigorous exercise abruptly. When the leg muscles suddenly cease contracting and relaxing, less blood returns to the heart, which continues to beat rapidly. If the heart is weak or damaged, this inadequate blood flow may cause the heart to malfunction. To reduce the risk of stressing the heart excessively, athletes are encouraged to follow hard exercise with moderate activity, such as walking, to "cool down" until their heart rate approaches its resting level.

Capillary Function

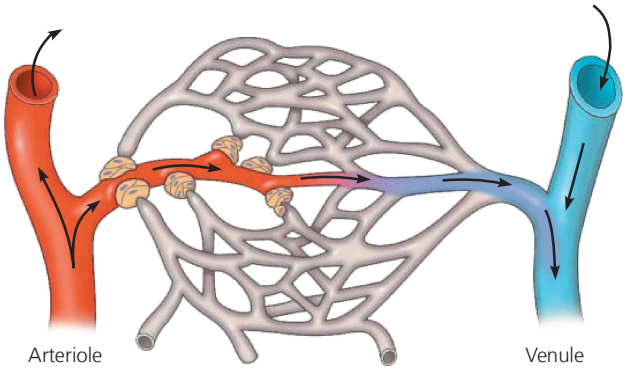
At any given time, blood is flowing through only 5–10% of the body's capillaries. However, each tissue has many capillaries, so every part of the body is supplied with blood at all times. Capillaries in the brain, heart, kidneys, and liver usually remain at capacity, but at many other sites the blood supply varies over time as blood is diverted from one destination to another. For example, blood supply to the digestive tract increases after a meal. In contrast, blood is diverted from the digestive tract and supplied more generously to skeletal muscles during strenuous exercise.

Given that capillaries lack smooth muscle, how is blood flow in capillary beds altered? One mechanism is constriction or dilation of the arterioles that supply capillary beds. A second mechanism involves precapillary sphincters, rings of smooth muscle located at the entrance to capillary beds **(Figure 42.13)**. The opening and closing of these muscular rings regulate the passage of blood into particular sets of capillaries. The signals regulating blood flow by these mechanisms include nerve impulses, hormones traveling throughout the bloodstream, and chemicals produced locally. For example, the chemical histamine released by cells at a wound

▼ Figure 42.13 Blood flow in capillary beds. Precapillary sphincters regulate the passage of blood into capillary beds. Some blood flows directly from arterioles to venules through capillaries called thoroughfare channels, which are always open.



(a) Sphincters relaxed



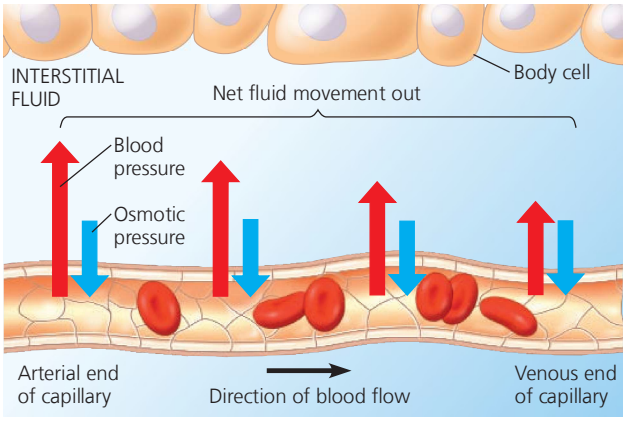
(b) Sphincters contracted

site causes vasodilation. The result is increased blood flow and increased access of disease-fighting white blood cells to invading microorganisms.

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. How does exchange occur? A few macromolecules 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 **(Figure 42.14)**. Many blood proteins (and all blood cells) are too large to pass readily through the

▼ Figure 42.14 Fluid exchange between capillaries and the interstitial fluid. This diagram shows a hypothetical capillary in which blood pressure exceeds osmotic pressure throughout the entire length of the capillary. In other capillaries, blood pressure may be lower than osmotic pressure along all or part of the capillary.



endothelium, so 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.

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 the proteins within it are recovered and returned to the blood via the **lymphatic system**.

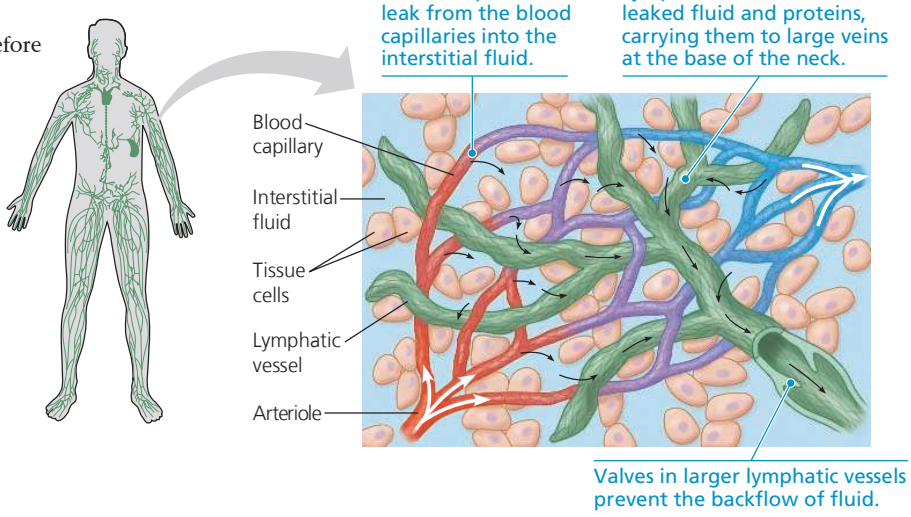
As shown in **Figure 42.15**, fluid diffuses into the lymphatic system via a network of tiny vessels intermingled with capillaries. The recovered fluid, called **lymph**, circulates within the lymphatic system before draining into a pair of large veins of the cardiovascular system at the base of the neck. This joining of the lymphatic and cardiovascular systems completes the recovery of fluid lost from capillaries as well as the transfer of lipids from the small intestine to the blood (see Figure 41.13).

The movement of lymph from peripheral tissues to the heart relies on many of 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.

Disruptions in the movement of lymph often result in fluid accumulation, or edema, in affected tissues. In some circumstances, the consequence is severe. For example, certain species of parasitic worms that lodge in lymph vessels and thereby block lymph movement cause elephantiasis, a condition marked by extreme swelling in limbs or other body parts.

Along a lymph vessel are small, lymph-filtering organs called **lymph nodes**, which play an important role in the body's defense. Inside each lymph node is a honeycomb of connective tissue with spaces filled by white blood cells, which function in defense. When the body is fighting an infection, the white blood cells multiply rapidly, and the lymph nodes become swollen and tender. This is why your doctor may check for swollen lymph nodes in your neck, armpits, or groin when you feel sick. Because lymph nodes may also trap circulating cancer cells, examining the lymph nodes of patients with cancer may reveal the spread of the disease.

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



▶ Figure 42.15 The close association of lymphatic vessels and blood capillaries. The lymphatic system, shown in green, extends throughout the body, terminating in narrow vessels intermingled with blood capillaries. The terminal lymphatic vessels have closed ends, but are permeable to interstitial liquid flowing in from surrounding tissue. Before reaching the heart, fluid in the lymphatic system undergoes filtering and monitoring by the immune system at small, bean-shaped structures called lymph nodes.

CONCEPT CHECK 42.3

1. What is the primary cause of the low velocity of blood flow in capillaries?
2. What short-term changes in an animal's cardiovascular function might facilitate using skeletal muscles to 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 42.4

Blood components function in exchange, transport, and defense

As you read in Concept 42.1, the fluid transported by an open circulatory system is continuous with the fluid that surrounds all of the body cells and thus has the same composition. In contrast, the fluid in a closed circulatory system can be much more 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 42.16)**. The remainder is plasma.

Plasma

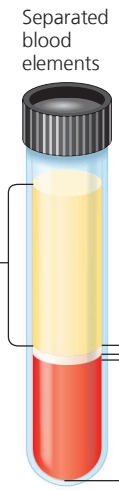
Dissolved in the plasma are ions and proteins that, together with the blood cells, function in osmotic regulation, transport, and defense. Inorganic salts in the form of dissolved ions are an essential component of the blood. Some buffer the blood, while others help maintain osmotic balance. In addition, 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. For plasma to serve all of these functions, plasma electrolytes must remain within narrow concentration ranges.

Like dissolved ions, plasma proteins such as albumins act as buffers against pH changes and help maintain the osmotic balance between blood and interstitial fluid. A number of plasma proteins have additional functions. Immunoglobulins, or antibodies, combat viruses and other foreign agents that invade the body (see Figure 43.10). Apolipoproteins escort lipids, which are insoluble in water and can travel in blood only when bound to proteins. Fibrinogens act as 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.)

▼ Figure 42.16 The composition of mammalian blood. Centrifuged blood separates into three layers: plasma, leukocytes and platelets, and erythrocytes.

Plasma 55%

Constituent	Major functions
Water	Solvent
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
Immunoglobulins (antibodies)	Defense and immunity
Apolipoproteins	Lipid transport
Fibrinogen	Blood clotting
Substances transported by blood Nutrients (such as glucose, fatty acids, vitamins), waste products of metabolism, respiratory gases (O_2 and CO_2), and 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

Plasma also contains many other substances in transit, including nutrients, metabolic wastes, respiratory gases, and hormones. Plasma has a much higher protein concentration than interstitial fluid, although the two fluids are otherwise similar. (Capillary walls, remember, are not very permeable to proteins.)

Cellular Elements

Blood contains two classes of cells: red blood cells, which transport O_2, and white blood cells, which function in defense (see Figure 42.16). Also suspended in blood plasma are **platelets**, cell fragments that are involved in the clotting process.

Erythrocytes Red blood cells, or **erythrocytes**, are by far the most numerous blood cells. 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 5.18). Erythrocytes also lack mitochondria and generate their ATP exclusively by anaerobic metabolism. Oxygen transport would be less efficient if erythrocytes were aerobic and consumed some of the O_2 they carry.

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 1 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 5.19).

Sickle-cell disease significantly impairs the function of the circulatory system. Sickled cells often lodge in arterioles and capillaries, preventing delivery of O_2 and nutrients and removal of CO_2 and wastes. Blood vessel blockage and resulting organ swelling can result in severe pain. In addition, sickled cells frequently rupture, reducing the number of red blood cells available for transporting O_2. The average life span of a sickled erythrocyte is only 20 days—one-sixth that of a normal erythrocyte. The rate of erythrocyte loss outstrips their production rate. Short-term therapy includes replacement of erythrocytes by blood transfusion; long-term treatments are generally aimed at inhibiting aggregation of Hb^S.

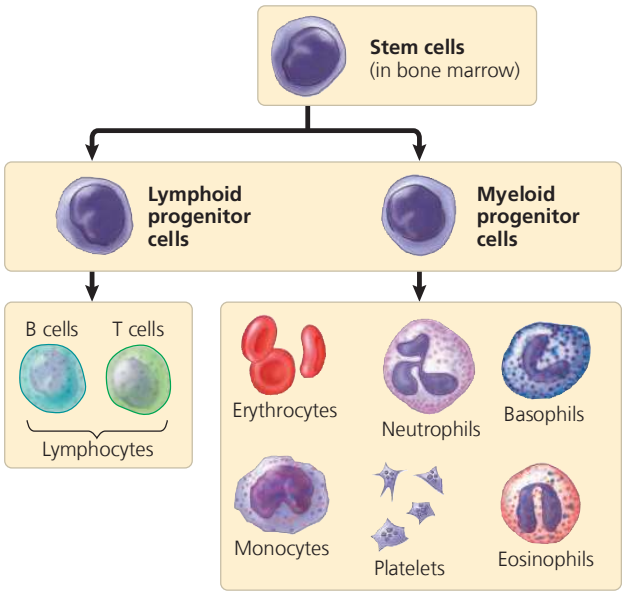
Leukocytes The blood contains five major types of white blood cells, or **leukocytes**. Their function is to fight infections. Some are phagocytic, engulfing and digesting microorganisms and debris from the body's own dead cells. Other leukocytes, called lymphocytes, mount immune responses against foreign substances (as we'll discuss in Concepts 43.2 and 43.3). 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 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.

Stem Cells and the Replacement of Cellular Elements

Erythrocytes, leukocytes, and platelets all develop from stem cells that are dedicated to replenishing the body's blood cell populations. As described in Concept 20.3, a **stem cell** can reproduce indefinitely, dividing mitotically to produce one daughter cell that remains a stem cell and another that adopts a specialized function. The stem cells that produce the cellular elements of blood cells are located in the red marrow inside bones, particularly the ribs, vertebrae, sternum, and pelvis. As they divide and self-renew, these stem cells give rise to two sets of progenitor cells with a more limited capacity for self-renewal **(Figure 42.17)**. One set, the lymphoid

▼ Figure 42.17 Differentiation of blood cells. Cell divisions of stem cells in bone marrow give rise to two specialized sets of cells. One set—the lymphoid progenitor cells—gives rise to immune cells called lymphocytes, primarily B and T cells. The second set—myeloid progenitor cells—gives rise to other immune cells, red blood cells (erythrocytes), and cell fragments called platelets.



progenitors, produces lymphocytes. The other set, the myeloid progenitors, produces all other white blood cells, red blood cells, and platelets.

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 feedback mechanism sensitive to O_2 level controls erythrocyte production. If the O_2 level falls, the kidneys synthesize and secrete a hormone called **erythropoietin (EPO)** that stimulates the generation of more erythrocytes.

Today, EPO produced by recombinant DNA technology is used to treat disorders such as *anemia*, a condition of lower-than-normal erythrocyte or hemoglobin level that decreases the oxygen-carrying capacity of the blood. Some athletes inject themselves with EPO to increase their erythrocyte level. Because this practice is banned by most major sports organizations, runners, cyclists, and other athletes caught using EPO-related drugs have forfeited their records and been banned from future competitions.

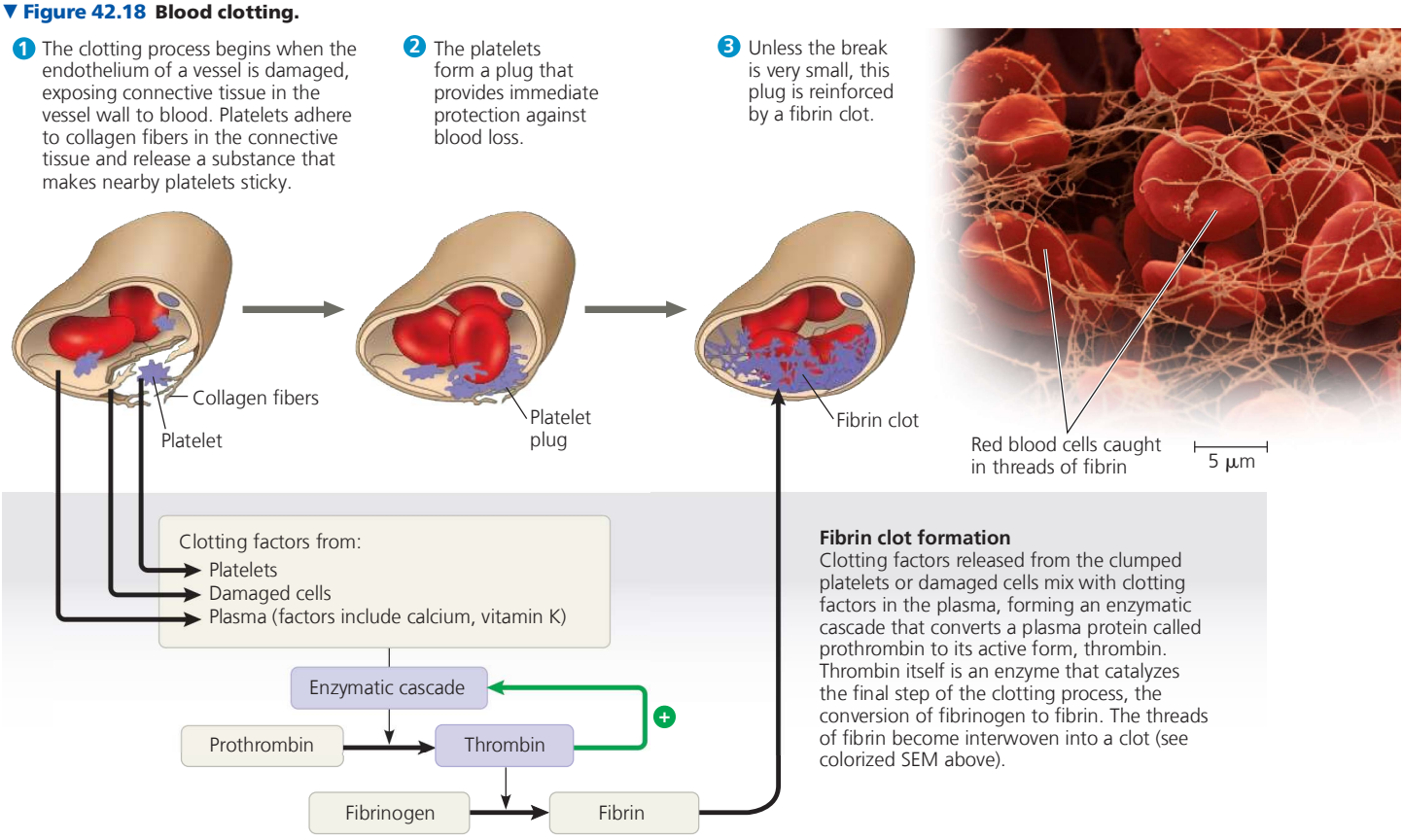
Blood Clotting

When blood vessels are broken by an injury such as a small cut or scrape, a chain of events ensues that quickly seals the break, halting blood loss and exposure to infection. The key mechanical event in this response is coagulation, the conversion of the liquid components of blood into a solid—a blood clot.

In the absence of injury, the coagulant, or sealant, circulates in an inactive form called fibrinogen. Blood clotting begins when injury exposes the proteins in a broken blood vessel wall to blood constituents. The exposed proteins attract platelets, which gather at the site of injury and release clotting factors. These clotting factors trigger a cascade of reactions leading to the formation of an active enzyme, *thrombin*, from an inactive form, prothrombin **(Figure 42.18)**. Thrombin in turn converts fibrinogen to fibrin, which aggregates into threads that form the framework of the clot. Any mutation that blocks a step in the clotting process can cause hemophilia, a life-threatening disease characterized by excessive bleeding and bruising from even minor cuts and bumps (see Concept 15.2).

As shown in Figure 42.18, clotting involves a positive feedback loop. Initially, the clotting reactions convert only some of the prothrombin at the clot site to thrombin. However, thrombin itself stimulates the enzymatic cascade, leading to more conversion of prothrombin to thrombin and thus driving clotting to completion.

▼ Figure 42.18 Blood clotting.



Fibrin clot formation
Clotting factors released from the clumped platelets or damaged cells mix with clotting factors in the plasma, forming an enzymatic cascade that converts a plasma protein called prothrombin to its active form, thrombin. Thrombin itself is an enzyme that catalyzes the final step of the clotting process, the conversion of fibrinogen to fibrin. The threads of fibrin become interwoven into a clot (see colorized SEM above).

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** (plural, *thrombi*). We'll explore shortly how thrombi form and the dangers they pose.

Cardiovascular Disease

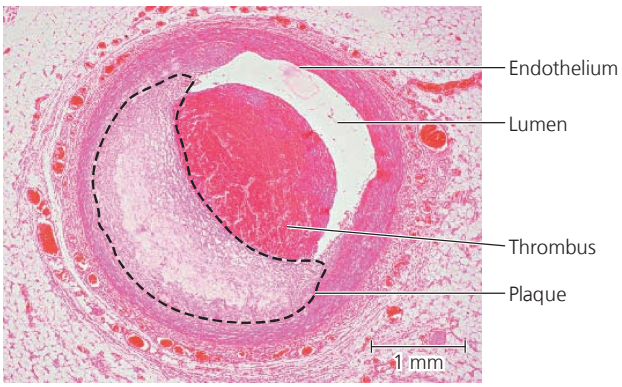
Each year, cardiovascular diseases—disorders of the heart and blood vessels—kill more than 750,000 people in the United States. These diseases range from minor disturbances of vein or heart valve function to life-threatening disruptions of blood flow to the heart or brain.

Atherosclerosis, Heart Attacks, and Stroke

Healthy arteries have a smooth inner lining that reduces resistance to blood flow. However, damage or infection can roughen the lining and lead to **atherosclerosis**, the hardening of the arteries by accumulation of fatty deposits. A key player in the development of atherosclerosis is cholesterol, a steroid that is important for maintaining normal membrane fluidity in animal cells (see Figure 7.5).

In atherosclerosis, damage to the arterial lining results in *inflammation*, the body's reaction to injury. Leukocytes are attracted to the inflamed area and begin to take up lipids, including cholesterol. 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. If the plaque ruptures, a thrombus can form in the artery **(Figure 42.19)**, potentially triggering a heart attack or a stroke.

▼ Figure 42.19 Atherosclerosis. In atherosclerosis, thickening of an arterial wall by plaque formation can restrict blood flow through the artery. If a plaque ruptures, a thrombus can form, further restricting blood flow. Fragments of a ruptured plaque can also 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 **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 oxygen-rich blood to the heart muscle. The coronary arteries are small in diameter and therefore especially vulnerable to obstruction by atherosclerotic plaques or thrombi. Such blockage can destroy cardiac muscle quickly because the constantly beating heart muscle requires a steady supply of O_2. If a large enough portion of the heart is affected, the heart will stop beating. Such cardiac arrest causes death if a heartbeat is not restored within minutes by cardiopulmonary resuscitation (CPR) or some other emergency procedure.

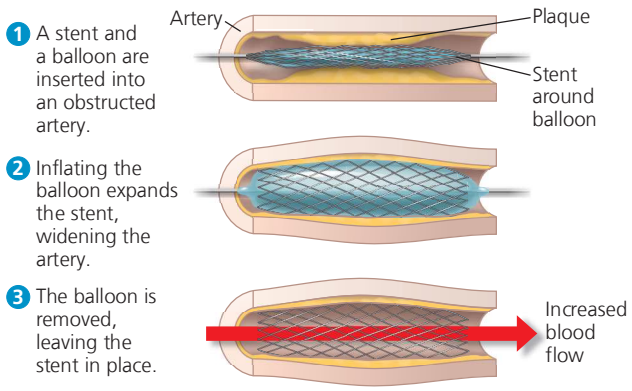
A **stroke** is the death of nervous tissue in the brain due to a lack of O_2. Strokes usually result from rupture or blockage of arteries in the neck or head. The effects of a stroke and the individual's chance of survival depend on the extent and location of the damaged brain tissue. If a stroke results from arterial blockage by a thrombus, 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. The pain is most likely to be felt when the heart is laboring under stress, and it signals that part of the heart is not receiving enough O_2. An obstructed artery may be treated surgically, either by inserting a mesh tube called a stent to expand the artery **(Figure 42.20)** or by transplanting a healthy blood vessel from the chest or a limb to bypass the blockage.

Risk Factors and Treatment of Cardiovascular Disease

Cholesterol travels in blood plasma mainly 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

▼ Figure 42.20 Inserting a stent to widen an obstructed artery.



for return to the liver. Individuals with a high ratio of LDL to HDL are at substantially increased risk for atherosclerosis.

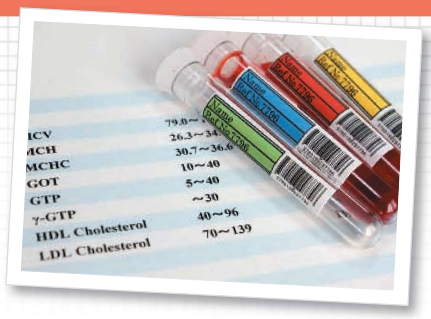
Although the tendency to develop particular cardiovascular diseases is inherited, it is also strongly influenced by lifestyle. For example, exercise decreases the LDL/HDL ratio, reducing the risk of cardiovascular disease. In contrast, consumption of certain processed vegetable oils called *trans fats*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

Mastering Biology **BBC Video: The Impact of Smoking**

Scientific Skills Exercise

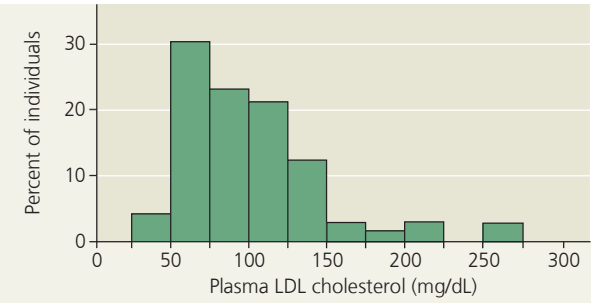
Making and Interpreting Histograms

Does Inactivating the PCSK9 Enzyme Lower LDL Levels? Researchers interested in genetic factors affecting susceptibility to cardiovascular disease examined the DNA of 15,000 individuals. They found that 3% of the individuals had a mutation that inactivates one copy of the gene for PCSK9, a liver enzyme. Because mutations that *increase* the activity of PCSK9 are known to *increase* the level of LDL cholesterol in the blood, the researchers hypothesized that *inactivating* mutations in this gene would *lower* the LDL level. In this exercise, you will interpret the results of an experiment they carried out to test this hypothesis.

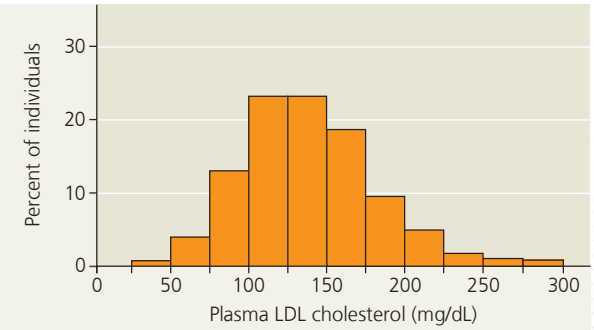


How the Experiment Was Done Researchers measured the LDL cholesterol level in blood plasma from 85 individuals with one copy of the *PCSK9* gene inactivated (the study group) and from 3,278 individuals with two functional copies of the gene (the control group).

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 a 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 and control groups that had an LDL level of 100 mg/dL or less. (For additional information about histograms, see the Scientific Skills Review in Appendix D.)
2. Compare the two histograms. Do you find support for the researchers' hypothesis? Explain.
3. What if instead of graphing the data, the researchers had compared the range of concentrations for plasma LDL cholesterol (low to high) in the control and study groups? How would their conclusions have differed?
4. What does the fact that the two histograms overlap as much as they do indicate about the extent to which PCSK9 determines plasma LDL cholesterol level?
5. Comparing these two histograms allowed researchers to draw a conclusion regarding the effect of *PCSK9* mutations on LDL cholesterol levels in blood. Consider two individuals with a plasma LDL level cholesterol of 160 mg/dL, one from the study group and one from the control group. **(a)** What do you predict regarding their relative risk of developing cardiovascular disease? **(b)** Explain how you arrived at your prediction. What role did the histograms play in making your prediction?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

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).

The recognition that inflammation plays a central role in atherosclerosis and thrombus formation is also influencing 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.

Hypertension (high blood pressure) is yet another contributor to heart attack and stroke. 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 can often be prevented and controlled by quitting any use of tobacco products, changing the diet, increasing exercise, taking medication, or a combination of these approaches.

CONCEPT CHECK 42.4

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, nitroglycerin is converted to nitric oxide (see Concept 42.3). Why would you expect nitroglycerin to relieve chest pain caused by narrowing of the cardiac arteries?
4. **MAKE CONNECTIONS** How do stem cells from the bone marrow of an adult differ from embryonic stem cells (see Concept 20.3)?

For suggested answers, see Appendix A.

CONCEPT 42.5

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 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.

Partial Pressure Gradients in Gas Exchange

To understand the driving forces for gas exchange, we must consider **partial pressure**, which is simply the pressure exerted by a particular gas in a mixture of gases. Determining partial pressures enables us to predict the net movement of a gas at an exchange surface: A gas always undergoes net diffusion from a region of higher partial pressure to a region of lower partial pressure.

To calculate partial pressures, we need to know the pressure that a gas 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, 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 state is reached such that 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 **(Table 42.1)**. Furthermore, the warmer and saltier the water is, the less dissolved O_2 it can hold.

Table 42.1 Comparing Air and Water as Respiratory Media

	Air (Sea Level)	Water (20°C)	Air-to-Water Ratio
O_2 partial pressure	160 mm	160 mm	1:1
O_2 concentration	210 ml/L	7 ml/L	30:1
Density	0.0013 kg/L	1 kg/L	1:770
Viscosity	0.02 cP	1 cP	1:50

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. As shown in Table 42.1, air is much less dense and less viscous than water, so it is easier to move and to force through small passageways. As a result, breathing air is relatively easy and the exchange does not need to not be particularly efficient. Humans, for example, extract only about 25% of the O_2 in inhaled air.

Water is a much more demanding gas exchange medium than air. 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 about 7 mL of dissolved O_2 per liter, a concentration roughly 30 times less than in air. 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.

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 net 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.

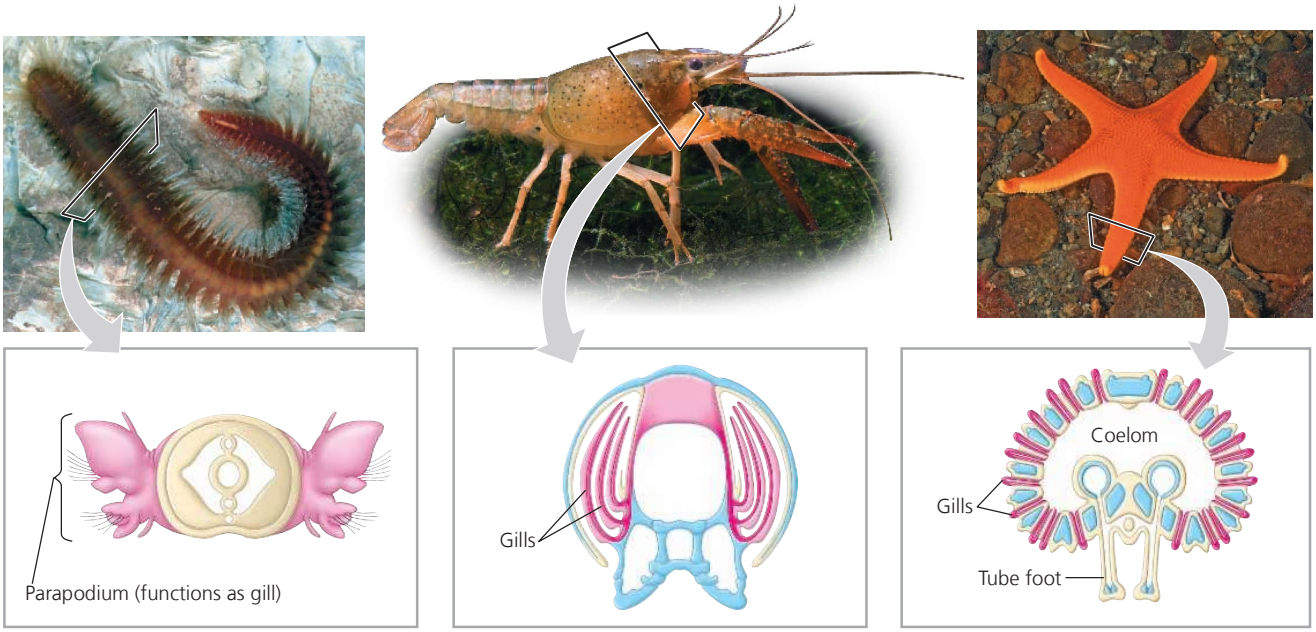
In some relatively simple animals, such as sponges, cnidarians, and flatworms, every cell in the body is close enough to the external environment that gases can diffuse quickly between any cell and the environment. In many animals, however, the bulk of the body's cells lack immediate access to the environment.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

For earthworms, as well as some amphibians and other animals, the skin serves as a respiratory organ. A dense network of capillaries just below the skin 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. As illustrated in **Figure 42.21** (and in Figure 42.1), the distribution of gills over the body can vary considerably.

▼ Figure 42.21 Diversity in the structure of gills, external body surfaces that function in gas exchange.



(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) Crayfish. Crayfish and other crustaceans have long, feathery gills covered by the exoskeleton. Specialized body appendages drive water over the gill surfaces.

(c) 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 tube feet surfaces also function in gas exchange.

Regardless of their distribution, gills often have a total surface area much greater than that of the rest of the body's exterior.

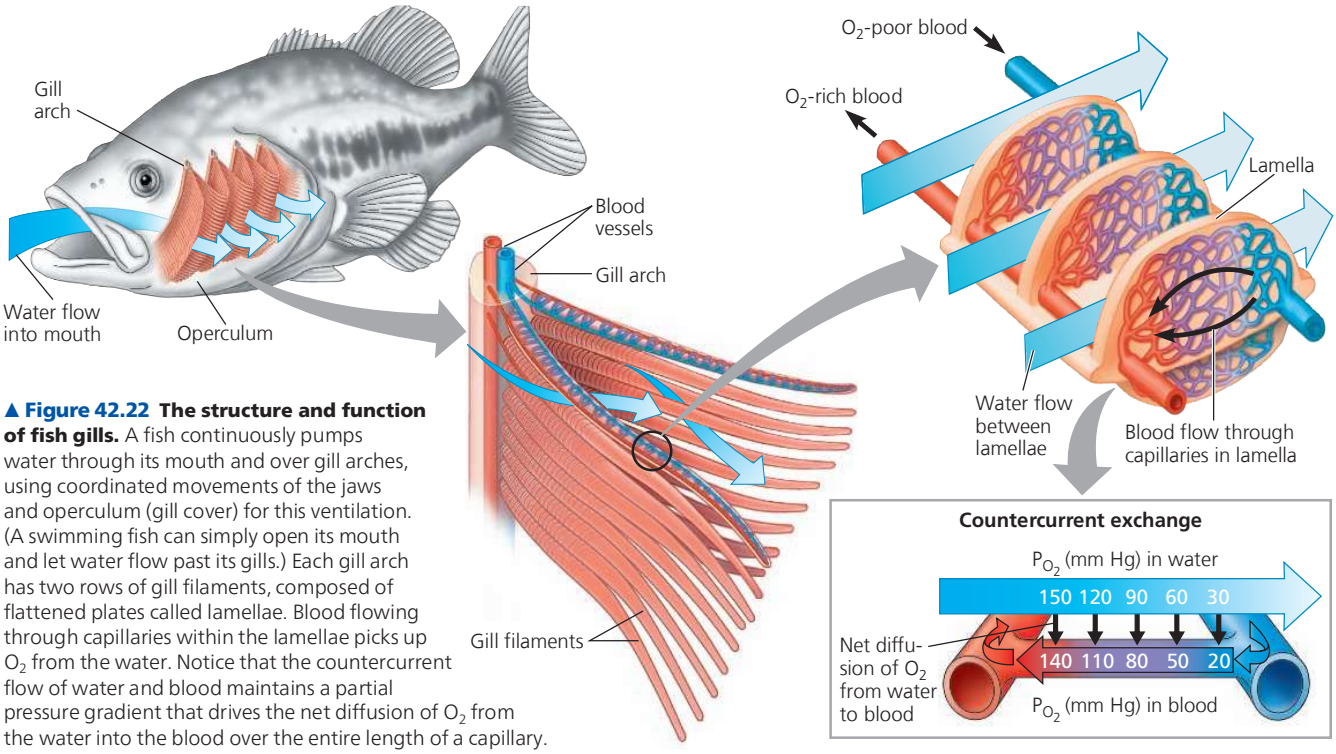
Movement of the respiratory medium over the respiratory surface, a process called **ventilation**, maintains the partial pressure gradients of O_2 and CO_2 across the gill that are necessary for gas exchange. To promote ventilation, most gill-bearing animals either move their gills through the water 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 significant side benefit of getting about by jet propulsion. Fishes use the motion of swimming or coordinated movements of the mouth and gill covers to ventilate their gills. In both cases, a current of water enters the mouth of the fish, passes through slits in the pharynx, flows over the gills, and then exits the body **(Figure 42.22)**.

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. In a fish gill, the two fluids are blood and water. Because blood flows in the direction opposite to that of water passing over the gills, at each point in its travel blood is less saturated with O_2 than the water it meets (see Figure 42.22). 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. The result is a partial pressure gradient that favors the diffusion of O_2 from water to blood along the entire length of the capillary.

Countercurrent exchange mechanisms are remarkably efficient. In the fish gill, more than 80% of the O_2 dissolved in the water is removed as the water passes over the respiratory surface. In other settings, countercurrent mechanisms contribute to temperature regulation and to the functioning of the mammalian kidney (see Concepts 40.3 and 44.4).

Tracheal Systems in Insects

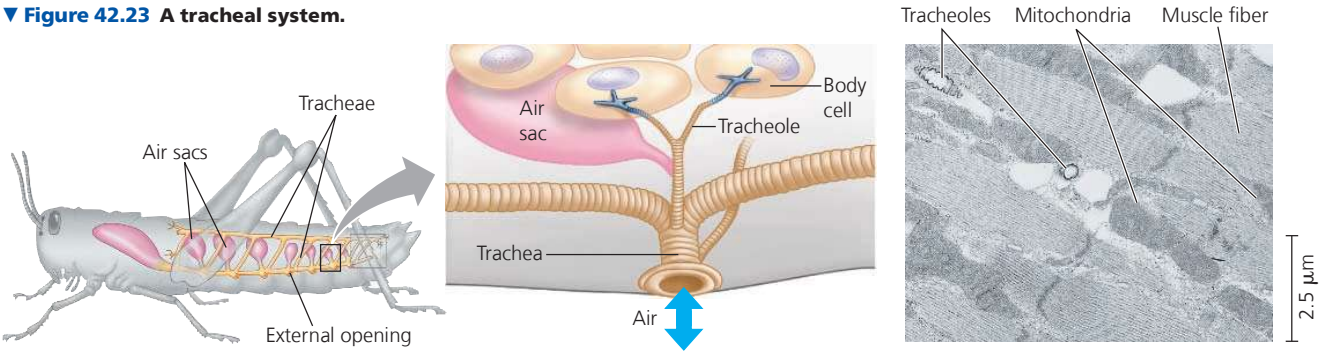
In most terrestrial animals, respiratory surfaces are enclosed within the body, exposed to the atmosphere only through narrow tubes. Although the most familiar example of such an arrangement is the lung, the most common is the insect **tracheal system**, a network of air tubes that branch throughout the body. The largest tubes, called tracheae,



▲ Figure 42.22 The structure and function of fish gills. A fish continuously pumps water through its mouth and over 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 that drives the net diffusion of O_2 from the water into the blood over the entire length of a capillary.

Mastering Biology Figure Walkthrough • Animation: Gas Exchange in Fish Gills

▼ Figure 42.23 A tracheal system.



(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) This micrograph above (TEM) 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.

open to the outside **(Figure 42.23)**. At the tips of the finest branches, a moist epithelial lining enables gas exchange by diffusion. Because the tracheal system brings air within a very short distance of virtually every body cell in an insect, the efficient exchange of O_2 and CO_2 does not require the participation of the animal's open circulatory system.

Tracheal systems often exhibit adaptations directly related to bioenergetics. Consider, for example, a flying insect, which consumes 10 to 200 times more O_2 when in flight than it does at rest. In many flying insects, cycles of flight muscle contraction and relaxation pump air rapidly through the tracheal system. This pumping improves ventilation, bringing ample O_2 to the densely packed mitochondria that support the high metabolic rate of flight muscle (see Figure 42.23).

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 both in organisms with open circulatory systems, such as spiders and land snails, and in vertebrates.

Among vertebrates that lack gills, the use of lungs for gas exchange varies. Amphibians rely heavily on diffusion across external 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. Turtles are an exception; they supplement lung breathing with gas exchange across moist epithelial surfaces continuous with their mouth or anus. Lungs and air breathing also 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 level of a pond recedes).

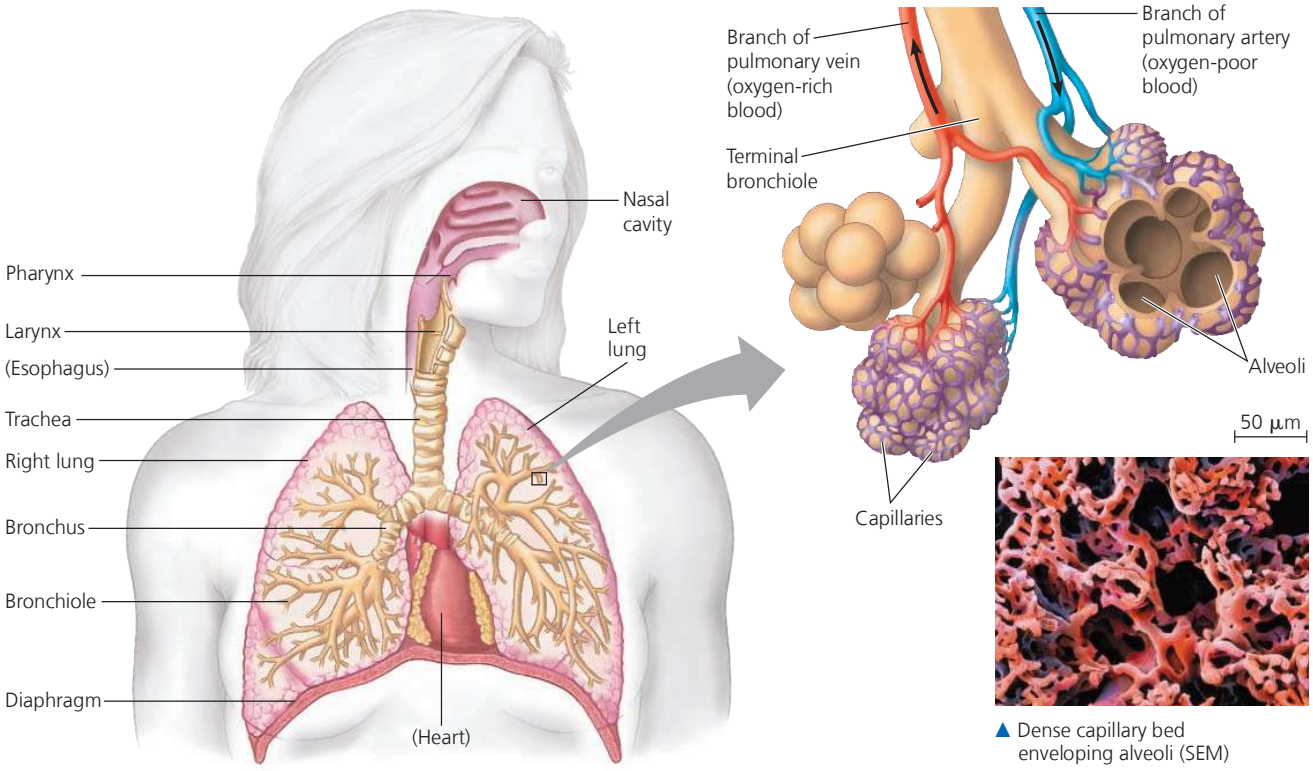
Mammalian Respiratory Systems: A Closer Look

In mammals, branching ducts convey air to the lungs, which are located in the *thoracic cavity*, enclosed by the ribs and diaphragm. 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 **(Figure 42.24)**. When food is swallowed, the **larynx** (the upper part of the respiratory tract) moves upward and tips the epiglottis over the glottis, which is the opening of the **trachea**, or windpipe. This allows food to go down the esophagus to the stomach (see Figure 41.9). The rest of the time, the glottis is open, enabling breathing.

From the larynx, air passes into the trachea. The cartilage that reinforces the walls of both the larynx and the trachea keeps this part of the airway open. Within the larynx of most mammals, the 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 that they vibrate. High-pitched sounds result from tightly stretched cords vibrating rapidly; low-pitched sounds come from looser cords vibrating slowly.

The trachea branches into two **bronchi** (singular, *bronchus*), one leading to each lung. Within the lung, the

▼ Figure 42.24 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.



▲ Dense capillary bed enveloping alveoli (SEM)

Mastering Biology **Animation: The Human Respiratory System**

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 42.24), 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 diffuses 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 smoking or vaping enter the alveoli and 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 Concept 3.2). Given their tiny diameter (about 0.25 mm), alveoli would be expected to collapse under high surface tension. It turns out, however, that these air sacs produce a mixture of phospholipids and proteins called **surfactant**, for *surf*ace-*act*ive agent, which coats the alveoli and reduces surface tension.

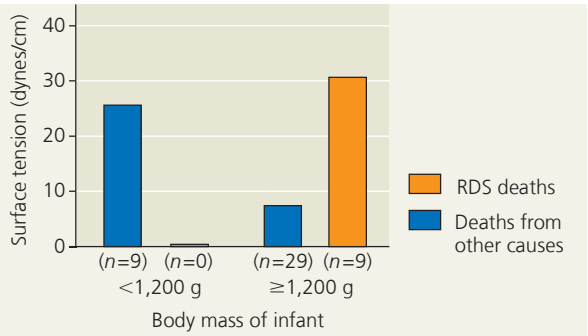
In the 1950s, Mary Ellen Avery did the first experiment linking surfactant deficiency to *respiratory distress syndrome* (RDS), a life-threatening disease of newborns that at the

▼ Figure 42.25 Inquiry

What causes respiratory distress syndrome?

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

Results Avery noted a pattern when she separated out samples from infants with body mass less than 1,200 g, the average mass of a fetus at 29–30 weeks of pregnancy.



Data from 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).

Conclusion For infants with a body mass of 1,200 g or greater, samples from those who had died of RDS exhibited much higher surface tension than samples from those who had died from other causes. Avery inferred that infants' lungs normally contain a surface-tension-reducing substance (now called surfactant) and that RDS occurs when this substance is lacking. The results from infants with a body mass less than 1,200 g were similar to those from infants who had died from RDS, suggesting that surfactant is not normally produced until a fetus reaches this size.

WHAT IF? *If the researchers had measured the amount of surfactant in lung samples from the infants, what relationship would you expect between the amount of surfactant and infant body mass?*

time killed 10,000 infants annually in the United States **(Figure 42.25)**. RDS is most common among infants born before 32 weeks of pregnancy. (The average full-term human pregnancy is 38 weeks.) Later studies revealed that surfactant typically appears in the lungs after 33 weeks of gestation. Artificial surfactants are now used to treat early preterm infants, and treated babies with a body mass over 900 g (2 pounds) at birth usually survive without long-term health problems. For her contributions, Avery received the National Medal of Science.

Having surveyed the route that air follows when we breathe, we'll turn next to the process of breathing itself.

CONCEPT CHECK 42.5

1. Why is an internal location for gas exchange tissues advantageous 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 similarities in the countercurrent exchange that facilitates respiration in fish and thermoregulation in geese (see Concept 40.3).

For suggested answers, see Appendix A.

CONCEPT 42.6

Breathing ventilates the lungs

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 breathing in amphibians, birds, and mammals.

How an Amphibian Breathes

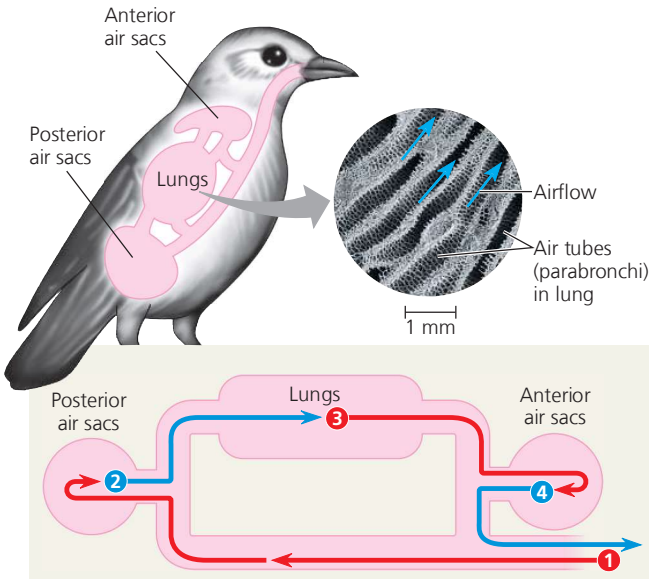
An amphibian such as a frog ventilates its lungs by **positive pressure breathing**, inflating the lungs with forced airflow. Inhalation begins when muscles lower the floor of an amphibian's oral cavity, drawing in air through its nostrils. Next, with the nostrils and mouth closed, the floor of the oral cavity rises, forcing air down the trachea. Exhalation follows as air is expelled by the elastic recoil of the lungs and by compression of the muscular body wall. When male frogs puff themselves up in aggressive or courtship displays, they disrupt this breathing cycle, taking in air several times without allowing any release.

How a Bird Breathes

When a bird breathes, it passes air over the gas exchange surface in only one direction. Air sacs situated on either side of the lungs act as bellows that direct air flow through the lungs. Within the lungs, tiny channels called *parabronchi* serve as the sites of gas exchange. Passage of air through the entire system—air sacs and lungs—requires two cycles of inhalation and exhalation **(Figure 42.26)**.

Ventilation in birds is highly efficient. One reason is that birds pass air over the gas exchange surface in only one direction during breathing. In addition, incoming fresh air does not mix with air that has already carried out gas exchange, maximizing the partial pressure difference with blood flowing through the lungs.

▼ Figure 42.26 The avian respiratory system. This diagram traces a breath of air through the respiratory system of a bird.



Two cycles of inhalation and exhalation are required to pass one breath through the system:

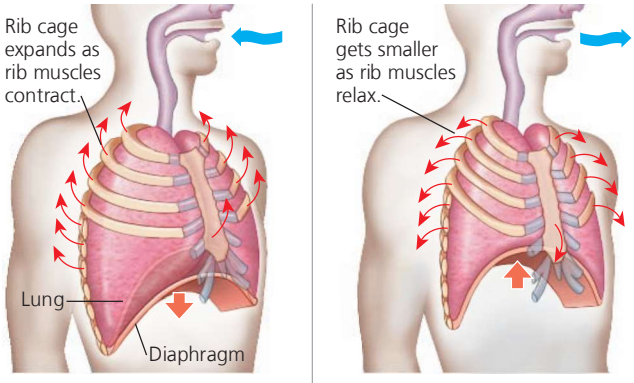
1. First inhalation: Air fills the posterior air sacs.
2. First exhalation: Posterior air sacs contract, pushing air into lungs.
3. Second inhalation: Air passes through lungs and fills anterior air sacs.
4. Second exhalation: As anterior air sacs contract, air that entered body at first inhalation is pushed out of body.

How a Mammal Breathes

To understand how a mammal breathes, think about filling a syringe. By pulling back on the plunger, you lower the pressure in the syringe, drawing gas or fluid through the needle into the syringe chamber. Similarly, mammals employ **negative pressure breathing**—pulling, rather than pushing, air into their lungs **(Figure 42.27)**. Using muscle contraction to actively expand the thoracic cavity, mammals lower air pressure in their lungs below that of the air outside their body. Because gas flows from a region of higher pressure to a region of lower pressure, the lowered air pressure in the lungs causes air to rush through the nostrils and mouth and down the breathing tubes to the alveoli.

Expanding the thoracic cavity during inhalation involves the animal's rib muscles and the **diaphragm**, a sheet of skeletal muscle that forms the bottom wall of the cavity. Contracting the rib muscles pulls the ribs upward and the sternum outward, expanding the rib cage, the front wall of the thoracic cavity. At the same time, the diaphragm contracts, expanding the thoracic cavity downward. It is this descending movement of the diaphragm that is analogous to a plunger being drawn out of a syringe.

▼ Figure 42.27 Negative pressure breathing. A mammal breathes by changing the air pressure within its lungs relative to the pressure of the outside atmosphere.



1. INHALATION: Diaphragm contracts (moves down).
2. EXHALATION: Diaphragm relaxes (moves up).

WHAT IF? *The walls of alveoli contain elastic fibers that allow the alveoli to expand and contract with each breath. If the alveoli lost their elasticity, how would that affect gas exchange in the lungs?*

Mastering Biology BioFlix® Animation: Mechanics of Breathing

Whereas inhalation is always active and requires work, exhalation is usually passive. During exhalation, the muscles controlling the thoracic cavity relax, and the volume of the cavity is reduced. The increased air pressure in the alveoli forces air up the breathing tubes and out of the body.

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 rib muscles and diaphragm are sufficient to change lung volume when a mammal is at rest. During exercise, other muscles of the neck, back, and chest increase the volume of the thoracic cavity by raising the rib cage. In kangaroos and some other mammals, locomotion causes a rhythmic movement of organs in the abdomen, including the stomach and liver. The result is a piston-like pumping motion that pushes and pulls on the diaphragm, further increasing the volume of air moved in and out of the lungs.

The volume of air inhaled and exhaled with each breath, called **tidal volume**, averages about 500 mL in resting humans. The tidal volume during maximal inhalation and exhalation is the **vital capacity**, 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**.

With age, the 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. The maximum P_{O_2} in lungs is also less for mammals than for birds, which have a unidirectional flow of air through the lungs. This is one reason why mammals function less well than birds at high altitude. For example, humans have great difficulty obtaining enough O_2 when climbing at high elevations, such as those 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 42.28)**. Neural circuits in the medulla form a pair of *breathing control centers* that establish the breathing rhythm.

In regulating breathing, the medulla uses the pH of the fluid in which it is bathed as an indicator of blood CO_2 concentration. The pH can be used in this way because 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 H_2CO_3 can then dissociate into a bicarbonate ion (HCO_3^-) and a hydrogen ion (H^+):

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

Consider what happens when metabolic activity increases, for example, during exercise. Increased metabolism raises the concentration of CO_2 in the blood and cerebrospinal fluid. Through the reactions shown above, the higher CO_2 concentration leads to an increase in the concentration of H^+, lowering pH. 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 42.28). 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. The regulation of breathing is modulated by additional neural circuits, primarily in the pons, a part of the brain next to the medulla.

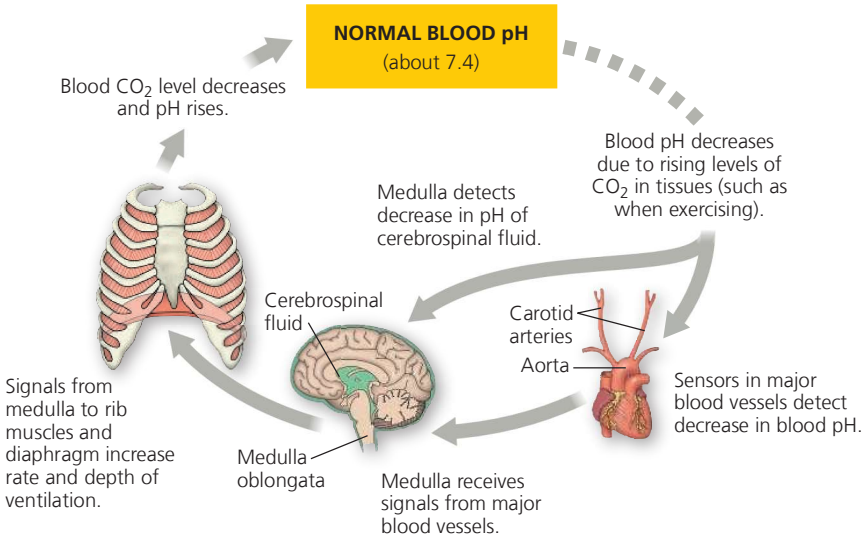
Breathing control is effective only if ventilation is matched to blood flow through alveolar capillaries. During exercise, for instance, such coordination couples an increased breathing rate, which enhances O_2 uptake and CO_2 removal, with an increase in cardiac output. When you breathe deeply, a negative-feedback 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.

CONCEPT CHECK 42.6

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.

▼ Figure 42.28 Homeostatic control of breathing.



VISUAL SKILLS *Suppose a person began breathing very rapidly while resting. Tracing a path along this negative-feedback control circuit, describe the effect on the CO_2 level in the blood and the steps by which homeostasis would be restored.*

CONCEPT 42.7

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. Here we'll examine how blood molecules called respiratory pigments facilitate this exchange through their interaction with O_2 and CO_2. We'll also investigate physiological adaptations that enable animals to be active under conditions of high metabolic load or very limiting P_{O_2}. As a basis for exploring these topics, let's summarize the basic gas exchange circuit in humans.

Coordination of Circulation and Gas Exchange

To appreciate how the gas exchange and circulatory systems function together, let's track the variation in partial pressure for O_2 and CO_2 across these systems **(Figure 42.29)**. 1 During inhalation, fresh air mixes with air remaining in the lungs. 2 The resulting mixture formed in the alveoli has a higher P_{O_2} than the blood flowing through the alveolar capillaries. Consequently, there is a net diffusion of O_2 down its partial pressure gradient from the air in the alveoli to the blood.

Meanwhile, the presence of a P_{CO_2} in the alveoli that is higher in the capillaries than in the air drives the net diffusion of CO_2 from blood to air. 3 By the time the blood leaves the lungs in the pulmonary veins, its P_{O_2} and P_{CO_2} match the values for the air in alveoli. After returning to the heart, this blood is pumped through the systemic circuit.

4 In the systemic 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. 5 Having unloaded O_2 and loaded CO_2, the blood is returned to the heart and pumped to the lungs again. 6 There, exchange occurs across the alveolar capillaries, resulting in exhaled air enriched in CO_2 and partially depleted of O_2.

Respiratory Pigments

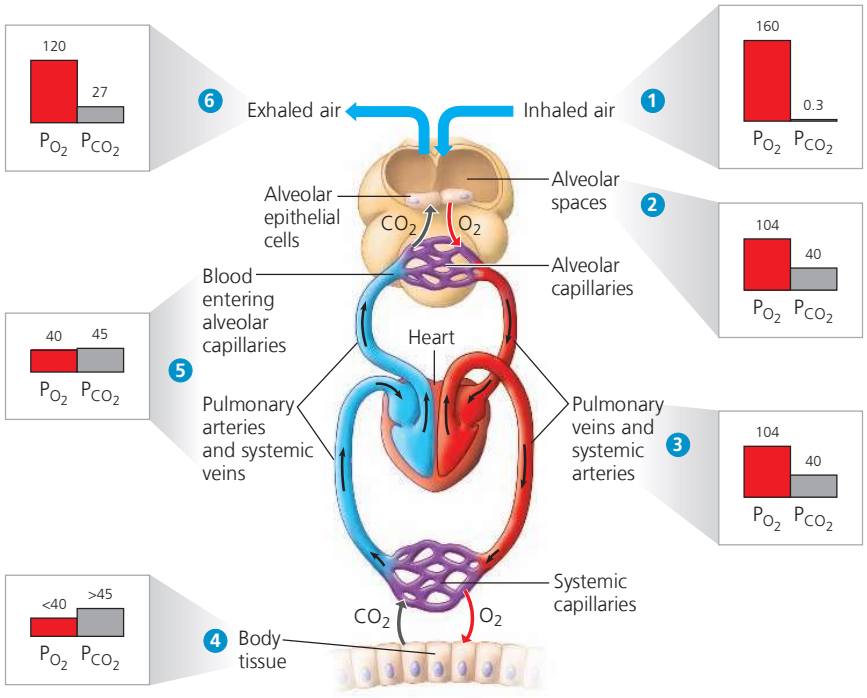
The low solubility of O_2 in water (and thus in blood) poses a problem for animals that rely on the circulatory system to deliver O_2. For example, a person requires almost 2 L of O_2 per minute during intense exercise, and all of it must be carried in the blood from the lungs to the active tissues. At normal body temperature and air pressure, however, only 4.5 mL of O_2 can dissolve into a liter of blood in the lungs. Even if 80% of the dissolved O_2 were delivered to the tissues, 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 (from 4.5 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 in animals. 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 invertebrate species and almost all species

▼ **Figure 42.29 Loading and unloading of respiratory gases.** The partial pressures of O_2 and CO_2 are given in mm Hg.

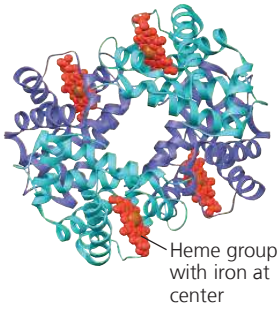


WHAT IF? *If you consciously forced more air out of your lungs each time you exhaled, how would that affect the values shown in the figure?*

Mastering Biology BioFlix® Animation: Gas Exchange in the Human Body

of vertebrates is hemoglobin (see Concept 42.4). In vertebrates, it is contained in erythrocytes and has four subunits. Each consists of a polypeptide and a heme group, a cofactor that has an iron atom at its center **(Figure 42.30)**. Each iron atom binds one molecule of O_2, so a hemoglobin molecule can carry four O_2 molecules. Like all respiratory pigments, hemoglobin binds O_2 reversibly, loading O_2 in the lungs or gills and unloading it elsewhere in the body. This process is enhanced by cooperativity between the hemoglobin subunits (see Concept 8.5). When O_2 binds to one subunit, the others change shape slightly, increasing affinity for O_2. 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 change in shape lowers their affinity for O_2.

▼ Figure 42.30 Ribbon model of hemoglobin.



Cooperativity in O_2 binding and release is evident in the dissociation curve for hemoglobin **(Figure 42.31a)**. 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. 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 subunit cooperativity, a slight drop in P_{O_2} causes a relatively large increase in the amount of O_2 the blood unloads.

Hemoglobin is especially efficient at delivering O_2 to tissues actively consuming O_2. However, this increased efficiency results not from O_2 consumption, but rather from CO_2 production. As tissues consume O_2 in cell respiration, they also produce CO_2. As we have seen, CO_2 reacts with water, forming carbonic acid, which lowers the pH of its surroundings. Low pH decreases the affinity of hemoglobin for O_2, an effect called the **Bohr shift** **(Figure 42.31b)**. Thus, where CO_2 production is greater, hemoglobin releases more O_2, which can then be used to support more cellular respiration.

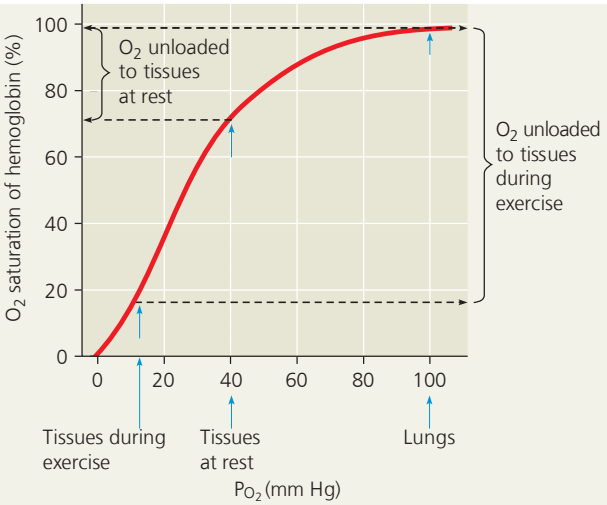
Hemoglobin also assists in buffering the blood—that is, preventing harmful changes in pH. In addition, it has a minor role in CO_2 transport, the topic we'll explore next.

Carbon Dioxide Transport

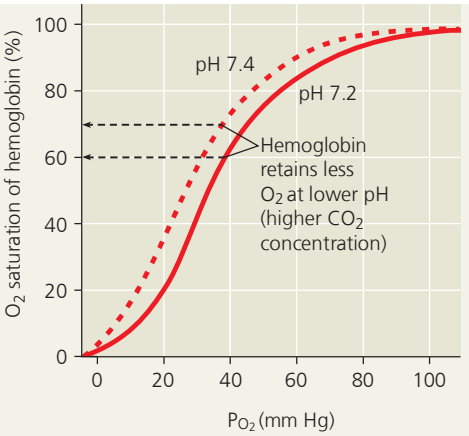
Only about 7% of the CO_2 released by respiring cells is transported in solution in blood plasma. The rest diffuses from plasma into erythrocytes and reacts with water (assisted by the enzyme carbonic anhydrase), forming H_2CO_3. The H_2CO_3 readily dissociates into H^+ and HCO_3^-. Most H^+ binds to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

▼ Figure 42.31 Dissociation curves for hemoglobin at 37°C.



(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 resting tissues, 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. In very active tissues, CO_2 from cellular respiration reacts with water to form carbonic acid, decreasing pH. Because hydrogen ions affect hemoglobin shape, a drop in pH shifts the O_2 dissociation curve toward the right (the Bohr shift). For a given P_{O_2}, hemoglobin releases more O_2 at a lower pH, supporting increased cellular respiration.

Mastering Biology **Animation: Transport of Respiratory Gases**

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 drive a 10–15% reduction in P_{CO_2} during passage of blood through the lungs (see Figure 42.29).

Respiratory Adaptations of Diving Mammals

EVOLUTION Animals vary greatly in their ability to spend time in environments in which there is no access to their normal respiratory medium—for example, when an air-breathing mammal swims underwater. Whereas most humans cannot swim deeper than 20 m or hold their breath longer than 2–3 minutes, the Weddell seal of Antarctica routinely plunges to 200–500 m and remains there for a period ranging from 20 minutes to more than an hour **(Figure 42.32)**. Another diving mammal, the Cuvier's beaked whale, can reach depths of 2,900 m—nearly 2 miles—and stay submerged for more than 2 hours! What enables these amazing feats?

▼ Figure 42.32 A Weddell seal, adapted to deep, long dives.

One evolutionary adaptation of diving mammals to prolonged stays underwater is a capacity to store large amounts of O_2 in their bodies. The volume of blood per kilogram of body mass in a Weddell seal is about twice that in a human. Furthermore, the muscles of seals and other diving mammals contain a high concentration of an oxygen-storing protein called **myoglobin** in their 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 for prolonged periods. During a dive, their heart rate and O_2 consumption rate decrease, and most blood is routed to vital tissues: the brain, spinal cord, eyes, adrenal glands, and, in pregnant seals, the placenta. Blood supply to the muscles is restricted or, during extended dives, shut off altogether. During these dives, a Weddell seal's muscles deplete the O_2 stored in myoglobin and then derive their ATP from fermentation instead of respiration (see Concept 9.5).

How might such adaptations have arisen over the course of evolution? All mammals, including humans, have a diving reflex triggered by a plunge or fall into water: When the face contacts cold water, the heart rate immediately decreases and blood flow to body extremities is reduced. Genetic changes that strengthened this reflex would have provided a selective advantage to seal ancestors foraging underwater. Also, genetic variations that increased traits such as blood volume or myoglobin concentration would have improved diving ability and therefore been favored during selection over many generations.

CONCEPT CHECK 42.7

1. What determines whether O_2 and CO_2 undergo net diffusion into or out of 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 is the doctor assuming about the patient's blood chemistry?

For suggested answers, see Appendix A.

42 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 42.1

Circulatory systems link exchange surfaces with cells throughout the body *(pp. 922–926)*

- In animals with simple body plans, a **gastrovascular cavity** mediates exchange between the environment and cells that can be reached by **diffusion**. Because 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 the **capillaries**, 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 circulation. Air-breathing vertebrates have two pumps combined in a single heart. Variations in ventricle

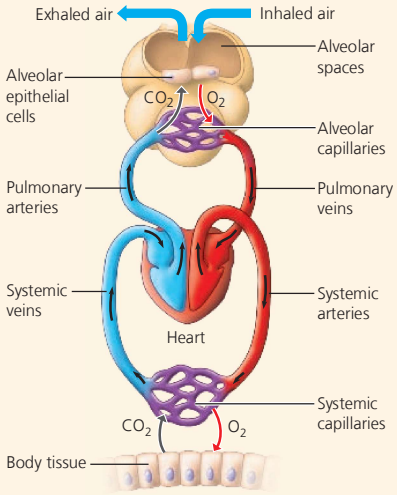
number and separation reflect adaptations to different environments and metabolic needs.

? *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 42.2

Coordinated cycles of heart contraction drive double circulation in mammals *(pp. 926–929)*

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



- The **cardiac cycle**, a complete sequence of the heart's pumping and filling, consists of a period of contraction, called **systole**, and a period of relaxation, called **diastole**. Heart function can be assessed by measuring the **pulse** (number of times the heart beats each minute) and **cardiac output** (volume of blood pumped by each ventricle per minute).
- The heartbeat originates with impulses at the **sinoatrial (SA) node** (pacemaker) of the right atrium. They trigger atrial contraction, are delayed at the **atrioventricular (AV) node**, and are then conducted along the bundle branches and Purkinje fibers, triggering ventricular contraction. The nervous system, hormones, and body temperature affect pacemaker activity.

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

CONCEPT 42.3

Patterns of blood pressure and flow reflect the structure and arrangement of blood vessels *(pp. 929–934)*

- 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.
- The velocity of blood flow is lowest in the capillary beds as a result of their large total cross-sectional area. Blood pressure is altered by changes in cardiac output and by variable constriction of arterioles.
- Fluid leaks out of capillaries and is returned to blood by the **lymphatic system**, which also defends against infection.

? *If while standing you placed your forearm on your head, how, if at all, would the blood pressure in that arm change? Explain.*

CONCEPT 42.4

Blood components function in exchange, transport, and defense *(pp. 934–939)*

- 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. Five types of white blood cells, or **leukocytes**, function in defense against microorganisms and foreign substances in the blood. Platelets function in blood clotting, a cascade of reactions that converts plasma fibrinogen to fibrin.
- A variety of diseases impair function of the circulatory system. In **sickle-cell disease**, an aberrant form of **hemoglobin** disrupts erythrocyte shape and function, leading to blockage of small blood vessels and a decrease in the oxygen-carrying capacity of the blood. 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 42.5

Gas exchange occurs across specialized respiratory surfaces *(pp. 939–944)*

- 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.
- The structure and organization of respiratory surfaces differ among animal species. Gills are outfoldings of the body surface 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 bring O_2 directly to cells. Spiders, land snails, and most terrestrial vertebrates have internal **lungs**. In mammals, air inhaled through the nostrils 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 42.6

Breathing ventilates the lungs *(pp. 944–946)*

- **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, preventing the mixing of incoming and outgoing air. Mammals ventilate their lungs by **negative pressure breathing**, which pulls air into the lungs when the rib muscles and **diaphragm** contract. Incoming and outgoing air mix, decreasing the efficiency of ventilation.
- Sensors detect the pH of cerebrospinal fluid (reflecting CO_2 concentration in the blood), and a control center in the brain adjusts breathing

rate and depth to match metabolic demands. Additional input to the control center is provided 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 42.7

Adaptations for gas exchange include pigments that bind and transport gases *(pp. 947–949)*

- 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 hemocyanin and 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 mammals stockpile O_2 in blood and other tissues and deplete it slowly.

? *How are the roles of a respiratory pigment and an enzyme similar?*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

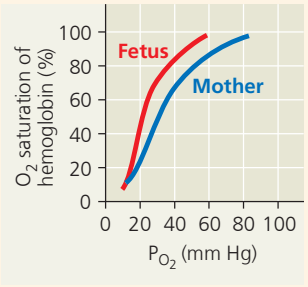
1. Which of the following respiratory systems is independent from a fluid-based circulatory system?
   (A) the lungs of a vertebrate
   (B) the gills of a fish
   (C) the tracheal system of an insect
   (D) the skin of an earthworm
2. Blood returning to the mammalian heart in a pulmonary vein drains first into the
   (A) left atrium. (C) left ventricle.
   (B) right atrium. (D) right ventricle.
3. Pulse is a direct measure of
   (A) blood pressure. (C) cardiac output.
   (B) stroke volume. (D) heart 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 (C) rising CO_2
   (B) falling O_2 (D) falling CO_2
5. One feature that amphibians and humans have in common is
   (A) the number of heart chambers.
   (B) a complete separation of circuits for circulation.
   (C) the number of circuits for circulation.
   (D) a low blood pressure in the systemic circuit.

Levels 3-4: Applying/Analyzing

6. A molecule of CO_2 released into the blood in your left toe can be exhaled from your nose without passing through which of the following structures?
   (A) the pulmonary vein. (C) the right atrium.
   (B) the trachea. (D) the right ventricle.
7. Compared with the interstitial fluid that bathes active muscle cells, blood reaching these cells in arterioles has a
   (A) higher P_{O_2}.
   (B) higher P_{CO_2}.
   (C) greater bicarbonate concentration.
   (D) lower pH.

Levels 5-6: Evaluating/Creating

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. **EVOLUTION CONNECTION** One opponent of the movie monster Godzilla is Mothra, a mothlike creature with a wingspan of several dozen meters. The largest known insects were Paleozoic dragonflies with half-meter wingspans. Focusing on respiration and gas exchange, explain why giant insects are improbable.
10. **SCIENTIFIC INQUIRY • INTERPRET THE DATA** The hemoglobin of a human fetus differs from adult hemoglobin. Compare the dissociation curves of the two hemoglobins in the graph at right. Describe how they differ, and propose a hypothesis to explain the benefit of this difference.



11. **SCIENCE, TECHNOLOGY, AND SOCIETY** Hundreds of studies have linked smoking with cardiovascular and lung disease. According to most health authorities, smoking is the leading cause of preventable, premature death in the United States. What are some arguments in favor of a total ban on cigarette advertising? What are arguments in opposition? Do you favor or oppose such a ban? Explain.
12. **WRITE ABOUT A THEME: INTERACTIONS** Some athletes prepare for competition at sea level by sleeping in a tent in which P_{O_2} is kept low. When climbing high peaks, some mountaineers breathe from bottles of pure O_2. In a short essay (100–150 words), relate these behaviors to the mechanism of O_2 transport in the human body and to physiological interactions with our gaseous environment.
13. **SYNTHESIZE YOUR KNOWLEDGE**

The diving bell spider (*Argyroneta aquatica*) stores air underwater in a net of silk. Explain why this adaptation could be more advantageous than having gills, taking into account differences in gas exchange media and gas exchange organs among animals.

For selected answers, see Appendix A.

43 The Immune System

KEY CONCEPTS

43.1 **In innate immunity, recognition and response rely on traits common to groups of pathogens** *p. 953*

43.2 **In adaptive immunity, receptors provide pathogen-specific recognition** *p. 957*

43.3 **Adaptive immunity defends against infection of body fluids and body cells** *p. 963*

43.4 **Disruptions in immune system function can elicit or exacerbate disease** *p. 970*

Study Tip

Make a table: As you study innate and adaptive immunity, compare and contrast these two forms of immune defense by continuing to fill in this table.

Defense mechanism	Key role in innate defense?	Key role in adaptive defense?	Effect on pathogen	Example of cell involved
Barrier	Yes	No	Entry into host tissues prevented	Epithelial cell
Phagocytosis				
Secreted molecules				
Destruction of infected host cells				

Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 43
- BioFlix® Animation: Activation of a Helper T cell
- BioFlix® Animation: Adaptive Defenses

For Instructors to Assign (in Item Library)
- Activity: The Inflammatory Response
- Tutorial: Acquired Immunity

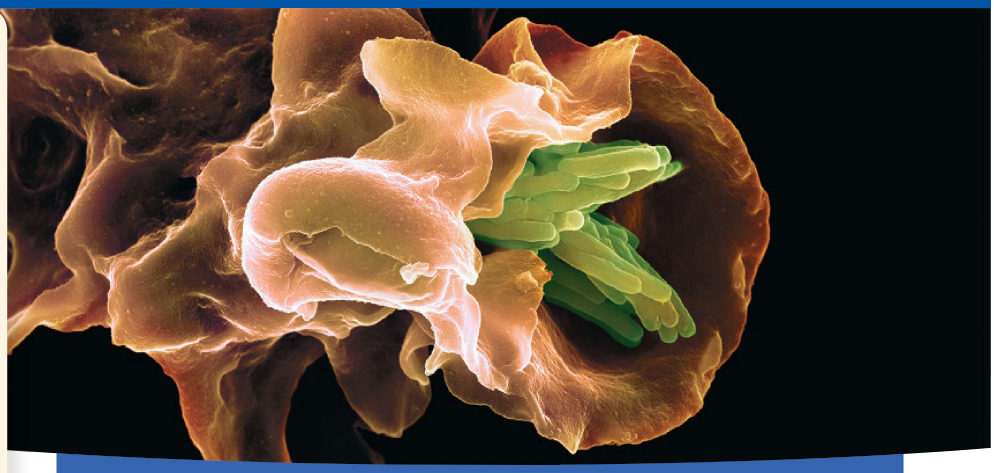
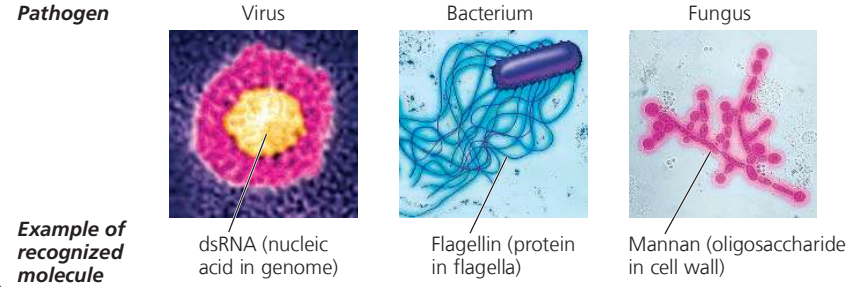


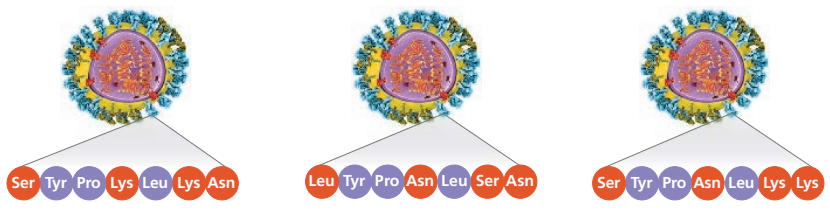
Figure 43.1 Dedicated immune cells in most animals specifically interact with and attack pathogens, disease-causing agents such as bacteria or viruses. Here, an immune cell called a macrophage (brown) is engulfing bacteria (green).

How do immune cells recognize pathogens?

Innate recognition Each of a small set of receptors recognizes a molecule absent from animals, but common to a type of pathogen, as shown by these examples.



Adaptive recognition Each of a vast number of receptors is specific for a particular part of a protein in one pathogen, such as a surface protein of the influenza (flu) virus. In this example, a different adaptive immune receptor would recognize each of the flu strains based on the proteins' amino acid sequences, which differ at the positions colored orange.



Recognition by either type of immunity triggers a **response** that can eliminate or inactivate the pathogen, protecting the infected animal.

CONCEPT 43.1

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

For a **pathogen**—a bacterium, fungus, virus, or other disease-causing agent—the internal environment of an animal offers a source of nutrients, a protected setting, and a means of transport to new environments. From the animal's vantage point, the situation is not so ideal. Fortunately, adaptations have arisen over the course of evolution that protect animals against many pathogens. The body's defenses make up the **immune system**, which enables an animal to avoid or limit many infections. (Note that a foreign molecule or cell doesn't have to be pathogenic to elicit an immune response, but we'll focus on the immune system's role in defending against pathogens.)

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 skin or a shell, blocks entry by many pathogens. 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 pathogens 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 molecules, particles, and cells.

Two types of immune defenses are found among animals. This concept focuses on **innate immunity**, the set of immune defenses common to all animals. The remainder of the chapter explores **adaptive immunity**, a set of molecular and cellular defense found only among vertebrates.

Innate Immunity of Invertebrates

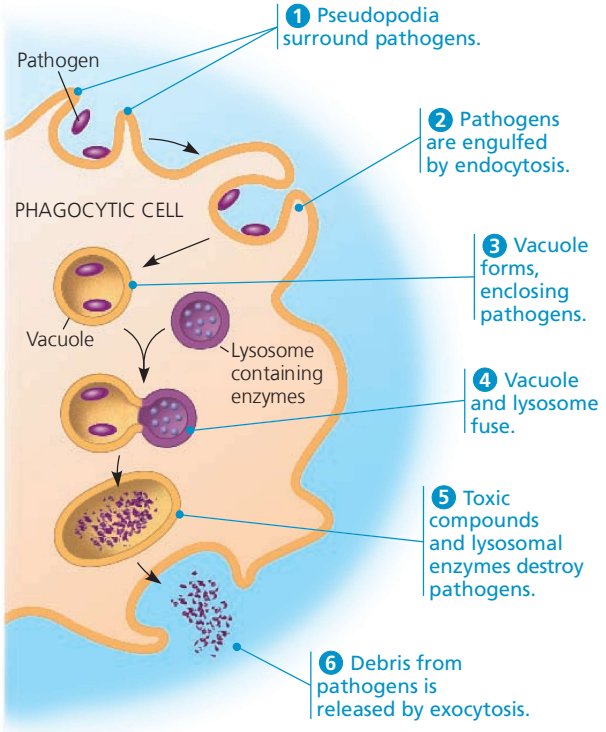
The great success of insects in terrestrial and freshwater habitats teeming with diverse pathogens highlights the effectiveness of invertebrate innate immunity. One part of this defense system is a set of barrier defenses, including the insect exoskeleton. Composed largely of the polysaccharide chitin, the exoskeleton provides a physical barrier against most pathogens. Chitin also lines the insect intestine, where it blocks infection by many pathogens. In the digestive system, **lysozyme**, an enzyme that breaks down bacterial cell walls, acts as a chemical barrier against any pathogens ingested with food.

Any pathogen that breaches an insect's barrier defenses encounters internal immune defenses. Insect immune cells produce a set of recognition proteins, each of which binds to a molecule common to a broad class of pathogens. Many of these molecules are components of fungal or bacterial cell walls. Because such molecules are not normally found in animal cells, they function as "identity tags" for pathogen recognition. Once bound to a pathogen molecule, a recognition protein triggers an innate immune response.

In insects, the major immune cells are called *hemocytes*. Like amoebas, some hemocytes are phagocytic cells: They ingest and break down microorganisms by a process known as **phagocytosis** (Figure 43.2). One class of hemocytes produces a type of defense molecule that helps entrap larger pathogens, such as *Plasmodium*, the single-celled parasite of mosquitoes that causes malaria in humans. Many other hemocytes release *antimicrobial peptides*, which circulate throughout the body of the insect and inactivate or kill bacteria or fungi by disrupting their plasma membranes.

The innate immune response of insects is specific for particular classes of pathogens. For example, if a fungus infects an insect, binding of recognition proteins to fungal cell wall molecules activates a transmembrane receptor called Toll. Toll in turn activates production and secretion of antimicrobial peptides that specifically kill fungal cells. Remarkably,

▼ **Figure 43.2 Phagocytosis.** This diagram depicts events in the ingestion and destruction of pathogens by a typical phagocytic cell.



phagocytic mammalian cells use receptor proteins very similar to the Toll receptor to recognize viral, fungal, and bacterial components, a discovery that was recognized with the Nobel Prize in Physiology or Medicine in 2011.

Insects also have specific defenses that protect against infection by viruses. Many viruses that infect insects have a genome consisting of a single strand of RNA. When the virus replicates in the host cell, this RNA strand is the template for the synthesis of double-stranded RNA. Because animals do not produce double-stranded RNA, its presence can trigger a specific defense against the invading virus, as illustrated in **Figure 43.3**.

Innate Immunity of Vertebrates

In 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. In this section, we'll consider the innate defenses that are similar to those found among invertebrates—barrier defenses, phagocytosis, and antimicrobial peptides—as well as some that are unique to vertebrates, such as natural killer cells, interferons, and the inflammatory response.

Barrier Defenses

The barrier defenses of mammals, which block the entry of many pathogens, include the mucous membranes and the skin. The mucous membranes that line the digestive, respiratory, urinary, and reproductive tracts produce *mucus*, a viscous fluid that traps pathogens and other particles. In the airway, ciliated epithelial cells sweep mucus and any entrapped material upward, helping prevent infection of the lungs. Saliva, tears, and mucous secretions that bathe various exposed epithelia provide a washing action that also inhibits colonization by fungi and bacteria.

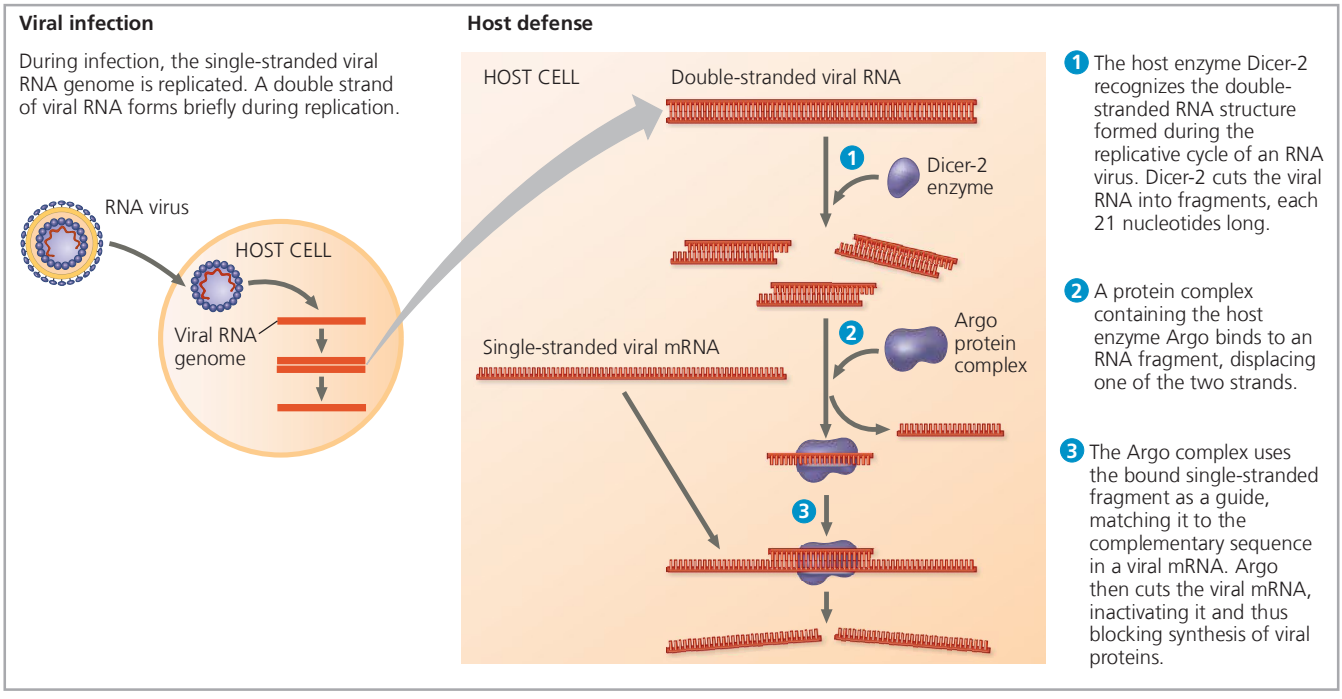
Beyond their physical role in inhibiting microbial entry, body secretions create an environment that is hostile to many pathogens. Lysozyme in tears, saliva, and mucous secretions destroys the cell walls of susceptible bacteria as they enter the openings around the eyes or the upper respiratory tract. Pathogens in food or water and those in swallowed mucus must also contend with the acidic environment of the stomach (pH 2), 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

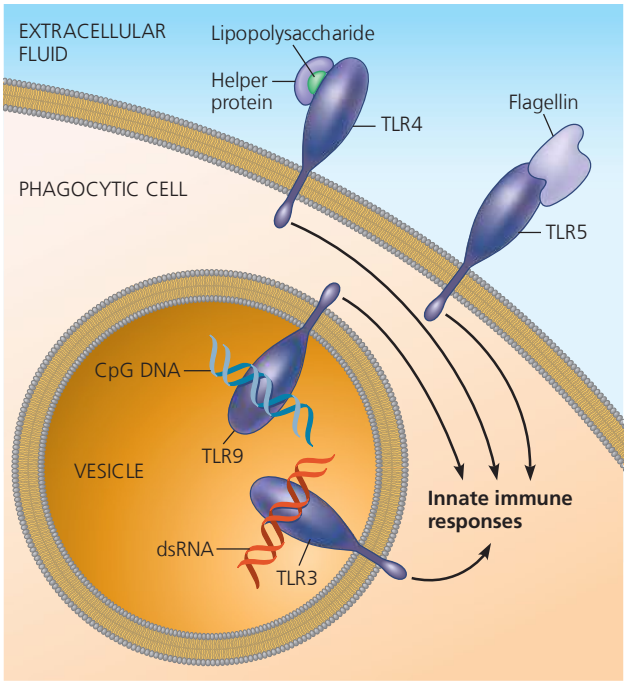
In mammals, as in insects, there are phagocytic innate immune cells dedicated to detecting, devouring, and destroying pathogens. In recognizing viral, fungal, or bacterial components, phagocytic mammalian cells rely on several types of receptors. As mentioned above, some are very similar to the insect innate immune receptor Toll. Each mammalian **Toll-like receptor (TLR)** binds to fragments of molecules

▼ Figure 43.3 Antiviral defense in insects. In defending against an infecting RNA virus, an insect cell turns the viral genome against itself, cutting the viral genome into small fragments that it then uses as guide molecules to find and destroy viral messenger RNAs (mRNAs).

VISUAL SKILLS *Compare and contrast the specificity of the Dicer-2 and Argo enzymes in terms of the size, number of strands, and sequence of the RNA molecules they each bind or act upon.*



▼ Figure 43.4 TLR signaling. Each mammalian Toll-like receptor (TLR) recognizes a molecular pattern shared by a group of pathogens. Lipopolysaccharide, flagellin, CpG DNA (DNA containing unmethylated CG sequences), and double-stranded (ds) RNA are found in bacteria, fungi, or viruses but not in animal cells. Once bound to such a pathogen molecule, TLR proteins trigger internal innate immune defenses, including production of cytokines and antimicrobial peptides.



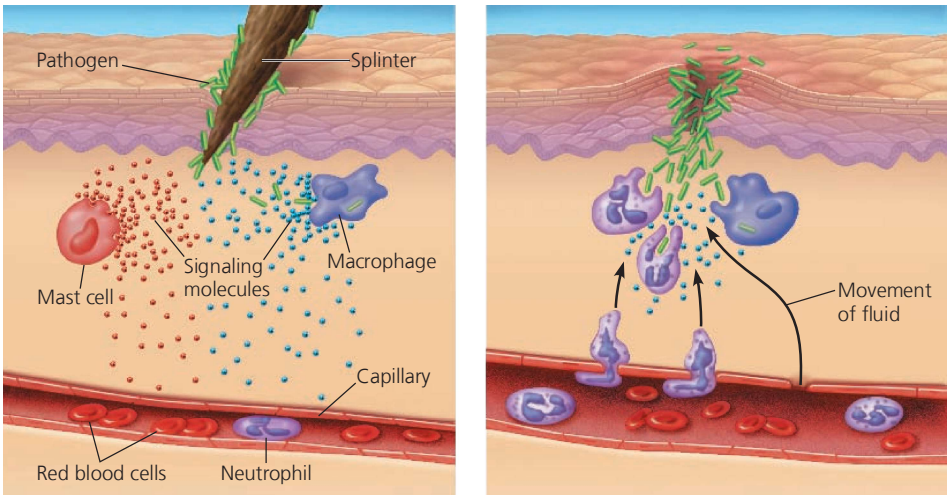
VISUAL SKILLS *Observe the locations of the TLR proteins and then suggest a possible benefit of their distribution.*

characteristic of a set of pathogens **(Figure 43.4)**. For example, TLR3, on the inner surface of vesicles formed by endocytosis, binds to double-stranded RNA, a form of nucleic acid produced by certain viruses. Similarly, TLR4, located on immune cell plasma membranes, recognizes lipopolysaccharide, a type of molecule found on the surface of many bacteria, and TLR5 recognizes flagellin, the main protein of bacterial flagella.

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 and then engulf and destroy the infecting pathogens. **Macrophages** ("big eaters"), like the one shown in Figure 43.1, are larger phagocytic cells. Some migrate throughout the body, whereas others reside permanently 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 are often trapped. Macrophages and neutrophils are both key components of the inflammatory response, as discussed shortly. In addition to these cells, a number of more specialized cell types also contribute to innate immune defenses:

- **Dendritic cells** mainly populate tissues, such as skin, that contact the environment. They stimulate adaptive immunity against pathogens that they engulf.
- **Eosinophils**, often found beneath an epithelium, are important in defending against multicellular invaders, such as parasitic worms. Upon encountering such parasites, eosinophils discharge destructive enzymes.
- **Natural killer cells** circulate through the body and detect the abnormal surface proteins found on some virus-infected and cancerous cells. Natural killer cells do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting spread of the virus or cancer.
- **Mast cells** are found in connective tissue and make key contributions to the inflammatory response, described next, as well as to allergies, discussed later.

▼ Figure 43.5 Major events in a local inflammatory response.



1 At the injury site, mast cells release histamines, and macrophages secrete cytokines. Some of these signaling molecules cause nearby capillaries to dilate, while others attract neutrophils.

2 Capillaries widen and become more permeable, allowing fluid containing antimicrobial peptides, as well as neutrophils, to enter the tissue. These immune cells digest pathogens and cell debris, allowing the tissue to heal.

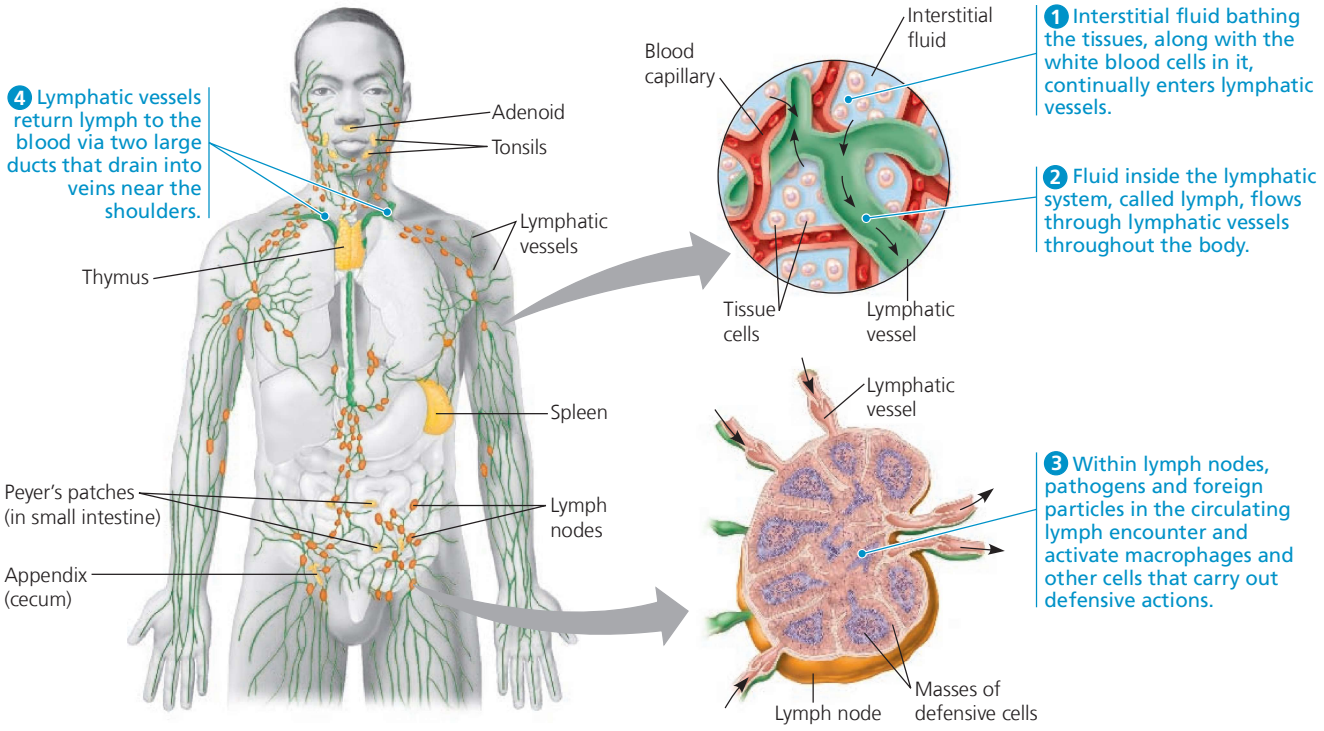
? *From your experience with splinters, deduce whether the signals mediating an inflammatory response are short- or long-lived. Explain your answer.*

Mastering Biology Animation: Overview of the Inflammatory Response

Local Inflammatory Response

When a splinter lodges under your skin, the surrounding area becomes swollen and warm. As **Figure 43.5** depicts, both changes reflect a local **inflammatory response**, a set of events triggered by signaling molecules released upon injury or infection.

▼ Figure 43.6 The human lymphatic system. The lymphatic system consists of lymphatic vessels (shown in green), through which lymph travels, and structures that trap foreign substances. These structures include lymph nodes (orange) and lymphoid organs (yellow): the adenoids, tonsils, thymus, spleen, Peyer's patches, and appendix. Steps 1–4 trace the flow of lymph and illustrate the role of lymph nodes in activating adaptive immunity. (Concept 42.3 describes the relationship between the lymphatic and circulatory systems.)



A local inflammatory response begins when activated macrophages discharge *cytokines*, signaling molecules that recruit neutrophils to the site of injury or infection. In addition, mast cells release the signaling molecule **histamine** at sites of damage. Histamine triggers nearby blood vessels to dilate and become more permeable. The resulting increase in local blood supply produces the redness and increased skin temperature typical of the inflammatory response (from the Latin *inflammare*, to set on fire).

Cycles of signaling and response continue the process of inflammation. Activated complement proteins promote further histamine release, attracting more phagocytic cells to the site of injury and infection. At the same time, enhanced blood flow to the site helps deliver antimicrobial peptides, which, as in insects, typically kill or inactivate pathogens by disrupting membrane integrity. The result is an accumulation of *pus*, a fluid rich in white blood cells, dead pathogens, and debris from damaged tissue.

At the end of the local inflammatory response, pus and excess fluid are taken up as lymph, the fluid transported in the network of vessels known as the lymphatic system **(Figure 43.6)**. Small organs called *lymph nodes* scattered within the lymphatic system contain macrophages, which engulf pathogens that enter 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.

Systemic and Chronic Inflammation

A minor injury or infection causes a local inflammatory response, but more extensive 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 the case of a severe infection, such as meningitis or appendicitis, the number of white blood cells in the bloodstream may increase severalfold within only a few hours.

A systemic inflammatory response sometimes involves fever. In response to certain pathogens, substances released by activated macrophages cause the body's thermostat to reset to a higher temperature (see Concept 40.3). 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 200,000 people each year in the United States.

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

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. A number of these, 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 interferon proteins that induce nearby uninfected cells to produce substances that inhibit viral replication. In this way, these 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 pathogens. 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 as well as in the adaptive defenses discussed later in the chapter.

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*, is a major cause of pneumonia and meningitis in humans (see Concept 16.1).

Some bacteria are recognized but resist breakdown after being engulfed by a host cell. One example is *Mycobacterium tuberculosis*, the bacterium shown in Figure 43.1. Rather than being destroyed, this bacterium grows and reproduces within host cells, effectively hidden from the body's immune defenses. The result of this infection is tuberculosis (TB), a disease that attacks the lungs and other tissues. Worldwide, TB kills more than 1 million people a year.

CONCEPT CHECK 43.1

1. Pus is both a sign of infection and 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 11.2)?
3. **WHAT IF?** Parasitic wasps inject their eggs into host larvae of other insects. If the host immune system doesn't kill the wasp egg, the egg hatches and the wasp larva devours the host larva as food. Suggest an explanation for why some insect species initiate an innate immune response to a wasp egg, but others cannot.

For suggested answers, see Appendix A.

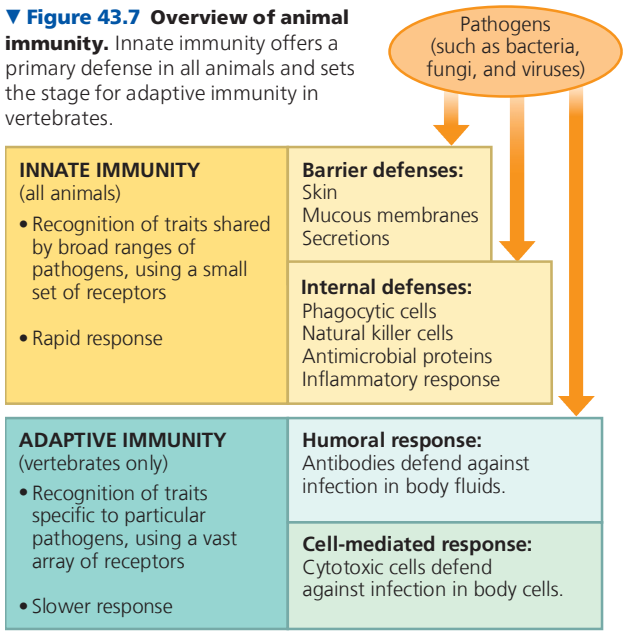
CONCEPT 43.2

In adaptive immunity, receptors provide pathogen-specific recognition

Vertebrates are unique in having adaptive as well as innate immunity. 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 remarkable specificity.

The adaptive immune response, also known as the acquired immune response, is activated after the innate immune response and develops more slowly. Unlike innate immunity, the adaptive response is enhanced by previous exposure to the infecting pathogen. **Figure 43.7** highlights

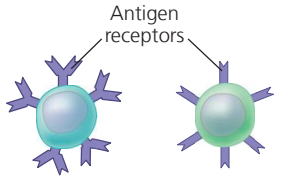
▼ Figure 43.7 Overview of animal immunity. Innate immunity offers a primary defense in all animals and sets the stage for adaptive immunity in vertebrates.



these and other fundamental similarities and differences between adaptive and innate immunity.

Adaptive immunity relies on T cells and B cells, which are types of white blood cells called **lymphocytes** (Figure 43.8). Like all blood cells, lymphocytes originate from stem cells in the bone marrow. Some migrate from the bone marrow to the **thymus**, an organ in the thoracic cavity above the heart (see Figure 43.6). These lymphocytes mature into **T cells**. Lymphocytes that remain and mature in the bone marrow develop as **B cells**. (Lymphocytes of a third type remain in the blood and become the natural killer cells active in innate immunity.)

▼ Figure 43.8 B and T lymphocytes.



Antigens as the Trigger for Adaptive Immunity

Any substance that elicits a B or T cell response is 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**. Each antigen receptor binds to just one part of one molecule from a particular pathogen, such as a species of bacteria or strain of virus.

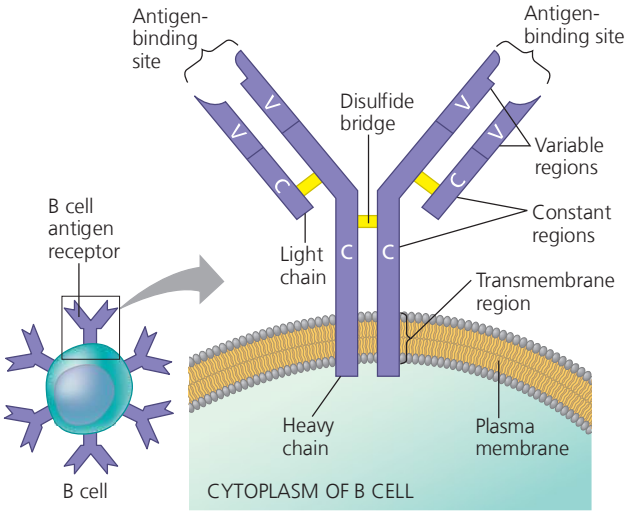
The cells of the immune system produce millions of different antigen receptors. A given lymphocyte, however, produces just one variety; all of the antigen receptors made by a single B or T cell are identical. Infection by a virus, bacterium, or other pathogen triggers activation of B and T cells with antigen receptors specific for parts of that pathogen. Although drawings of B and T cells typically include just a few antigen receptors, a single B or T cell actually has about 100,000 antigen receptors on its surface.

Antigens are usually foreign and are typically large molecules, either proteins or polysaccharides. Many antigens protrude from the surface of foreign cells or viruses. Other antigens, such as toxins secreted by bacteria, are released into the extracellular fluid.

The small, accessible portion of an antigen that binds to an antigen receptor is called an **epitope**. An example is a group of amino acids in a particular protein. A single antigen usually has several epitopes, each binding 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 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.

▼ Figure 43.9 The structure of a B cell antigen receptor.



Antigen Recognition by B Cells and Antibodies

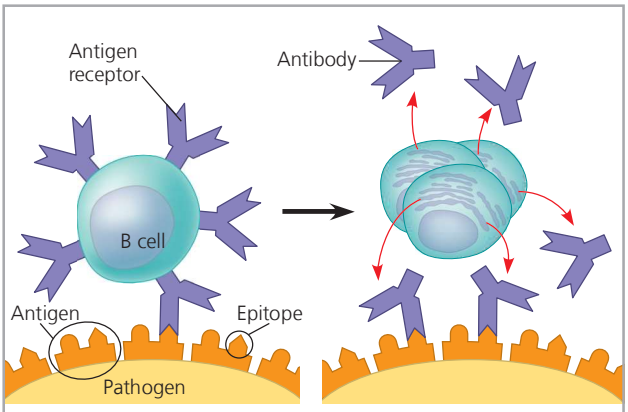
Each B cell antigen receptor is a Y-shaped protein consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains** (Figure 43.9). Disulfide bridges link the chains together.

Each light chain or heavy chain has a *constant (C) region*, where amino acid sequences vary little among the receptors on different B cells. The constant region of heavy chains contains a transmembrane region, which anchors the receptor in the cell's plasma membrane. As shown in Figure 43.9, each light or heavy chain also 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. Therefore, each B cell antigen receptor has two identical antigen-binding sites.

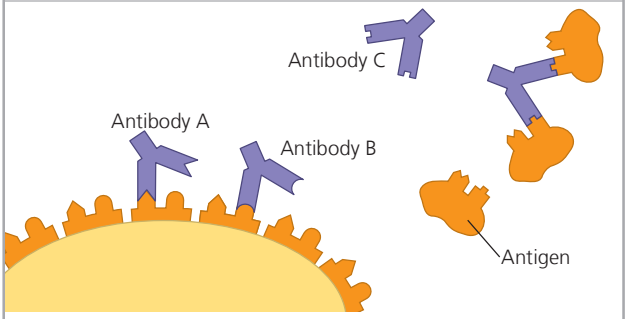
Binding of a B cell antigen receptor to an antigen is an early step in B cell activation, leading eventually to formation of cells that secrete a soluble form of the receptor (Figure 43.10a). This secreted protein is called an **antibody**, also known as an **immunoglobulin (Ig)**. Antibodies have the same Y-shaped structure as B cell antigen receptors but lack a membrane anchor. As you'll see later, antibodies provide a direct defense against pathogens in body fluids.

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. This stable interaction involves many noncovalent bonds between an epitope and the surface of the binding site. Differences in the amino acid sequences of variable regions provide the variation in binding surfaces that enables binding to be highly specific.

▼ Figure 43.10 Antigen recognition by B cells and antibodies.



(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 an antibody: a soluble form of the receptor that is specific for the same epitope as the original antigen receptor.



(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.

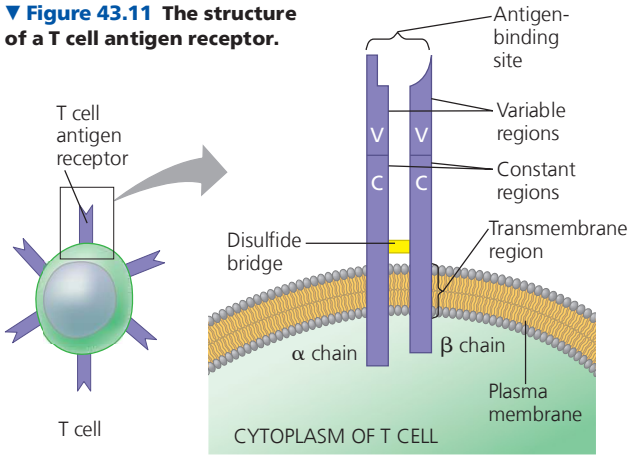
MAKE CONNECTIONS *The interactions depicted here involve a highly specific binding between antigen and receptor (see also Figure 5.17). How is this type of interaction similar to an enzyme-substrate interaction (see Figure 8.15)?*

B cell antigen receptors and antibodies bind to intact antigens in the blood and lymph. As illustrated in **Figure 43.10b** 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 43.11)**. Near the base of the 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 the α and β chains together form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

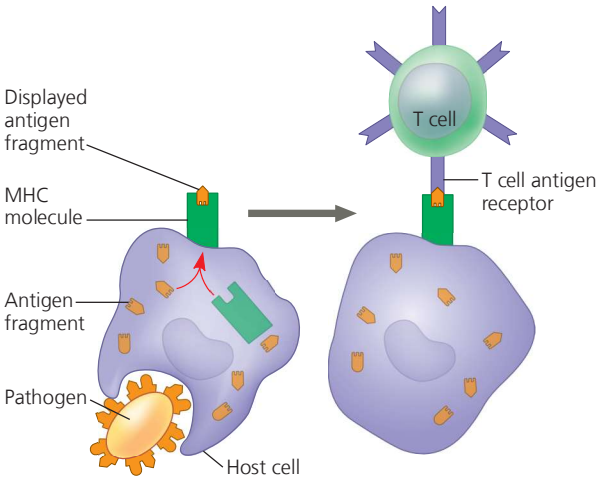
▼ Figure 43.11 The structure of a T cell antigen receptor.



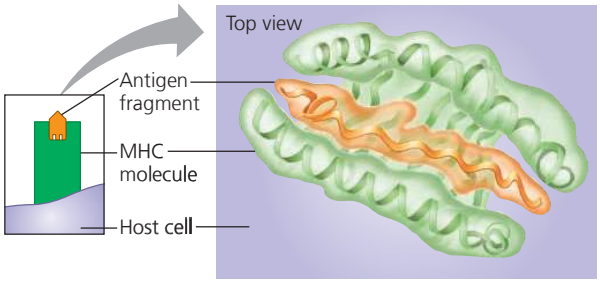
Whereas the antigen receptors of B cells bind to epitopes of *intact* antigens protruding from pathogens or circulating free in body fluids, antigen receptors of T cells bind only to fragments of antigens that are displayed, or presented, on the surface of host cells. The host protein that displays the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

The display of protein antigens occurs when a pathogen infects a cell of the animal host or when an immune cell engulfs pathogen proteins or a whole pathogen **(Figure 43.12)**. Inside the animal cell, enzymes cleave each antigen into antigen fragments, which are small peptides. Each antigen fragment binds to an MHC molecule, which transports the bound peptide to the cell surface. The result is

▼ Figure 43.12 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.



▼ Figure 43.13 A closer look at antigen presentation. As shown in this ribbon model, the top of the MHC molecule cradles an antigen fragment, like a bun holding a hot dog. An MHC molecule can display many different antigen fragments, but the antigen receptor of a T cell is specific for a single antigen fragment.



antigen presentation, the display of the antigen fragment in an exposed groove of the MHC protein.

Figure 43.13 shows a close-up view of antigen presentation. In effect, antigen presentations 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 triggers an adaptive immune response, as we'll explore in Concept 43.3.

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, the immense repertoire of lymphocytes and receptors enables detection of antigens and 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*, which we'll explore later in the chapter.

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.

The Basis 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 so many different antigen receptors? The answer lies in combinations. Think of selecting a cell phone model that comes in three sizes and six colors. There are 18 (3×6) combinations to consider. Similarly, by combining variable elements, the immune system assembles millions of different receptors from a very small collection of parts.

To understand the origin of receptor diversity, let's consider an immunoglobulin (Ig) gene that encodes the light chain of both membrane-bound B cell antigen receptors and secreted antibodies (immunoglobulins). 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. The alternative copies of the *V* and *J* segments are arrayed along the gene in a series **(Figure 43.14)**. 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.

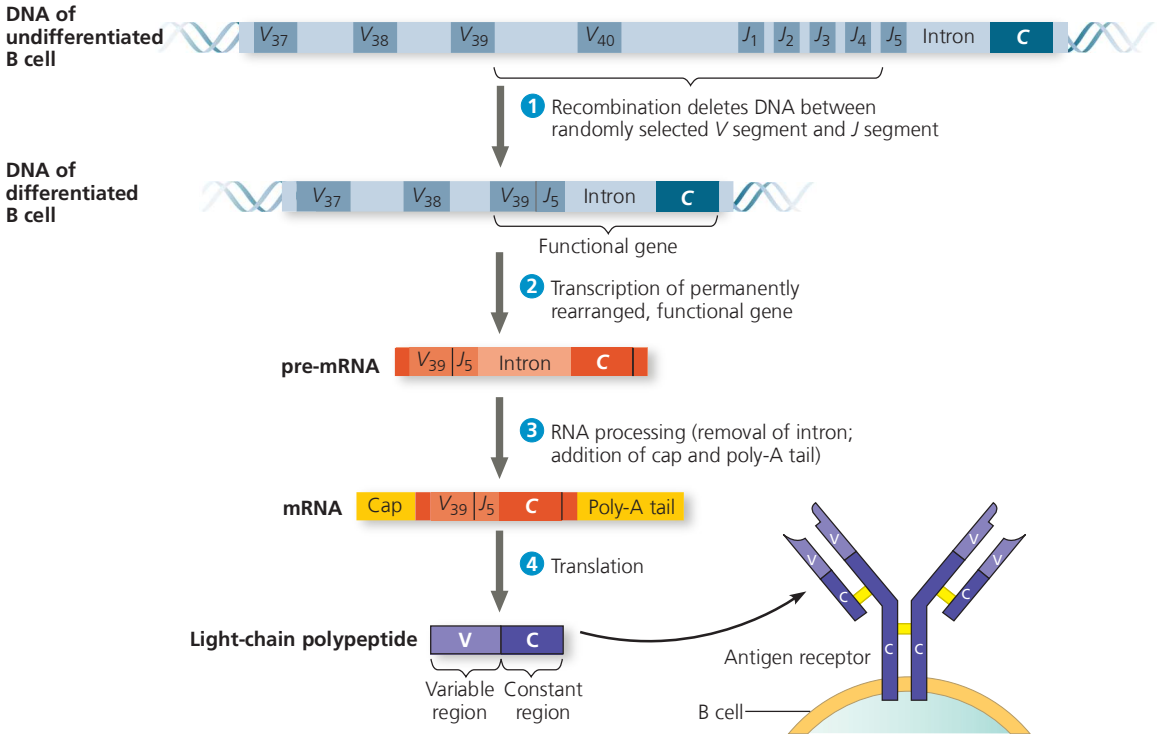
Antigen Receptor Gene Rearrangement

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*.

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 been 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 43.14). 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

▼ Figure 43.14 Immunoglobulin (antibody) gene rearrangement. The joining of randomly selected *V* and *J* gene segments (V_{39} and J_5 in the example shown) 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 diploid 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 (see Figure 18.14). How do these processes differ?*

variation, making the number of 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 *apoptosis*, which is a programmed cell death (see Concept 11.5). The remaining self-reactive lymphocytes are typically rendered nonfunctional, leaving only those lymphocytes that react to foreign molecules. Since the 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 43.6) until a match is made. A successful match between an antigen receptor and an epitope initiates events that activate the lymphocyte bearing the receptor.

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**, mostly short-lived cells that take effect immediately against the antigen and any pathogens producing that antigen.

For B cells, the effector forms are *plasma cells* **(Figure 43.15)**, which secrete antibodies. For T cells, the effector forms are helper T cells and cytotoxic T cells, whose roles we'll explore in Concept 43.3. 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 43.15 A plasma cell.

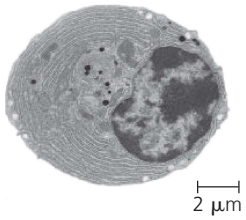


Figure 43.16 summarizes the proliferation of lymphocyte into a clone of cells occurs in response to binding to an antigen, using B cells as an example. The process is called **clonal selection** because an encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells specific for a particular epitope.

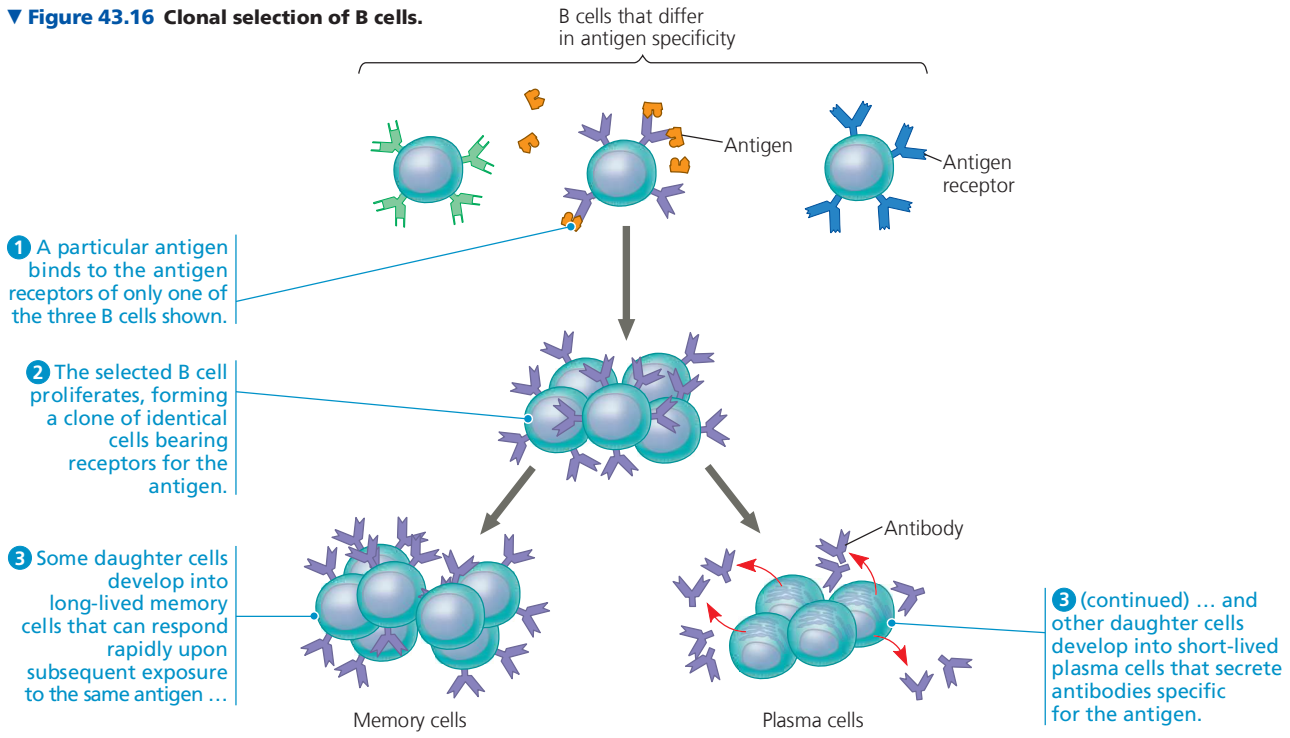
Immunological Memory

Immunological memory is responsible for the long-term protection that a prior infection provides against many diseases, such as chicken pox. 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 effector cells formed by clones of lymphocytes after an initial exposure to an antigen produce a **primary immune response**. The primary response peaks about 10–17 days after the initial exposure. If the same antigen is encountered again later, there is a **secondary immune response**, a response that is faster (typically peaking only 2–7 days after exposure), of greater magnitude, and more prolonged. These differences between primary and secondary immune responses are readily apparent in a graph of the concentrations of specific antibodies in blood over time **(Figure 43.17)**.

The secondary immune response relies on the reservoir of T and B memory cells generated upon initial exposure to an antigen. Because these cells are long-lived, they provide the basis for immunological memory, which can span many

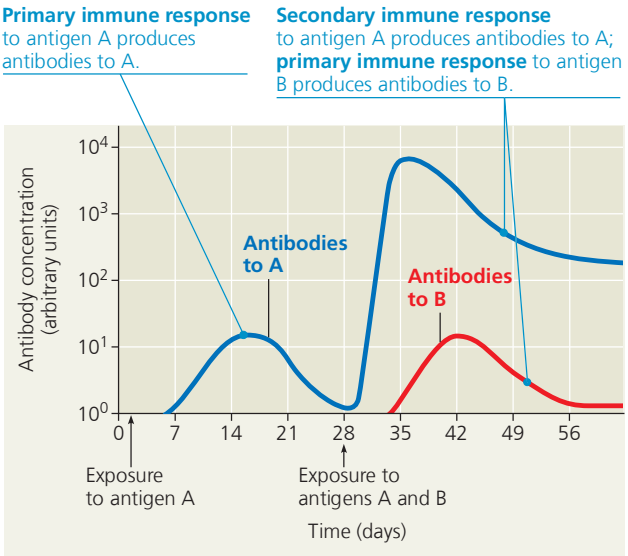
▼ Figure 43.16 Clonal selection of B cells.



VISUAL SKILLS *For the purpose of illustration, this figure shows only a few of each type of cell or molecule. Based on what you have read in Concept 43.2, provide estimates of the number of different B cells and number of antigen receptors on each B cell.*

Mastering Biology **Animation: Clonal Selection**

▼ Figure 43.17 The specificity of immunological memory. Long-lived memory cells that are generated in the primary response to antigen A give rise to a heightened secondary response to the same antigen but don't affect the primary response to another antigen (B).



INTERPRET THE DATA *Assume that on average one out of every 10^5 B cells in the body is specific for antigen A on day 16 and that the number of B cells producing a specific antibody is proportional to the concentration of that antibody. What would you predict is the frequency of B cells specific for antigen A on day 36?*

decades. (Most 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 that are 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 in Concept 43.3.

CONCEPT CHECK 43.2

1. **DRAW IT** Sketch a B cell antigen receptor. Label the V and C regions of the light and heavy chains. Where are the antigen-binding sites, disulfide bridges, and transmembrane region located relative to these regions?
2. Explain how memory cells strengthen the immune response 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 43.3

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 humoral and cell-mediated immune responses. The **humoral immune response** protects the blood and lymph (once called body *humors*, or fluids). In this response, antibodies help neutralize or eliminate toxins and pathogens in body fluids. In the **cell-mediated immune response**, specialized T cells destroy infected host cells. Both humoral and cellular immunity can include a primary and a secondary immune response, with memory cells enabling the secondary response.

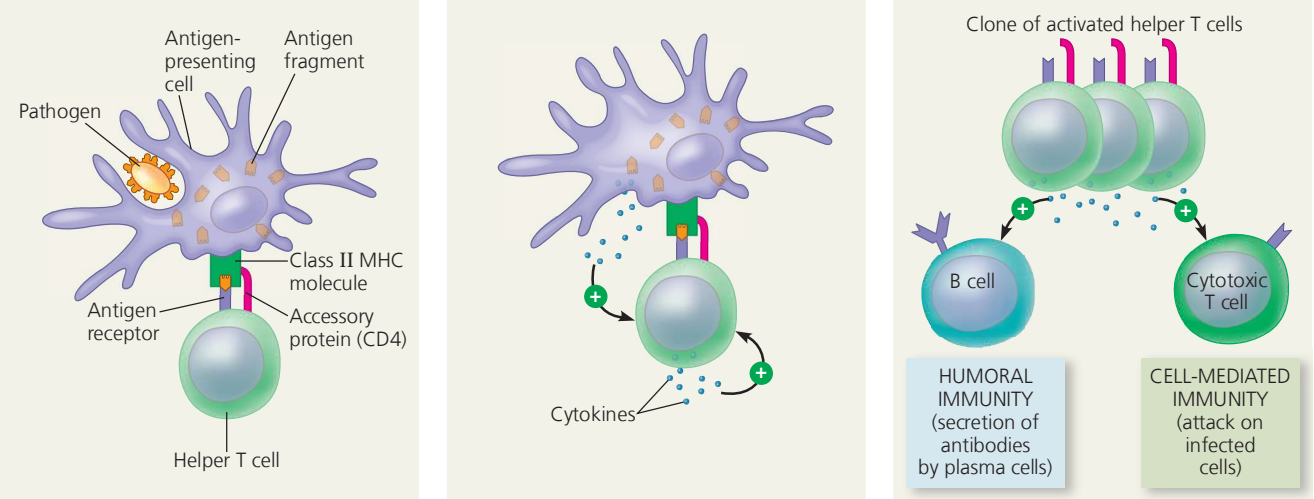
Helper T Cells: Activating Adaptive Immunity

A type of T cell called a **helper T cell** activates humoral and cell-mediated immune responses. Before this can happen, however, two conditions must be met. First, a foreign molecule must be present that can bind specifically to the antigen receptor of the helper T cell. Second, this antigen must be displayed on the surface of an **antigen-presenting cell**. An antigen-presenting cell can be a dendritic cell, macrophage, or B cell.

Like immune cells, infected cells can display foreign antigens on their surface. What then distinguishes antigen-presenting cells from infected cells? The answer lies in two distinct types, or *classes*, of MHC molecules. Most body cells have only the 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. 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 **(Figure 43.18)**. 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 are exchanged in the form of cytokines. For example, the cytokines secreted from a dendritic cell act in combination with the antigen to stimulate the helper T cell, causing it to produce its own set of cytokines. Also, extensive contact between the cell surfaces enables further information exchange.

▼ Figure 43.18 The central role of helper T cells in humoral and cell-mediated immune responses. Here, a helper T cell responds to a dendritic cell displaying an antigen.



1 An antigen-presenting cell engulfs a pathogen, degrades it, and displays antigen fragments complexed with class II MHC molecules on the cell surface. A specific helper T cell binds to this complex via its antigen receptor and an accessory protein called CD4.

2 Binding of the helper T cell promotes secretion of cytokines by the antigen-presenting dendritic cell. These cytokines, along with cytokines from the helper T cell itself, activate the helper T cell and stimulate its proliferation.

3 Cell proliferation produces a clone of activated helper T cells. All cells in the clone have receptors for the same antigen. These cells secrete other cytokines, which help activate B cells and cytotoxic T cells with the same antigen specificity.

Mastering Biology BioFlix® Animation: Activation of a Helper T Cell by a Dendritic Cell (Example: Infection by a Rhinovirus)

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. In contrast, B cells present antigens to *already* activated helper T cells, which in turn activate the B cells. Activated helper T cells also help stimulate cytotoxic T cells, as we'll discuss shortly.

B Cells and Antibodies: A Response to Extracellular Pathogens

Secretion of antibodies by clonally selected B cells is the hallmark of the humoral immune response. It begins with activation of the B cells.

Activation of B Cells

As illustrated in **Figure 43.19**, 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.

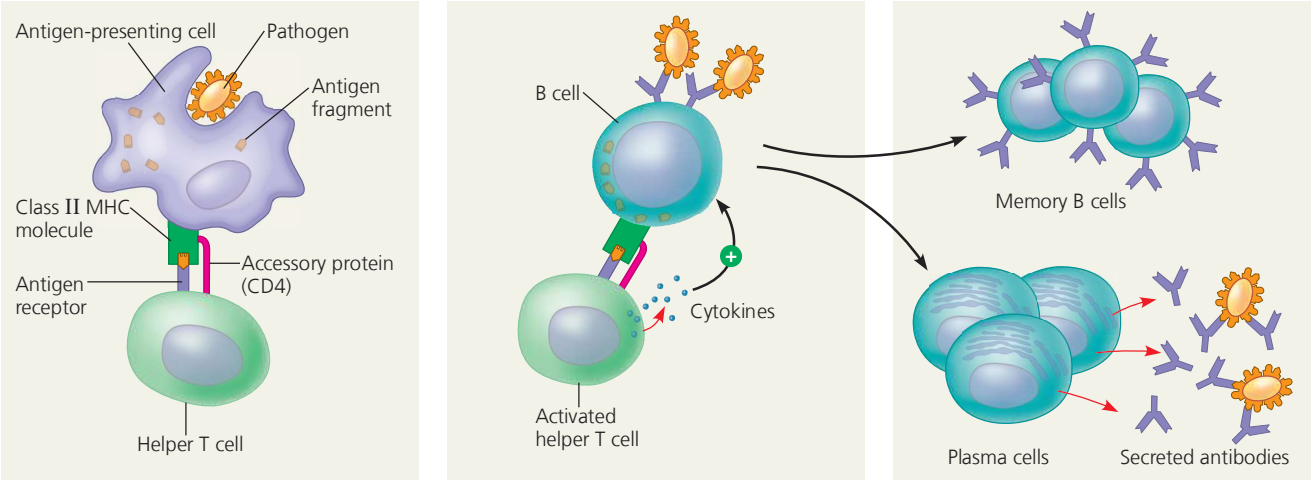
The pathway for antigen processing and display in B cells differs from that in other antigen-presenting cells. A macrophage or dendritic cell can present fragments from a wide variety of protein antigens, whereas a B cell presents only the antigen to which it specifically binds. When an antigen first binds to receptors on the surface of a B cell, the cell takes in a few foreign molecules by receptor-mediated endocytosis (see Figure 7.19). The class II MHC protein of the B cell then presents an antigen fragment to a helper T cell. This direct cell-to-cell contact is usually critical to B cell activation (see step 2 in Figure 43.19).

B cell activation leads to a robust humoral immune response: A single activated B cell gives rise to thousands of identical plasma cells. These plasma cells stop expressing a membrane-bound antigen receptor and begin producing and secreting antibodies (see step 3 in Figure 43.19). Each plasma cell secretes approximately 2,000 antibodies every second during its four- to five-day life span, nearly a trillion antibody molecules in total. Furthermore, most antigens recognized by B cells contain multiple epitopes. An exposure to a single antigen therefore normally activates a variety of B cells, which give rise to different plasma cells producing antibodies directed against different epitopes on the common antigen.

Antibody Function

Antibodies do not directly kill pathogens, but by binding to antigens, they interfere with pathogen activity or mark

▼ Figure 43.19 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.



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.

? *Looking at the steps in this figure, propose a function for the cell-surface antigen receptors of memory B cells.*

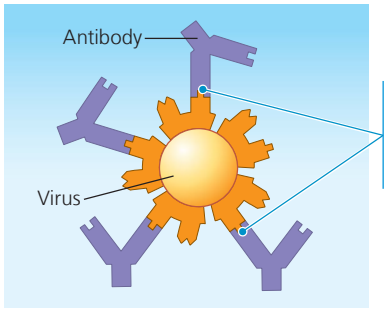
Mastering Biology BioFlix® Animation: Adaptive Defenses: B Cells (Example: Infection by a Rhinovirus)

pathogens in various ways for inactivation or destruction. Consider, for example, *neutralization*, a process in which antibodies bind to proteins on the surface of a virus **(Figure 43.20a)**. The bound antibodies prevent viral 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.

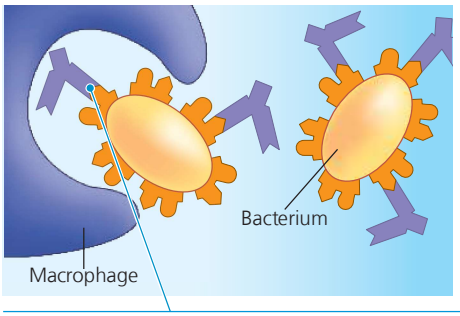
In *opsonization*, antibodies that are bound to antigens on bacteria do not block infection, but instead present a readily recognized structure for macrophages or neutrophils, thereby promoting phagocytosis **(Figure 43.20b)**. Because each antibody has two antigen-binding sites, antibodies can also facilitate phagocytosis by linking bacterial cells, viruses, or other foreign substances into aggregates.

When antibodies facilitate phagocytosis, as in opsonization, they also help fine-tune the humoral immune response. Recall that phagocytosis enables macrophages and dendritic cells to present antigens to and stimulate helper T cells, which in turn stimulate the very B cells whose antibodies contribute to phagocytosis. This positive feedback between innate and adaptive immunity contributes to a coordinated, effective response to infection.

▼ Figure 43.20 Two mechanisms of antibody function.

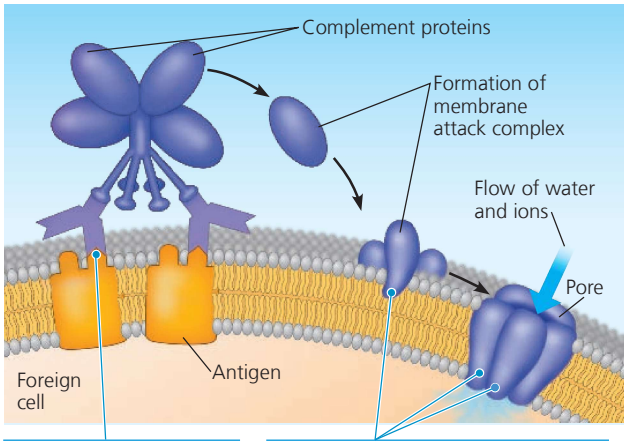


(a) Neutralization



(b) Opsonization

▼ Figure 43.21 Activation of complement system and pore formation.



Binding of antibodies to antigens on the surface of a foreign cell activates the complement system.

After activation of the complement system, the membrane attack complex forms pores in the cell's membrane, allowing water and ions to rush in. The cell swells and lyses.

Antibodies sometimes work together with the proteins of the complement system **(Figure 43.21)**. (The name *complement* reflects the fact that these proteins add to 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.

Although antibodies are the cornerstones of the response in body fluids, there is also a mechanism by which they can bring about the death of infected body cells. When a virus uses a cell's biosynthetic machinery to produce viral proteins, these viral products can appear on the cell surface. If antibodies specific for epitopes on these viral proteins bind to the exposed proteins, the presence of bound antibody at the cell surface can recruit a natural killer cell. The natural killer cell then releases proteins that cause the infected cell to undergo apoptosis. Thus the activities of the innate and adaptive immune systems are once again closely linked.

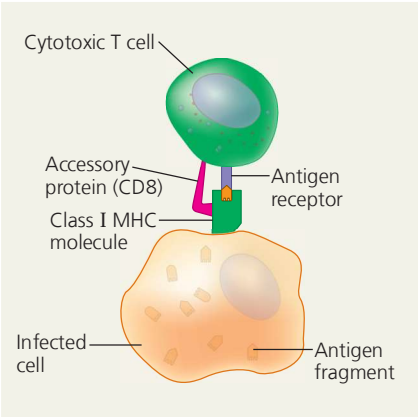
B cells can express five different types, or *classes*, of immunoglobulin (IgA, IgD, IgE, IgG, and IgM). For a given B cell, each class has an identical antigen-binding specificity but a distinct heavy-chain C region. The B cell antigen receptor, known as IgD, is exclusively membrane bound. The other four classes of Ig have soluble forms, such as the antibodies found in blood, tears, saliva, and breast milk.

Cytotoxic T Cells: A Response to Infected Host Cells

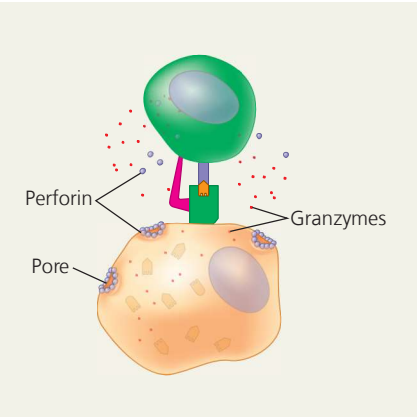
In the absence of an immune response, pathogens can reproduce in and kill infected cells. In the cell-mediated immune response, **cytotoxic T cells** use toxic proteins to kill cells infected by viruses or other intracellular pathogens before pathogens fully mature **(Figure 43.22)**. To become active, 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

▼ Figure 43.22 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.

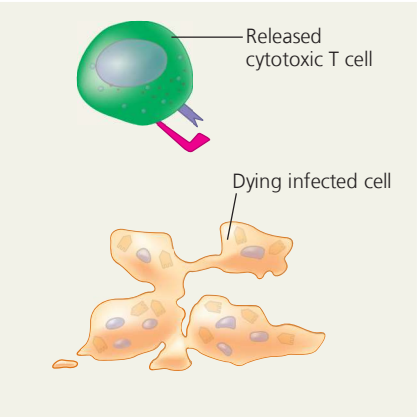
Mastering Biology BioFlix® Animation: Adaptive Defenses: Cytotoxic T Cells (Example: Infection by a Rhinovirus)



1 An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on an infected cell via the T cell's 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 via the perforin pores.



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

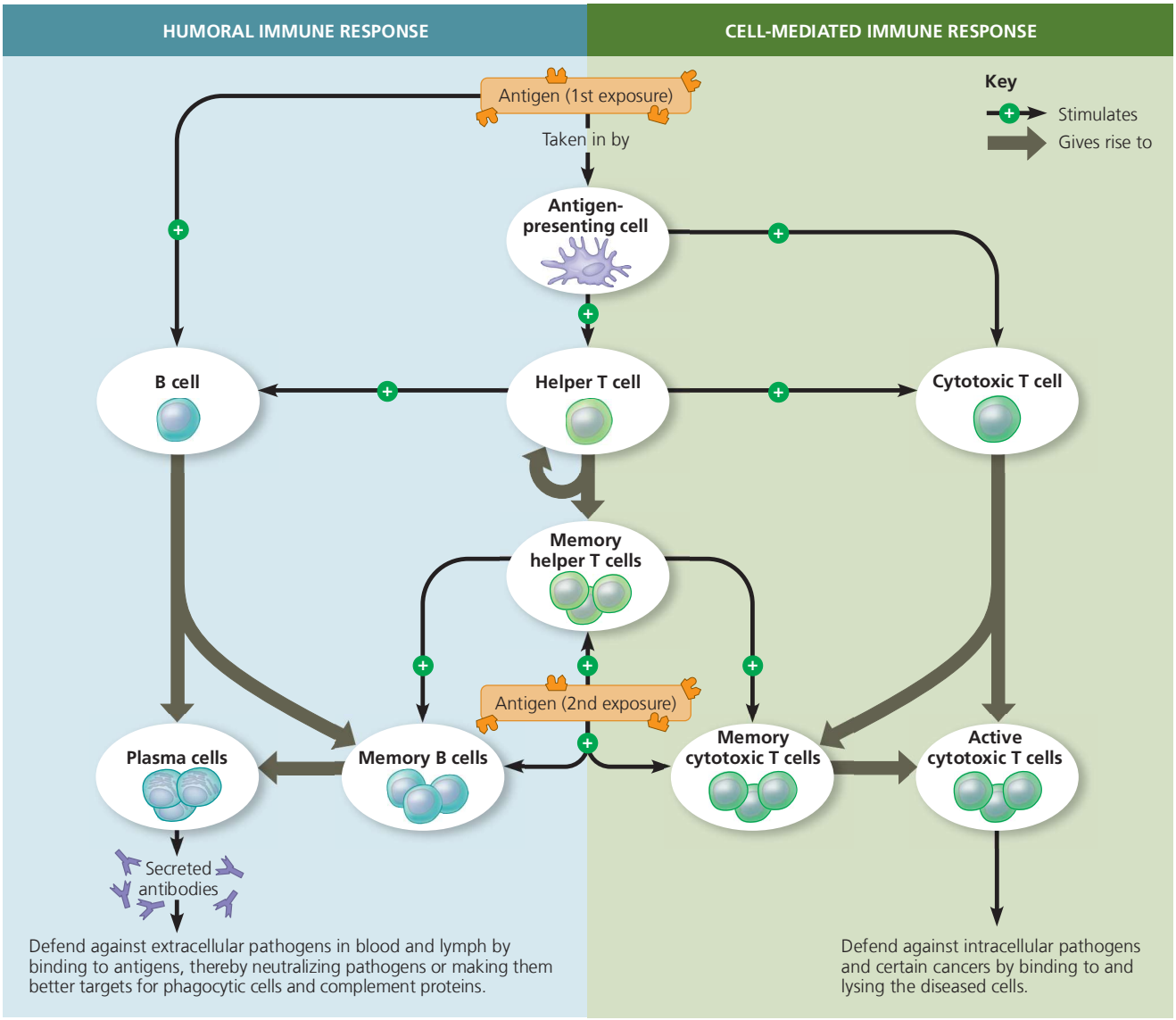
T cells. Like helper T cells, cytotoxic T cells have an accessory protein that can bind to an MHC molecule. The interaction of this accessory protein, called CD8, with a class I MHC molecule displaying antigen targets the infected cell for cytotoxic T cell activity.

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 (apoptosis; see Figure 43.22). The death of the infected cell not only deprives the pathogen of a place to multiply but also exposes cell contents to circulating antibodies, which mark released antigens for disposal.

Summary of the Humoral and Cell-Mediated Immune Responses

As noted earlier, both humoral and cell-mediated immunity 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 43.23** summarizes adaptive immunity, reviews the events that initiate humoral and cell-mediated immune responses, highlights the difference in

▼ Figure 43.23 An overview of the adaptive immune response.



VISUAL SKILLS *Identify each arrow as representing part of the primary response or secondary response.*

Mastering Biology **BioFlix® Animation: Summary of the Adaptive Immune Response (Example: Infection by a Rhinovirus)**

response to pathogens in body fluids versus in body cells, and emphasizes the central role of the helper T cell.

Immunization

The protection provided by a second immune response provides the basis for **immunization**, the use of antigens artificially introduced into the body to generate an adaptive immune response and memory cell formation. In 1796, Edward Jenner noted that milkmaids who had cowpox, a mild disease usually seen only in cows, did not contract smallpox, a far more dangerous disease. In the first documented immunization (or *vaccination*, from the Latin *vacca,* cow), Jenner used the cowpox virus to induce adaptive immunity against the closely related smallpox virus. The *vaccines* used today for immunizations may be made from inactivated bacterial toxins, killed or weakened pathogens, or even genes encoding microbial proteins. Because all of these agents induce a primary immune response and immunological memory, an encounter with the pathogen from which the vaccine was derived triggers a rapid and strong secondary immune response (see Figure 43.17).

Vaccination programs have been successful against many infectious diseases that once killed or incapacitated large numbers of people. A worldwide vaccination campaign led to eradication of smallpox in the late 1970s. In industrialized nations, routine immunization of infants and children has dramatically reduced the incidence of sometimes devastating diseases, such as polio and measles **(Figure 43.24)**. Unfortunately, not all pathogens are easily managed by vaccination. Furthermore, some vaccines are not readily available in impoverished areas of the globe.

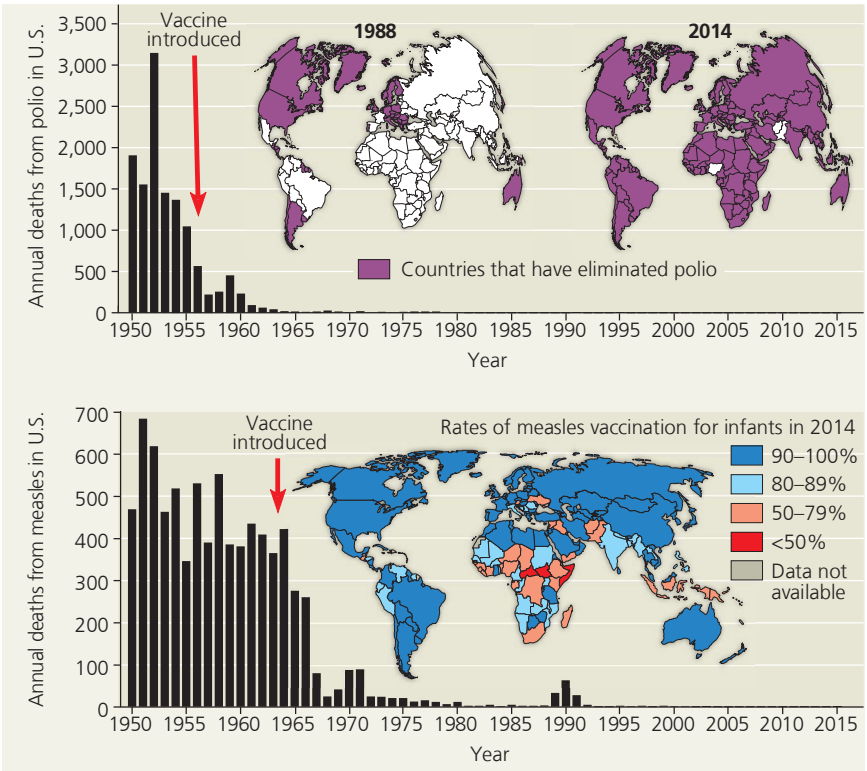
Misinformation about vaccine safety and disease risk has led to a growing public health problem. Consider measles as just one example. The vaccine is highly effective and very safe—fewer than one in a million children experience a significant allergic reaction. Indeed, a vaccination campaign had effectively eliminated the disease in the United States by 2000. However, the disease remains quite dangerous to this day, killing more than 200,000 people worldwide each year. Recently, a decline in vaccination rates in the United States has led to multiple outbreaks since 2010. A multi-state outbreak in 2019 was the worst in two decades, with more than 1,100 cases in the first six months of the year. Even with modern medical care, measles kills on average one out of every 1,000 infected individuals.

Active and Passive Immunity

Our discussion of adaptive immunity has to this point focused on **active immunity**, the defenses that arise when a pathogen infection or immunization prompts an immune response. A different type of immunity results when, for example, the IgG 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). IgA antibodies present in breast milk provide additional passive immunity to the infant's digestive tract while the infant's immune system develops. Passive immunity persists only as long as the transferred antibodies last (up to a few months).

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, the antibodies in antivenin can neutralize toxins in the venom before the toxins do massive damage.

▼ Figure 43.24 Vaccine-based protection against two life-threatening communicable diseases. The graphs show deaths by year in the United States caused by polio and measles. The maps show examples of the global progress against these two diseases.



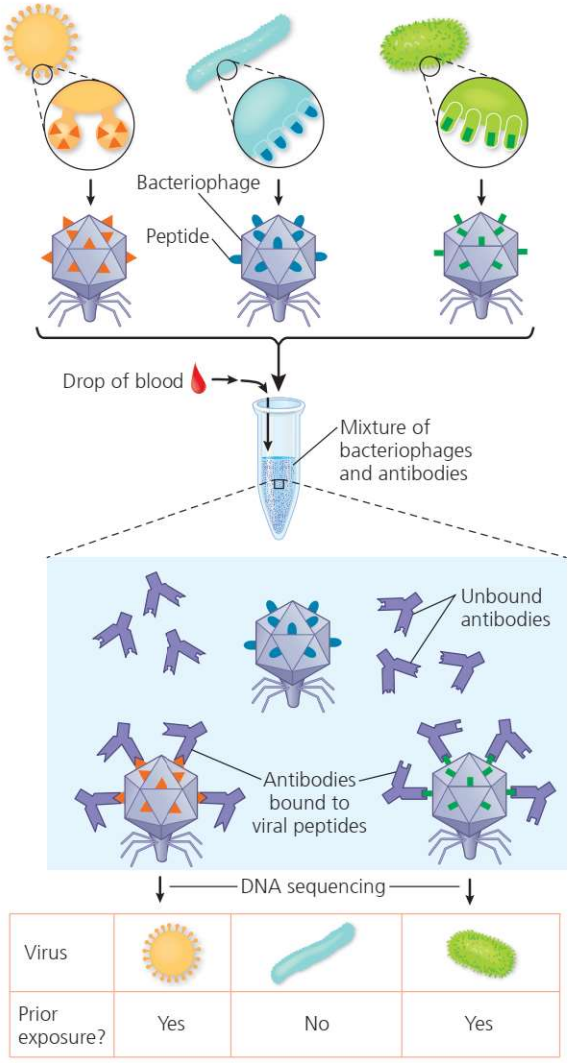
Antibodies as Tools

Antibodies that an animal produces after exposure to an antigen are the products of many different clones of plasma cells, each specific for a different epitope. However, antibodies can also be prepared from a single 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 Concept 46.5), 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 being used as therapies for a growing number of human diseases, including many cancers.

One recently developed antibody tool uses a single drop of blood to identify every virus that a person has encountered through infection or vaccination **(Figure 43.25)**. To detect the antibodies formed against these viruses, researchers generated a set of nearly 100,000 bacteriophages, each of which displays a different peptide from one of the roughly 200 species of viruses that infect humans.

▼ Figure 43.25 A comprehensive test for past viral encounters. By combining the power of DNA sequencing with the specificity of antigen recognition by antibodies, researchers can identify every virus that a person's immune system has encountered during the person's lifetime.



1. Viruses that infect humans have unique peptides on their surface (insets). By introducing short DNA sequences from all known human viruses into copies of a bacteriophage genome, researchers generated a collection of 100,000 bacteriophages, each displaying many copies of one viral peptide.
2. The bacteriophages are combined with serum from a drop of a person's blood. The serum contains antibodies, some of which were produced in response to exposure to viruses. Any antibody that is specific for a viral peptide binds to a bacteriophage displaying that peptide. Bacteriophages displaying peptides from viruses never encountered are not recognized.
3. DNA sequencing of bacteriophages to which antibodies are bound identifies the complete set of viruses to which a person has been exposed.

WHAT IF? *All of the antibodies are shown with just one antigen-binding site occupied. If a single antibody bound to two bacteriophages, how would this affect the results?*

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. It turns out that MHC molecules are a primary cause of rejection. Why? Each of us expresses MHC proteins from more than a dozen different MHC genes. Furthermore, there are more than 100 different versions, or alleles, of human MHC genes. As a consequence, the sets of MHC proteins on cell surfaces are likely to differ between any two people, except identical twins. Such differences can stimulate an immune response in the recipient of a transplant or graft, causing rejection. To minimize rejection of a transplant or graft, surgeons 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).

Blood Groups

In the case of blood transfusions, the recipient's immune system can recognize glycoproteins on the surface of blood cells as foreign, 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. Red blood

cells are designated as type A if they have the A carbohydrate on their surface. Similarly, the B carbohydrate is found on the surface of type B red blood cells; both A and B carbohydrates are found on type AB red blood cells; and neither carbohydrate is found on type O red blood cells (see Figure 14.11).

Why does the immune system recognize particular sugars on red blood cells? It turns out that we are frequently exposed to certain bacteria that have epitopes very similar to the carbohydrates on blood cells. A person with type A blood will respond to the bacterial epitope similar to the B carbohydrate and make antibodies that will react with any B carbohydrate encountered upon a transfusion. However, that same person doesn't make antibodies against the bacterial epitope similar to the A carbohydrate because lymphocytes that would be reactive with the body's own cells and molecules were inactivated or eliminated during development.

To understand how ABO blood groups affect transfusions, let's consider further the example of a person with type A blood receiving a transfusion of type B blood. The person's anti-B antibodies would cause the transfused red blood cells to undergo lysis, triggering chills, fever, shock, and perhaps kidney malfunction. At the same time, anti-A antibodies in the donated type B blood would act against the recipient's red blood cells. Applying the same logic to a type O person, we can see that such interactions would cause a problem upon transfusion of any other blood type. Fortunately, the discovery of enzymes that can cleave the A and B carbohydrates from red blood cells may eliminate this problem in the future.

CONCEPT CHECK 43.3

1. If a child were born without a thymus gland, what cells and functions of the immune system would be deficient? Explain.
2. Treatment of antibodies with a particular protease clips the heavy chains in half, releasing the two arms of the Y-shaped molecule. How might the antibodies continue to function?
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 have a harmful side effect?

For suggested answers, see Appendix A.

CONCEPT 43.4

Disruptions in immune system function can elicit or exacerbate disease

Although adaptive immunity protects against many pathogens, it is not fail-safe. Here we'll first examine the disorders and diseases that arise when adaptive immunity is blocked or misregulated. We'll then turn to some of the evolutionary adaptations of pathogens that diminish the effectiveness of adaptive immune responses in the host.

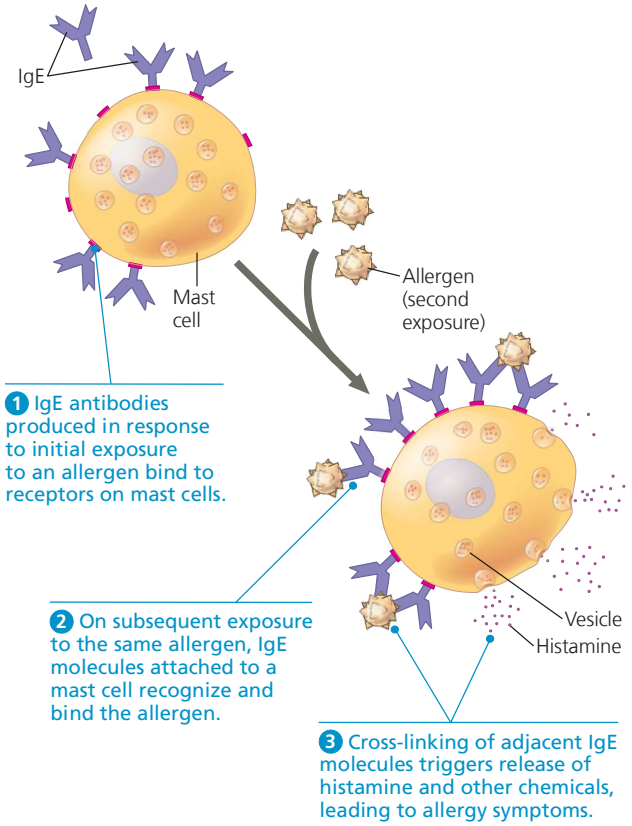
Exaggerated, Self-Directed, and Diminished Immune Responses

The highly regulated interplay among lymphocytes, other body cells, and foreign substances generates an immune response that provides extraordinary protection against many pathogens. When allergic, autoimmune, or immunodeficiency disorders disrupt this delicate balance, the effects are frequently severe.

Allergies

Allergies are exaggerated (hypersensitive) responses to certain antigens called *allergens*. The most common allergies involve antibodies of the IgE class. Hay fever, for instance, occurs when plasma cells secrete IgE antibodies specific for antigens on the surface of pollen grains **(Figure 43.26)**. Some IgE antibodies attach by their base to mast cells in connective tissues. Pollen grains that enter the body later attach to the antigen-binding sites of these IgE antibodies. Such attachment cross-links adjacent IgE molecules, inducing the mast cell to release histamine and other inflammatory chemicals. Acting on a variety of cell types, these chemicals bring about the typical allergy symptoms: sneezing, runny nose, teary eyes, and smooth muscle contractions in the lungs that can inhibit effective breathing.

▼ **Figure 43.26 Mast cells, IgE, and the allergic response.** In this example, pollen grains act as the allergen.



Drugs known as antihistamines block receptors for histamine, diminishing allergy symptoms (and inflammation).

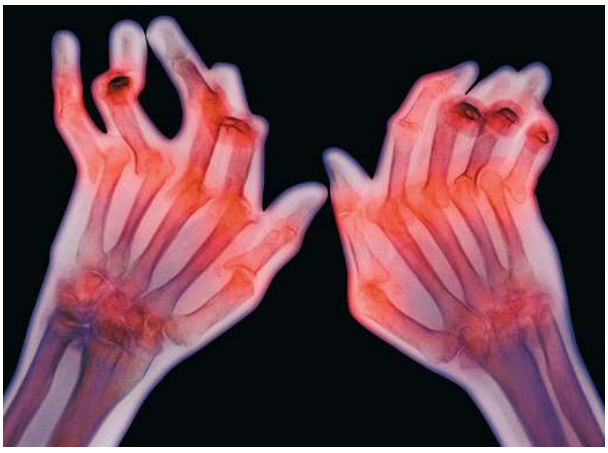
An acute allergic response sometimes leads to a life-threatening reaction called *anaphylactic shock*. Inflammatory chemicals released from immune cells trigger constriction of bronchioles and sudden dilation of peripheral blood vessels, which causes a precipitous drop in blood pressure. Death may occur within minutes due to the inability to breathe and lack of blood flow. Substances that can cause anaphylactic shock in allergic individuals include bee venom, penicillin, peanuts, and shellfish. People with severe hypersensitivities often carry an autoinjector containing the hormone epinephrine. An injection of epinephrine rapidly counteracts this allergic response, constricting peripheral blood vessels, reducing swelling in the throat, and relaxing muscles in the lungs to help breathing (see Figure 45.20b).

Autoimmune Diseases

In some people, the immune system is active against particular molecules of the body, causing an **autoimmune disease**. Such a loss of self-tolerance has many forms. In systemic lupus erythematosus, commonly called *lupus*, the immune system generates antibodies against histones and DNA released by the normal breakdown of body cells. These self-reactive antibodies cause skin rashes, fever, arthritis, and kidney dysfunction. Other targets of autoimmunity include the insulin-producing beta cells of the pancreas (in type 1 diabetes) and the myelin sheaths that encase many neurons (in multiple sclerosis).

Heredity, gender, and environment all influence susceptibility to autoimmune disorders. For example, members of certain families show an increased susceptibility to particular autoimmune disorders. In addition, many autoimmune diseases affect females more often than males. Women are nine times as likely as men to have 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 43.27)**. The causes of this sex bias, as well as the rise in autoimmune disease frequency in industrialized countries, are areas of active research and debate.

▼ Figure 43.27 X-ray of hands that are deformed by rheumatoid arthritis.



An additional focus of current research on autoimmune disorders is the activity of *regulatory T cells*, nicknamed Tregs. These specialized T cells help modulate immune system activity and prevent response to self-antigens.

Exertion, Stress, and the Immune System

Many forms of exertion and stress influence immune system function. For example, moderate exercise improves immune system function and significantly reduces susceptibility to the common cold and other infections of the upper respiratory tract. In contrast, exercise to the point of exhaustion leads to more frequent infections and more severe symptoms. Psychological stress likewise disrupts immune system regulation, altering the interplay of the hormonal, nervous, and immune systems (see Figure 45.20). Research has also shown that rest is important for immunity: Adults who averaged fewer than 7 hours of sleep got sick three times as often when exposed to a cold virus as those who averaged at least 8 hours.

Immunodeficiency Diseases

A disorder in which an immune system response to antigens is defective or absent is called an immunodeficiency. Whatever its cause and nature, an immunodeficiency can lead to frequent and recurrent infections and increased susceptibility to certain cancers.

An *inborn immunodeficiency* results from a genetic or developmental defect in the production of immune system cells or of specific proteins, such as antibodies or the proteins of the complement system. Depending on the specific defect, either innate or adaptive defenses—or both—may be impaired. In severe combined immunodeficiency (SCID), functional lymphocytes are rare or absent. Lacking an adaptive immune response, SCID patients are susceptible to infections that can cause death in infancy, such as pneumonia and meningitis. Treatments include bone marrow and stem cell transplantation.

Later in life, exposure to chemicals or biological agents can cause an *acquired immunodeficiency*. Drugs used to fight autoimmune diseases or prevent transplant rejection suppress the immune system, leading to an immunodeficient state. Certain cancers also suppress the immune system, especially Hodgkin's disease, which damages the lymphatic system. Acquired immunodeficiencies range from temporary states that may arise from physiological stress to the devastating disease AIDS (acquired immune deficiency syndrome), which we'll explore in the next section.

Evolutionary Adaptations of Pathogens That Underlie 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. Using human pathogens

as examples, we'll examine some common mechanisms: antigenic variation, latency, and direct attack on the immune system.

Antigenic Variation

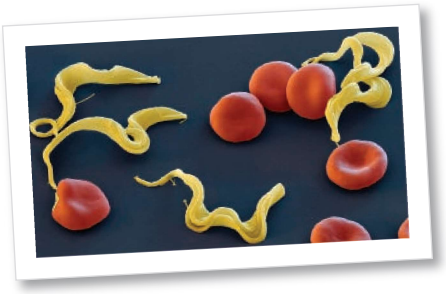
One mechanism for escaping the body's defenses involves a pathogen altering how it appears to the immune system. If a pathogen changes the epitopes that it expresses to ones that a host has not previously encountered, it can reinfect or remain in the host without triggering the rapid and robust response mediated by memory cells. Such changes in epitope expression are called *antigenic variation*. The parasite that causes sleeping sickness (trypanosomiasis) provides an extreme example, periodically switching at random among 1,000 versions of the protein found over its entire surface. In the **Scientific Skills Exercise**, you will interpret data on this form of antigenic variation and the body's response.

Antigenic variation is the main reason the influenza, or "flu," virus remains a major public health problem. As it

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. The glycoproteins covering a trypanosome's surface are encoded by a gene that is duplicated more than 1,000 times in the organism's genome. Each copy is slightly different. By periodically switching among these genes, the trypanosome can display a series of surface glycoproteins with different molecular structures. In this exercise, you will interpret two data sets to explore hypotheses about the benefits to the trypanosome of its ever-shifting surface glycoproteins in avoiding the host's immune response.



Day of infection	Study A: Millions of parasites/mL blood	Study B: Antibody specific to Variant A	Study B: Antibody specific to Variant B
4	0.1	0	0
6	0.3	0	0
8	1.2	0.2	0
10	0.2	0.5	0
12	0.2	1	0
14	0.9	1	0.1
16	0.6	1	0.3
18	0.1	1	0.9
20	0.7	1	1
22	1.2	1	1
24	0.2	1	1

Data from L. J. Morrison et al., Probabilistic order in antigenic variation of *Trypanosoma brucei*, *International Journal for Parasitology* 35:961–972 (2005); and L. J. Morrison et al., Antigenic variation in the African trypanosome: molecular mechanisms and phenotypic complexity, *Cellular Microbiology* 1:1724–1734 (2009).

Data from the Studies Study A measured the abundance of parasites in the blood of one human patient during the first few weeks of a chronic infection. The results are shown in the second column of the data table. 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 third and fourth columns of the table list the relative abundance of two such antibodies during the early period of chronic infection, using an index ranging from 0 (absent) to 1.

Part A: INTERPRET THE DATA

1. Which of the first two columns represents the independent variable and which the dependent variable? Plot the data from Study A as a line graph, putting the independent variable on the *x*-axis. (For additional information about graphs, see the Scientific Skills Review in Appendix D.)
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: INTERPRET THE DATA

4. Note that the data for Study B were collected over the same period of infection (days 4–24) as the parasite abundance data in Study 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 question 3? Do they prove it? 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?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

replicates in one human host after another, the human flu virus undergoes frequent mutations. As a result, a new flu vaccine must be developed, produced, and distributed each year. In addition, the human flu virus occasionally forms new strains by exchanging genes with influenza viruses that infect domesticated animals, such as pigs or chickens. When this exchange of genes occurs, the new strain 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.

Latency

Some viruses avoid an immune response by infecting cells and then entering a largely inactive state called *latency*. In latency, the production of most viral proteins and free viruses ceases; as a result, latent viruses do not trigger an adaptive immune response. Nevertheless, the viral genome persists in the nuclei of infected cells, either as a separate DNA molecule or as a copy integrated into the host genome. Latency typically persists until conditions arise that are favorable for viral transmission or unfavorable for host survival, such as when the host is infected by another pathogen. Such circumstances trigger the synthesis and release of free viruses that can infect new hosts.

Herpes simplex viruses provide a good example of latency. A number of these herpesviruses infect only humans and cause symptoms ranging from mild to life-threatening **(Table 43.1)**. The type 1 herpesvirus causes most oral herpes infections (often inaccurately called "cold" sores), whereas the sexually transmitted type 2 herpesvirus is responsible for most cases of genital herpes. People infected with either the type 1 or type 2 herpesvirus often have no symptoms. Instead, these viruses remain latent in certain neurons until a stimulus such as fever, emotional stress, or a hormonal change associated with the menstrual cycle reactivates the virus. Activation of the type 1 herpesvirus can result in the appearance of blisters around the mouth. Infections of the type 2 herpesvirus pose a serious threat to the babies of infected mothers and can increase transmission of HIV.

Table 43.1 Latency as a Shared Characteristic of Human Herpesviruses

Human Herpesvirus	Main Sites of Latency	Associated Diseases or Disorders
Herpes simplex virus-1 (HSV-1)	Clusters of neurons in spinal nerves	Cold sores
Herpes simplex virus-2 (HSV-2)	Clusters of neurons in spinal nerves	Genital ulcers
Varicella-zoster virus (VZV)	Clusters of neurons in spinal nerves	Chicken pox, shingles
Epstein-Barr virus (EBV)	Memory B cells	Some lymphoma, mononucleosis
Cytomegalovirus (CMV)	Monocytes and lymphocytes	Abnormal fetal development
Human herpesvirus 8 (HHV-8)	B cells	Kaposi's sarcoma

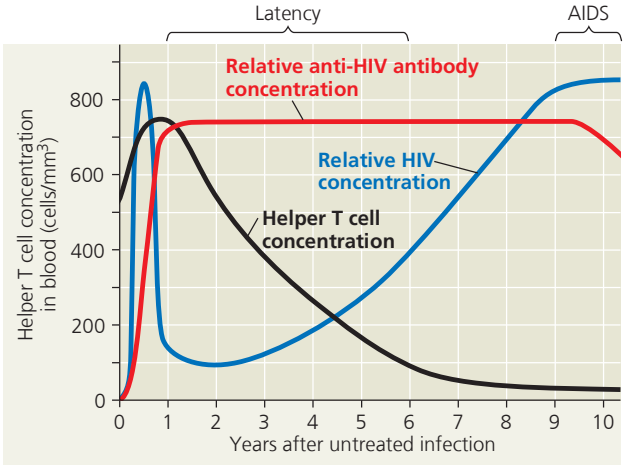
Attack on the Immune System: HIV

The **human immunodeficiency virus (HIV)**, the pathogen that causes AIDS, both escapes and attacks the adaptive immune response. HIV infects helper T cells with high efficiency by binding specifically to the CD4 accessory protein. HIV also infects some cell types that have low levels of CD4, such as macrophages and brain cells. Inside cells, the HIV RNA genome is reverse-transcribed, and the product DNA is integrated into the host cell's genome (see Figure 19.8). In this form, the viral genome can direct the production of new viruses.

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 replicate and mutate further. HIV thus evolves within the body.

Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it **(Figure 43.28)**. Viral replication and cell death triggered by the virus lead to loss of helper T cells, impairing both humoral and cell-mediated immune responses. The eventual result is **acquired immunodeficiency syndrome (AIDS)**, an impairment in immune responses that leaves the body susceptible to infections and cancers that a healthy immune system would usually defeat. For example, *Pneumocystis jirovecii*, a common fungus that does not cause disease in

▼ Figure 43.28 The progress of an untreated HIV infection.



Mastering Biology
Interview with Flossie Wong-Staal: Characterizing HIV

healthy individuals, can result in severe pneumonia in people with AIDS. Such opportunistic diseases, as well as nerve damage and body wasting, are the primary causes of death from AIDS, rather than HIV itself.

Transmission of HIV requires the transfer of virus particles or infected cells from person to person via body fluids such as semen, blood, or breast milk. Unprotected sex (that is, without using a condom) and transmission via HIV-contaminated needles (often among intravenous drug users) cause the vast majority of HIV infections. The virus can enter the body through mucosal linings of the vagina, vulva, penis, or rectum during intercourse or via the mouth during oral sex. 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 no cure has been found for HIV infection, drugs that can significantly slow HIV replication and the progression to AIDS are available.

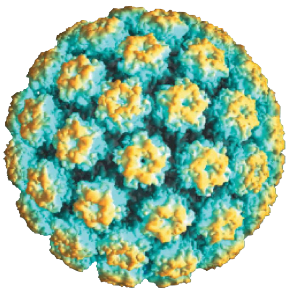
Mastering Biology Animation: HIV Reproductive Cycle

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 patients with untreated AIDS than for people who are healthy. This observation was initially puzzling. 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 (see Table 43.1). 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 specific for human papillomavirus (HPV) marked a major victory against cervical cancer, as well as oral cancers that are becomingly increasingly common among men. The computer graphic image of an HPV particle in **Figure 43.29** illustrates the abundant copies of the capsid protein (yellow) that is used as the antigen in vaccination.

▼ Figure 43.29 Human papillomavirus.



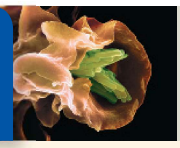
Mastering Biology
Interview with Harald zur Hausen: Discovering the cause of cervical cancer

CONCEPT CHECK 43.4

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 is myasthenia gravis?
2. People with herpes simplex type 1 viruses often get mouth sores when they have a cold or similar infection. How might this location benefit the virus?
3. **WHAT IF?** How would a macrophage deficiency likely affect a person's innate and adaptive defenses?

For suggested answers, see Appendix A.

43 Chapter Review



Go to Mastering Biology for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the Vocab Self-Quiz in the Mastering Biology eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 43.1

In innate immunity, recognition and response rely on traits common to groups of pathogens
(pp. 953–957)

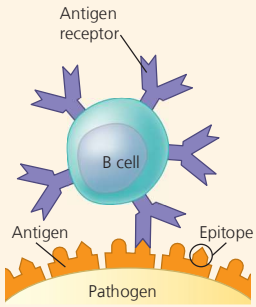
- **Innate immunity** is mediated by physical and chemical barriers as well as cell-based defenses. Recognition proteins in innate immunity are specific for broad classes of **pathogens**. Pathogens that penetrate barrier defenses are ingested by phagocytic cells, which in vertebrates include **macrophages** and **dendritic cells**. Additional cellular defenses include **natural killer cells**, which can induce the death of virus-infected cells. **Complement system** proteins, **interferons**, and other antimicrobial peptides also act against pathogens. In the **inflammatory response, histamine** and other chemicals that are released at the injury site promote changes in blood vessels that enhance immune cell access and action.
- Pathogens sometimes evade innate immune defenses. For example, some bacteria have an outer capsule that prevents recognition, while others are resistant to breakdown within lysosomes.

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

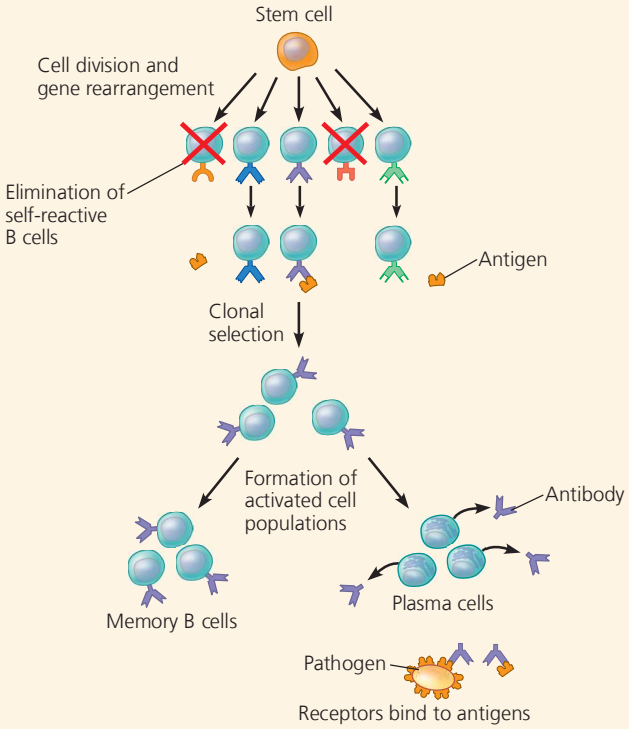
CONCEPT 43.2

In adaptive immunity, receptors provide pathogen-specific recognition *(pp. 957–963)*

- **Adaptive immunity** relies on two types of **lymphocytes: B cells** and **T cells**. Lymphocytes have cell-surface **antigen receptors** for foreign molecules (**antigens**). All receptor proteins on a single B or T cell are the same, but there are millions of B and T cells in the body that differ in the foreign molecules that their receptors recognize. Upon infection, B and T cells specific for the pathogen are activated. Some T cells help other lymphocytes; others kill infected host cells. B cells called **plasma cells** produce soluble proteins called **antibodies**, which bind to foreign molecules and cells. B and T **memory cells** defend against future infections by the same pathogen.



- Recognition of foreign molecules by B cells and T cells 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 circulating in the blood or lymph. T cells recognize protein epitopes in small antigen fragments (peptides) that are presented on the surface of host cells by **major histocompatibility complex (MHC) molecules**. This interaction activates a T cell, enabling it to participate in adaptive immunity.
- 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 43.3

Adaptive immunity defends against infection of body fluids and body cells *(pp. 963–970)*

- **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 **humoral immune response**, antibodies help eliminate antigens by facilitating phagocytosis and complement-mediated lysis. In the **cell-mediated immune response**, activated **cytotoxic T cells** trigger destruction of infected cells.
- **Active immunity** develops in response to infection or to **immunization**. The transfer of antibodies in **passive immunity** provides immediate, short-term protection.
- Tissues or cells transferred from one person to another are subject to immune rejection. In tissue grafts and organ transplants, MHC molecules stimulate rejection. Lymphocytes in bone marrow transplants may cause a graft-versus-host reaction.

? *Is immunological memory after a natural infection fundamentally different from immunological memory after vaccination? Explain.*

CONCEPT 43.4

Disruptions in immune system function can elicit or exacerbate disease *(pp. 970–974)*

- 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. Inborn immunodeficiencies result from defects that interfere with innate, humoral, or cell-mediated defenses. **AIDS** is an acquired immunodeficiency caused by **HIV**.
- Antigenic variation, latency, and direct assault on the immune system allow some pathogens to thwart immune responses.

? *Is being infected with HIV the same as having AIDS? Explain.*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. Which of these is absent from insect immunity?
   (A) antibacterial digestive enzymes
   (B) activation of natural killer cells
   (C) phagocytosis by hemocytes
   (D) production of antimicrobial peptides
2. An epitope associates with which part of an antigen receptor or antibody?
   (A) the tail
   (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
3. Which statement best describes the difference between responses of effector B cells (plasma cells) and those of cytotoxic T cells?
   (A) B cells confer active immunity; cytotoxic T cells confer passive immunity.
   (B) B cells respond the first time a pathogen is present; cytotoxic T cells respond subsequent times.
   (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.

Levels 3-4: Applying/Analyzing

4. Which of the following statements is true?
   (A) An antibody has one antigen-binding site.
   (B) A lymphocyte has receptors for a single antigen.
   (C) Every antigen has a single epitope.
   (D) A liver or muscle cell makes two classes 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 set of immune cells eliminated as self-reactive

Levels 5-6: Evaluating/Creating

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) MHC molecules that can present an antigen.
7. Which of the following is least likely to 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
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 clonal selection with Lamarck's idea for the inheritance of acquired characteristics (see Concept 22.1).
10. **EVOLUTION CONNECTION** Describe one invertebrate mechanism of defense against pathogens and discuss how it is an evolutionary adaptation retained in vertebrates.
11. **SCIENTIFIC INQUIRY** A major cause of septic shock is the presence in blood of lipopolysaccharide (LPS) from bacteria. Suppose you have available purified LPS and several strains of mice, each with a mutation that inactivates a particular TLR gene. Explain how you might use these mice to test the feasibility of treating septic shock with a drug that blocks TLR signaling.
12. **WRITE ABOUT A THEME: 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 DNA as heritable biological information, focusing on similarities between cellular and organismal generations.
13. **SYNTHESIZE YOUR KNOWLEDGE**

This child is receiving an oral vaccine against polio, a disease caused by a virus that infects neurons. Given that the body cannot replace most neurons, why must a polio vaccine stimulate both a cell-mediated and a humoral response?

For selected answers, see Appendix A.

Explore Scientific Papers with Science in the Classroom AAAS
How do immunizations affect deaths from infectious disease?
Go to "One Vaccine to Rule Them All"
at www.scienceintheclassroom.org.
Instructors: Questions can be assigned in Mastering Biology.

44 Osmoregulation and Excretion

KEY CONCEPTS

Study Tip

Make a table: As you read Concept 44.2, complete a table like the one shown to help organize information about the major forms of nitrogenous waste. In the first three rows, use the terms "high," "medium," or "low" to describe the relevant properties of these forms.

Waste attribute	Waste product		
	Ammonia	Urea	Uric acid
Toxicity			
Energy cost to produce			
Water loss during excretion			
Example of organism excreting this product			

Go to Mastering Biology

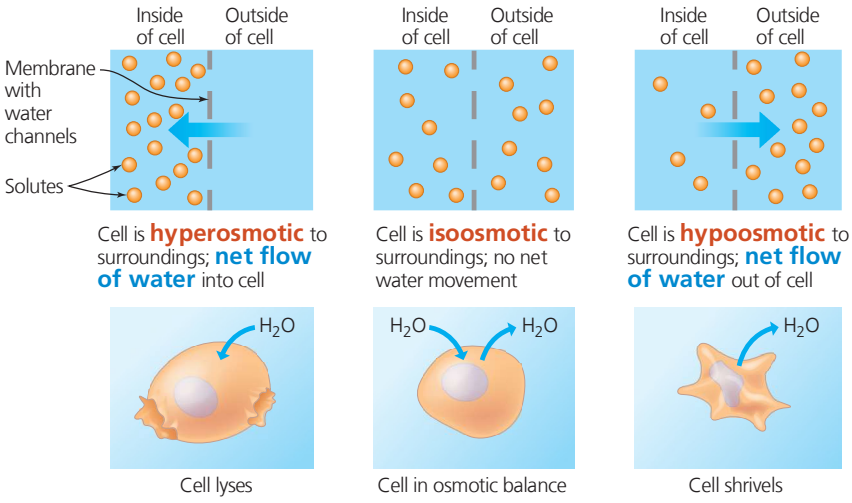
For Students (in eText and Study Area)
- Get Ready for Chapter 44
- Figure 44.14 Walkthrough: How the Human Kidney Concentrates Urine
- BioFlix® Animation: Membrane Transport

For Instructors to Assign (in Item Library)
- Tutorial: Kidney Structure and Function
- Scientific Skills Exercise: Describing and Interpreting Quantitative Data

Figure 44.1 At 3.5 m, the wingspan of a wandering albatross (*Diomedea exulans*) is the largest of any living bird. This massive bird remains at sea day and night throughout the year, returning to land only to reproduce. Despite drinking only seawater, the albatross keeps its body salts and water in balance.

How do animals regulate water and salt concentrations in their tissues?

Lacking a means to pump water across cell membranes, animals transport salts and thereby direct water movement into or out of cells by **osmosis**, in which water undergoes net diffusion from an area of higher free H_2O concentration (lower solute concentration) to an area of lower free H_2O concentration (higher solute concentration).



As you'll read, excretory systems not only maintain salt and water balance, but also rid the body of **nitrogen-containing wastes**.

For both an albatross and a human, maintaining fluid balance requires that the relative concentrations of water and solutes be kept within narrow limits. In addition, ions such as sodium and calcium must be kept 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 and balance water gain and loss.

In safeguarding their internal fluids, animals must also deal with ammonia, a toxic metabolite produced by the dismantling of *nitrogenous* (nitrogen-containing) molecules, chiefly proteins and nucleic acids. Several mechanisms have evolved for ridding the body of nitrogenous metabolites and other metabolic waste products, a process called **excretion**. Because systems for osmoregulation and excretion are structurally and functionally linked in many animals, we'll consider both of these processes in this chapter.

CONCEPT 44.1

Osmoregulation balances the uptake and loss of water and solutes

Osmoregulation requires controlled movement of water and solutes across plasma membrane. Ultimately, the driving force for the movement of both water and solutes is a concentration gradient of one or more solutes across the membrane.

Osmosis and Osmolarity

Water enters and leaves cells by osmosis, which occurs when two solutions separated by a membrane differ in total solute concentration. The unit of measurement for solute concentration is **osmolarity**, the number of moles of solute per liter of solution. The osmolarity of human blood is about 300 milliosmoles per liter (mOsm/L), whereas that of seawater is about 1,000 mOsm/L.

Two solutions with the same osmolarity are said to be *isoosmotic*. If a selectively permeable membrane separates the solutions, water molecules will continually cross the membrane at equal rates in both directions. Thus, there is no *net* movement of water by osmosis between isoosmotic solutions. When two solutions differ in osmolarity, the solution with the higher 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, thus reducing the concentration difference for both solutes and free water (see the diagram on the first page of the chapter).

In this chapter, we use the terms *isoosmotic, hypoosmotic*, and *hyperosmotic*, which refer specifically to osmolarity, instead of *isotonic, hypotonic*, and *hypertonic*. The latter set of terms applies to the response of animal cells—whether they swell or shrink—in solutions of known solute concentrations.

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. Because an osmoconformer's internal osmolarity is the same as that of its environment, there is no tendency to gain or lose water. Many osmoconformers live in water that has a stable composition and hence have a constant internal osmolarity.

The second way to maintain water balance is to be an **osmoregulator**: to control internal osmolarity independent of that of the external environment. In a hypoosmotic environment, an osmoregulator must discharge excess water. In a hyperosmotic environment, it must instead take in water to offset osmotic loss. Osmoregulation enables animals to live in environments that are uninhabitable for osmoconformers, such as freshwater and terrestrial habitats, or to move between marine and freshwater environments **(Figure 44.2)**.

Whether osmoconformers or osmoregulators, most animals cannot tolerate substantial changes in external osmolarity and are said to be *stenohaline* (from the Greek *stenos*, narrow, and *halos*, salt). In contrast, *euryhaline* animals (from the Greek *eurys*, broad) can survive large fluctuations in external osmolarity. Euryhaline osmoconformers include barnacles and mussels in estuaries that are alternately exposed to fresh and salt water; euryhaline osmoregulators include striped bass and the various species of salmon (see Figure 44.2).

Next, we'll examine adaptations for osmoregulation that have evolved in marine, freshwater, and terrestrial animals.

Marine Animals

Most marine invertebrates are osmoconformers. Their osmolarity is the same as that of seawater. Therefore, they face no

▼ Figure 44.2 Sockeye salmon (*Oncorhynchus nerka*), osmoregulators that migrate between rivers and the ocean.

substantial challenges in water balance. Nevertheless, they actively transport *specific* solutes that they maintain at levels different from those in the ocean. For example, homeostatic mechanisms in the Atlantic lobster (*Homarus americanus*) maintain a magnesium ion (Mg^{2+}) concentration in hemolymph (circulatory fluid) of less than 9 m*M* (millimolar, or 10^{-3} mol/L), far below the 50 m*M* concentration of Mg^{2+} in their environment.

Two osmoregulatory strategies evolved among marine vertebrates that address the challenges of a strongly dehydrating environment. One is found among marine "bony fishes," a group that includes ray-finned and lobe-finned fishes. The other is found in marine sharks and most other chondrichthyans (cartilaginous animals; see Concept 34.3).

Cod, shown in **Figure 44.3a**, and other marine bony fishes constantly lose water by osmosis. They balance water loss by drinking a lot of seawater. The excess salts ingested with seawater are eliminated through the gills and kidneys.

Like bony fishes, sharks have an internal salt concentration much lower than that of seawater. However, shark tissues have a high concentration of several other solutes, including urea and another organic molecule, trimethylamine oxide (TMAO). Because the total solute concentration is somewhat higher than 1,000 mOsm/L, water slowly *enters* the shark's body by osmosis and in food (sharks do not drink).

The small influx of water into the shark's body is disposed of in urine produced by the kidneys. The urine also removes some of the salt that diffuses into the shark's body; the rest is lost in feces or is secreted from a specialized gland.

Freshwater Animals

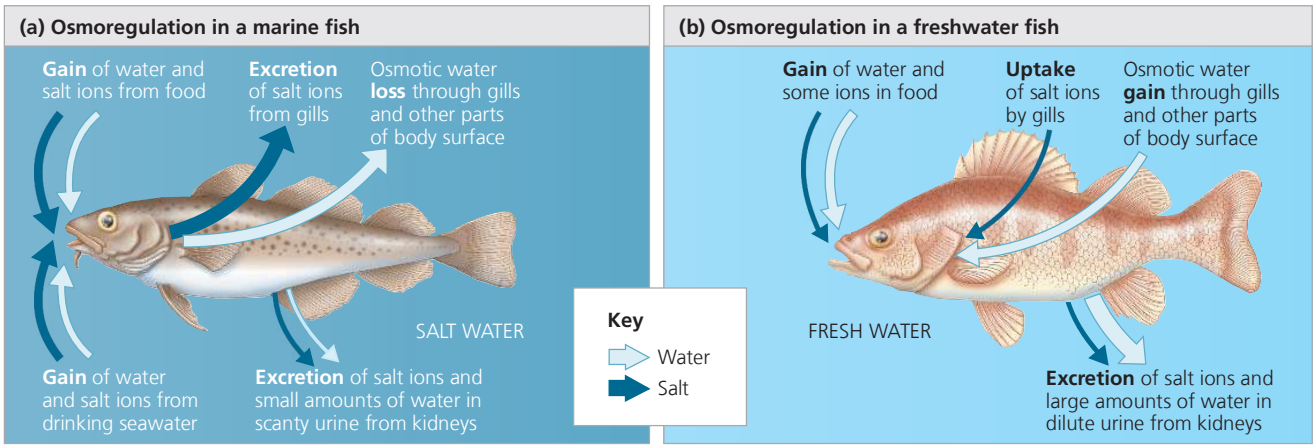
The osmoregulatory problems of freshwater animals are the opposite of those of marine animals. The body fluids of freshwater animals must be hyperosmotic because animal cells cannot tolerate salt concentrations as low as that of lake or river water. Since freshwater animals have internal fluids with an osmolarity higher than that of their surroundings, they face the problem of gaining water by osmosis. For the perch and many other freshwater animals, water balance relies on excreting large amounts of very dilute urine and drinking almost no water **(Figure 44.3b)**. In addition, salts lost by diffusion and in the urine are replenished by eating and by taking up salt across their gills.

Salmon and other euryhaline fishes that migrate between fresh water and seawater undergo dramatic changes in osmoregulatory status. When living in rivers and streams, salmon osmoregulate like other freshwater fishes, producing large amounts of dilute urine and taking up salt from the dilute environment through their gills. When they migrate to the ocean, salmon acclimatize (see Concept 40.2). They produce more of the steroid hormone cortisol, which increases the number and size of specialized salt-secreting cells. These and other physiological changes enable salmon in salt water to excrete excess salt from their gills and produce only small amounts of urine—just like bony fishes that spend their entire lives in salt water.

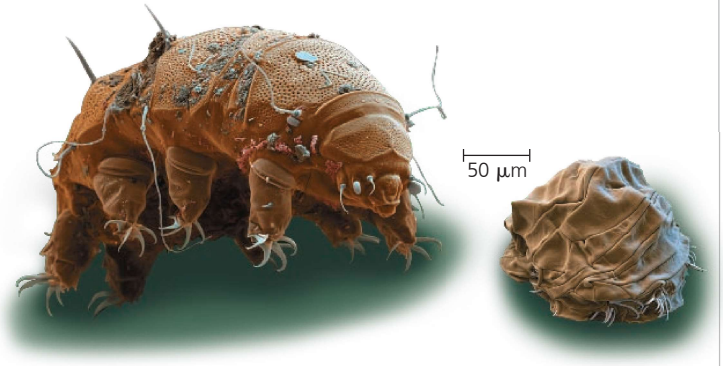
Animals That Live in Temporary Waters

Extreme dehydration, or *desiccation*, is fatal for most animals. However, a few aquatic invertebrates that live in temporary ponds and in films of water around soil particles can lose almost all their body water and survive. These animals enter a dormant state when their habitats dry up, an adaptation called **anhydrobiosis** ("life without water"). Among the most striking examples are the tardigrades, or water bears, tiny invertebrates less than

▼ Figure 44.3 Osmoregulation in marine and freshwater bony fishes: a comparison.



▼ **Figure 44.4 Anhydrobiosis.** When hydrated, tardigrades (SEM images) inhabit temporary ponds as well as droplets of water in soil and on moist plants.



1 mm long **(Figure 44.4)**. In their active, hydrated state, they contain about 85% water by weight, but they can dehydrate to less than 2% water and survive in an inactive state, dry as dust, for a decade or more. Just add water, and within hours the rehydrated tardigrades are moving about and feeding.

Anhydrobiosis requires adaptations that keep cell membranes intact. Researchers are just beginning to learn how tardigrades survive drying out, but studies of anhydrobiotic roundworms (phylum Nematoda; see Concept 33.4) show that desiccated individuals contain large amounts of sugars. In particular, a disaccharide called trehalose seems to protect the cells by replacing the water that is normally associated with proteins and membrane lipids. Many insects that survive freezing in the winter also use trehalose as a membrane protectant, as do some plants resistant to desiccation.

Recently, scientists began applying lessons learned from the study of anhydrobiosis to the preservation of biological materials. Traditionally, samples of protein, DNA, and cells have been kept in ultracold freezers (−80°C), consuming large amounts of energy. Today, the manufacture of materials modeled after the protectants of anhydrobiotic species has enabled room temperature storage of such samples.

Land Animals

The threat of dehydration is a major regulatory problem for terrestrial plants and animals. Adaptations that reduce water loss are key to survival on land. Much as a waxy cuticle contributes to the success of land plants, the body coverings of most terrestrial animals help prevent dehydration. Examples are the waxy layers of insect exoskeletons, the shells of land snails, and the layers of dead, keratinized skin cells covering most terrestrial vertebrates, including humans.

Many terrestrial animals, especially desert-dwellers, are nocturnal, which reduces evaporative water loss because of the lower temperature and higher humidity of night air.

Despite anatomical and behavioral adaptations that conserve water, most terrestrial animals lose water through a variety of routes: in urine and feces, across the skin, and from the epithelial surfaces of gas exchange organs and airways. Land animals maintain water balance by drinking and eating moist foods and by producing water metabolically through cellular respiration.

A number of desert animals are well enough adapted for minimizing water loss that they can survive for long periods of time without drinking. Camels, for example, tolerate a 7°C rise in body temperature, greatly reducing the amount of water lost in sweat production. They can also lose 25% of their body water and survive. (In contrast, a human who loses half this fraction of body water will die from heart failure.) In the **Scientific Skills Exercise**, you can examine water balance in another desert species, the sandy inland mouse.

Energetics of Osmoregulation

Maintaining an osmolarity difference between an animal's body and its external environment carries an energy cost. Because diffusion tends to equalize concentrations in a system, osmoregulators must expend energy to maintain the osmotic gradients that cause water to move in or out. They do so by using active transport to manipulate solute concentrations in their body fluids.

The energy cost of osmoregulation depends on how different an animal's osmolarity is from its surroundings, how easily water and solutes can move across the animal's surface, and how much work is required to pump solutes across the membrane. Osmoregulation accounts for 5% or more of the resting metabolic rate of many fishes. For brine shrimp, small crustaceans that live in extremely salty lakes, the gradient between internal and external osmolarity is very large, and the cost of osmoregulation is correspondingly high—as much as 30% of the resting metabolic rate.

The energy cost to an animal of maintaining water and salt balance is minimized by having body fluids that are adapted to the salinity of the animal's habitat. Thus, the body fluids of most animals that live in fresh water (which has an osmolarity of 0.5–15 mOsm/L) have lower solute concentrations than the body fluids of their closest relatives that live in seawater (1,000 mOsm/L). For instance, whereas marine molluscs have body fluids with solute concentrations of approximately 1,000 mOsm/L, some freshwater molluscs maintain the osmolarity of their body fluids at just 40 mOsm/L. In each case, minimizing the osmotic difference between body fluids and the surrounding environment decreases the energy cost of osmoregulation.

Scientific Skills Exercise

Describing and Interpreting Quantitative Data

How Do Desert Mice Maintain Osmotic Homeostasis?
The sandy inland mouse (now known scientifically as *Pseudomys 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 kept in an environmentally controlled room and given birdseed (10% water by weight) to eat. In part A of the study, the mice had unlimited access to tap water for drinking; in part B of the study, the mice were not given any drinking water for 35 days, similar to conditions in their natural habitat. At the end of parts A and B, the researchers measured the osmolarity and urea concentration of the urine and blood of each mouse. The mice were also weighed three times a week.

Data from the Experiment

Access to Water	Mean Osmolarity (mOsm/L)		Mean Urea Concentration (m*M*)	
	Urine	Blood	Urine	Blood
Part A: Unlimited	490	350	330	7.6
Part B: None	4,700	320	2,700	11
In part A, the mice 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 can you draw from these ratios?
3. If you learned that the amount of urine produced in part A were different from that in part B, how would that affect your calculation? Explain.

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

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).

Transport Epithelia in Osmoregulation

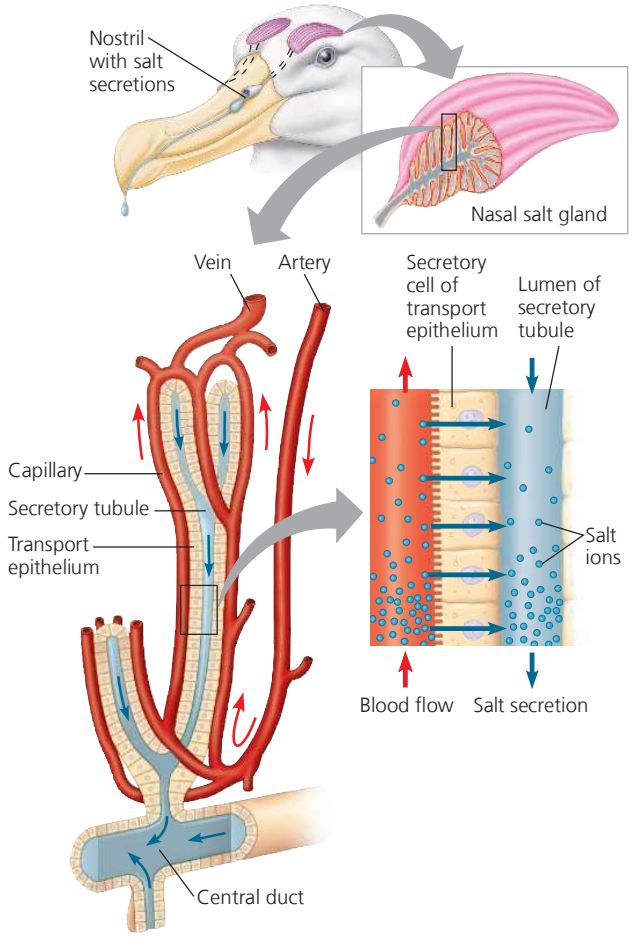
Although the ultimate function of osmoregulation is to control solute concentrations in cells, most animals do this indirectly, managing instead the solute content of the body fluid that bathes the cells. In insects and other animals with an open circulatory system, the fluid surrounding cells is hemolymph. In vertebrates and other animals with a closed circulatory system, the cells are bathed in an interstitial fluid that contains a mixture of solutes controlled indirectly by the blood. Maintaining the composition of such fluids depends on structures ranging from individual cells that regulate solute movement to complex organs such as the vertebrate kidney.

In most animals, 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 into tubular networks with extensive surface areas. Some transport epithelia face the outside environment directly, whereas others line channels connected to the outside by an opening on the body surface.

The transport epithelium that enables the albatross and other marine birds to survive on seawater remained undiscovered for many years. To find it, researchers gave captive marine birds only seawater to drink. Although very little salt appeared in the birds' urine, tests revealed that fluid dripping from the tip of their beaks was a concentrated solution of salt (NaCl). The source of this solution turned out to be a pair of nasal salt glands packed with transport epithelia **(Figure 44.5)**. Salt glands, which are also found in sea turtles and marine iguanas, use active transport of ions to secrete a fluid much saltier than the ocean. Even though drinking seawater brings in a lot of salt, the salt gland enables these marine vertebrates to achieve a net gain of water. By contrast, humans who drink a given volume of seawater must use a *greater* volume of water to excrete the salt load, with the result that they become dehydrated.

Transport epithelia that function in maintaining water balance also often function in disposal of metabolic wastes. We'll see examples of this coordinated function in our upcoming consideration of earthworm and insect excretory systems as well as the vertebrate kidney.

▼ Figure 44.5 Salt secretion in the nasal glands of a marine bird. A transport epithelium moves salt from the blood into secretory tubules, which drain into central ducts leading to the nostrils.



CONCEPT CHECK 44.1

1. The movement of salt from the surrounding water to the blood of a freshwater fish requires the expenditure of energy in the form of ATP. Why?
2. Why aren't any freshwater animals osmoconformers?
3. **WHAT IF?** Researchers found that a camel in the sun required much more water when its fur was shaved off, although its body temperature was the same. What can you conclude about the relationship between osmoregulation and the insulation provided by fur?

For suggested answers, see Appendix A.

CONCEPT 44.2

An animal's nitrogenous wastes reflect its phylogeny and habitat

In regulating and safeguarding their internal fluids, animals must deal with **ammonia**, a toxic metabolite produced by the dismantling of *nitrogenous* (nitrogen-containing) molecules, chiefly proteins and nucleic acids. Several mechanisms have evolved for ridding the body of ammonia and other metabolic waste products, a process called **excretion**. 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.

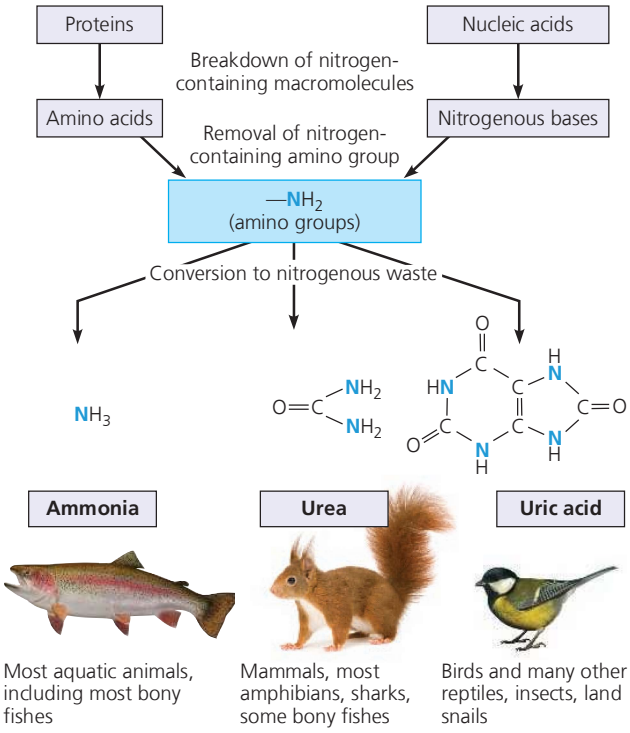
Forms of Nitrogenous Waste

Although some animal species excrete ammonia directly, others excrete alternative forms of nitrogenous waste, either urea or uric acid **(Figure 44.6)**. These different forms vary significantly in their toxicity, their solubility, and the energy costs of producing them.

Ammonia

Ammonia is very toxic, in part because its ion, ammonium (NH_4^+), can interfere with oxidative phosphorylation. Because ammonia can be tolerated only at very low concentrations, animals that excrete ammonia need access to lots of water. Therefore, ammonia excretion is most common in aquatic species. The highly soluble ammonia molecules, which interconvert between NH_3 and NH_4^+, easily pass through membranes and are readily lost by diffusion to the surrounding water. In many invertebrates, ammonia release occurs across the whole body surface.

▼ Figure 44.6 Variations in forms of nitrogenous waste among animal species.



Urea

Although ammonia excretion works well in many aquatic species, it is much less suitable for land animals. Ammonia is so toxic that it can be safely transported through and excreted from the body only in large volumes of very dilute solutions. Most terrestrial animals and many marine species simply do not have access to sufficient water to routinely excrete ammonia. Instead, they mainly excrete a different nitrogenous waste, **urea**. In vertebrates, urea is the product of an energy-consuming metabolic cycle that combines ammonia with carbon dioxide in the liver.

The main advantages of urea for nitrogenous waste excretion are its very low toxicity and its high solubility in water. The main disadvantage is its energy cost: Animals must expend energy to produce urea from ammonia. From a bioenergetic standpoint, we would predict that animals that spend part of their lives in water and part on land would switch between excreting ammonia (thereby saving energy) and excreting urea (reducing excretory water loss). Indeed, many amphibians excrete mainly ammonia when they are aquatic tadpoles and switch largely to urea excretion when they become land-dwelling adults.

Uric Acid

Insects, land snails, and many reptiles, including birds, excrete **uric acid** as their primary nitrogenous waste **(Figure 44.7)**. 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 than urea, requiring considerable ATP for synthesis from ammonia.

Although they are not primarily uric acid producers, humans and some other animals generate a small amount of uric acid from metabolism. Diseases that alter this process reflect problems that can arise when a metabolic product is insoluble. For example, a genetic defect predisposes Dalmatian dogs to form uric acid stones in their bladder. In humans, adult males are particularly susceptible to *gout*, a painful joint inflammation caused by deposits of uric acid crystals. Some dinosaurs appear to have been similarly affected: Fossilized bones of *Tyrannosaurus rex* exhibit joint damage characteristic of gout.

▼ Figure 44.7 Guano (bird excrement) is rich in uric acid.

The Influence of Evolution and Environment on Nitrogenous Wastes

EVOLUTION As a result of natural selection, the type and amount of nitrogenous waste a species produces are matched to its environment. One key factor in a habitat is the availability of water. For example, terrestrial turtles (which often live in dry areas) excrete mainly uric acid, whereas aquatic turtles excrete both urea and ammonia.

In some cases, an animal's egg is the immediate environment of relevance to the type of nitrogenous waste excreted. In an amphibian egg, which lacks a shell, ammonia or urea can simply diffuse out of the egg. Similarly, soluble wastes produced by a mammalian embryo can be carried away by the mother's blood. In the case of birds and other reptiles, however, the egg is surrounded by a shell that is permeable to gases but not to liquids. As a result, any soluble nitrogenous wastes released by the embryo would be trapped within the egg and could accumulate to dangerous levels. For this reason, using uric acid as an insoluble waste product conveys a selective advantage in reptiles. Stored within the egg as a harmless solid, the uric acid is left behind when the animal hatches.

Regardless of the type of nitrogenous waste, the amount produced is coupled to the animal's energy budget. Endotherms, which use energy at high rates, eat more food and produce more nitrogenous waste than ectotherms. The amount of nitrogenous waste is also linked to diet. Predators, which derive much of their energy from protein, excrete more nitrogen than animals that rely mainly on lipids or carbohydrates as energy sources.

Having surveyed the forms of nitrogenous waste and their interrelationship with habitat and energy consumption, we'll turn next to the processes and systems animals use to excrete these and other wastes.

CONCEPT CHECK 44.2

1. What advantage does uric acid offer as a nitrogenous waste in arid environments?
2. **WHAT IF?** Suppose a bird and a human both have gout. Why might reducing purine in their diets help the human much more than the bird?

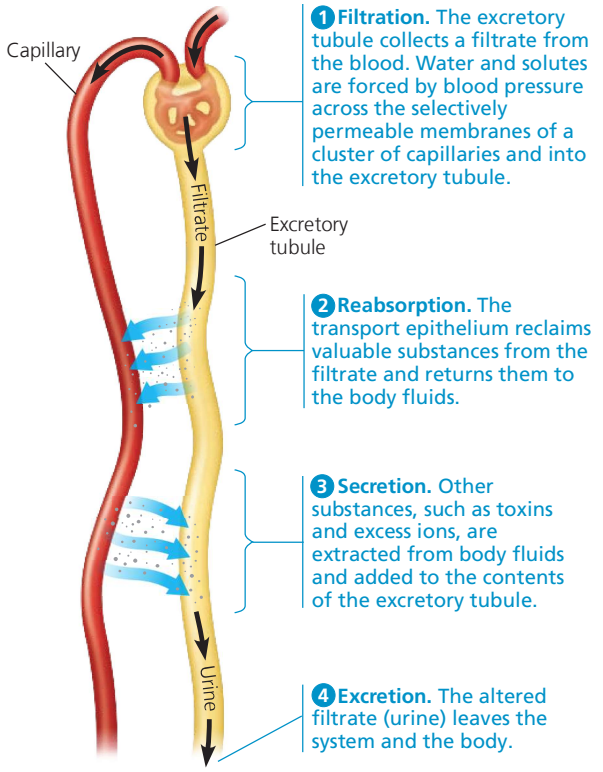
For suggested answers, see Appendix A.

CONCEPT 44.3

Diverse excretory systems are variations on a tubular theme

By both disposing of metabolic wastes and controlling body fluid composition, excretory systems play a central role in homeostasis. Excretory processes begin when body fluid (blood, coelomic fluid, or hemolymph) is brought

▼ Figure 44.8 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.



in contact with the selectively permeable membrane of a transport epithelium **(Figure 44.8)**. 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 fluid. 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 in turn determines whether water moves by osmosis into or out of the filtrate. In the last step—excretion—the processed filtrate containing nitrogenous wastes is released from the body as a fluid waste called urine.

Survey of Excretory Systems

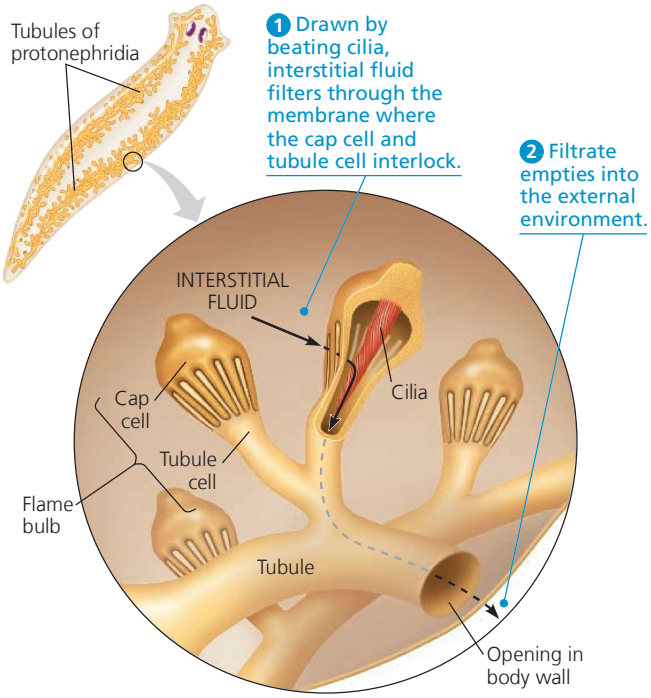
The systems that perform the basic excretory functions outlined in Figure 44.8 vary widely among animal groups. However, they are generally built on a complex network of tubules that provide a large surface area for the exchange of water and solutes, including nitrogenous wastes. We'll examine the excretory systems of flatworms, earthworms, insects, and vertebrates as examples of evolutionary variations on tubule networks.

Protonephridia

As illustrated in **Figure 44.9**, flatworms (phylum Platyhelminthes), which lack a coelom or body cavity, have excretory systems called **protonephridia** (singular, *protonephridium*). Protonephridia consist of a network of dead-end tubules that branch throughout the body. Cellular units called flame bulbs cap each branch. Each flame bulb, consisting of a tubule cell and a cap cell, 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 name *flame bulb* derives from the moving cilia's resemblance to a flickering flame.) The processed filtrate moves outward through the tubules and empties as urine via external openings. Because the urine excreted by freshwater flatworms is low in solutes, its production helps to balance the osmotic uptake of water from the environment.

▼ Figure 44.9 Protonephridia in a planarian.



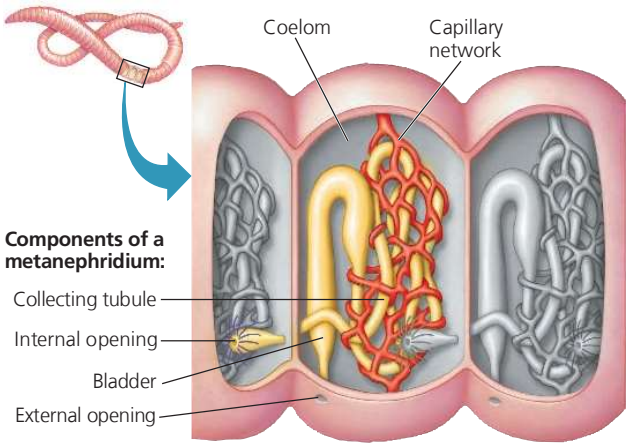
Protonephridia are also found in rotifers, some annelids, mollusc larvae, and lancelets (see Figure 34.4). In the freshwater flatworms, protonephridia serve chiefly in osmoregulation. Most metabolic wastes diffuse out of the animal across the body surface or are excreted into the gastrovascular cavity and eliminated through the mouth (see Figure 33.9). In contrast, parasitic flatworms that are isoosmotic to the surrounding fluids of their host organisms have protonephridia that primarily function in the disposal of nitrogenous wastes. Natural selection has thus adapted protonephridia to different tasks in different environments.

Metanephridia

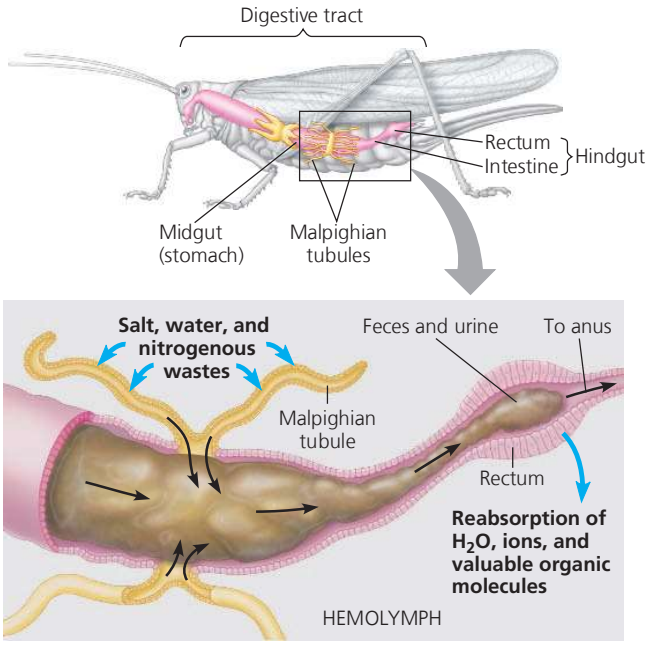
Most annelids, such as earthworms, have **metanephridia** (singular, *metanephridium*), excretory organs that collect fluid directly from the coelom **(Figure 44.10)**. A pair of metanephridia are found in each segment of an annelid, where they are immersed in coelomic fluid and enveloped by a capillary network. A ciliated funnel surrounds the internal opening of each metanephridium. As the cilia beat, fluid is drawn into a collecting tubule, which includes a storage bladder that opens to the outside.

Earthworms inhabit damp soil and therefore usually experience a net uptake of water by osmosis through their skin. Their metanephridia balance the water influx by producing urine that is dilute (hypoosmotic to body fluids). In producing a hypoosmotic filtrate, the transport epithelium reabsorbs most solutes and returns them to the blood in the capillaries. Nitrogenous wastes, however, remain in the tubule and are excreted to the environment. The metanephridia of an earthworm thus serve both an excretory and an osmoregulatory function.

▼ Figure 44.10 Metanephridia of an earthworm. Each segment of the worm contains a pair of metanephridia, which collect coelomic fluid from the adjacent anterior segment. The region highlighted in yellow illustrates the organization of one metanephridium of a pair; the other would be behind it.



▼ Figure 44.11 Malpighian tubules of insects. Malpighian tubules are outpocketings of the digestive tract that remove nitrogenous wastes and function in osmoregulation.



Malpighian Tubules

Insects and other terrestrial arthropods have organs called **Malpighian tubules** that remove nitrogenous wastes and that also function in osmoregulation **(Figure 44.11)**. The Malpighian tubules extend from dead-end tips immersed in hemolymph to openings into the digestive tract. The filtration step common to other excretory systems is absent. Instead, the transport epithelium that lines the tubules secretes certain solutes, including nitrogenous wastes, from the hemolymph into the lumen of the tubule. Water follows the solutes into the tubule by osmosis.

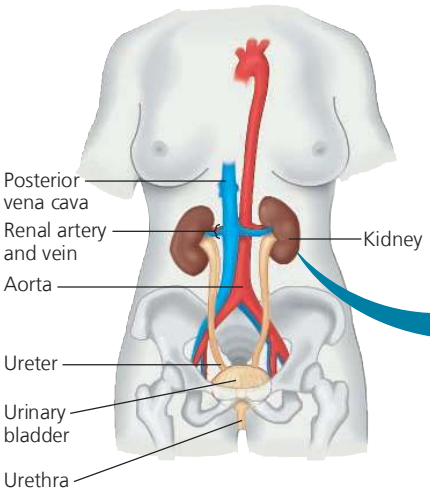
As fluid passes from the tubules into the rectum, most solutes are pumped back into the hemolymph; water reabsorption by osmosis follows. The nitrogenous wastes—mainly insoluble uric acid—are eliminated as nearly dry matter along with the feces. The insect excretory system is capable of conserving water very effectively, a key adaptation contributing to the tremendous success of insects on land.

Kidneys

In vertebrates and some other chordates, a compact organ called the **kidney** functions in both osmoregulation and excretion. Like the excretory organs of most animal phyla, kidneys consist of tubules. The tubules of kidneys are

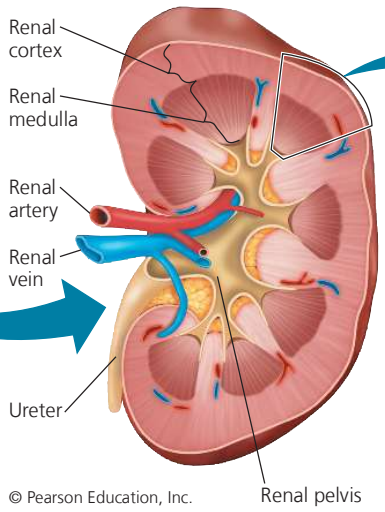
▼ Figure 44.12 Exploring the Mammalian Excretory System

Excretory Organs



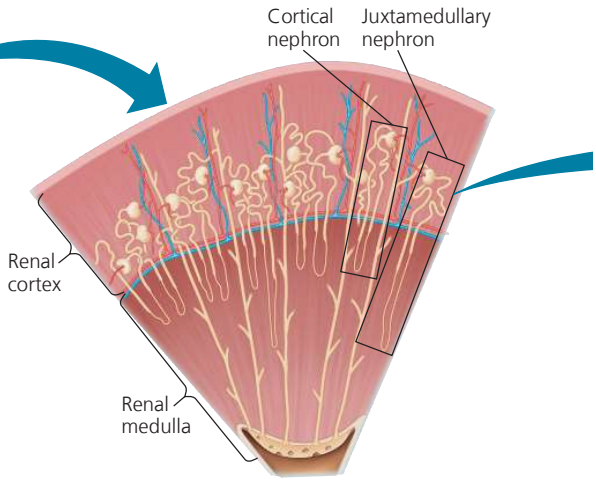
In humans, the excretory system consists of **kidneys**, a pair of organs each about 10 cm in length, as well as organs for transporting and storing urine. Urine produced by each kidney exits through a duct called the **ureter**; the two ureters drain into a common sac called the **urinary bladder**. 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 excretory tubules carry and process a filtrate produced from the blood entering the kidney. Nearly all of the fluid in the filtrate is reabsorbed into the surrounding blood vessels and exits the kidney in the renal vein. The remaining fluid leaves the excretory tubules as urine, is collected in the inner **renal pelvis**, and exits the kidney via the ureter.

Nephron Types



Weaving back and forth across the renal cortex and medulla are the **nephrons**, the functional units of the vertebrate kidney. Of the roughly 1 million nephrons in a human kidney, 85% 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, a key adaptation for water conservation in mammals.

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.

Vertebrate kidneys are typically nonsegmented. However, hagfishes, which are jawless vertebrates (see Concept 34.2), have kidneys with segmentally arranged excretory tubules. Because hagfishes and other vertebrates share a common chordate ancestor, it is possible that the excretory structures of vertebrate ancestors were also segmented.

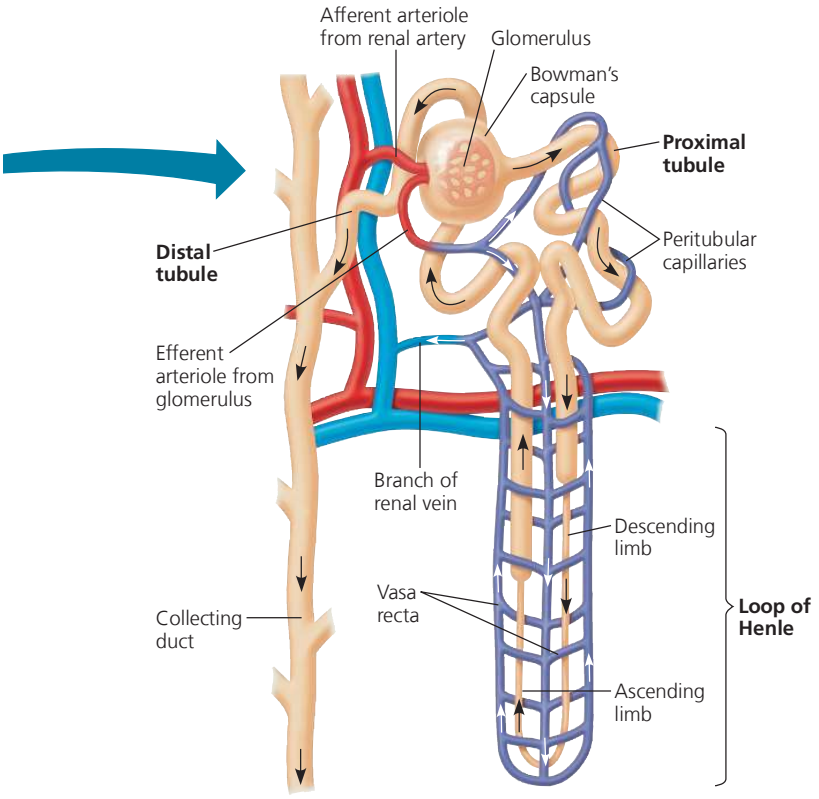
We conclude this introduction to excretory systems with an exploration of the anatomy of the mammalian kidney and associated structures **(Figure 44.12)**. Familiarizing yourself with the terms and diagrams in this figure will provide you with a solid foundation for learning about filtrate processing in the kidney, the focus of the next section of this chapter.

CONCEPT CHECK 44.3

1. Compare and contrast the ways that metabolic waste products enter the excretory systems of flatworms, earthworms, and insects.
2. Where and how does filtrate originate in the vertebrate kidney, and by what two routes do the components of the filtrate exit the kidney?
3. **WHAT IF?** Kidney failure is often treated by hemodialysis, in which blood diverted out of the body is filtered and then allowed to flow on one side of a semipermeable membrane. Fluid called dialysate flows in the opposite direction on the other side of the membrane. In replacing the reabsorption and secretion of solutes in a functional kidney, the makeup of the starting dialysate is critical. What initial solute composition would work well?

For suggested answers, see Appendix A.

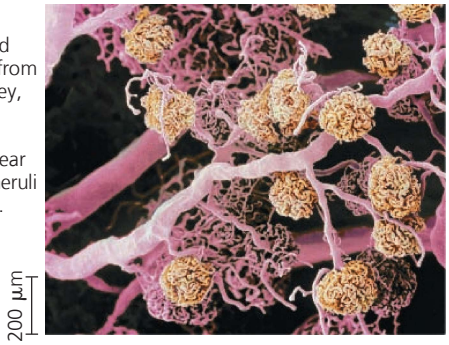
Nephron Organization



Each nephron consists of a single long tubule as well as 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 hairpin 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, including the long loop of Henle of juxtamedullary nephrons.

▶ In this SEM of densely packed blood vessels from a human kidney, arterioles and peritubular capillaries appear pink; the glomeruli appear yellow.



Mastering Biology **Animation: Kidney Structure**

CONCEPT 44.4

The nephron is organized for stepwise processing of blood filtrate

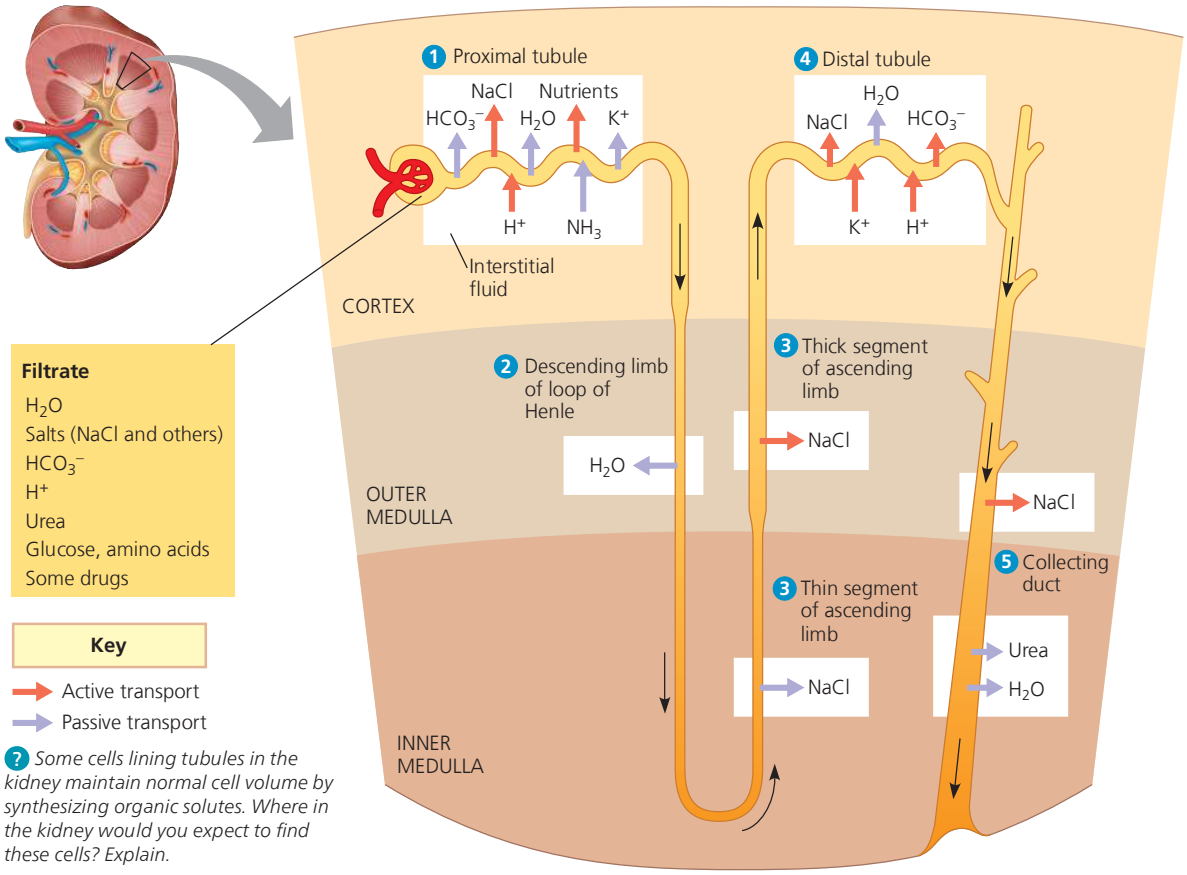
In the human kidney, filtrate forms when fluid passes from the bloodstream to the lumen of Bowman's capsule. The glomerular capillaries and specialized cells of Bowman's capsule retain blood cells and large molecules, such as plasma proteins, but are permeable to water and small solutes. Thus, the filtrate 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.

Under normal conditions, roughly 1,600 L of blood flows through a pair of human kidneys each day, yielding about 180 L of initial filtrate. Both the volume and the composition of the filtrate are changed dramatically as processing occurs. About 99% of 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.

From Blood Filtrate to Urine: *A Closer Look*

To explore how filtrate is processed into urine, we'll follow the filtrate along its path in the nephron. Each circled number in the text and the figure refers to the processing

▼ Figure 44.13 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 maintain normal cell volume by synthesizing organic solutes. Where in the kidney would you expect to find these cells? Explain.*

Mastering Biology **Animation: Nephron Function**

in transport epithelia as the filtrate moves through the kidney cortex and medulla **(Figure 44.13)**.

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. There, Na^+ ions are transferred to the interstitial fluid by active transport (see Concept 7.4). 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, reducing filtrate volume considerably. The salt and water that exit the filtrate 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.

Processing of filtrate in the proximal tubule helps maintain a relatively constant pH in body fluids. Cells of the transport epithelium secrete H^+ into the lumen of the tubule but also synthesize and secrete ammonia, which acts as a buffer to trap H^+ in the form of ammonium ions (NH_4^+). The more acidic the filtrate is, the more ammonia the cells produce and secrete, and a mammal's urine usually contains some ammonia from this source (even though most nitrogenous waste is excreted as urea). The proximal tubules also reabsorb about 90% of the buffer bicarbonate (HCO_3^-) from the filtrate, contributing further to pH balance in body fluids.

As the filtrate passes through the proximal tubule, materials to be excreted become concentrated. Many wastes leave the body fluids during the nonselective filtration process and remain in the filtrate while water and salts are reabsorbed. Urea, for example, is reabsorbed at a much lower rate than are salt and water. In addition, some materials are actively secreted into the filtrate from surrounding tissues. For example, drugs and toxins that have been processed in the liver pass from the peritubular capillaries into the interstitial fluid. These molecules are then actively secreted by the transport epithelium into the lumen of the proximal tubule.

2 Descending limb of the loop of Henle. Upon leaving the proximal tubule, filtrate enters the loop of Henle, which further reduces filtrate volume via distinct stages of water and salt movement. In the first portion of the loop, the descending limb, 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 cortex through the medulla. As a result, the filtrate loses water and increases in solute concentration all along its journey down the descending limb. The highest osmolarity (about 1,200 mOsm/L) occurs at the elbow of the loop of Henle.

3 Ascending limb of the loop of Henle. The filtrate reaches the tip of the loop and then returns to the cortex in the ascending limb. Unlike the descending limb, the ascending limb has a transport epithelium that lacks water channels. Consequently, the epithelial membrane that faces the filtrate in the ascending limb 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 highly 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.

Although the loop of Henle has a small net effect on filtrate composition, it is a major site for the recovery of water (descending loop) and salt (ascending loop) from the filtrate. It is this recovery that underlies water conservation in land-dwelling vertebrates, as we will explore shortly.

4 Distal tubule. The distal tubule plays a key role in regulating the K^+ and NaCl concentration 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. The distal tubule also contributes to pH regulation by the controlled secretion of H^+ and reabsorption of HCO_3^-.

5 Collecting duct. The collecting duct processes the filtrate into urine, which it carries to the renal pelvis (see Figure 44.12). As filtrate passes along the transport epithelium of the collecting duct, hormonal control of permeability and transport 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. At the same time, the epithelium remains impermeable to salt and, in the renal cortex, to urea. As the collecting duct traverses the gradient of osmolarity in the kidney, 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. Along with NaCl, this urea contributes to the high osmolarity of the interstitial fluid in the medulla. The net result is urine that is hyperosmotic to the general body fluids.

When producing dilute rather than concentrated urine, the collecting duct actively absorbs salts without allowing water to follow by osmosis. At these times, the epithelium lacks aquaporin channels, and NaCl is actively transported out of filtrate. As we'll see, the presence of water channels in the collecting duct epithelium is controlled by hormones that regulate blood pressure, volume, and osmolarity.

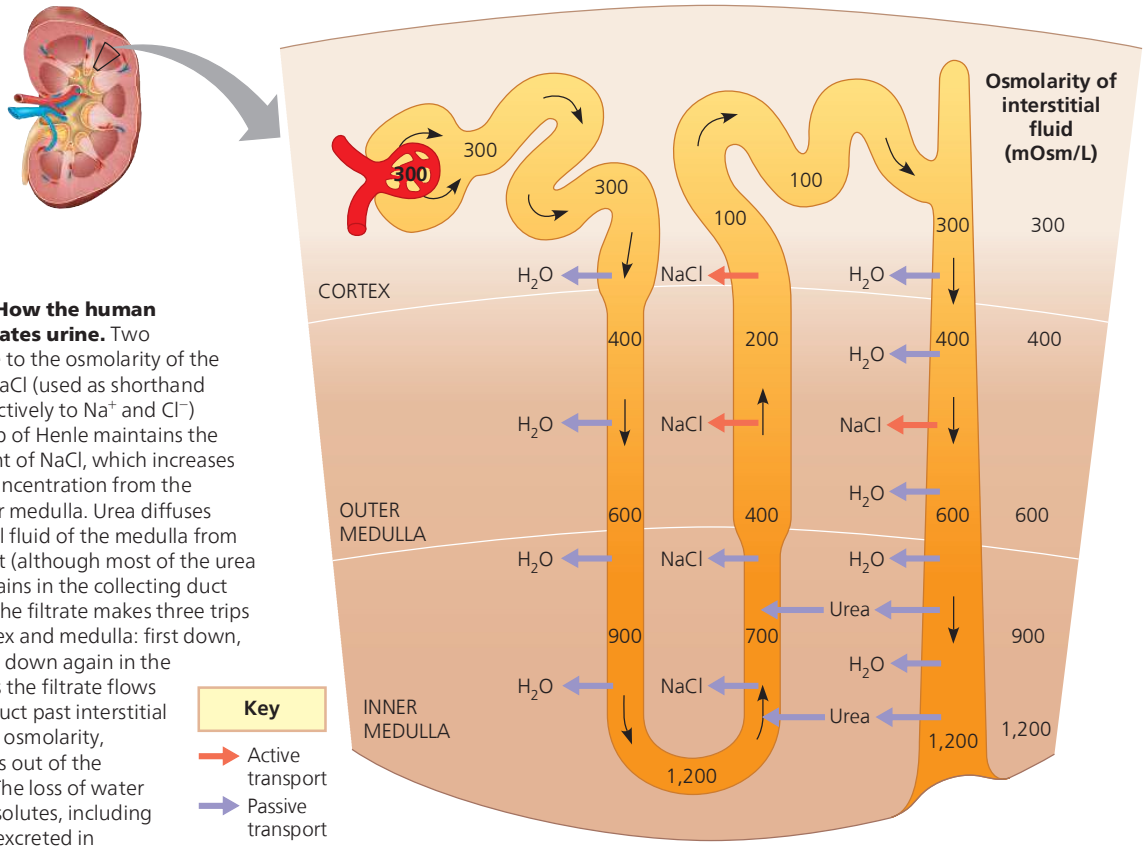
Solute Gradients and Water Conservation

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

In a mammalian kidney, the production of hyperosmotic urine is possible only because considerable energy is expended for the active transport of solutes against concentration gradients. The nephrons—particularly the loops of Henle—can be thought of as energy-consuming machines that produce an osmolarity gradient suitable for extracting water from the filtrate in the collecting duct. The primary solutes affecting osmolarity are NaCl, which is concentrated in the renal medulla by the loop of Henle, and urea, which passes across the epithelium of the collecting duct in the inner medulla.

Concentrating Urine in the Mammalian Kidney

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 juxtamedullary nephrons maintain an osmolarity gradient in the tissues that surround the loop of Henle and how they use that gradient to excrete hyperosmotic urine



▶ Figure 44.14 How the human kidney concentrates urine. 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 (although 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?*

Mastering Biology Figure Walkthrough

(Figure 44.14). 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. Diffusion of salt out of the tubule is maximal 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 and that countercurrent gas exchange in fish gills maximizes oxygen absorption (see Figures 40.13 and 42.21). In those cases, the countercurrent mechanisms involve passive movement along either an oxygen concentration gradient or 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 countercurrent systems, which expend energy to create concentration gradients, are called **countercurrent multiplier systems**.

What prevents the capillaries of the vasa recta from dissipating the gradient by carrying away the high concentration of NaCl in the medulla's interstitial fluid? As shown in Figure 44.12, the descending and ascending vessels of the vasa recta carry blood in opposite directions through the kidney's osmolarity gradient. As the descending vessel conveys blood toward the inner medulla, water is lost from the blood and NaCl is gained by diffusion. These net fluxes are reversed as blood flows back toward the cortex in the ascending vessel of the vasa recta, with water reentering the

blood and salt diffusing out. Thus, the vasa recta can supply the kidney with nutrients and other important substances carried by the blood without interfering with the osmolarity gradient in the inner and outer medulla.

The countercurrent-like characteristics of the loop of Henle and the vasa recta help to generate the steep osmotic gradient between the medulla and cortex. However, diffusion will eventually eliminate any osmotic gradient within animal tissue unless energy is expended to maintain the gradient. In the kidney, this expenditure largely occurs in the thick segment of the ascending limb of the loop of Henle, where NaCl is actively transported out of the tubule. Even with the benefits of countercurrent exchange, this process—along with other renal active transport systems—consumes considerable ATP. Thus, for its size, the kidney has one of the highest metabolic rates of any organ.

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 and encounters interstitial fluid of increasing osmolarity. This process concentrates salt, urea, and other solutes in the filtrate. Some urea passes out of the lower portion of the collecting duct and contributes to the high interstitial osmolarity of the inner medulla. (This urea is recycled by diffusion into the loop of Henle, but continual leakage from the collecting duct maintains a high interstitial urea concentration.) When the kidney concentrates urine maximally, the urine reaches 1,200 mOsm/L, the osmolarity of the interstitial fluid in the inner medulla. Although *isoosmotic* to the inner medulla's interstitial fluid, the urine is *hyperosmotic* to blood and interstitial fluid elsewhere in the body. This high osmolarity allows the solutes remaining in the urine to be excreted from the body with minimal water loss.

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. Comparing vertebrates across environments reveals adaptive variations in nephron structure and function. In the case of mammals, for example, the presence of juxtamedullary nephrons is a key adaptation that enables these terrestrial animals to shed salts and nitrogenous wastes without squandering water. Differences among species in the length of the loop of Henle in the juxtamedullary nephrons and in the relative numbers of juxtamedullary and cortical nephrons help to fine-tune osmoregulation to particular habitats.

Mammals

Mammals that excrete the most hyperosmotic urine, such as Australian hopping mice, North American kangaroo rats, and other desert mammals, have many juxtamedullary nephrons with 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.

In contrast, beavers, muskrats, and other aquatic mammals that spend much of their time in fresh water and rarely face problems of dehydration have mostly cortical nephrons, resulting in a much lower ability to concentrate urine. Terrestrial mammals living in moist conditions have loops of Henle of intermediate length and the capacity to produce urine intermediate in concentration to that produced by freshwater and desert mammals.

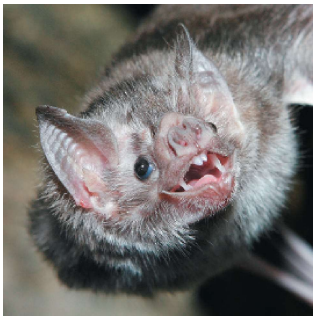
Case Study: *Kidney Function in the Vampire Bat*

The South American vampire bat in **Figure 44.15** 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 is typically not seriously harmed). Anticoagulants in the bat's saliva prevent the blood from clotting.

A vampire bat may search for hours and fly long distances to locate a suitable victim. When it does find prey, it benefits from consuming as much blood as possible. Often drinking more than half its body mass, the bat is at risk of becoming too heavy to fly. As the bat feeds, however, its kidneys 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.

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

▶ Figure 44.15 A vampire bat (*Desmodus rotundus*), a mammal with unique excretory challenges.



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 vampire bat's ability to alternate rapidly between producing large amounts of dilute urine and small amounts of very hyperosmotic urine is an essential part of its adaptation to an unusual food source.

Birds and Other Reptiles

Most birds, including the albatross (see Figure 44.1) and the ostrich **(Figure 44.16)**, live in environments that are dehydrating. Like mammals but no other species, birds have kidneys with juxtamedullary nephrons. However, the nephrons of 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 having uric acid as the nitrogenous waste molecule.

The kidneys of other reptiles have only cortical nephrons, and they produce urine that is isoosmotic or hypoosmotic to body fluids. However, the epithelium of the cloaca from which urine and feces leave the body conserves fluid by reabsorbing water from these wastes. Like birds, most other reptiles excrete their nitrogenous wastes as uric acid.

▼ Figure 44.16 An ostrich (*Struthio camelus*), an animal well adapted to its dry environment.

Freshwater Fishes and Amphibians

Hyperosmotic to their surroundings, freshwater fishes produce large volumes of very dilute urine. Their kidneys, which are packed with cortical nephrons, produce filtrate at a high rate. Salt conservation relies on the reabsorption of ions from the filtrate in the distal tubules.

Amphibian kidneys function much like those of freshwater fishes. When frogs are in fresh water, their kidneys excrete dilute urine while their skin accumulates certain salts from the water by active transport. On land, where dehydration is the most pressing problem of osmoregulation, frogs conserve body fluid by reabsorbing water across the epithelium of the urinary bladder.

Marine Bony Fishes

Compared with freshwater fishes, marine fishes have fewer and smaller nephrons, and their nephrons lack a distal tubule. In addition, their kidneys have small glomeruli or lack glomeruli entirely. In keeping with these features, filtration rates are low and very little urine is excreted.

The main function of kidneys in marine bony fishes is to get rid of divalent ions (those with a charge of 2+ or 2–) such as calcium (Ca^{2+}), magnesium (Mg^{2+}), and sulfate (SO_4^{2-}). Marine fishes take in divalent ions by incessantly drinking seawater. They rid themselves of these ions by secreting them into the proximal tubules of the nephrons and excreting them in urine. Osmoregulation in marine bony fishes also relies on specialized *chloride cells* in the gills. By establishing ion gradients that enable secretion of salt (NaCl) into seawater, the chloride cells maintain proper levels of monovalent ions (charge of 1+ or 1–) such as Na^+ and Cl^-.

The generation of ion gradients and the movement of ions across membranes are central to salt and water balance in marine bony fishes. These events, however, are by no means unique to these organisms nor to homeostasis. As illustrated by the examples in **Figure 44.17**, osmoregulation by chloride cells is but one of many diverse physiological processes that are driven by the movement of ions across a membrane.

CONCEPT CHECK 44.4

1. What do the number and length of nephrons in a fish's kidney indicate about the fish's habitat? How do they correlate with urine production?
2. Many medications make the epithelium of the collecting duct less permeable to water. How would taking such a medication 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.

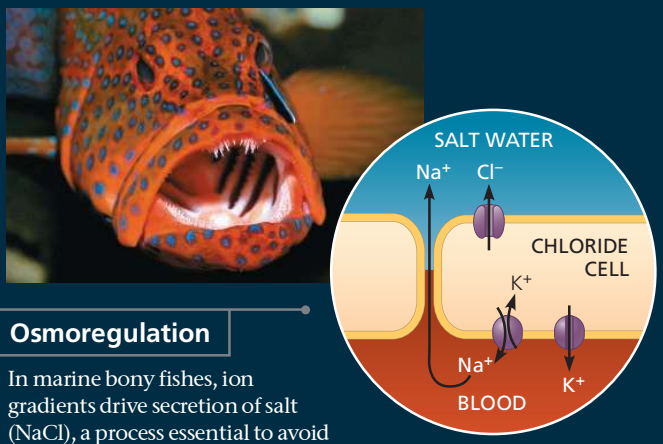
For suggested answers, see Appendix A.

▼ **Figure 44.17**

MAKE CONNECTIONS

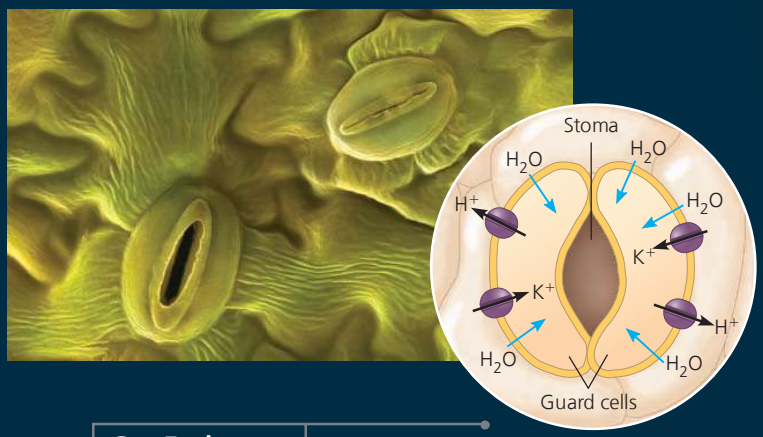
Ion Movement and Gradients

The transport of ions across the plasma membrane of a cell is a fundamental activity of all animals, and indeed of all living things. By generating ion gradients, ion transport provides the potential energy that powers processes ranging from an organism's regulation of salts and gases in internal fluids to its perception of and locomotion through its environment.



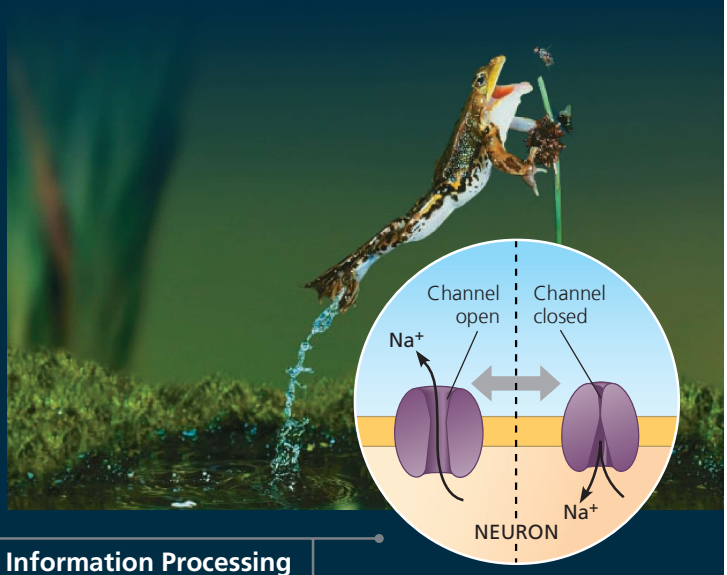
Osmoregulation

In marine bony fishes, ion gradients drive secretion of salt (NaCl), a process essential to avoid dehydration. Within gills, the pumps, cotransporters, and channels of specialized chloride cells function together to drive salt from the blood across the gill epithelium and into the surrounding salt water. (See Figure 44.3.)



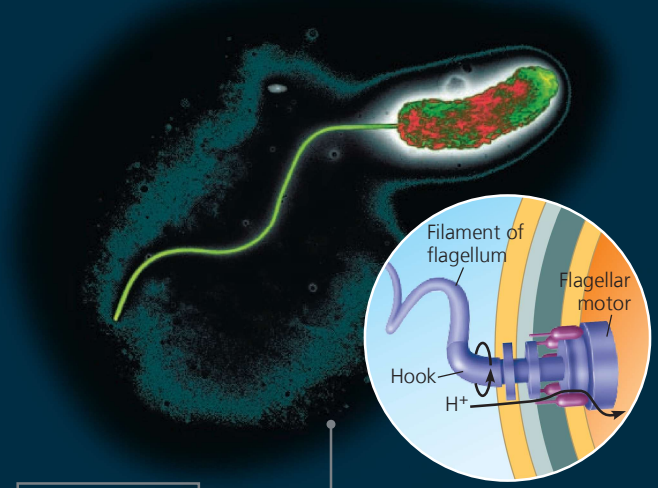
Gas Exchange

Ion gradients provide the basis for the opening of a plant stoma by surrounding guard cells. Active transport of H^+ out of a guard cell generates a voltage (membrane potential) that drives inward movement of K^+. This uptake of K^+ by guard cells triggers an osmotic influx of water that changes cell shape, bowing the guard cells outward and thereby opening the stoma. (See Concept 36.4.)



Information Processing

In neurons, transmission of information as nerve impulses is made possible by the opening and closing of channels selective for sodium or other ions. These signals enable nervous systems to receive and process input and to direct appropriate output, such as this leap of a frog capturing prey. (See Concept 48.3 and Concept 50.5.)



Locomotion

A gradient of H^+ powers the bacterial flagellum. An electron transport chain generates this gradient, establishing a higher concentration of H^+ outside the bacterial cell. Protons reentering the cell provide a force that causes the flagellar motor to rotate. The rotating motor turns the curved hook, causing the attached filament to propel the cell. (See Concept 9.4 and Figure 27.7.)

MAKE CONNECTIONS

Explain why the set of forces driving ion movement across the plasma membrane of a cell is described as an electrochemical (electrical and chemical) gradient (see Concept 7.4).

Mastering Biology BioFlix® Animation: Membrane Transport

CONCEPT 44.5

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

In mammals, both the volume and osmolarity of urine are adjusted according to an animal's water and salt balance and its rate of urea production. In situations of high salt intake and low water availability, a mammal can excrete urea and salt in small volumes of hyperosmotic urine with minimal water loss. If salt is scarce and fluid intake is high, the kidney can instead eliminate the excess water with little salt loss by producing large volumes of hypoosmotic urine. At such times, the urine can be as dilute as 70 mOsm/L, less than one-fourth the osmolarity of human blood.

How are urine volume and osmolarity regulated so effectively? As we'll explore in this final portion of the chapter, two major control circuits that respond to different stimuli together restore and maintain normal water and salt balance.

Homeostatic Regulation of the Kidney

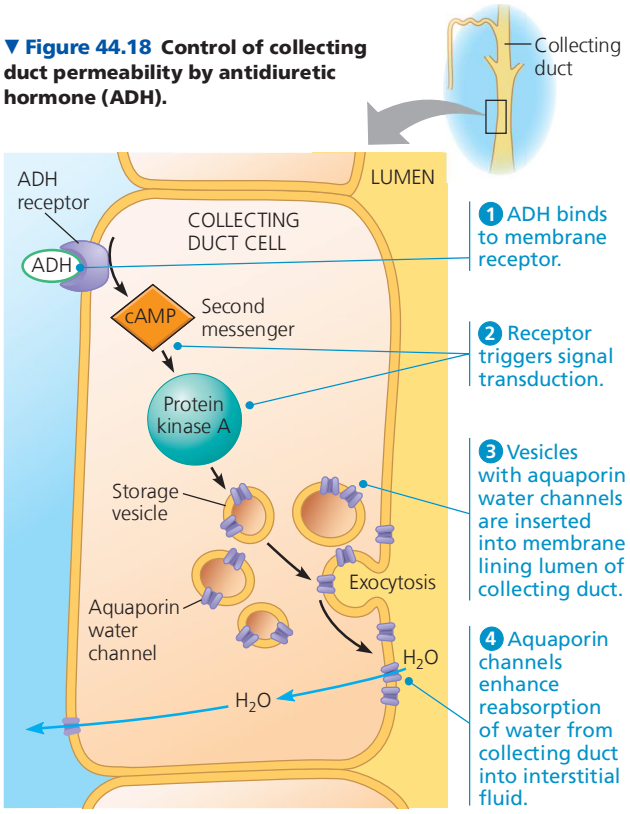
A combination of nervous and hormonal controls manages the osmoregulatory function of the mammalian kidney. Through their effects on the amount and osmolarity of urine, these controls contribute to homeostasis for both blood pressure and blood volume.

Antidiuretic Hormone

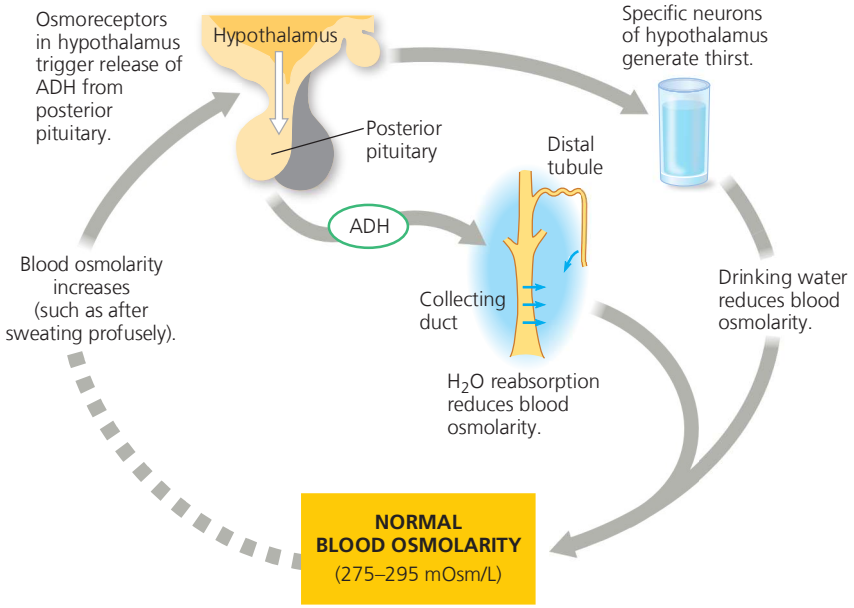
One key hormone in of the kidney is **antidiuretic hormone (ADH)**, also called *vasopressin*. ADH molecules released from the posterior pituitary bind to and activate membrane receptors on the surface of collecting duct cells. The activated receptors initiate a signal transduction cascade that directs insertion of aquaporin proteins into the membrane lining the collecting duct **(Figure 44.18)**. More aquaporin channels result in more water recapture, reducing urine volume. (A high level of urine production is called diuresis; ADH is therefore called *anti*diuretic hormone.)

To understand the regulatory circuitry based on ADH, let's consider first what occurs when blood osmolarity rises, such as after eating salty food or losing water through sweating **(Figure 44.19)**. When osmolarity rises above the normal range (275–295 mOsm/L), osmoreceptor cells in the hypothalamus trigger increased

▼ Figure 44.18 Control of collecting duct permeability by antidiuretic hormone (ADH).



▼ Figure 44.19 Regulation of fluid retention in the kidney. Osmoreceptors in the hypothalamus monitor blood osmolarity via its effect on the net diffusion of water into or out of the receptor cells. When blood osmolarity increases, signals from the osmoreceptors trigger a release of ADH from the posterior pituitary and generate thirst. Water reabsorption in the collecting duct and water intake restore normal blood osmolarity, inhibiting further ADH secretion.



Mastering Biology **Animation: Control of Water Reabsorption**

release of ADH from the posterior pituitary. The resulting increase in water reabsorption in the collecting duct concentrates urine, reduces urine volume, and lowers blood osmolarity back toward the normal range. As the osmolarity of the blood falls, a negative-feedback mechanism reduces the osmoreceptor cell activity 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? Blood osmolarity falls below the normal range, causing a drop in ADH secretion to a very low level. The resulting decrease in permeability of the collecting ducts reduces water reabsorption, resulting in discharge of large volumes of dilute urine.

Contrary to common belief, caffeinated drinks increase urine production to no greater degree than water of comparable volume: Numerous studies of coffee and tea drinkers have found no diuretic effect for caffeine.

Blood osmolarity, ADH release, and water reabsorption in the kidney are normally linked in a feedback circuit that contributes to homeostasis. Anything that disrupts this circuit can interfere with water balance. For example, alcohol inhibits ADH release, leading to excessive urinary water loss and dehydration (which may cause some of the symptoms of a hangover).

Mutations that prevent ADH production or that inactivate the ADH receptor gene disrupt homeostasis by blocking the insertion of additional aquaporin channels in the collecting duct membrane. The resulting disorder can cause severe dehydration and solute imbalance due to production of copious dilute urine. These symptoms give the disorder its name: *diabetes insipidus* (from the Greek for "to pass through" and "having no flavor"). Could mutations in an aquaporin gene have a similar effect? **Figure 44.20** describes an experimental approach that addressed this question.

The Renin-Angiotensin-Aldosterone System

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. Given that this will not affect ADH release, how does the body respond? It turns out that an endocrine circuit called the **renin-angiotensin-aldosterone system (RAAS)** also regulates kidney function. The RAAS responds to the drop in blood volume and pressure by increasing water and Na^+ reabsorption.

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. When blood pressure or volume drops in the afferent

▼ Figure 44.20 Inquiry

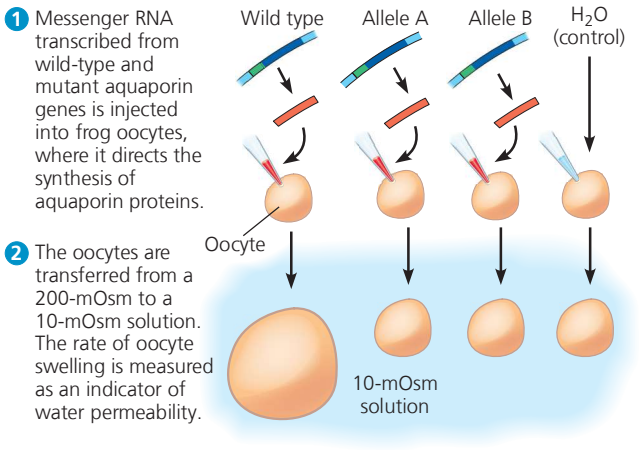
Can aquaporin mutations cause diabetes?

Experiment Researchers studied a patient with diabetes insipidus who had a normal ADH receptor gene but two mutant alleles (A and B) of the aquaporin-2 gene. The resulting changes are shown below in an alignment of protein sequences that includes other species.

Source of Aquaporin-2 Gene Sequence	Amino Acids 183–191* in Encoded Protein	Amino Acids 212–220* in Encoded Protein
Frog (*Xenopus laevis*)	MNPARSFAP	GIFASLIYN
Lizard (*Anolis carolinensis*)	MNPARSFGP	AVVASLLYN
Chicken (*Gallus gallus*)	MNPARSFAP	AAAASIIYN
Human (*Homo sapiens*)	MNPARSLAP	AILGSLLYN
Conserved residues	MNPARS–P	–S–YN
Patient's gene: allele A	MNPACSLAP	AILGSLLYN
Patient's gene: allele B	MNPARSLAP	AILGPLLYN

*The numbering is based on the human aquaporin-2 protein sequence.

Each mutation changed the protein sequence at a highly conserved position. To test the hypothesis that the changes affect function, researchers used frog oocytes, cells that will express foreign messenger RNA and can be readily collected from adult female frogs.



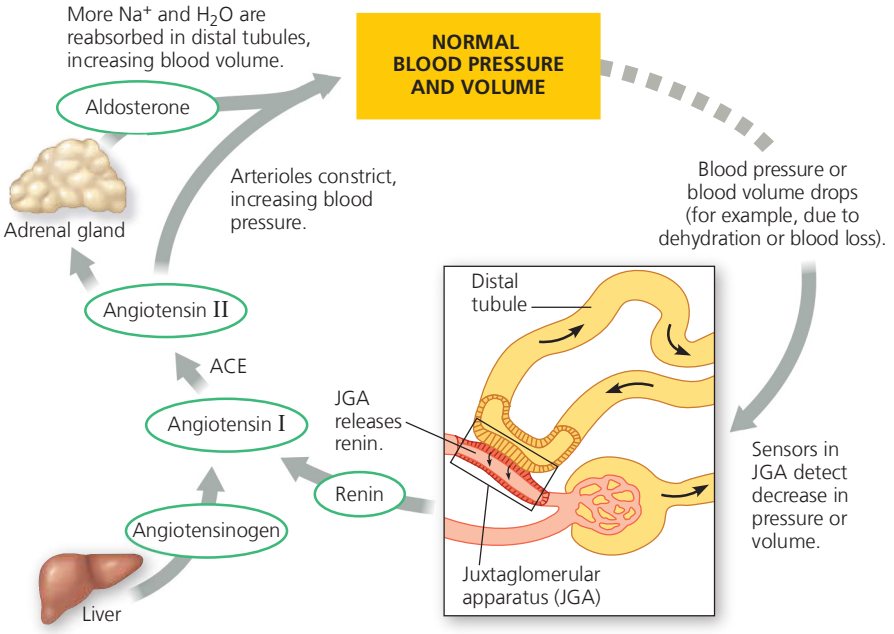
Results

Source of Injected mRNA	Rate of Swelling (μm/sec)
Human wild type	196
Patient's allele A	17
Patient's allele B	18
None (H_2O control)	20

Conclusion Because each mutation renders aquaporin inactive as a water channel, researchers concluded that these mutations cause the disorder common to the patients.

Data from P. M. Deen et al., Requirement of human renal water channel aquaporin-2 for vasopressin-dependent concentration of urine, *Science* 264:92–95 (1994).

WHAT IF? *If you measured ADH levels in patients with ADH receptor mutations and in patients with aquaporin mutations, what would you expect to find, compared with wild-type subjects?*



▶ Figure 44.21 Regulation of blood volume and blood pressure by the renin-angiotensin-aldosterone system (RAAS).

VISUAL SKILLS *Label each arrow that represents the secretion of a hormone.*

arteriole (for instance, as a result of dehydration), the JGA releases the enzyme renin. Renin initiates a sequence of steps that cleave a plasma protein called angiotensinogen, ultimately yielding a peptide called *angiotensin II* **(Figure 44.21)**.

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*. Aldosterone causes the nephrons' distal tubules and collecting duct to reabsorb more Na^+ and water, increasing blood volume and pressure.

Because angiotensin II results in increased 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.

The RAAS 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.

Coordinated Regulation of Salt and Water Balance

Both ADH and RAAS increase water reabsorption in the kidney. However, whereas ADH alone would lower blood Na^+ concentration via water reabsorption in the kidney, the RAAS helps maintain body fluid osmolarity within the normal range by stimulating Na^+ reabsorption.

Another hormone, **atrial natriuretic peptide (ANP)**, opposes the RAAS. The walls of the atria of the heart release ANP in response to an increase in blood volume and pressure. ANP inhibits the release of renin from the JGA, inhibits NaCl reabsorption by the collecting ducts, and reduces aldosterone release from the adrenal glands. These actions lower blood volume and pressure. Thus, ADH, the RAAS, and ANP provide an elaborate system of checks and balances that regulate the kidney's ability to control blood osmolarity, salt concentration, volume, and pressure.

Thirst plays an essential role in the control of water and salt balance. Recently, researchers have identified neurons in the hypothalamus dedicated to regulating thirst. Stimulating one set of neurons in mice causes intense drinking behavior, even if the animal is fully hydrated. Stimulating a second set causes an immediate halt in water consumption, even in dehydrated animals. Follow-up studies are focused on identifying the cellular and molecular pathways linking these neurons to the behavioral responses.

CONCEPT CHECK 44.5

1. How does alcohol affect regulation of water balance in the body?
2. Why could it be dangerous to drink a very large amount of water in a short period of time?
3. **WHAT IF?** Conn's syndrome is a condition caused by tumors of the adrenal cortex that secrete high amounts of aldosterone in an unregulated manner. What would you expect to be the major symptom of this disorder?

For suggested answers, see Appendix A.

44 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 44.1

Osmoregulation balances the uptake and loss of water and solutes *(pp. 978–982)*

Animal	Inflow/Outflow	Urine
Freshwater fish. Lives in water less concentrated than body fluids; fish tends to gain water, lose salt	Does not drink water Salt in (active transport by gills) H_2O in Salt out H_2O out	Large volume of urine Urine is less concentrated than body fluids
Marine bony fish. Lives in water more concentrated than body fluids; fish tends to lose water, gain salt	Drinks water Salt in H_2O out Salt out (active transport by gills)	Small volume of urine Urine is slightly less concentrated than body fluids
Terrestrial vertebrate. Terrestrial environment; tends to lose body water to air	Drinks water Salt in (by mouth) H_2O and salt out	Moderate volume of urine Urine is more concentrated than body fluids

- 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.
- **Osmoconformers** are isoosmotic with their marine environment and do not regulate their **osmolarity**. In contrast, **osmoregulators** control water uptake and loss in a hypoosmotic or hyperosmotic environment, respectively. Water-conserving excretory organs help terrestrial animals avoid desiccation, which can be life-threatening. Animals that live in temporary waters may enter a dormant state called **anhydrobiosis** when their habitats dry up.
- **Transport epithelia** contain specialized epithelial cells that control the solute movements required for waste disposal and osmoregulation.

? *Under what environmental conditions does water move into a cell by osmosis?*

CONCEPT 44.2

An animal's nitrogenous wastes reflect its phylogeny and habitat *(pp. 982–983)*

- Protein and nucleic acid metabolism generates **ammonia**. Most aquatic animals excrete ammonia. Mammals and most adult amphibians convert ammonia to the less toxic **urea**, which is excreted with a minimal loss of water. Insects and many reptiles, including birds, convert ammonia to **uric acid**, a mostly insoluble waste excreted in a paste-like urine.
- The kind of nitrogenous waste excreted depends on an animal's habitat, whereas the amount excreted is coupled to the animal's energy budget and dietary protein intake.

MAKE CONNECTIONS *Metabolism of carbohydrates and fats requires several nitrogen-containing molecules, such as NAD^+/NADH (see Figure 9.12), but is not a significant source of nitrogen-containing waste. Why?*

CONCEPT 44.3

Diverse excretory systems are variations on a tubular theme *(pp. 983–987)*

- Most excretory systems carry out **filtration, reabsorption, secretion**, and **excretion**. Invertebrate excretory systems include the **protonephridia** of flatworms, the **metanephridia** of earthworms, and the **Malpighian tubules** of insects. **Kidneys** function in both excretion and osmoregulation in vertebrates.
- Excretory tubules (consisting of **nephrons** and **collecting ducts**) and blood vessels pack the mammalian kidney. Blood pressure forces fluid from blood in the **glomerulus** into the lumen of **Bowman's capsule**. Following reabsorption and secretion, **filtrate** flows into a collecting duct. The **ureter** conveys urine from the **renal pelvis** to the **urinary bladder**.

? *What is the function of the filtration step in excretory systems?*

CONCEPT 44.4

The nephron is organized for stepwise processing of blood filtrate *(pp. 987–993)*

- 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; water moves by osmosis into the interstitial fluid. The ascending limb is permeable to salt but not water; salt leaves by diffusion and by active transport. The **distal tubule** and collecting duct regulate K^+ and NaCl levels in body fluids.
- In mammals, **a countercurrent multiplier system** involving the loop of Henle maintains the gradient of salt concentration in the kidney interior. Urea exiting the collecting duct contributes to the osmotic gradient of the kidney.
- Natural selection has shaped the form and function of nephrons in various vertebrates to the osmoregulatory 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,** whereas mammals in moist habitats have shorter loops and excrete more dilute urine.

? *How do cortical and juxtamedullary nephrons differ with respect to reabsorbing nutrients and concentrating urine?*

CONCEPT 44.5

Hormonal circuits link kidney function, water balance, and blood pressure *(pp. 994–996)*

- The posterior pituitary gland releases **antidiuretic hormone (ADH)** when blood osmolarity rises above the normal range, such as when water intake is inadequate. ADH increases the permeability to water of the collecting ducts by increasing the number of epithelial **aquaporin** channels.
- When blood pressure or blood volume in the afferent arteriole drops, the **juxtaglomerular apparatus** releases renin. Angiotensin II formed in response to renin constricts arterioles and triggers release of the hormone aldosterone, raising blood pressure and reducing the release of renin. This **renin-angiotensin-aldosterone system** has functions that overlap with those of ADH and are opposed by **atrial natriuretic peptide**.

? *Why can only some patients with diabetes insipidus be treated effectively with ADH?*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. *Unlike* an earthworm's metanephridia, a mammalian nephron
   (A) is intimately associated with a capillary network.
   (B) functions in both osmoregulation and excretion.
   (C) receives filtrate from blood instead of coelomic fluid.
   (D) has a transport epithelium.
2. Which process in the nephron is *least* selective?
   (A) filtration (C) active transport
   (B) reabsorption (D) secretion
3. Which of the following animals generally has the lowest volume of urine production?
   (A) vampire bat (C) marine bony fish
   (B) salmon in fresh water (D) freshwater flatworm

Levels 3-4: Applying/Analyzing

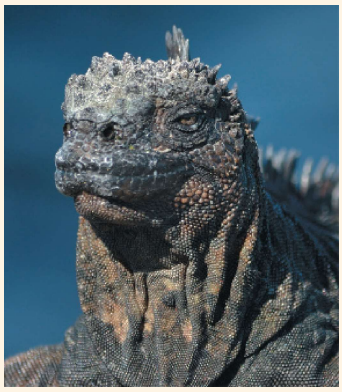
4. The high osmolarity of the renal medulla is maintained by which of the following?
   (A) active transport of salt from the upper region of the descending limb.
   (B) the loose packing of juxtamedullary nephrons.
   (C) diffusion of urea into the collecting duct.
   (D) diffusion of salt from the descending limb of the loop of Henle.
5. In which of the following species should natural selection favor the highest proportion of juxtamedullary nephrons?
   (A) a river otter
   (B) a mouse species living in a temperate broadleaf forest
   (C) a mouse species living in a desert
   (D) a beaver
6. African lungfish, which are often found in small, stagnant pools of fresh water, produce urea as a nitrogenous waste. What is an advantage of this adaptation?
   (A) Urea takes less energy to synthesize than ammonia.
   (B) Small, stagnant pools do not provide enough water to dilute ammonia, which is toxic.
   (C) Urea forms an insoluble precipitate.
   (D) Urea makes lungfish tissue hypoosmotic to the pool.

Levels 5-6: Evaluating/Creating

7. **INTERPRET THE DATA** (a) Use the data below to draw four pie charts for the average daily water gain and loss in a kangaroo rat and a human.

	Kangaroo Rat	Human
Average Water Gain (mL/day)		
Ingested in food	0.2	750
Ingested in liquid	0	1,500
Derived from metabolism	1.8	250
Average Water Loss (mL/day)		
Urine	0.45	1,500
Feces	0.09	100
Evaporation	1.46	900

   (b) Which routes of water gain and loss make up a much larger share of the total in a kangaroo rat than in a human?
8. **EVOLUTION CONNECTION** Merriam's kangaroo rats (*Dipodomys merriami*) live in North American habitats ranging from moist, cool woodlands to hot deserts. Based on the hypothesis that there are adaptive differences in water conservation between *D. merriami* populations, predict how the rates of evaporative water loss would differ for populations that live in moist versus dry environments. Propose a test of your prediction, using a humidity sensor to detect evaporative water loss by kangaroo rats.
9. **SCIENTIFIC INQUIRY** You are exploring kidney function in kangaroo rats. You measure urine volume and osmolarity, as well as the amount of chloride (Cl^-) and urea in the urine. If the water source provided to the animals were switched from tap water to a 2% NaCl solution, indicate what change in urine osmolarity you would expect. How would you determine if this change was more likely due to a change in the excretion of Cl^- or urea?
10. **WRITE ABOUT A THEME: 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.
11. **SYNTHESIZE YOUR KNOWLEDGE**



The marine iguana (*Amblyrhynchus cristatus*), which spends long periods under water feeding on seaweed, relies on both salt glands and kidneys for homeostasis of its internal fluids. Describe how these organs together meet the particular osmoregulatory challenges of this animal's environment.

For selected answers, see Appendix A.

45 Hormones and the Endocrine System

KEY CONCEPTS

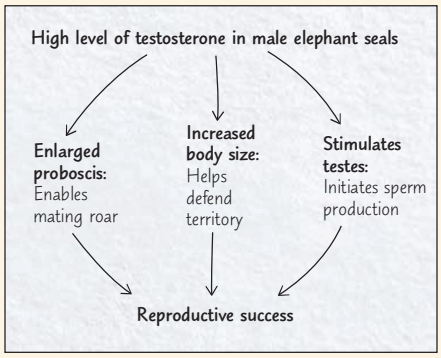
45.1 **Hormones and other signaling molecules bind to target receptors, triggering specific response pathways** *p. 1000*

45.2 **Feedback regulation and coordination with the nervous system are common in hormone pathways** *p. 1004*

45.3 **Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior** *p. 1011*

Study Tip

Make a flowchart: Many hormones, such as insulin, parathyroid hormone, and epinephrine, have multiple physiological effects in a single organism. To keep track of the action and function of each such hormone, make a flowchart like this example. Use arrows to indicate how the hormone's diverse effects contribute to an overall outcome for the organism.



Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 45
- Animation: Water-Soluble Hormone Pathway
- Animation: Steroid Hormone Pathway

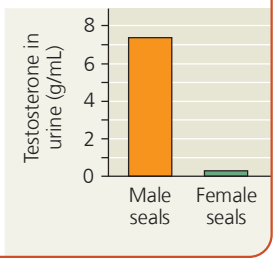
For Instructors to Assign (in Item Library)
- Scientific Skills Exercise: Designing a Controlled Experiment
- Problem-Solving Exercise: Is Thyroid Regulation Normal in this Patient?

Figure 45.1 Male and female elephant seals (*Mirounga angustirostris*) differ greatly in appearance and behavior. The male is much larger, and only he has the prominent proboscis for which the species is named. The male is also far more territorial, using the proboscis to emit loud roars during mating season. Underlying each of these differences is a single hormone—testosterone. Like all hormones, testosterone is an endocrine signaling molecule that circulates in the blood throughout the body.

What variables shape a hormone's effect on an animal's body and behavior?

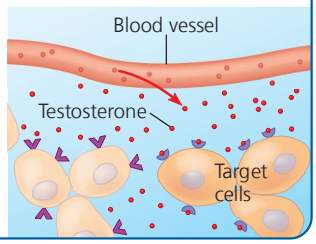
Concentration of the hormone in the body:

Testosterone is present in both male and female mammals, but typically at a much higher concentration in males.



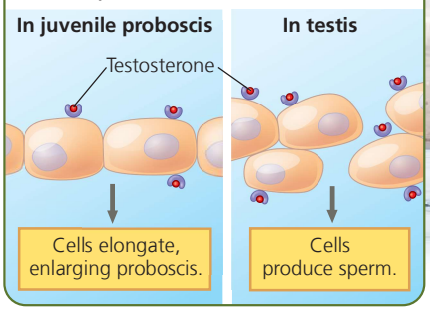
Presence of the hormone receptor in a cell:

A hormone circulates throughout the bloodstream, but cells only respond to a hormone if they have a receptor that binds that hormone specifically.



Response of the cell when the receptor binds the hormone:

Cells in different tissues may respond differently to the same hormone.



▼ **Male elephant seals sparring**

CONCEPT 45.1

Hormones and other signaling molecules bind to target receptors, triggering specific response pathways

A **hormone** (from the Greek *horman*, to excite) is a secreted molecule that circulates throughout the body and stimulates specific cells. Although a given hormone reaches all cells of the body, it only elicits a response—such as a change in metabolism—in specific *target cells*, those that have a receptor that binds the hormone specifically. Cells lacking a receptor for that hormone are unaffected.

Chemical signaling by hormones is the function of the **endocrine system**, one of the two basic systems for communication and regulation in the animal body. The other major communication and control system is the **nervous system**, a network of specialized cells—neurons—that transmit signals along dedicated pathways. These signals in turn regulate neurons, muscle cells, and endocrine cells. Because signaling by neurons can regulate the release of hormones, the nervous and endocrine systems often overlap in function.

As a background to our further exploration of the endocrine system, we'll begin with an overview of the diverse ways that animal cells use chemical signals to communicate.

Intercellular Information Flow

Communication between animal cells via secreted signals is often classified by two criteria: the type of secreting cell and the route taken by the signal in reaching its target. **Figure 45.2** illustrates five forms of signaling distinguished in this manner.

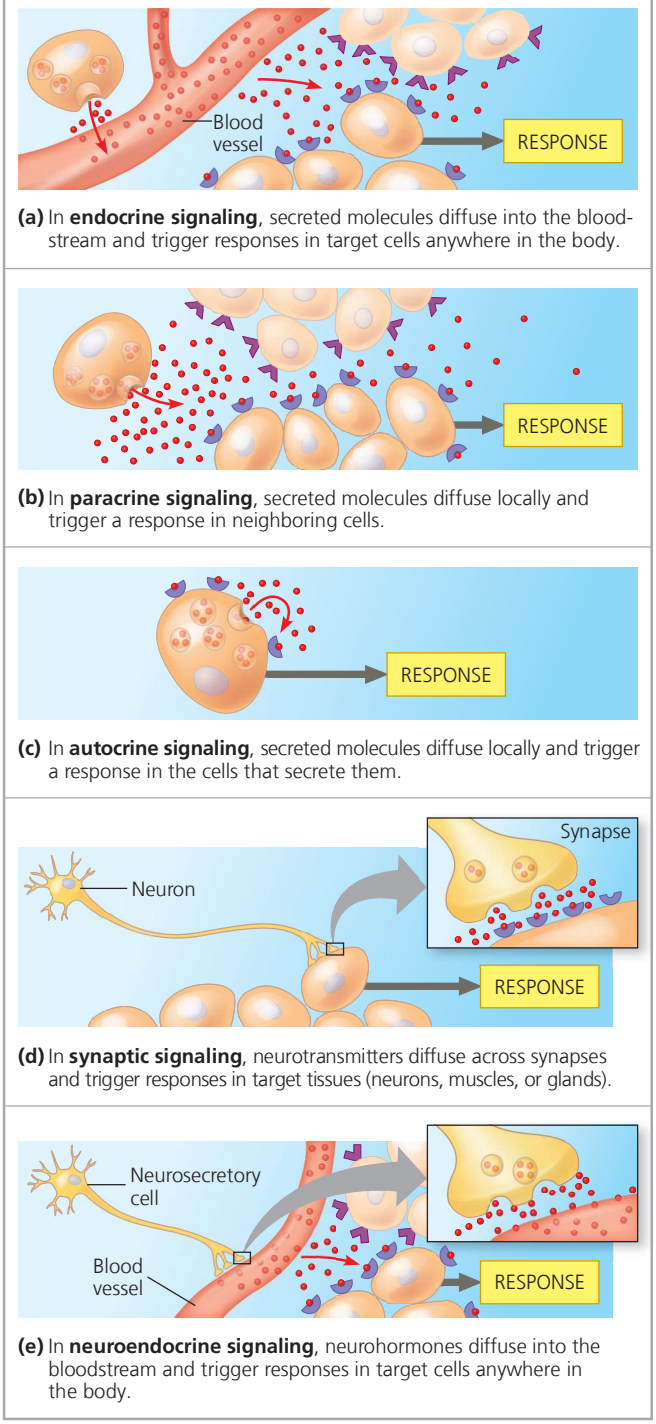
Endocrine Signaling

In endocrine signaling (see Figure 45.2a), hormones secreted into extracellular fluid by endocrine cells reach target cells via the bloodstream (or hemolymph). One function of endocrine signaling is to maintain homeostasis. Hormones regulate properties that include blood pressure and volume, energy metabolism and allocation, and solute concentrations in body fluids. Endocrine signaling also mediates responses to environmental stimuli, regulates growth and development, and triggers physical and behavioral changes underlying sexual maturity and reproduction (see Figure 45.1).

Paracrine and Autocrine Signaling

Many types of cells produce and secrete **local regulators**, molecules that act over short distances, reach their target cells solely by diffusion, and act on their target cells within seconds or even milliseconds. Local regulators play roles in many physiological processes, including blood pressure regulation, nervous system function, and reproduction.

▼ Figure 45.2 Intercellular communication by secreted molecules. In each type of signaling, secreted molecules (•) bind to a specific receptor protein ( ) expressed by target cells. Some receptors are located inside cells, but for simplicity, here all are drawn on the cell surface.



(a) In **endocrine signaling**, secreted molecules diffuse into the bloodstream and trigger responses in target cells anywhere in the body.

(b) In **paracrine signaling**, secreted molecules diffuse locally and trigger a response in neighboring cells.

(c) In **autocrine signaling**, secreted molecules diffuse locally and trigger a response in the cells that secrete them.

(d) In **synaptic signaling**, neurotransmitters diffuse across synapses and trigger responses in target tissues (neurons, muscles, or glands).

(e) In **neuroendocrine signaling**, neurohormones diffuse into the bloodstream and trigger responses in target cells anywhere in the body.

Depending on the target cell, signaling by local regulators is in general either paracrine or autocrine. In **paracrine** signaling (from the Greek *para*, to one side of), target cells

lie near the secreting cell (see Figure 45.2b). In **autocrine** signaling (from the Greek *auto*, self), the secreting cells themselves are the target cells (see Figure 45.2c).

One group of local regulators are the **prostaglandins**, which are produced throughout the body and have diverse functions. In the immune system, for example, prostaglandins promote inflammation and the sensation of pain in response to injury. Drugs that block prostaglandin synthesis, such as aspirin and ibuprofen, prevent these activities, producing both anti-inflammatory and pain-relieving effects.

Prostaglandins are modified fatty acids. Many other local regulators are polypeptides, including cytokines, which enable immune cell communication (see Figure 43.16 and Figure 43.17), and growth factors, which promote cell growth, division, and development.

Some local regulators, such as **nitric oxide (NO)**, are gases. When the level of oxygen in the blood falls, endothelial cells in blood vessel walls synthesize and release NO. After diffusing into the surrounding smooth muscle cells, NO activates an enzyme that relaxes the cells. The result is vasodilation, which increases blood flow to tissues.

In human males, NO's ability to promote vasodilation enables sexual function by increasing blood flow into the penis, producing an erection. The drug Viagra (sildenafil citrate), a treatment for male erectile dysfunction, sustains an erection by prolonging activity of the NO response pathway.

Synaptic and Neuroendocrine Signaling

Secreted molecules are essential for the function of the nervous system. Neurons communicate with target cells, such as other neurons and muscle cells, via specialized junctions called synapses. At most synapses, neurons secrete molecules called **neurotransmitters** that diffuse a very short distance (a fraction of a cell diameter) and bind to receptors on the target cells (see Figure 45.2d). Such *synaptic signaling* is central to sensation, memory, cognition, and movement (as we'll explore in Chapters 48–50).

In *neuroendocrine signaling*, neurons called neurosecretory cells secrete **neurohormones**, which diffuse from nerve cell endings into the bloodstream (see Figure 45.2e). One example of a neurohormone is antidiuretic hormone, which functions in kidney function and water balance as well as courtship behavior. Many neurohormones regulate endocrine signaling, as we'll discuss later in this chapter.

▼ Figure 45.3 Signaling by pheromones. Using their lowered antennae, these Asian army ants (*Leptogenys distinguenda*) carry pupae and larvae along a pheromone-marked trail to a new nest site.

Signaling by Pheromones

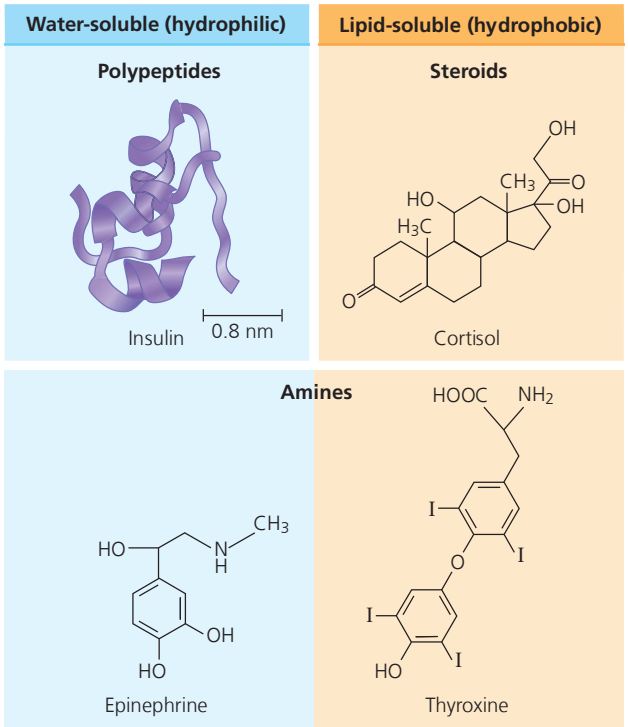
Not all secreted signaling molecules act within the body. Members of a particular animal species sometimes communicate with each other via **pheromones**, chemicals that are released into the external environment. For example, when a foraging ant discovers a new food source, it marks its path back to the nest with a pheromone. Ants also use pheromones for guidance when a colony migrates to a new location **(Figure 45.3)**.

Pheromones serve a wide range of functions that include defining territories, warning of predators, and attracting potential mates. The polyphemus moth (*Antheraea polyphemus*) provides a noteworthy example: The sex pheromone released into the air by a female enables her to attract a male of the species from up to 4.5 km away. You'll read more about pheromone function when we take up the topic of animal behavior in Chapter 51.

Chemical Classes of Hormones

Hormones fall into three major chemical classes: polypeptides, steroids, and amines **(Figure 45.4)**. The hormone insulin, for example, is a polypeptide that contains two chains in its active form. Steroid hormones, such as cortisol, are lipids

▼ Figure 45.4 Variation in hormone solubility and structure.



MAKE CONNECTIONS *Cells synthesize epinephrine from the amino acid tyrosine. On the structure of epinephrine shown above, draw a circle around the portion of the molecule corresponding to the R group of tyrosine (see Figure 5.14).*

that contain four fused carbon rings; all are derived from the steroid cholesterol (see Figure 5.12). Epinephrine and thyroxine are amine hormones, each synthesized from a single amino acid, either tyrosine or tryptophan.

As Figure 45.4 indicates, hormones vary in their solubility in aqueous and lipid-rich environments. Polypeptides and most amine hormones are water-soluble, whereas steroid hormones and other largely nonpolar (hydrophobic) hormones, such as thyroxine, are lipid-soluble.

Cellular Hormone Response Pathways

Water-soluble and lipid-soluble hormones differ in their response pathways. One key difference is the location of the receptor proteins in target cells. Water-soluble hormones are secreted by exocytosis and travel freely in the bloodstream. Being insoluble in lipids, they cannot diffuse through the plasma membranes of target cells. Instead, these hormones bind to cell-surface receptors, inducing changes in cytoplasmic molecules and sometimes altering gene transcription **(Figure 45.5a)**. In contrast, lipid-soluble hormones exit endocrine cells by diffusing out across the membranes. They then bind to transport proteins, which keep them soluble in blood. After circulating in the blood, they diffuse into target cells and typically bind to receptors in the cytoplasm or nucleus **(Figure 45.5b)**. The hormone-bound receptor then triggers changes in gene transcription.

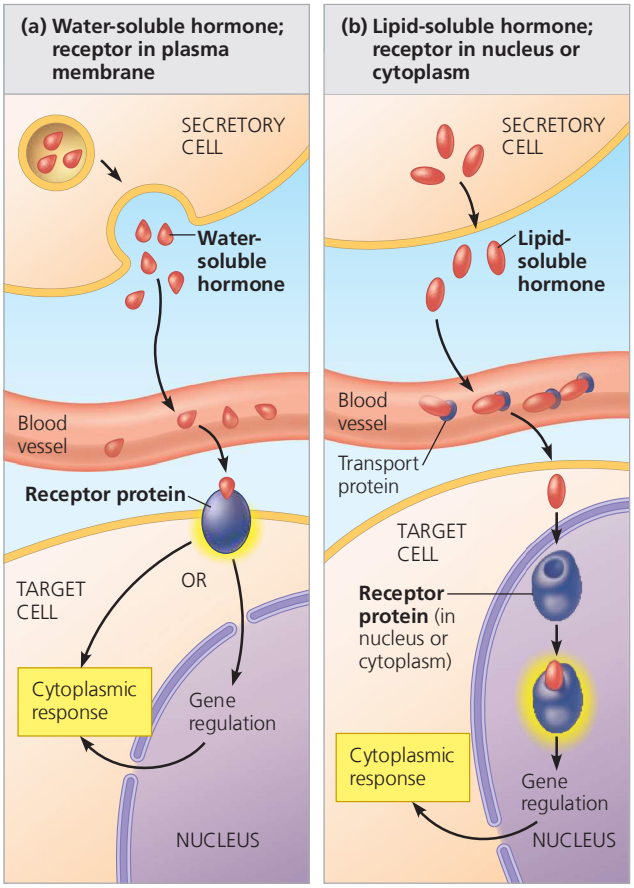
To explore further the distinct cellular responses to water-soluble and lipid-soluble hormones, we'll examine the two response pathways in turn.

Response Pathway for Water-Soluble Hormones

The binding of a water-soluble hormone to a cell-surface receptor protein triggers a cellular response. The response may be the activation of an enzyme, a change in the uptake or secretion of specific molecules, or a rearrangement of the cytoskeleton. In some cases, cell-surface receptors cause proteins in the cytoplasm to move into the nucleus and alter the transcription of specific genes.

The chain of events that converts the extracellular chemical signal to a specific intracellular response is called **signal transduction**. As an example, we'll consider one response to short-term stress. When you are in a stressful situation, perhaps running to catch a bus, the adrenal glands that lie atop your kidneys secrete the water-soluble hormone **epinephrine**, also known as *adrenaline*. Epinephrine regulates many organs, including the liver, where it binds to a G protein-coupled receptor in the plasma membrane of target cells. As shown in **Figure 45.6**, this interaction triggers a cascade of events involving synthesis of cyclic AMP (cAMP) as a short-lived *second messenger*. Activation of protein kinase A by cAMP leads to activation of an enzyme required for breakdown of

▼ Figure 45.5 Variation in hormone receptor location.



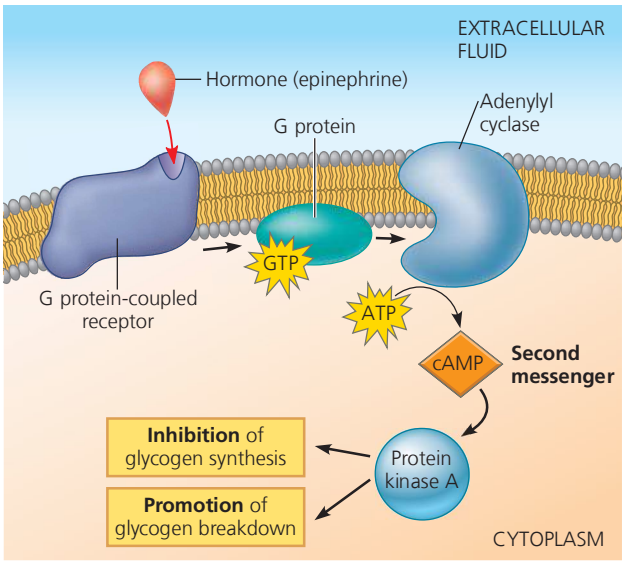
WHAT IF? *Suppose you are studying a cell's response to a particular hormone. You observe that the cell produces the same response to the hormone whether or not the cell is treated with a chemical that blocks transcription. What can you surmise about the hormone and its receptor?*

Mastering Biology **Animation: Binding of Hormones**

glycogen into glucose, as well as inactivation of an enzyme needed for glycogen synthesis.

Note that there are three enzymes in this signal transduction cascade—adenylyl cyclase (which converts AMP to its cyclic form), protein kinase A, and, for example, the enzyme that breaks down glycogen into glucose. Each enzyme-catalyzed step in the cascade provides an opportunity for signal amplification: One enzyme molecule can catalyze many reactions, thereby generating multiple signals at that step in the cascade. Furthermore, because the three enzymes act at different steps in the same pathway, the net effect can be enormous. If, for instance, each enzyme carried out 1,000 reactions, the binding of one molecule of epinephrine to its receptor would trigger cleavage of a billion (10^3 X 10^3 x 10^3) glycogen molecules. The net result is that the liver releases a substantial quantity of glucose into the bloodstream, quickly providing the body with extra fuel.

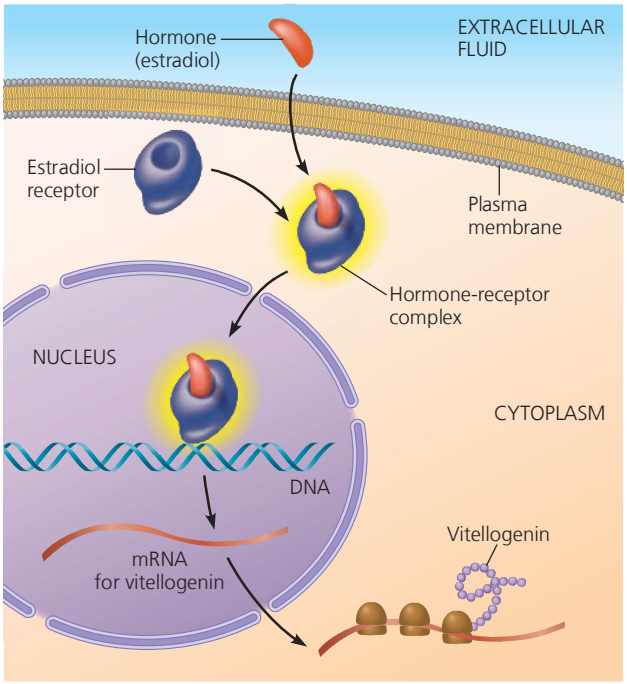
▼ Figure 45.6 Signal transduction triggered by a cell-surface hormone receptor.



VISUAL SKILLS *A series of arrows represents the steps linking epinephrine to protein kinase A. How does the event represented by the arrow between ATP and cAMP differ from the other four?*

Mastering Biology **Animation: Water-Soluble Hormone Pathway**

▼ Figure 45.7 Direct regulation of gene expression by a steroid hormone receptor.



Mastering Biology **Animation: Steroid Hormone Pathway**

Response Pathway for Lipid-Soluble Hormones

Intracellular receptors for lipid-soluble hormones perform the entire task of transducing a signal within a target cell. The hormone activates the receptor, which then directly triggers the cell's response. In most cases, the response to a lipid-soluble hormone is a change in gene expression.

Most steroid hormone receptors are located in the cytosol prior to binding to a hormone. Binding of a steroid hormone to its cytosolic receptor forms a complex that moves into the nucleus (see Figure 11.9). There, the receptor portion of the complex interacts with a specific DNA-binding protein or response element in the DNA, altering transcription of particular genes. (In some cell types, steroid hormones trigger additional responses by interacting with other kinds of receptor proteins located at the cell surface).

Among the best-characterized steroid hormone receptors are those that bind to estrogens, steroid hormones necessary for female reproductive function in vertebrates. For example, in female birds and frogs, estradiol, a form of estrogen, binds to a cytoplasmic receptor in liver cells. Binding of estradiol to this receptor activates transcription of the vitellogenin gene **(Figure 45.7)**. Following translation of the messenger RNA, vitellogenin protein is secreted and transported in the blood to the reproductive system, where it is used to produce egg yolk.

Thyroxine, vitamin D, and other lipid-soluble hormones that are not steroids typically have receptors in the nucleus. These receptors bind to hormone molecules that diffuse from the bloodstream across both the plasma membrane and nuclear envelope. Once bound to a hormone, the receptor binds to specific sites in the cell's DNA and stimulates the transcription of specific genes.

Multiple Responses to a Single Hormone

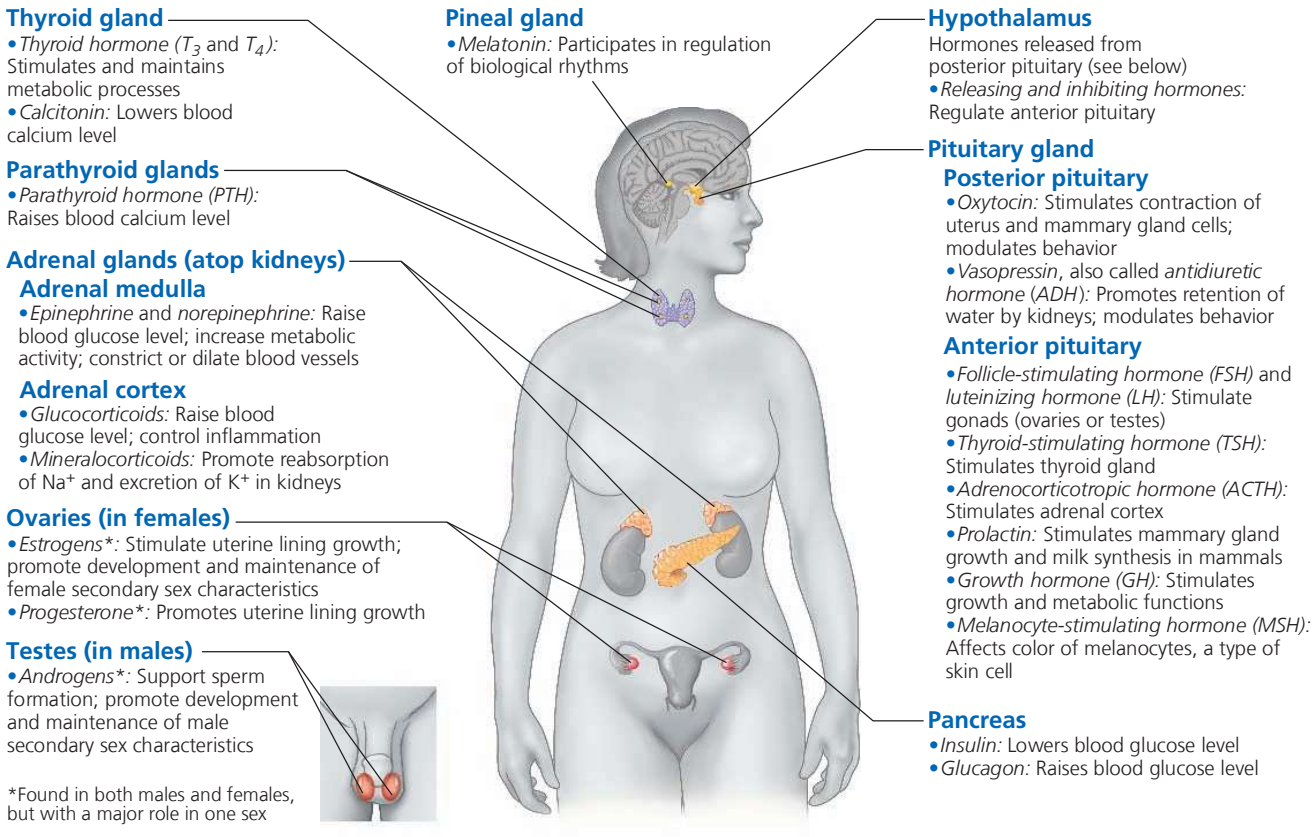
Although hormones bind to specific receptors, a particular hormone can vary in its effects. A hormone can elicit distinct responses in particular target cells if those cells differ in receptor type or in the molecules that produce the response. In this way a single hormone can trigger a range of activities that together bring about a coordinated response to a stimulus. For example, the multiple effects of epinephrine form the basis for the "fight-or-flight" response, a rapid response to stress that you'll read about in Concept 45.3.

Endocrine Tissues and Organs

Some endocrine cells are found in organs that are part of other organ systems. For example, the stomach contains isolated endocrine cells that help regulate digestive processes by secreting the hormone gastrin. More often, endocrine cells are grouped in ductless organs called **endocrine glands**,

▼ Figure 45.8 Human endocrine glands and their hormones. This figure highlights the location and primary functions of the major human endocrine glands. Endocrine tissues and cells are also located in the thymus, heart, liver, stomach, kidneys, and small intestine.

Mastering Biology Animation: Endocrine System Anatomy



such as the thyroid and parathyroid glands and the gonads, either testes in males or ovaries in females **(Figure 45.8)**.

Note that endocrine glands secrete hormones directly into the surrounding fluid. In contrast, *exocrine glands* have ducts that carry secreted substances, such as sweat or saliva, onto body surfaces or into body cavities. This distinction is reflected in the glands' names: The Greek *endo* (within) and *exo* (out of) refer to secretion into or out of body fluids, while *crine* (from the Greek word meaning "separate") refers to movement away from the secreting cell. In the case of the pancreas, endocrine and exocrine tissues are found in the same gland: Ductless tissues secrete hormones, whereas tissues with ducts secrete enzymes and bicarbonate.

CONCEPT CHECK 45.1

1. How do response mechanisms in target cells differ for water-soluble and lipid-soluble hormones?
2. What type of gland would you expect to secrete pheromones? Explain.
3. **WHAT IF?** Predict what would happen if you injected a water-soluble hormone into the cytosol of a target cell.

For suggested answers, see Appendix A.

CONCEPT 45.2

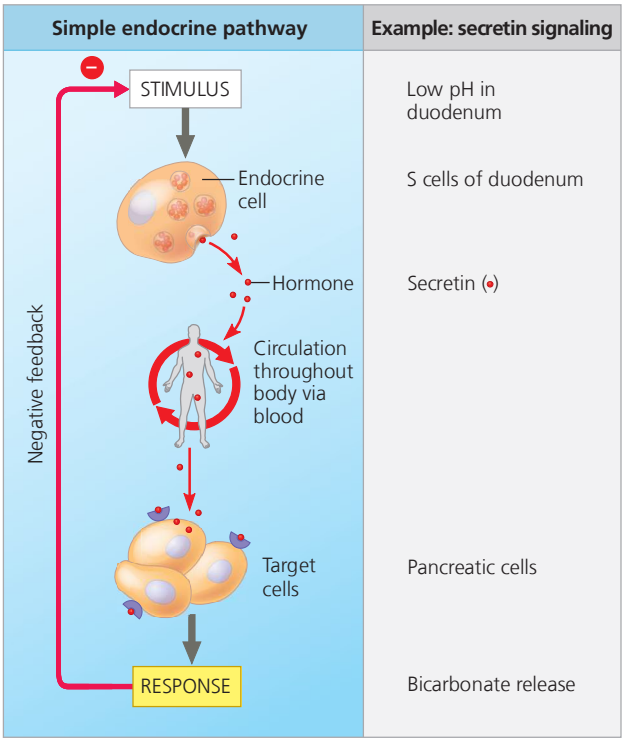
Feedback regulation and coordination with the nervous system are common in hormone pathways

Having explored hormone structure, recognition, and response, we now consider how regulatory pathways controlling hormone secretion are organized.

Simple Endocrine Pathways

In a *simple endocrine pathway*, 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 physiological response.

▼ Figure 45.9 A simple endocrine pathway. Endocrine cells respond to a change in some internal or external variable—the stimulus—by secreting hormone molecules that binds to a specific receptor protein expressed by target cells, triggering a particular response. In the case of secretin signaling, the simple endocrine pathway is self-limiting because the response to secretin (bicarbonate release) reduces the stimulus (low pH) through negative feedback.



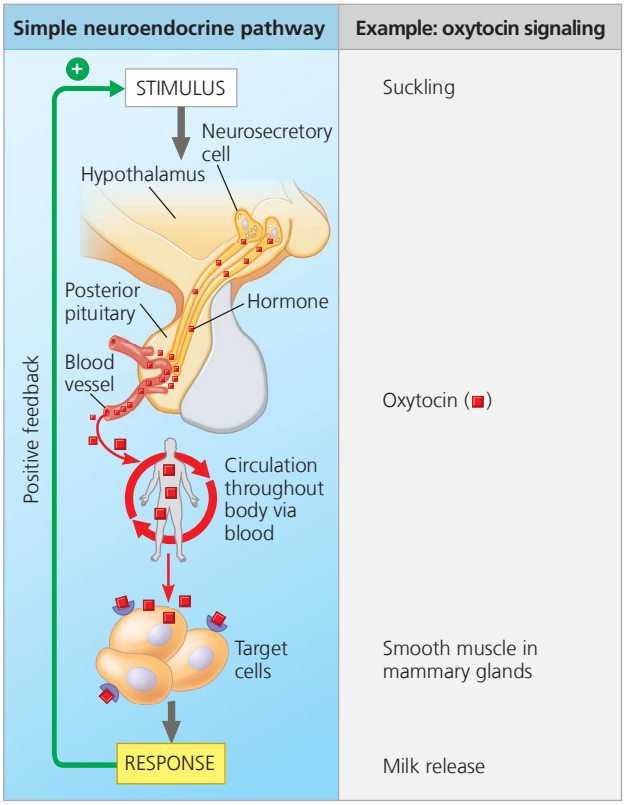
The activity of endocrine cells in the duodenum, the first part of the small intestine, provides a useful example of a simple endocrine pathway. During digestion, the partially processed food that enters the duodenum contains highly acidic digestive juices secreted by the stomach. Before further digestion can occur, this acidic mixture must be neutralized. **Figure 45.9** outlines the simple endocrine pathway that ensures neutralization takes place.

The low pH of partially digested food entering the small intestine is detected by S cells, which are endocrine cells in the lining of the duodenum. In response, the S cells secrete the hormone *secretin*, which diffuses into the blood. Traveling throughout the circulatory system, secretin reaches the pancreas. Target exocrine cells in the pancreas have receptors for secretin and respond by releasing bicarbonate into ducts that lead to the duodenum. In the last step of the pathway, the bicarbonate released into the duodenum raises the pH, neutralizing the stomach acid.

Simple Neuroendocrine Pathways

In a *simple neuroendocrine pathway*, the stimulus is received by a sensory neuron rather than endocrine tissue. The sensory neuron in turn stimulates a neurosecretory cell. In response, the neurosecretory cell secretes a neurohormone. Like other hormones, the neurohormone diffuses into the bloodstream and travels in the circulation to target cells.

▼ Figure 45.10 A simple neuroendocrine pathway. Sensory neurons respond to a stimulus by sending nerve impulses to a neurosecretory cell, triggering secretion of a neurohormone. Upon reaching its target cells, the neurohormone binds to its receptor, triggering a specific response. In oxytocin signaling, the response increases the stimulus, forming a positive-feedback loop that amplifies signaling.



As an example of a simple neuroendocrine pathway, consider the regulation of milk release during nursing in mammals **(Figure 45.10)**. When an infant suckles, it stimulates sensory neurons in the nipples, generating nerve impulses that reach the hypothalamus. This input triggers the secretion of the neurohormone **oxytocin** from the posterior pituitary gland. Oxytocin then causes contraction of mammary gland cells, forcing milk from reservoirs in the gland.

Feedback Regulation

A feedback loop linking a response back to an initial stimulus is a feature of many control pathways. Often, this loop involves **negative feedback**, in which the response reduces the initial stimulus. For instance, bicarbonate released in response to secretin increases pH in the intestine, eliminating

the stimulus and thereby shutting off secretin release (see Figure 45.9). By decreasing hormone signaling, negative-feedback regulation prevents excessive pathway activity.

Whereas negative feedback dampens a stimulus, **positive feedback** reinforces a stimulus, driving a process to completion. For example, in the pathway outlined in Figure 45.10, the mammary glands secrete milk in response to circulating oxytocin. The released milk in turn leads to more suckling and thus more stimulation. Activation of the pathway is sustained until the baby is full and stops suckling. Other functions of oxytocin, such as stimulating contractions of the uterus during birthing, also exhibit positive feedback.

Comparing negative and positive feedback, we see that only negative feedback helps restore a preexisting state. It is not surprising, therefore, that hormone pathways involved in homeostasis typically exhibit negative feedback. Often such pathways are paired, providing even more balanced control. For example, the blood glucose level is tightly regulated by the opposing, or antagonistic, effects of insulin and glucagon (see Figure 41.23).

Coordination of the Endocrine and Nervous Systems

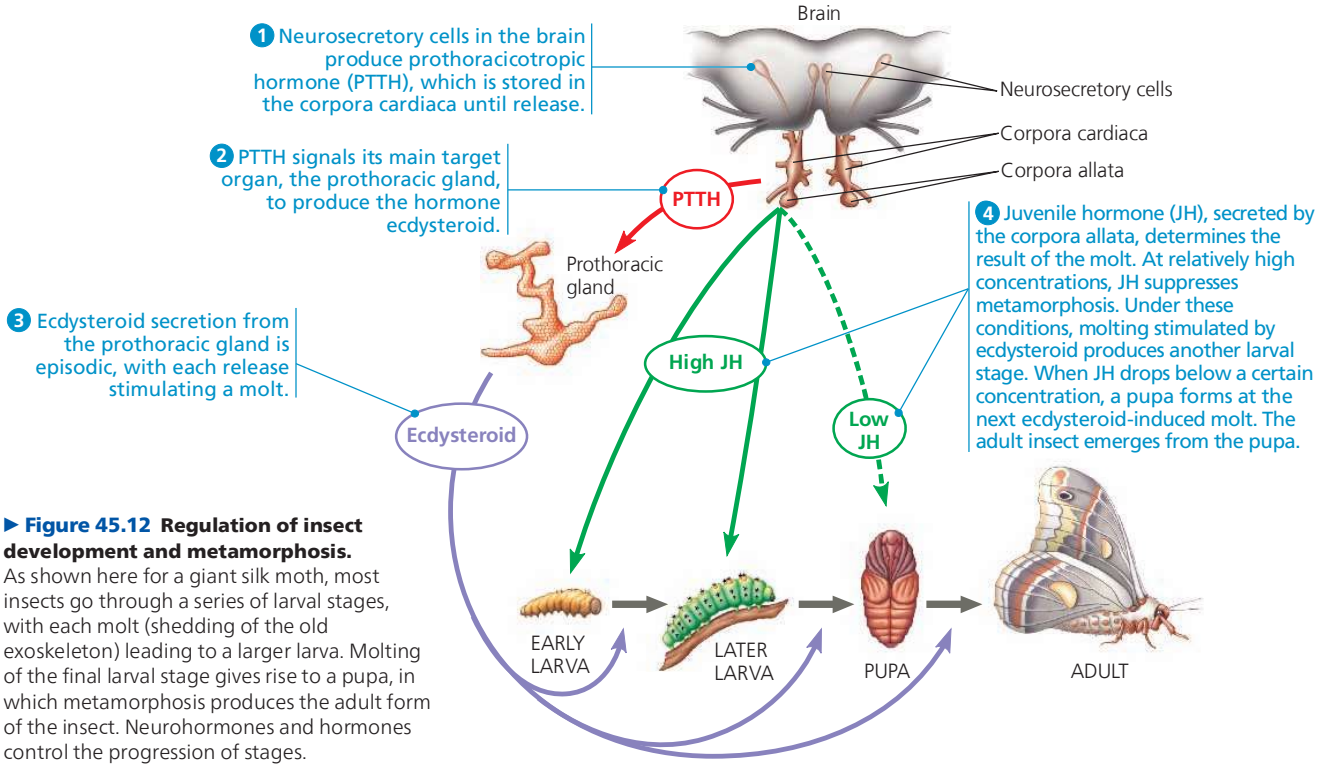
In a wide range of animals, endocrine organs in the brain integrate function of the endocrine system with that of the nervous system. We'll explore the basic principles of such integration in invertebrates and vertebrates.

Invertebrates

▼ Figure 45.11 Larva of the giant silk moth.

The control of development in a moth illustrates neuroendocrine coordination in invertebrates. A moth larva, such as the caterpillar of the giant silk moth (*Hyalophora cecropia*) shown in **Figure 45.11**, grows in stages. Because its exoskeleton cannot stretch, the larva must periodically molt, shedding the old exoskeleton and secreting a new one. The endocrine pathway that controls molting originates in the larval brain **(Figure 45.12)**. Neurosecretory cells in the brain produce PTTH, a polypeptide neurohormone. When PTTH in body fluids reaches an endocrine organ called the prothoracic gland, it directs release of a second hormone, *ecdysteroid*. Bursts of ecdysteroid trigger each successive molt.

Ecdysteroid also controls a remarkable change in form called metamorphosis. Within the larva lie islands of tissues that will become the eyes, wings, brain, and other adult structures. Once a plump, crawling larva becomes a stationary pupa, these islands of cells take over. They complete their program of development, while many larval tissues undergo programmed cell death. The end result is the transformation of the crawling caterpillar into a free-flying moth.



▶ Figure 45.12 Regulation of insect development and metamorphosis. As shown here for a giant silk moth, most insects go through a series of larval stages, with each molt (shedding of the old exoskeleton) leading to a larger larva. Molting of the final larval stage gives rise to a pupa, in which metamorphosis produces the adult form of the insect. Neurohormones and hormones control the progression of stages.

Given that ecdysteroid can cause either molting or metamorphosis, what determines which process takes place? The answer is another signal, juvenile hormone (JH), secreted by a pair of endocrine glands behind the brain. JH modulates ecdysteroid activity. When the level of JH in body fluids is high, ecdysteroid stimulates molting (and thus maintains the "juvenile" larval state). When the JH level drops, ecdysteroid instead induces formation of a pupa, within which metamorphosis occurs.

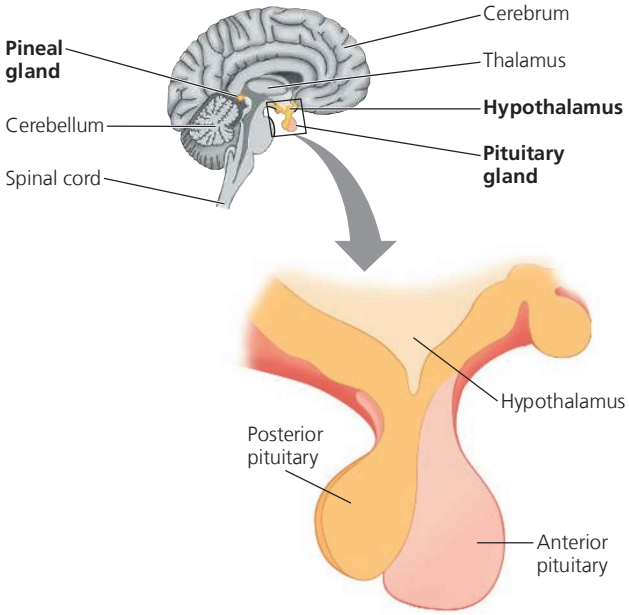
Knowledge of the coordination between the nervous system and endocrine system in insects has provided a basis for novel methods of agricultural pest control. For example, one tool to control insect pests is a chemical that binds to the ecdysteroid receptor, causing insect larvae to molt prematurely and die.

Vertebrates

In vertebrates, coordination of endocrine signaling relies heavily on the **hypothalamus** (Figure 45.13). The hypothalamus receives information from nerves throughout the body and, in response, initiates neuroendocrine signaling appropriate to environmental conditions. In many vertebrates, for example, nerve signals from the brain pass sensory information to the hypothalamus about seasonal changes. The hypothalamus, in turn, regulates the release of reproductive hormones required during the breeding season.

Signals from the hypothalamus travel to the **pituitary gland**, a gland located at the base of the hypothalamus (see Figure 45.13). Roughly the size and shape of a lima bean, the pituitary is made up of two glands that fused during development but remain as discrete posterior and anterior parts, or lobes, that perform very different functions. The **posterior pituitary** is an extension of the neural tissue of the hypothalamus. Hypothalamic axons that reach into the posterior pituitary secrete neurohormones synthesized in the hypothalamus. In contrast, the **anterior pituitary** is an endocrine gland that synthesizes and secretes hormones in response to hormones from the hypothalamus.

▼ Figure 45.13 Endocrine glands in the human brain. This side view of the brain indicates the position of the hypothalamus, the pituitary gland, and the pineal gland. (The pineal gland plays a role in regulating biological rhythms.)

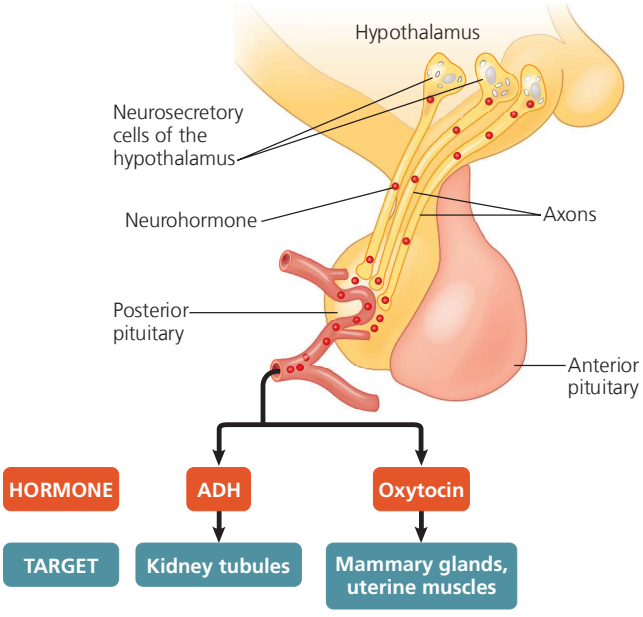


Posterior Pituitary Hormones Neurosecretory cells of the hypothalamus synthesize the two posterior pituitary hormones: antidiuretic hormone (ADH) and oxytocin. After traveling to the posterior pituitary within the long axons of the neurosecretory cells, these neurohormones are stored, to be released into the bloodstream in response to nerve impulses transmitted by the hypothalamus (Figure 45.14).

Antidiuretic hormone (ADH), or *vasopressin*, regulates kidney function. Circulating ADH increases water retention in the kidneys, helping maintain normal blood osmolarity (see Concept 44.5). ADH also has an important role in social behavior (see Concept 51.4).

Oxytocin has multiple functions related to reproduction. As we have seen, in female mammals oxytocin controls milk secretion by the mammary glands and regulates uterine contractions during birthing. In addition, oxytocin has targets in

▼ Figure 45.14 Production and release of posterior pituitary hormones. The posterior pituitary gland is an extension of the hypothalamus. Certain neurosecretory cells in the hypothalamus make antidiuretic hormone (ADH) and oxytocin, which are transported to the posterior pituitary, where they are stored. Nerve signals from the brain trigger release of these neurohormones.



the brain, where it influences behaviors related to maternal care, pair bonding, and sexual activity.

Anterior Pituitary Hormones Hormones secreted by the anterior pituitary control diverse processes in the human body, including metabolism, osmoregulation, and reproduction. As illustrated in **Figure 45.15**, many anterior pituitary hormones, but not all, regulate endocrine glands or tissues.

Hormones secreted by the hypothalamus control the release of all anterior pituitary hormones. Each hypothalamic hormone that regulates release of one or more hormones by the anterior pituitary is called a *releasing* or *inhibiting* hormone. *Prolactin-releasing hormone*, for example, is a hypothalamic hormone that stimulates the anterior pituitary to secrete **prolactin**, which has activities that include stimulating milk production. Each anterior pituitary hormone is controlled by at least one releasing hormone. Some, such as prolactin, have both a releasing hormone and an inhibiting hormone.

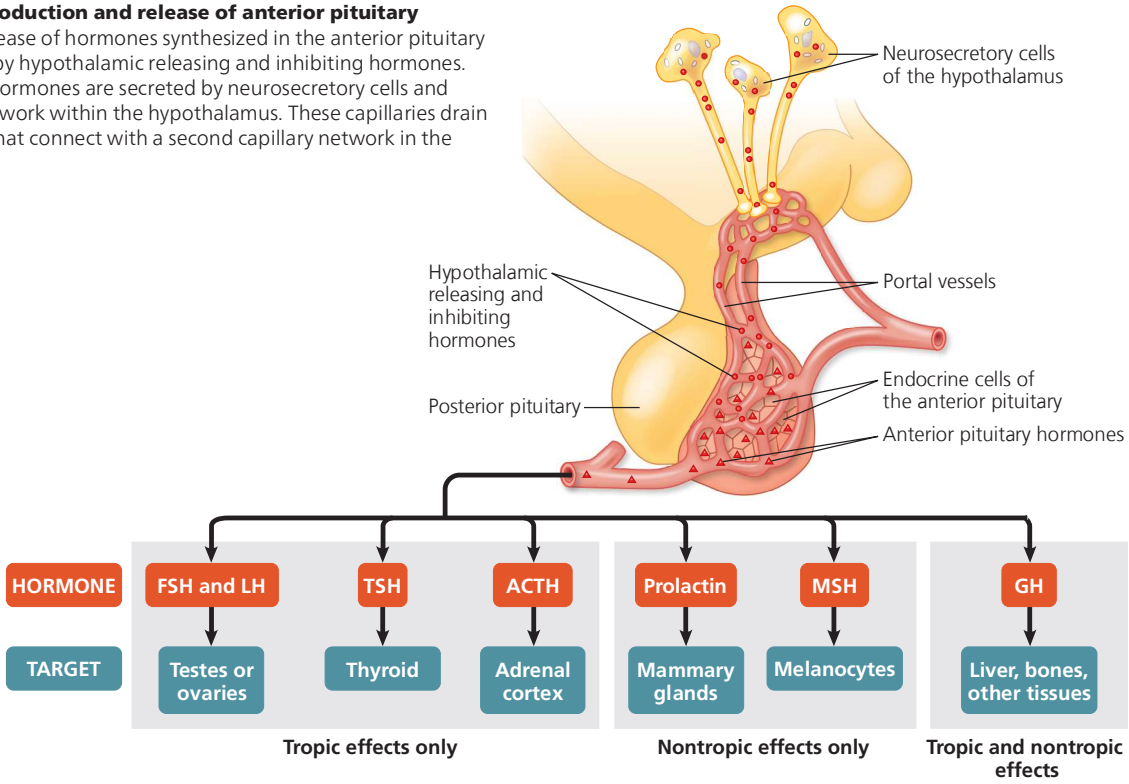
The hypothalamic releasing and inhibiting hormones are secreted near capillaries at the base of the hypothalamus. The capillaries drain into short blood vessels, called portal vessels, which subdivide into a second capillary bed within the anterior pituitary. Releasing and inhibiting hormones thus have direct access to the gland they control.

In neuroendocrine pathways, sets of hormones from the hypothalamus, the anterior pituitary, and a target endocrine gland are often organized into a *hormone cascade*, a form of regulation in which multiple endocrine organs and signals act in series. Signals to the brain stimulate the hypothalamus to secrete a hormone that stimulates or inhibits release of a specific anterior pituitary hormone. The anterior pituitary hormone in turn stimulates another endocrine organ to secrete yet another hormone, which affects specific target tissues. In reproduction, for example, the hypothalamus signals the anterior pituitary to release the hormones FSH and LH, which in turn regulate hormone secretion by the gonads (ovaries or testes).

In a sense, hormone cascade pathways redirect signals from the hypothalamus to other endocrine glands. For this reason, the anterior pituitary hormones in such pathways are called *tropic* hormones, or tropins, and are said to have a *tropic* effect (from the Greek *trope*, to turn). Thus, FSH and LH are gonadotropins because they convey signals from the hypothalamus to the gonads. To learn more about tropic hormones and hormone cascade pathways, we'll turn next to thyroid gland function and regulation.

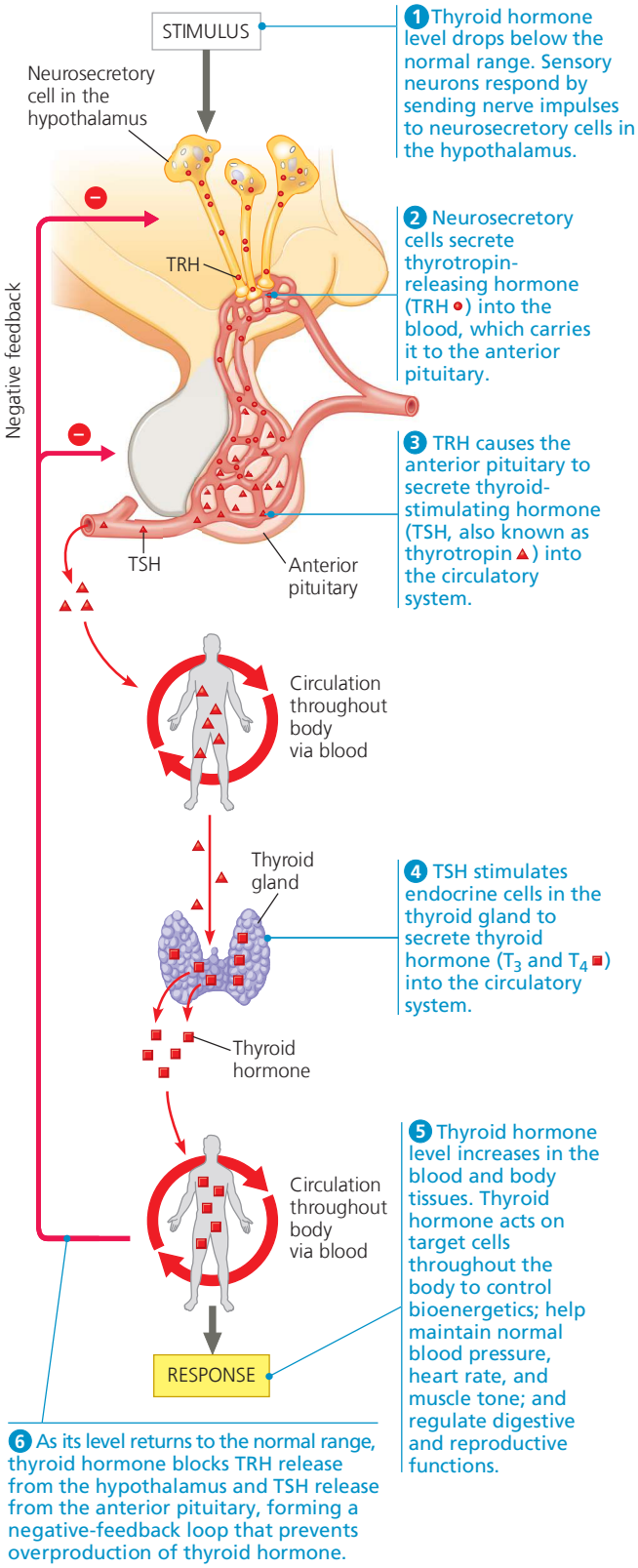
Thyroid Regulation: A Hormone Cascade Pathway

In mammals, **thyroid hormone** regulates bioenergetics; helps maintain normal blood pressure, heart rate, and muscle tone; and regulates digestive and reproductive functions. **Figure 45.16** provides an overview of the hormone cascade



▶ Figure 45.15 Production and release of anterior pituitary hormones. The release of hormones synthesized in the anterior pituitary gland is controlled by hypothalamic releasing and inhibiting hormones. The hypothalamic hormones are secreted by neurosecretory cells and enter a capillary network within the hypothalamus. These capillaries drain into portal vessels that connect with a second capillary network in the anterior pituitary.

▼ Figure 45.16 Regulation of thyroid hormone secretion: a hormone cascade pathway.



pathway that regulates thyroid hormone release. If the level of thyroid hormone in the blood drops, the hypothalamus secretes thyrotropin-releasing hormone (TRH), causing the anterior pituitary to secrete thyrotropin, a tropic hormone also known as thyroid-stimulating hormone (TSH). TSH in turn stimulates the **thyroid gland**, an organ in the neck consisting of two lobes on the ventral surface of the trachea. The thyroid gland responds by secreting thyroid hormone, which increases metabolic rate.

As with other hormone cascade pathways, feedback regulation often occurs at multiple levels. For example, thyroid hormone exerts negative feedback on the hypothalamus and on the anterior pituitary, in each case blocking release of the hormone that promotes its production (see Figure 45.16).

Disorders of Thyroid Function and Regulation

Disruption of thyroid hormone production and regulation can result in serious disorders. One such disorder reflects the unusual chemical makeup of thyroid hormone, the only iodine-containing molecule synthesized in the body. *Thyroid hormone* is actually a pair of very similar molecules derived from the amino acid tyrosine. *Triiodothyronine* (T_3) contains three iodine atoms, whereas tetraiodothyronine, or *thyroxine* (T_4), contains four (see Figure 45.4).

Although iodine is readily obtained from seafood or iodized salt, people in many parts of the world lack enough iodine in their diet to synthesize adequate amounts of thyroid hormone. With only a low blood level of thyroid hormone, the pituitary receives no negative feedback and continues to secrete TSH. An elevated TSH level in turn causes the thyroid gland to enlarge, resulting in goiter, a marked swelling of the neck.

Hormonal Regulation of Growth

Growth hormone (GH), which is secreted by the anterior pituitary, stimulates growth through both tropic and nontropic effects. A major target, the liver, responds to GH by releasing *insulin-like growth factors* (*IGFs*), which circulate in the blood and directly stimulate bone and cartilage growth. (IGFs also appear to play a key role in aging in many animal species.) In the absence of GH, the skeleton of an immature animal stops growing. GH also exerts diverse metabolic effects that tend to raise the blood glucose level, thus opposing the effects of insulin.

Abnormal production of GH in humans can result in several disorders, depending on when the problem occurs and whether it involves hypersecretion (too much) or hyposecretion (too little). Hypersecretion of GH during childhood can lead to gigantism, in which the person grows unusually tall but retains relatively normal body

PROBLEM-SOLVING EXERCISE

Is thyroid regulation normal in this patient?

Normal health requires proper regulation of the thyroid gland. Hypothyroidism, the secretion of too little thyroid hormone (T_3 and T_4), can cause weight gain, lethargy, and intolerance to cold in adults. In contrast, excessive secretion of thyroid hormone, known as hyperthyroidism, can lead to high body temperature, profuse sweating, weight loss, muscle weakness, irritability, and high blood pressure. Thyroid-stimulating hormone (TSH) stimulates the thyroid to release thyroid hormone. Testing for levels of T_3, T_4, and TSH in the blood can help diagnose various medical conditions.

In this exercise, you will determine whether a 35-year-old man who came to the emergency room with episodes of paralysis has thyroid problems.

Your Approach As the emergency physician, you order a set of blood tests, including four that measure thyroid function. To determine whether the thyroid activity of your patient is normal, you will compare his blood test results with the normal range, as determined from a large set of healthy people.

Your Data

#	Test*	Patient	Normal Range	Comments
1	Total triiodothyronine (T_3)	2.93 nmol/L	0.89–2.44 nmol/L	
2	Free thyroxine (T_4)	27.4 pmol/L	9.0–21.0 pmol/L	
3	TSH	5.55 mU/L	0.35–4.94 mU/L	
4	TSH receptor autoantibody	0.2 U/mL	0–1.5 U/mL	

*T_3 and T_4 levels are measured as the number of molecules per unit volume: here, nanomoles (nmol, 10^{-9} moles) or picomoles (pmol, 10^{-12} moles) per liter (L). The levels of TSH and the autoantibody for its receptor are measured as activity, expressed in units (U) or milliunits (mU) per unit volume.

Your Analysis

1. For each test, determine whether the patient's test value is high, low, or normal relative to the normal range. Then write *High, Low*, or *Normal* in the comments column of the table.
2. Based on tests 1–3, is your patient hypothyroid or hyperthyroid?
3. Test 4 measures the level of autoantibodies (self-reactive antibodies) that bind to and activate the body's receptor for TSH. A high level of autoantibodies causes sustained thyroid hormone production and the autoimmune disorder called Graves' disease. Is it likely that your patient has this disease? Explain.
4. A thyroid tumor increases the mass of cells producing T_3 and T_4, whereas a tumor in the anterior pituitary increases the mass of TSH-secreting cells. Would you expect either condition to result in the observed blood test values? Explain.

Instructors: A version of this Problem-Solving Exercise can be assigned in **Mastering Biology**.

proportions **(Figure 45.17)**. Excessive GH production in adulthood stimulates bony growth in the few body parts that are still responsive to the hormone—predominantly the face, hands, and feet. The result is an overgrowth of the extremities called acromegaly (from the Greek *acros*, extreme, and *mega*, large).

Hyposecretion of GH in childhood retards long-bone growth and can lead to pituitary dwarfism. People with this disorder are for the most part properly proportioned but generally reach a height of only about 1.2 m (4 feet). If diagnosed before puberty, pituitary dwarfism can be treated with human GH (also called HGH). Treatment with HGH produced by recombinant DNA technology is common.

Whereas the effects of altered growth hormone levels are readily related to a change in adult height, disrupting some endocrine pathways can have effects that appear unrelated to normal pathway function. The **Problem-Solving Exercise** explores one such example of a medical mystery difficult to diagnose based on symptoms alone.

▼ Figure 45.17 Effect of growth hormone overproduction. Shown here surrounded by his family, Robert Wadlow grew to a height of 2.7 m (8 feet 11 inches) by age 22, making him the tallest man in history. His height was due to excess secretion of growth hormone by his pituitary gland.

CONCEPT CHECK 45.2

1. What are the roles of oxytocin and prolactin in regulating the mammary glands?
2. How do the two fused glands of the pituitary gland differ in function?
3. **WHAT IF?** Propose an explanation for why defects in a particular hormone cascade pathway observed in patients typically affect the final gland in the pathway rather than the hypothalamus or pituitary.
4. **WHAT IF?** Lab tests of two patients, each diagnosed with excessive thyroid hormone production, revealed an elevated level of TSH in one but not the other. Was the diagnosis of one patient necessarily incorrect? Explain.

For suggested answers, see Appendix A.

CONCEPT 45.3

Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior

In the remainder of this chapter, we'll focus on endocrine function in homeostasis, development, and behavior. We'll begin with another example of a simple hormone pathway, the regulation of calcium ion concentration in the circulatory system.

Parathyroid Hormone and Vitamin D: Control of Blood Calcium

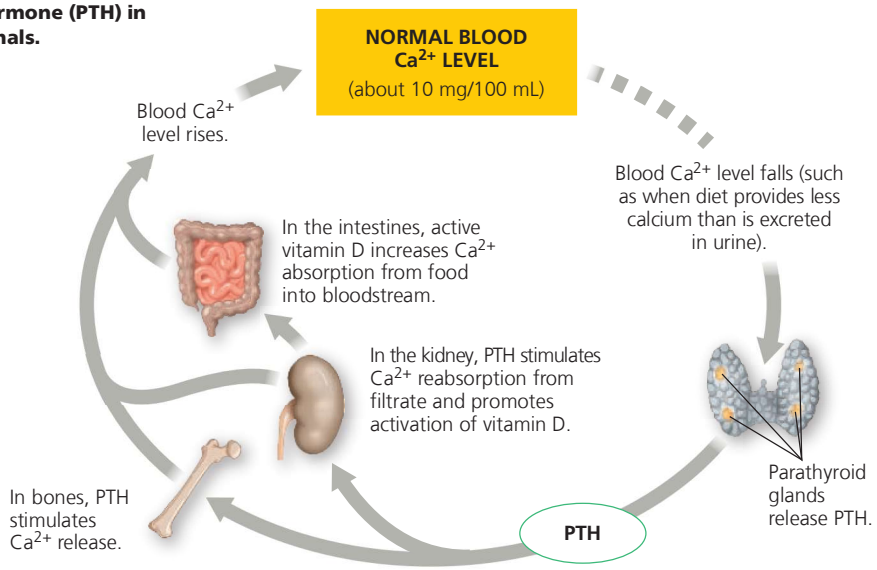
Because calcium ions (Ca^{2+}) are essential to the normal functioning of all cells, homeostatic control of the level of calcium in the blood is vital. If the blood Ca^{2+} level falls substantially, skeletal muscles begin to contract convulsively, a potentially fatal condition. If the blood Ca^{2+} level rises substantially, calcium phosphate can form precipitates in body tissues, leading to widespread organ damage.

In mammals, the **parathyroid glands**, a set of four small structures embedded in the posterior surface of the thyroid (see Figure 45.8), play a major role in blood Ca^{2+} regulation. When the blood Ca^{2+} level falls below a set point of about 10 mg/100 mL, these glands release **parathyroid hormone (PTH)**.

PTH raises the level of blood Ca^{2+} through direct effects in bones and the kidneys and an indirect effect on the intestines **(Figure 45.18)**. In bones, PTH causes the mineralized matrix to break down, releasing Ca^{2+} into the blood. In the kidneys, PTH directly stimulates reabsorption of Ca^{2+} through the renal tubules. In addition, PTH indirectly raises the blood Ca^{2+} level by promoting production of vitamin D. A precursor form of vitamin D is obtained from food or synthesized by skin exposed to sunlight. Conversion of this precursor to active vitamin D begins in the liver. PTH acts in the kidney to stimulate completion of the conversion process. Vitamin D in turn acts on the intestines, stimulating the uptake of Ca^{2+} from food. As the blood Ca^{2+} level rises, a negative-feedback loop inhibits further release of PTH from the parathyroid glands (not shown in Figure 45.18).

The thyroid gland can also contribute to calcium homeostasis. If the blood Ca^{2+} level rises above the set point, the thyroid gland releases **calcitonin**, a hormone that inhibits bone breakdown and enhances Ca^{2+} excretion by the kidneys. In fishes, rodents, and some other animals, calcitonin is required for Ca^{2+} homeostasis. In humans, however, calcitonin is apparently needed only during the extensive bone growth of childhood.

▶ Figure 45.18 The roles of parathyroid hormone (PTH) in regulating the blood calcium level in mammals.



Adrenal Hormones: Response to Stress

The adrenal glands of vertebrates play a major role in the response to *stress*, a state of threatened homeostasis. Located atop the kidneys (the *renal* organs), each **adrenal gland** is actually made up of two glands with different cell types, functions, and embryonic origins: the adrenal *cortex*, the outer portion, and the adrenal *medulla*, the central portion **(Figure 45.19)**. The adrenal cortex consists of true endocrine cells, whereas the secretory cells of the adrenal medulla develop from neural tissue. Thus, like the pituitary gland, each adrenal gland is a fused endocrine and neuroendocrine gland.

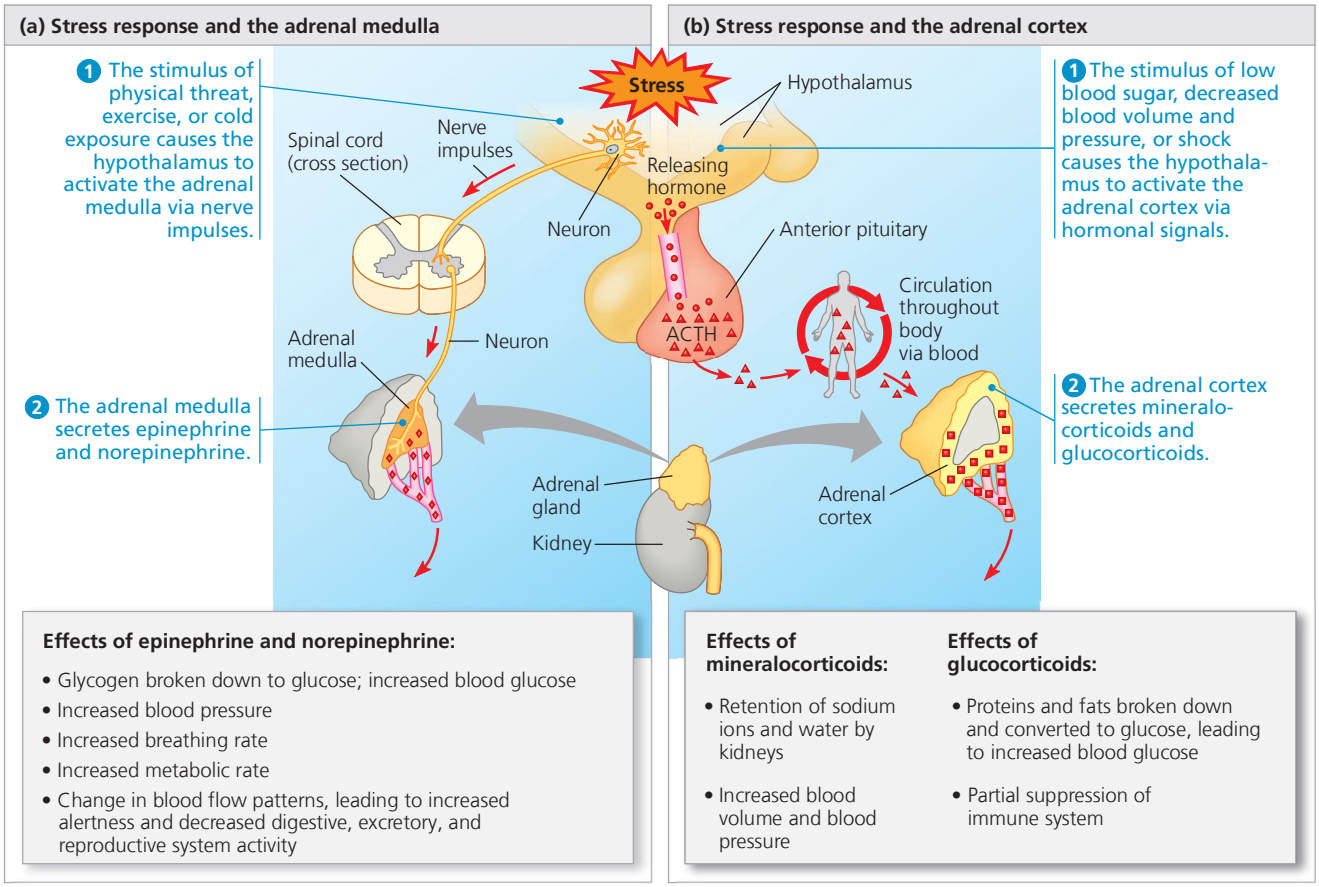
The Role of the Adrenal Medulla

Imagine that while walking in the woods at night you hear a growling noise nearby. "A bear?" you wonder. Your heart beats faster, your breathing quickens, your muscles tense, and your thoughts speed up. These and other rapid responses to perceived danger comprise the "fight-or-flight" response. This coordinated set of physiological changes is triggered by two hormones of the adrenal medulla, epinephrine (adrenaline) and **norepinephrine** (also known as noradrenaline). Both are *catecholamines*, a class of amine hormones synthesized from the amino acid tyrosine. Both molecules also function as neurotransmitters, as you'll read in Concept 48.4.

As hormones, epinephrine and norepinephrine increase the amount of chemical energy available for immediate use (see Figure 45.19a). Both catecholamines increase the rate of glycogen breakdown in the liver and skeletal muscles and promote the release of glucose by liver cells and of fatty acids from fat cells. The released glucose and fatty acids circulate in the blood and can be used by body cells as fuel.

Catecholamines also exert profound effects on the cardiovascular and respiratory systems. For example, they increase heart rate and stroke volume and dilate the bronchioles in the lungs, actions that raise the rate of oxygen delivery to body cells. For this reason, doctors may prescribe epinephrine as a heart stimulant or to open the airways during an asthma attack. Catecholamines also alter blood flow, causing constriction of some blood vessels and dilation of others. The overall effect is to shunt blood away from the skin, digestive organs, and kidneys while increasing the blood supply to the heart, brain, and skeletal muscles.

▼ Figure 45.19 Stress and the adrenal gland.



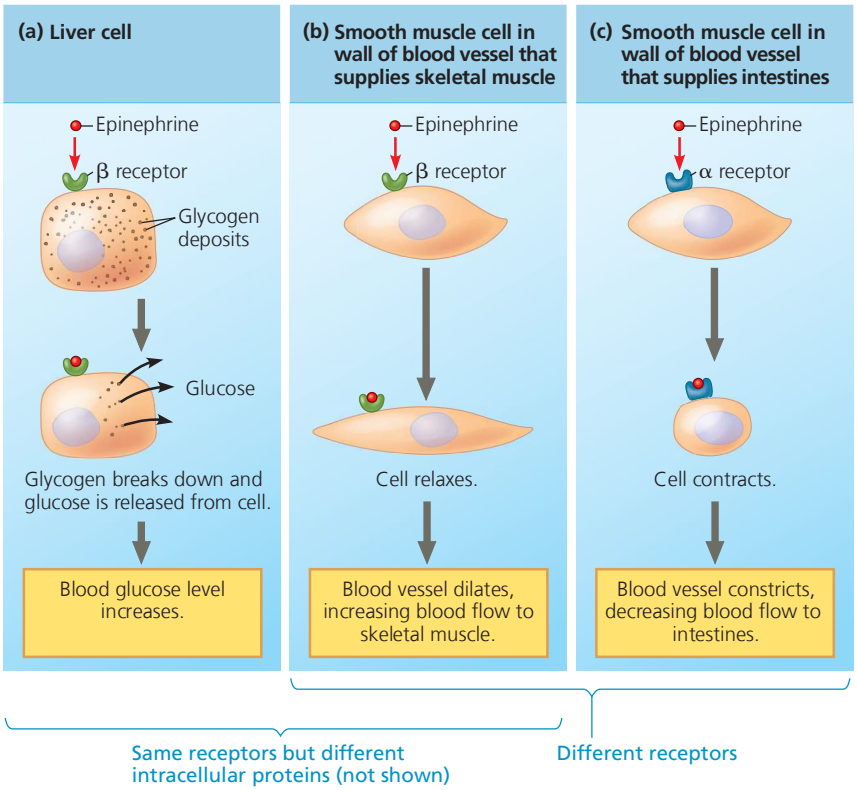
Mastering Biology Animation: Hormonal Response to Stress

Epinephrine's Multiple Effects: *A Closer Look* How can epinephrine coordinate a response to stress that involves widely varying effects in individual tissues? We can answer that question by examining different response pathways **(Figure 45.20)** in a range of target cells:

- In liver cells, epinephrine binds to a β-type receptor in the plasma membrane. This receptor activates the enzyme protein kinase A, which in turn regulates enzymes of glycogen metabolism, causing release of glucose into the blood (see Figure 45.20a). Note that this is the signal transduction pathway illustrated in Figure 45.6.
- In the smooth muscle cells that line blood vessels supplying skeletal muscle, the same kinase activated by the same epinephrine receptor inactivates a muscle-specific enzyme. The result is smooth muscle relaxation, leading to vasodilation and hence increased blood flow to skeletal muscles (see Figure 45.20b).
- In the smooth muscle cells lining blood vessels of the intestines, epinephrine binds to an α-type receptor (see Figure 45.20c). This receptor triggers a signaling pathway that involves enzymes other than protein kinase A and that causes smooth muscle contraction rather than relaxation. The resulting vasoconstriction reduces blood flow to the intestines, facilitating the redirection of blood to active skeletal muscle.

Thus, epinephrine elicits multiple responses if its target cells differ in the receptor protein they express or in the molecules activated by the receptor upon hormone binding. As illustrated in these examples, such variation in response plays a key role in enabling epinephrine to trigger a range of activities that together bring about a coordinated rapid response to stressful stimuli.

▼ Figure 45.20 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 or effector proteins; compare **(a)** with **(b)**. Target cells with different receptors for the hormone often exhibit different responses; compare **(b)** with **(c)**.



The Role of the Adrenal Cortex

Like the adrenal medulla, the adrenal cortex mediates an endocrine response to stress (see Figure 45.19b). The two portions of the adrenal gland differ, however, in both the types of stress that trigger a response and the targets of the hormones that are released.

The adrenal cortex becomes active under stressful conditions that include low blood sugar, decreased blood volume and pressure, and shock. Such stimuli cause the hypothalamus to secrete a releasing hormone that stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), a tropic hormone. When ACTH reaches the adrenal cortex via the bloodstream, it stimulates the endocrine cells to synthesize and secrete a family of steroids called *corticosteroids*. The two main types of corticosteroids in humans are glucocorticoids and mineralocorticoids.

Glucocorticoids, such as cortisol (see Figure 45.4), make more glucose available as fuel by promoting glucose synthesis from noncarbohydrate sources, such as proteins. Glucocorticoids also act on skeletal muscle, causing the breakdown of muscle proteins into amino acids. These are transported to the liver and kidneys, converted to glucose, and released into the blood. The synthesis of glucose upon the breakdown of muscle proteins provides circulating fuel when the body requires more glucose than the liver can mobilize from its glycogen stores.

If glucocorticoids are introduced into the body at a level above that normally present, they suppress certain components of the body's immune system. For this reason, glucocorticoids are sometimes used to treat inflammatory diseases such as arthritis. However, their long-term use can have serious side effects on metabolism. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as

Scientific Skills Exercise

Designing a Controlled Experiment

How Is Nighttime ACTH Secretion Related to Expected Sleep Duration? Humans secrete increasing amounts of adrenocorticotropic hormone (ACTH) during the late stages of normal sleep, with the peak secretion occurring at the time of spontaneous waking. Because ACTH is released in response to stressful stimuli, scientists hypothesized that ACTH secretion prior to waking might be an anticipatory response to the stress associated with transitioning from sleep to a more active state. If so, an individual's expectation of waking at a particular time might influence the timing of ACTH secretion. How can such a hypothesis be tested? In this exercise, you will examine how researchers designed a controlled experiment to study the role of expectation.

How the Experiment Was Done Researchers studied 15 healthy volunteers in their mid-20s over three nights. Each night, each subject was told when he or she would be awakened: 6:00 or 9:00 AM. The subjects went to sleep at midnight. Subjects in the "short" or "long" protocol group were awakened at the expected time (6:00 or 9:00 AM, respectively). Subjects in the "surprise" protocol group were told they would be awakened at 9:00 AM, but were actually awakened 3 hours early, at 6:00 AM. At set times, blood samples were drawn to determine plasma levels of ACTH. To determine the change (Δ) in ACTH concentration post-waking, the researchers compared samples drawn at waking and 30 minutes later.

Data from the Experiment

Sleep Protocol	Expected Wake Time	Actual Wake Time	Mean Plasma ACTH Level (pg/mL)		
			1:00 AM	6:00 AM	Δ in the 30 Minutes Post-waking
Short	6:00 AM	6:00 AM	9.9	37.3	10.6
Long	9:00 AM	9:00 AM	8.1	26.5	12.2
Surprise	9:00 AM	6:00 AM	8.0	25.5	22.1

Data from J. Born et al., Timing the end of nocturnal sleep, *Nature* 397:29–30 (1999).

INTERPRET THE DATA

1. Describe the role of the "surprise" protocol in the experimental design.
2. Each subject was given a different protocol on each of the three nights, and the order of the protocols was varied among the subjects that so that one-third had each protocol each night. What factors were the researchers attempting to control for with this approach?
3. For subjects in the short protocol, what was the mean ACTH level at waking? Using the data in the last two columns, calculate the mean level 30 minutes later. Was the rate of change faster or slower in that 30-minute period than during the interval from 1:00 to 6:00 AM?
4. How does the change in ACTH level between 1:00 and 6:00 AM for the surprise protocol compare to that for the short and long protocols? Does this result support the hypothesis being tested? Explain.
5. Using the data in the last two columns, calculate the mean ACTH concentration 30 minutes post-waking for the surprise protocol and compare to your answer for question 3. What do your results suggest about a person's physiological response immediately after waking?
6. What are some variables that weren't controlled for in this experiment that could be explored in a follow-up study?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

aspirin and ibuprofen, are therefore generally preferred for treating chronic inflammatory conditions.

Mineralocorticoids act principally in maintaining salt and water balance. For example, the mineralocorticoid *aldosterone* functions in ion and water homeostasis of the blood (see Figure 44.21). Like glucocorticoids, mineralocorticoids not only mediate stress responses, but also participate in homeostatic regulation of metabolism. In the **Scientific Skills Exercise**, you can explore an experiment investigating changes in ACTH secretion as humans awaken from sleep.

Sex Hormones

Sex hormones affect growth, development, reproductive cycles, and sexual behavior. Although the adrenal glands secrete small quantities of these hormones, the gonads (testes of males and ovaries of females) are their principal sources. The gonads produce and secrete three major types of steroid sex hormones: androgens, estrogens, and progesterone. All three types are found in both males and females but in different proportions.

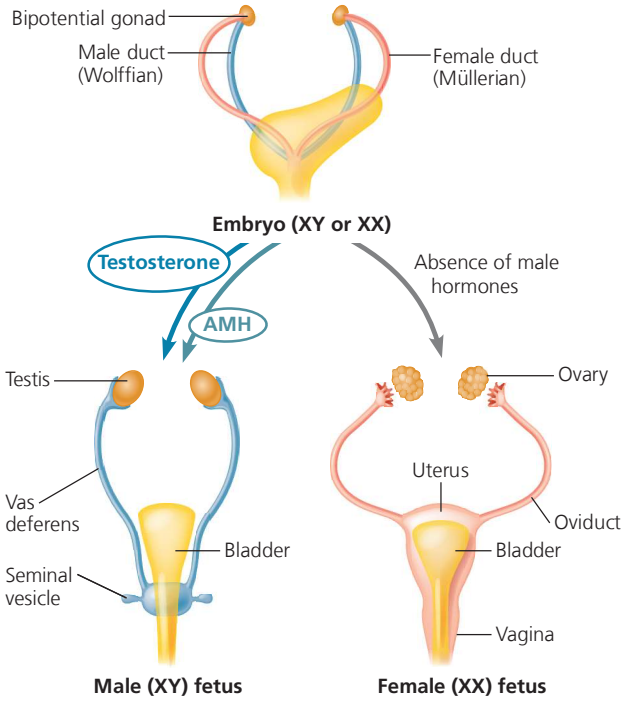
The testes primarily synthesize **androgens**, the main one being **testosterone**. In humans, testosterone first functions in male (XY) embryos, promoting development of male reproductive structures **(Figure 45.21)**. In female (XX) embryos, the absence of testosterone allows the development of female reproductive structures. You can learn more about this role of hormones in the development of an embryo as male or female in the Scientific Skills Exercise in Chapter 46.

Androgens play a major role again at puberty, when they are responsible for the development of male secondary sex characteristics. High concentrations of androgens lead to lengthening and thickening of the vocal cords that lower the voice, male patterns of hair growth, and increases in muscle and bone mass. The muscle-building, or anabolic, action of testosterone and related steroids has enticed some athletes to take them as supplements, despite prohibitions against their use in nearly all sports. Use of anabolic steroids, while effective in increasing muscle mass, can cause severe acne outbreaks and liver damage, as well as significant decreases in sperm count and testicular size.

Estrogens, of which the most important is **estradiol**, are responsible for the maintenance of the female reproductive system and for the development of female secondary sex characteristics. In contrast, **progesterone** is involved in preparing and maintaining tissues of the mammalian uterus required to support the growth and development of an embryo.

Gonadal androgens, estrogens, and progesterone are components of hormone cascade pathways. Synthesis of these hormones is primarily controlled by two gonadotropins from the anterior pituitary, follicle-stimulating hormone and luteinizing hormone (see Figure 45.15). Gonadotropin secretion is in turn controlled by GnRH (gonadotropin-releasing hormone) from the hypothalamus.

▼ Figure 45.21 Sex hormones regulate formation of internal reproductive structures in human development. In a male (XY) embryo, the bipotential gonads (gonads that can develop into either of two forms) become the testes, which secrete testosterone and anti-Müllerian hormone (AMH). Testosterone directs formation of sperm-carrying ducts (vas deferens and seminal vesicles), while AMH causes the female ducts to degenerate. In the absence of these testis hormones, the male ducts degenerate and female structures form, including the oviduct, uterus, and vagina.



VISUAL SKILLS *Looking at this figure, explain why the adjective* bipotential *is only used to describe the gonad.*

Mastering Biology **BBC Video: Male, Female, or Intersex?**

We'll examine the feedback relationships that regulate gonadal hormone secretion in detail in Chapter 46.

Endocrine Disruptors

Between 1938 and 1971, some pregnant women at risk for pregnancy complications were prescribed a synthetic estrogen called diethylstilbestrol (DES). What was not known until 1971 was that exposure to DES can alter reproductive system development in the fetus. Daughters of women who took DES more frequently developed certain reproductive abnormalities, including vaginal and cervical cancer, structural changes in the reproductive organs, and increased risk of miscarriage (spontaneous abortion). DES is now recognized as an *endocrine disruptor*, a foreign molecule that interrupts the normal function of a hormone pathway.

In recent years, some scientists have hypothesized that molecules in the environment also act as endocrine disruptors. For example, bisphenol A, a chemical used in making some plastics, has been studied for potential interference with normal reproduction and development. In addition, it has been suggested that some estrogen-like molecules, such as those present in soybeans and other edible plant products, have the beneficial effect of lowering breast cancer risk. Sorting out such effects, whether harmful or beneficial, has proven quite difficult, in part because enzymes in the liver change the properties of any such molecules entering the body through the digestive system.

Hormones and Biological Rhythms

There is still much to be learned about the hormone **melatonin**, a modified amino acid that regulates functions related to light and the seasons. Melatonin is produced by the **pineal gland**, a small mass of tissue near the center of the mammalian brain (see Figure 45.13).

Although melatonin affects skin pigmentation in many vertebrates, its primary effects relate to biological rhythms associated with reproduction and with the daily activity level (see Figure 40.9). Melatonin is secreted at night, and the amount released depends on the length of the night. In winter, for example, when days are short and nights are long, more melatonin is secreted. There is also good evidence that nightly increases in the level of melatonin play a significant role in promoting sleep.

The release of melatonin by the pineal gland is controlled by a group of neurons in the hypothalamus called the suprachiasmatic nucleus (SCN). The SCN functions as a biological clock and receives input from specialized light-sensitive neurons in the retina of the eye. Although the SCN regulates melatonin production during the 24-hour light/dark cycle, melatonin also influences SCN activity. We'll consider biological rhythms further in Concept 49.2, where we analyze experiments on SCN function.

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 45.16). 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 45.22)**.

▼ Figure 45.22 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.

▲ Tadpole

▲ Adult frog

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 indicate that prolactin is an ancient hormone with functions that have diversified during the evolution of vertebrate groups.

Melanocyte-stimulating hormone (MSH), secreted by the anterior pituitary, provides another example of a hormone with distinct functions in different evolutionary lineages. In amphibians, fishes, and reptiles, MSH regulates skin color by controlling pigment distribution in skin cells called melanocytes. In mammals, MSH functions in hunger and metabolism in addition to skin coloration.

The specialized action of MSH that has evolved in the mammalian brain may prove to be of particular medical importance. Many patients with late-stage cancer, AIDS, tuberculosis, and certain aging disorders develop a devastating wasting condition called cachexia. Characterized by weight loss, muscle atrophy, and loss of appetite, cachexia responds poorly to existing therapies. However, it turns out that activation of a brain receptor for MSH produces some of the same changes seen in cachexia. Moreover, in experiments on mice with mutations that cause cancer and consequently cachexia, treatment with drugs that blocked the brain receptor for MSH prevented cachexia. Whether such drugs can be used to treat cachexia in humans is an area of active study.

CONCEPT CHECK 45.3

1. If a hormone pathway produces a transient response to a stimulus, how would shortening the stimulus duration affect the need for negative feedback?
2. **WHAT IF?** Suppose you receive an injection of cortisone, a glucocorticoid, in an inflamed joint. What aspect of glucocorticoid activity would you be exploiting? If a glucocorticoid pill were also effective at treating the inflammation, why would it still be preferable to introduce the drug locally?
3. **MAKE CONNECTIONS** What parallels can you identify in the properties and effects of epinephrine and the plant hormone auxin (see Concept 39.2) with regard to their effects in different target tissues?

For suggested answers, see Appendix A.

45 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

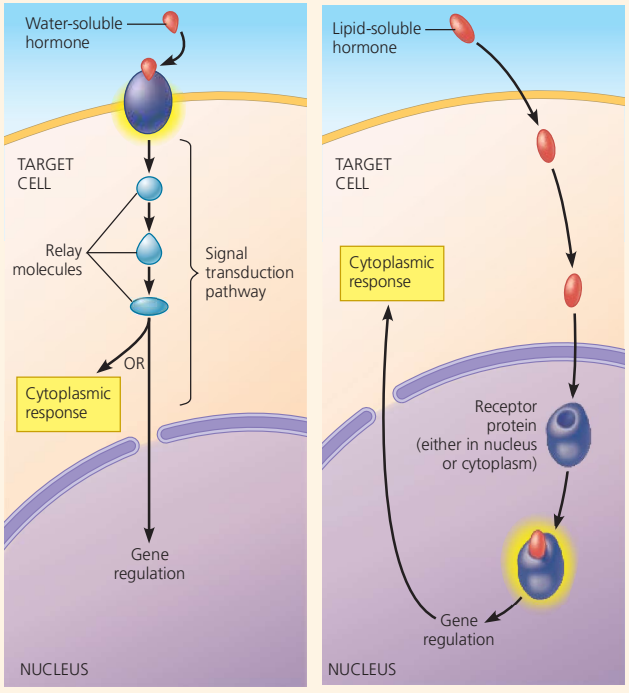
SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 45.1

Hormones and other signaling molecules bind to target receptors, triggering specific response pathways *(pp. 1000–1004)*

- The forms of signaling between animal cells differ in the type of secreting cell and the route taken by the signal to its target. **Endocrine** signals, or **hormones**, are secreted into the extracellular fluid by endocrine cells or ductless glands and reach target cells via circulatory fluids. There the binding of a hormone to a receptor specific for that particular hormone triggers a cellular response. **Paracrine** signals act on neighboring cells, whereas **autocrine** signals act on the secreting cell itself. **Neurotransmitters** also act locally, but **neurohormones** can act throughout the body. **Pheromones** are released into the environment for communication between animals of the same species.
- **Local regulators**, which carry out paracrine and autocrine signaling, include cytokines and growth factors (polypeptides), **prostaglandins** (modified fatty acids), and **nitric oxide** (a gas).
- Polypeptides, steroids, and amines comprise the major classes of animal hormones. Depending on whether they are water-soluble or lipid-soluble, hormones activate different response pathways. The endocrine cells that secrete hormones are often located in glands dedicated in part or in whole to endocrine signaling.

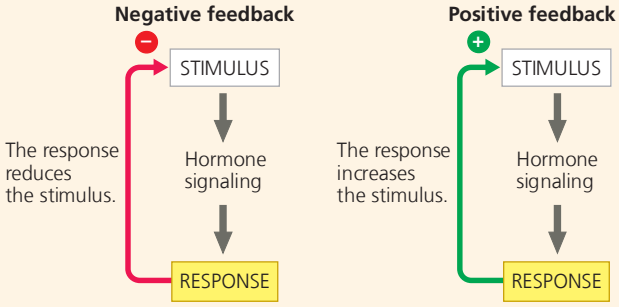


MAKE CONNECTIONS *What forms of signaling activate a helper T cell in immune responses (see Figure 43.18)?*

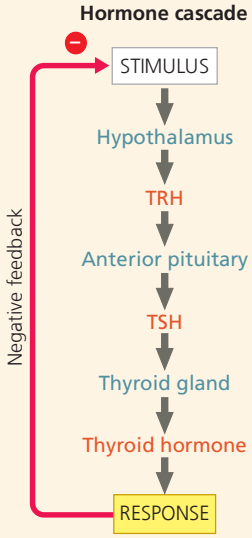
CONCEPT 45.2

Feedback regulation and coordination with the nervous system are common in hormone pathways *(pp. 1004–1011)*

- In a simple endocrine pathway, endocrine cells respond directly to a stimulus. By contrast, in a simple neuroendocrine pathway, a sensory neuron receives the stimulus.
- Hormone pathways may include **negative feedback**, which dampens the stimulus and thus limits the response, or **positive feedback**, which amplifies the stimulus and drives the response to completion.



- In insects, molting and development are controlled by three hormones: PTTH; ecdysteroid, whose release is triggered by PTTH; and juvenile hormone. Coordination of signals from the nervous and endocrine systems and modulation of one hormone activity by another bring about the sequence of developmental stages that lead to an adult form.
- In vertebrates, neurosecretory cells in the **hypothalamus** produce two hormones that are secreted by the **posterior pituitary** and that act directly on nonendocrine tissues: **oxytocin**, which induces uterine contractions and release of milk from mammary glands, and **antidiuretic hormone (ADH)**, which enhances water reabsorption in the kidneys.
- Other hypothalamic cells produce hormones that are transported to the **anterior pituitary**, where they stimulate or inhibit the release of particular hormones.
- Often, anterior pituitary hormones act in a cascade. For example, the secretion of thyroid-stimulating hormone (TSH) is regulated by thyrotropin-releasing hormone (TRH). TSH in turn induces the **thyroid gland** to secrete **thyroid hormone**, a combination of the iodine-containing hormones T_3 and T_4. Thyroid hormone stimulates metabolism and influences development and maturation.



- Most anterior pituitary hormones are tropic hormones, acting on endocrine tissues or glands to regulate hormone secretion. Tropic hormones of the anterior pituitary include TSH, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropic hormone (ACTH). **Growth hormone (GH)** has both tropic and nontropic effects. It promotes growth directly, affects metabolism, and stimulates the production of growth factors by other tissues.

? *Which major endocrine organs described in Figure 45.8 are regulated independently of the hypothalamus and pituitary?*

CONCEPT 45.3

Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior *(pp. 1011–1016)*

- **Parathyroid hormone (PTH)**, secreted by the **parathyroid glands**, causes bone to release Ca^{2+} into the blood and stimulates reabsorption of Ca^{2+} in the kidneys. PTH also stimulates the kidneys to activate vitamin D, which promotes intestinal uptake of Ca^{2+} from food. **Calcitonin**, secreted by the thyroid, has the opposite effects in bones and kidneys as PTH. Calcitonin is important for calcium homeostasis in adults of some vertebrates, but not humans.
- In response to stress, neurosecretory cells in the adrenal medulla release **epinephrine** and **norepinephrine**, which mediate various fight-or-flight responses. The adrenal cortex releases **glucocorticoids**, such as cortisol, which influence glucose metabolism and the immune system. It also releases **mineralocorticoids**, primarily aldosterone, which help regulate salt and water balance.
- Sex hormones regulate growth, development, reproduction, and sexual behavior. Although the adrenal cortex produces small amounts of these hormones, the gonads (testes and ovaries) serve as the major source. All three types—**androgens, estrogens**, and **progesterone**—are produced in males and females, but in different proportions.
- The **pineal gland**, located within the brain, secretes **melatonin**, which functions in biological rhythms related to reproduction and sleep. Release of melatonin is controlled by the SCN, the region of the brain that functions as a biological clock.
- Hormones have acquired distinct roles in different species over the course of evolution. **Prolactin** stimulates milk production in mammals but has diverse effects in other vertebrates. **Melanocyte-stimulating hormone (MSH)** influences fat metabolism in mammals and skin pigmentation in other vertebrates.

? *ADH and epinephrine act as hormones when released into the bloodstream and as neurotransmitters when released in synapses between neurons. What is similar about the endocrine glands that produce these two molecules?*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. Which statement is accurate?
(A) Hormones that differ in effect reach their target cells by different routes through the body.
(B) Pairs of hormones that have the same effect are said to have antagonistic functions.
(C) Hormones are often regulated through feedback loops.
(D) Hormones of the same chemical class usually have the same function.

2. The hypothalamus
   (A) synthesizes all of the hormones produced by the pituitary gland.
   (B) influences the function of only one lobe of the pituitary gland.
   (C) produces only inhibitory hormones.
   (D) regulates both reproduction and body temperature.

3. Growth factors are local regulators that
   (A) are produced by the anterior pituitary.
   (B) are modified fatty acids that stimulate bone and cartilage growth.
   (C) are found on the surface of cancer cells and stimulate abnormal cell division.
   (D) bind to cell-surface receptors and stimulate growth and development of target cells.

4. Which hormone is *correctly* paired with its action?
   (A) oxytocin—stimulates uterine contractions during childbirth
   (B) thyroxine—inhibits metabolic processes
   (C) ACTH—inhibits the release of glucocorticoids by the adrenal cortex
   (D) melatonin—raises blood calcium level

Levels 3-4: Applying/Analyzing

5. What do steroid and peptide hormones typically have in common?
   (A) their solubility in cell membranes
   (B) their requirement for travel through the bloodstream
   (C) the location of their receptors
   (D) their reliance on signal transduction in the cell

6. Which of the following is the most likely explanation for hypothyroidism in a patient whose iodine level is normal?
   (A) greater production of T_3 than of T_4
   (B) hyposecretion of TSH
   (C) hypersecretion of MSH
   (D) a decrease in the thyroid secretion of calcitonin

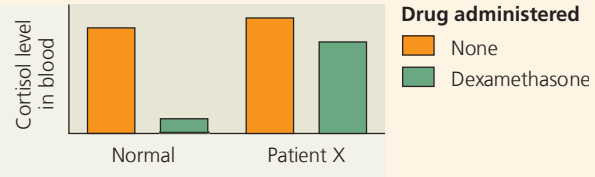
7. The relationship between the insect hormones ecdysteroid and PTTH is an example of
   (A) an interaction of the endocrine and nervous systems.
   (B) homeostasis achieved by positive feedback.
   (C) homeostasis maintained by antagonistic hormones.
   (D) competitive inhibition of a hormone receptor.

8. **DRAW IT** In mammals, milk production by mammary glands is controlled by prolactin and prolactin-releasing hormone. Draw a simple sketch of this pathway, including glands, tissues, hormones, routes for hormone movement, and effects.

Levels 5-6: Evaluating/Creating

9. **EVOLUTION CONNECTION** The intracellular receptors used by all the steroid and thyroid hormones are similar enough in structure that they are all considered members of one "superfamily" of proteins. Propose a hypothesis for how the genes encoding these receptors may have evolved. (Hint: See Figure 21.13.) Explain how you could test your hypothesis using DNA sequence data.

10. **SCIENTIFIC INQUIRY • INTERPRET THE DATA** A chronically high level of glucocorticoids can result in obesity, muscle weakness, and depression, a combination of symptoms called Cushing's syndrome. Excessive activity of either the pituitary or the adrenal gland can be the cause. To determine which gland has abnormal activity in a particular patient, doctors use the drug dexamethasone, a synthetic glucocorticoid that blocks ACTH release. Based on the graph, identify which gland is affected in patient X.



11. **WRITE ABOUT A THEME: INTERACTIONS** In a short essay (100–150 words), discuss the role of hormones in an animal's responses to changes in its environment. Use specific examples.

12. **SYNTHESIZE YOUR KNOWLEDGE**

The frog on the left was injected with MSH, causing a change in skin color within minutes due to a rapid redistribution of pigment granules in specialized skin cells. Using what you know about neuroendocrine signaling, explain how a frog could use MSH to match its skin coloration to that of its surroundings.

For selected answers, see Appendix A.

46 Animal Reproduction

KEY CONCEPTS

46.1 **Both asexual and sexual reproduction occur in the animal kingdom** *p. 1020*

46.2 **Fertilization depends on mechanisms that bring together sperm and eggs of the same species** *p. 1022*

46.3 **Reproductive organs produce and transport gametes** *p. 1025*

46.4 **The interplay of tropic and sex hormones regulates reproduction in mammals** *p. 1030*

46.5 **In placental mammals, an embryo develops fully within the mother's uterus** *p. 1034*

Study Tip

Make a table: To help you keep track of the roles of the tropic hormones in mammalian reproductive systems, make a table like the one shown here. Complete the last cell for GNRH, and fill in the rows for FSH and LH.

Hormone	Source	In males: Target/effect	In females: Target/effect
GNRH= gonado-tropin-releasing hormone	Hypo-thalamus	Anterior pituitary/ promote FSH and LH release	
FSH=			
LH=			

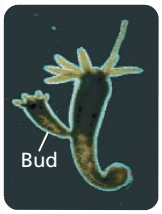
Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 46
- Animation: Human Spermatogenesis
- Animation: Human Oogenesis

For Instructors to Assign (in Item Library)
- Scientific Skills Exercise: Making Inferences and Designing an Experiment
- Tutorial: Sex Hormones and Mammalian Reproduction

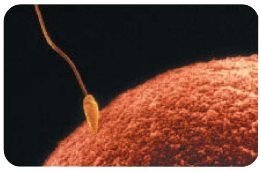
Figure 46.1 This colony of coral polyps is reproducing. Tiny yellow orbs packed with eggs and sperm emerge from the polyps, rise to the sea surface, and burst. There, the eggs and sperm form embryos that become larvae, eventually drifting down and establishing new coral colonies.

In what different ways do animals reproduce?



Asexual reproduction
No fusion of a sperm and an egg.

Sexual reproduction
Fusion of a sperm and an egg forms a zygote.



Hermaphroditism
An individual animal produces both male and female gametes.

Separate sexes
Male produces sperm and female produces eggs.

External fertilization
An egg encounters sperm outside of the female reproductive tract.

Internal fertilization
An egg encounters sperm inside the female reproductive tract. In some animals, including most mammals, the embryo develops internally and is born from the mother's body.

CONCEPT 46.1

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 13.8). The female gamete, the **egg**, is large and nonmotile, whereas the male gamete, the **sperm**, is generally much smaller and motile. In **asexual reproduction**, new individuals are generated without the fusion of egg and sperm. For most asexual animals, reproduction relies entirely on mitotic cell division. Asexual and sexual reproduction are both common among animals.

Mechanisms of Asexual Reproduction

Among animals, several simple forms of asexual reproduction are found exclusively in invertebrates. One of these is *budding*, in which new individuals arise from outgrowths of existing ones (see Figure 13.2). 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 splitting and separation of a parent organism into two individuals of approximately equal size.

Invertebrate asexual reproduction can also occur by *fragmentation*, the breaking of the body into several pieces, followed by *regeneration*, regrowth of lost body parts. If more than one piece grows and develops into a complete animal, the effect is reproduction. For example, certain annelid worms can split into several fragments, each regenerating a complete worm. Numerous corals, sponges, cnidarians, and tunicates also reproduce by fragmentation and regeneration.

A wide range of animal species reproduce asexually by **parthenogenesis**, in which an egg develops without being fertilized. Among invertebrates, parthenogenesis occurs in certain species of bees, wasps, and ants. The offspring can be either haploid or diploid. In the case of honeybees, males (drones) are fertile haploid adults that arise by parthenogenesis. In contrast, female honeybees, including both the sterile workers and the fertile queens, are diploid adults that develop from fertilized eggs.

Among vertebrates, parthenogenesis is thought to be a rare response to low population density. For example, female Komodo dragons, hammerhead sharks, and zebra sharks have been observed to produce offspring when kept in captivity apart from males of their species. In 2015, DNA analysis of a group of female sawfish from a Florida river identified specimens that had two identical copies of all loci tested, providing evidence of vertebrate parthenogenesis in the wild.

Variation in Patterns of Sexual Reproduction

In many animal species, including humans, sexual reproduction involves the mating of a female and a male. In certain circumstances, however, finding a partner for reproduction can be challenging. Adaptations that arose during the evolution of some species meet this challenge by blurring the distinction between male and female. One such adaptation is particularly common among sessile (stationary) animals, such as barnacles, burrowing animals, such as clams, and some parasites, including tapeworms. That adaptation is **hermaphroditism**, in which each individual has both male and female reproductive systems (the term *hermaphrodite* merges the names of Hermes and Aphrodite, a Greek god and goddess). Sessile animals have a very limited opportunity to find a mate, but 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 shown for a pair of sea slugs in **Figure 46.2**. In some species, including many corals, hermaphrodites can also self-fertilize, allowing a form of sexual reproduction that doesn't require any partner.

▼ Figure 46.2 Reproduction among hermaphrodites. In this mating of sea slugs, or nudibranchs (*Nembrotha chamberlaini*), each hermaphrodite is providing sperm to fertilize the eggs of the other.

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 to be lost. Instead, within a week the largest female in the harem transforms into a male and begins to produce sperm instead of eggs. What selective pressure in the evolution of the bluehead wrasse resulted in sex reversal for the 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.

Certain oyster species also undergo sex reversal. In this case, individuals reproduce as males and then later as females, when their size is greatest. Since the number of gametes produced generally increases with size much more for females than for males, sex reversal in this direction maximizes gamete production. The result is enhanced reproductive success: Because oysters are sedentary animals and release their gametes into the surrounding water rather than mating directly, releasing more gametes tends to result in more offspring.

Reproductive Cycles

Most animals, whether asexual or sexual, exhibit cycles in reproductive activity, often related to changing seasons. These cycles are controlled by hormones, whose secretion is in turn regulated by environmental cues. In this way, animals expend resources to reproduce only when sufficient energy sources are available and when environmental conditions favor the survival of offspring. For example, ewes (female sheep) have a reproductive cycle lasting 15–17 days. **Ovulation**, the release of mature eggs, occurs at the midpoint of each cycle. For ewes, reproductive cycles generally occur only during fall and early winter, and the length of any pregnancy is five months. Thus, most lambs are born in the early spring, when their chances of survival are optimal.

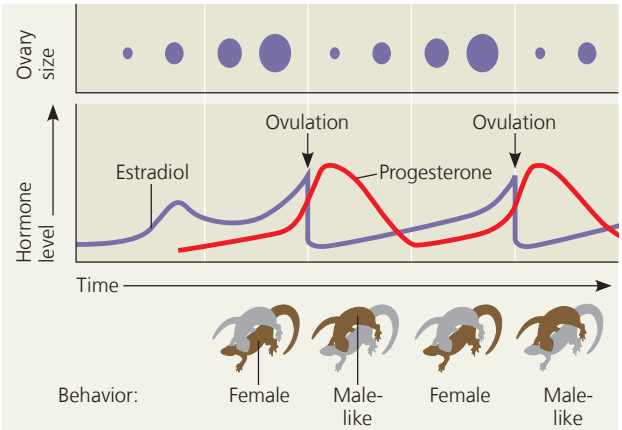
Because seasonal temperature is often an important cue for reproduction, climate change can decrease reproductive success. Researchers have discovered such an effect on caribou (wild reindeer) in Greenland. In spring, caribou migrate to calving grounds to eat sprouting plants, give birth, and care for their calves. Prior to 1993, the arrival of the caribou at the calving grounds coincided with the brief period during which the plants were nutritious and digestible. By 2006, however, average spring temperatures in the calving grounds had increased by more than 4°C, and the plants sprouted two weeks earlier. Because caribou migration is triggered by day length, not temperature, a mismatch arose between the timing of new plant growth and caribou birthing. Without adequate nutrition for the nursing females, production of caribou offspring has declined by more than 75% since 1993. To learn more about the effects of climate change on caribou and other organisms, see Make Connections Figure 56.31.

Reproductive cycles are also found among animals that can reproduce both sexually and asexually. Consider, for instance, the water flea (genus *Daphnia*). A female *Daphnia* can produce eggs of two types. One type of egg requires fertilization to develop, but the other type does not and develops instead by parthenogenesis. *Daphnia* reproduce asexually when environmental conditions are favorable and sexually during times of environmental stress. As a result, the switch between sexual and asexual reproduction is roughly linked to season.

For some asexual animal species, a cycle of reproductive behavior appears to reflect a sexual evolutionary past. In the parthenogenetic lizard species *Aspidoscelis uniparens*, reproduction is asexual, and all individuals are female. Nevertheless, these lizards have courtship and mating behaviors very similar to those of sexual species of *Aspidoscelis*. One member of each mating pair undergoes **ovulation**, the production and release of mature eggs. The other female mimics a male **(Figure 46.3a)**. Over the course of the breeding season, the two lizards alternate roles two or three times. An individual adopts female behavior prior to ovulation, when the concentration of the hormone estradiol is high, and then switches to male-like behavior after ovulation, when the concentration of the hormone progesterone is high **(Figure 46.3b)**. A female is more likely to ovulate if she is mounted at a critical time of the hormone cycle; isolated lizards lay fewer eggs than those that go through the motions of sex. These findings support the hypothesis that these parthenogenetic lizards evolved from species having two sexes and still require certain sexual stimuli for maximum reproductive success.

▼ Figure 46.3 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, but ovulation is stimulated by mating behavior.

(a) Both lizards in this photograph are *A. uniparens* females. The one on top is playing the role of a male. Individuals switch sex roles two or three times during the breeding season.



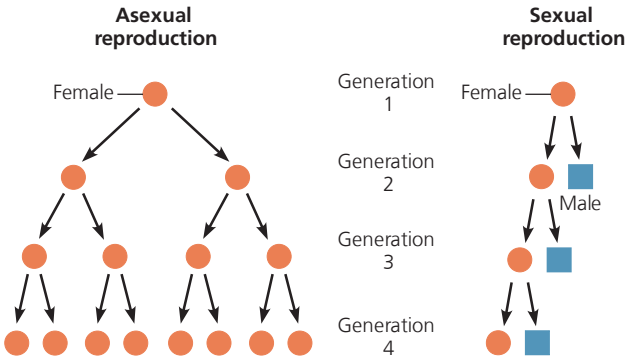
(b) The changes in sexual behavior of *A. uniparens* individuals are correlated with the cycles of ovulation and changing levels of the sex hormones estradiol and progesterone. These drawings track the changes in ovary size, hormone levels, and sexual behavior of one female lizard (shown in brown).

INTERPRET THE DATA *If you plotted hormone levels for the lizard shown in gray, how would your graph differ from the graph in part (b)?*

Sexual Reproduction: An Evolutionary Enigma

EVOLUTION Although our species and many others reproduce sexually, the existence of sexual reproduction is actually puzzling. To see why, imagine an animal population in which half the females reproduce sexually and half reproduce asexually. We'll assume that the number of offspring per female is a constant, two in this case. The two offspring of an

▼ Figure 46.4 The "reproductive handicap" of sex. These diagrams contrast asexual versus sexual reproduction over four generations, assuming two surviving offspring per female.



asexual female will both be daughters that will each give birth to two more reproductive daughters. In contrast, half of a sexual female's offspring will be male **(Figure 46.4)**. 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 sexual reproduction provide that counteracts its twofold cost? The answer remains uncertain. 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, asexual reproduction is expected to be most advantageous in stable, favorable environments because it can perpetuate successful genotypes precisely.

There are a number of reasons why the unique gene combinations formed during sexual reproduction might be advantageous. One is that beneficial gene combinations arising through recombination might speed up adaptation. Although this idea appears straightforward, the theoretical advantage is significant only when the rate of beneficial mutations is high and population size is small. Another idea is that the shuffling of genes during sexual reproduction might allow a population to rid itself of sets of harmful genes more readily.

CONCEPT CHECK 46.1

1. Compare and contrast the outcomes of asexual and sexual reproduction.
2. Parthenogenesis is the most common form of asexual reproduction in animals that at other times reproduce sexually. What characteristic of parthenogenesis might explain this observation?
3. **WHAT IF?** If a hermaphrodite self-fertilizes, will the offspring be identical to the parent? Explain.
4. **MAKE CONNECTIONS** What examples of plant reproduction are most similar to asexual reproduction in animals? (See Concept 38.2.)

For suggested answers, see Appendix A.

CONCEPT 46.2

Fertilization depends on mechanisms that bring together sperm and eggs of the same species

The union of sperm and egg—**fertilization**—can be external or internal. In species with *external fertilization*, the female releases eggs into the environment, where the male fertilizes them **(Figure 46.5)**. In species with *internal fertilization*, sperm deposited in or near the female reproductive tract fertilize eggs within the tract. (We'll discuss cellular and molecular details of fertilization in Concept 47.1.)

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 that one individual generates in releasing gametes trigger others 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 of the South Pacific, like the coral in Figure 46.1, times its spawning to both the season and the lunar cycle. 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

▼ Figure 46.5 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.

in such vast numbers that the sea appears milky with gametes. 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 (see Figure 46.5). 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 even when the external environment is dry. It typically requires sophisticated and compatible reproductive systems, as well as cooperative behavior that leads to copulation. 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 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 are active at very low concentrations (see Concept 45.1). Many pheromones function as mate attractants. For example, pheromones allow some female insects to be detected by males more than a kilometer away.

Evidence for human pheromones remains controversial. It was once argued that female roommates produce pheromones that trigger synchrony in menstrual cycles, but further statistical analyses have failed to support this finding.

Ensuring the Survival of Offspring

Typically, animals that fertilize eggs internally produce fewer gametes than species with external fertilization, but a higher fraction of their zygotes survive. 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 greater protection of the embryos and parental care of the young. For example, the internally fertilized eggs of birds and other reptiles have shells and internal membranes that protect against water loss and physical damage during the eggs' external development (see Figure 34.26). 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. The offspring of marsupial mammals, such as kangaroos and opossums, spend only a short period in the uterus as embryos; they then crawl out and complete development attached to a mammary gland in the mother's pouch. Embryos of eutherian (placental) mammals, such as zebras and 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.

▼ Figure 46.6 Parental care in an invertebrate. Compared with many other insects, giant water bugs of the genus *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. The male (shown here) carries the eggs for days, frequently fanning water over them to keep them moist, aerated, and free of parasites.

When a caribou or kangaroo is born or when a baby eagle hatches out of an egg, the newborn is not yet capable of independent existence. Instead, mammals nurse their offspring, and adult birds feed their young. Parental care of eggs or offspring is in fact widespread among animals, even including some invertebrates **(Figure 46.6)**.

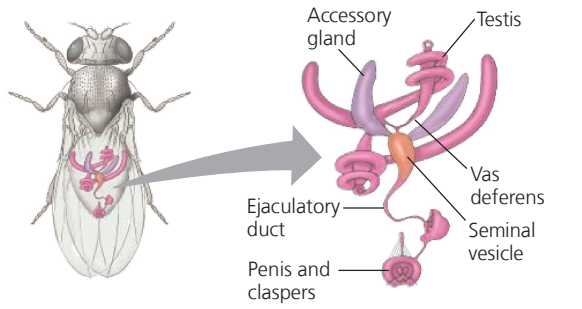
Gamete Production and Delivery

Sexual reproduction in animals relies on sets of cells that are precursors for eggs and sperm. Cells dedicated to this function are often established early in the formation of the embryo and remain inactive while the body plan takes shape. Cycles of growth and mitosis then increase, or *amplify*, the number of cells available for making gametes—eggs or sperm.

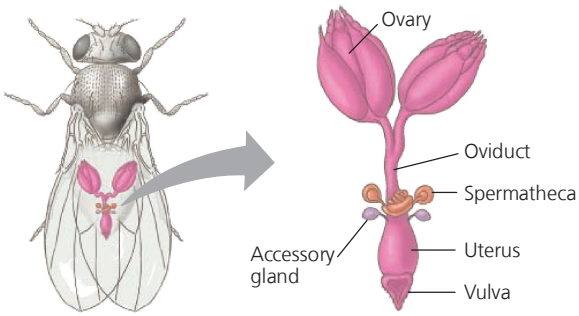
In producing gametes from the precursor cells and making them available for fertilization, animals employ a variety of reproductive systems. **Gonads**, organs that produce gametes, are found in many but not all animals. Exceptions include the palolo, discussed above. The palolo and most other polychaete worms (phylum Annelida) 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 open a portion of the body, 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. For example, fruit flies and most other insects have separate sexes with

▼ Figure 46.7 An example of insect reproductive anatomy.



(a) Male fruit fly. Sperm form in the testes, pass through a sperm duct (vas deferens), and are stored in the seminal vesicles. The male ejaculates sperm along with fluid from the accessory glands. (Males of some species of insects and other arthropods have appendages called claspers that grasp the female during copulation.)



(b) Female fruit fly. Eggs develop in the ovaries and then travel through the oviducts to the uterus. After mating, sperm are stored in the spermathecae, which are connected to the uterus by short ducts. The female uses a stored sperm to fertilize each egg as it enters the uterus before she passes the egg out through the vulva.

VISUAL SKILLS *Study the two drawings, and then describe the movement of fruit fly sperm from formation to fertilization.*

complex reproductive systems **(Figure 46.7)**. In many insect species, the female reproductive system includes one or more **spermathecae** (singular, *spermatheca*), sacs in which sperm may be kept alive and stored for extended periods, a year or more in some cases. Because the female releases male gametes from the spermathecae and thus fertilizes her eggs only in response to the appropriate stimuli, fertilization occurs under conditions likely to be well suited to survival of offspring.

Vertebrate reproductive systems display limited but significant variations. In some vertebrates, the uterus is divided into two chambers; in others, including humans and birds, it is a single structure. 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. Lacking a well-developed penis, males of these species instead release sperm by turning the cloaca inside out. In contrast, mammals generally lack a cloaca and have a separate opening for the digestive tract. In addition, most female mammals have separate openings for the excretory and reproductive systems.

Although fertilization involves the union of a single egg and sperm, animals often mate with more than one member of the other sex. Monogamy, the sustained sexual partnership of two individuals, is rare among animals, including most mammals. Mechanisms have evolved, however, that enhance the reproductive success of a male with a particular female and diminish the chance of that female mating successfully with another partner. For example, some male insects transfer secretions that make a female less receptive to courtship, reducing the likelihood of her mating again.

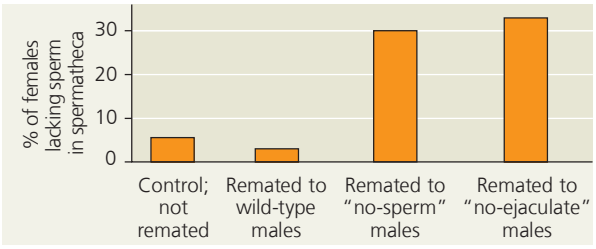
Can females also influence the relative reproductive success of their mates? This question intrigued two scientific collaborators working in Europe. Studying female fruit flies that copulated with one male and then another, the researchers traced the fate of sperm transferred in the first mating. As shown in **Figure 46.8**, females play a major role in determining the outcome of multiple matings. The processes by which gametes and individuals compete during reproduction remain a vibrant research area.

▼ Figure 46.8 Inquiry

Why is sperm usage biased when female fruit flies mate twice?

Experiment When a female fruit fly mates twice, 80% of the offspring result from the second mating. Scientists had hypothesized that ejaculate from the second mating displaces sperm from the first mating. To test this hypothesis, Rhonda Snook, at the University of Sheffield, and David Hosken, at the University of Zurich, used mutant males with altered reproductive systems. "No-ejaculate" males mate but do not transfer sperm or fluid to females. "No-sperm" males mate and ejaculate but make no sperm. The researchers allowed females to mate first with wild-type males and then with wild-type males, no-sperm males, or no-ejaculate males. As a control, some females were mated only once (to wild-type males). The scientists then dissected each female under a microscope and recorded whether sperm were absent from the spermathecae, the major sperm storage organs.

Results



Conclusion Because remating reduces sperm storage when no sperm or fluids are transferred, the hypothesis that ejaculate from a second mating displaces stored sperm is incorrect. Instead, it appears females may get rid of stored sperm in response to remating, perhaps allowing for replacing stored sperm, possibly of diminished fitness, with fresh sperm.

Data from R. R. Snook and D. J. Hosken, Sperm death and dumping in *Drosophila*, *Nature* 428:939–941 (2004).

WHAT IF? *Suppose males in the first mating had a mutant allele that resulted in smaller eyes as a dominant trait. What fraction of the females would produce some offspring with smaller eyes?*

CONCEPT CHECK 46.2

1. How does internal fertilization facilitate life on land?
2. What mechanisms have evolved in animals with (a) external fertilization and (b) internal fertilization that help offspring survive to adulthood?
3. **MAKE CONNECTIONS** What are the shared and distinct functions of the uterus of an insect and the ovary of a flowering plant? (See Figure 38.6.)

For suggested answers, see Appendix A.

CONCEPT 46.3

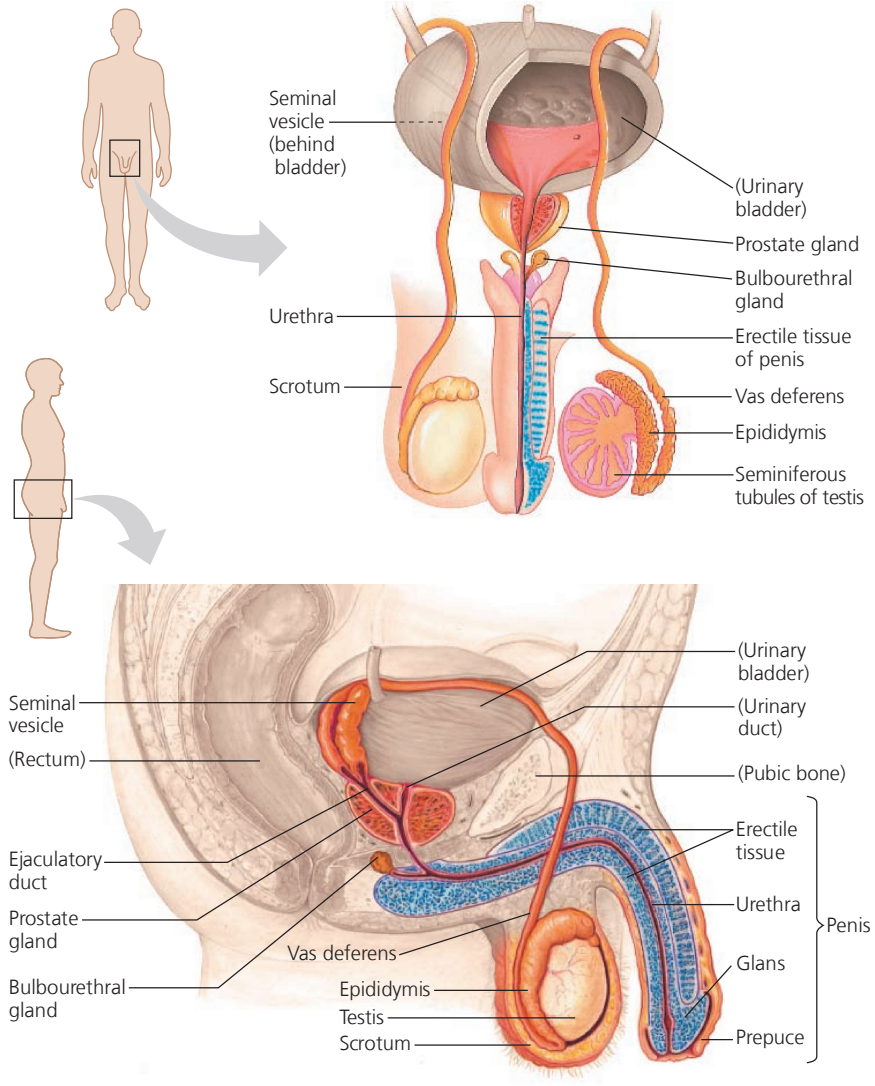
Reproductive organs produce and transport gametes

Having surveyed some of the general features of animal reproduction, we'll focus in the rest of the chapter on humans, beginning with the reproductive anatomy of each sex.

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 46.9)**.

▼ **Figure 46.9 Reproductive anatomy of the human male.** Labels in parentheses identify nonreproductive structures shown for orientation purposes.



Mastering Biology **Animation: Reproductive System of the Human Male**

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, testis temperature is maintained about 2°C below the core body temperature by the **scrotum**, a fold of the body wall.

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 three 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 (see Concept 45.1).

The **prostate gland** secretes its products directly into the urethra through small ducts. Thin and milky, the fluid from this gland contains anticoagulant enzymes and citrate (a sperm nutrient). 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. There is evidence that bulbourethral fluid carries some sperm released before ejaculation, which may contribute to 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 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 the local regulator nitric oxide (NO; see Concept 45.1); 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 dogs, raccoons, walruses, 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 of the penis, the male **glans**, has a much thinner outer layer and is much more sensitive to stimulation. A fold of skin called the *prepuce* covers the glans of humans. The male prepuce, or foreskin, is removed if 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 consist of gonads, which produce eggs and reproductive hormones, and a system of ducts and chambers, which receive and carry gametes and house the embryo and fetus **(Figure 46.10)**.

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, cilia on the epithelial lining of the oviduct begin beating. This motion draws fluid from the body cavity into the oviduct, bringing along the egg. Further motion of the cilia, together with wavelike contractions of the oviduct, conveys the egg down the duct to the uterus.

The **uterus**, also known as the womb, 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

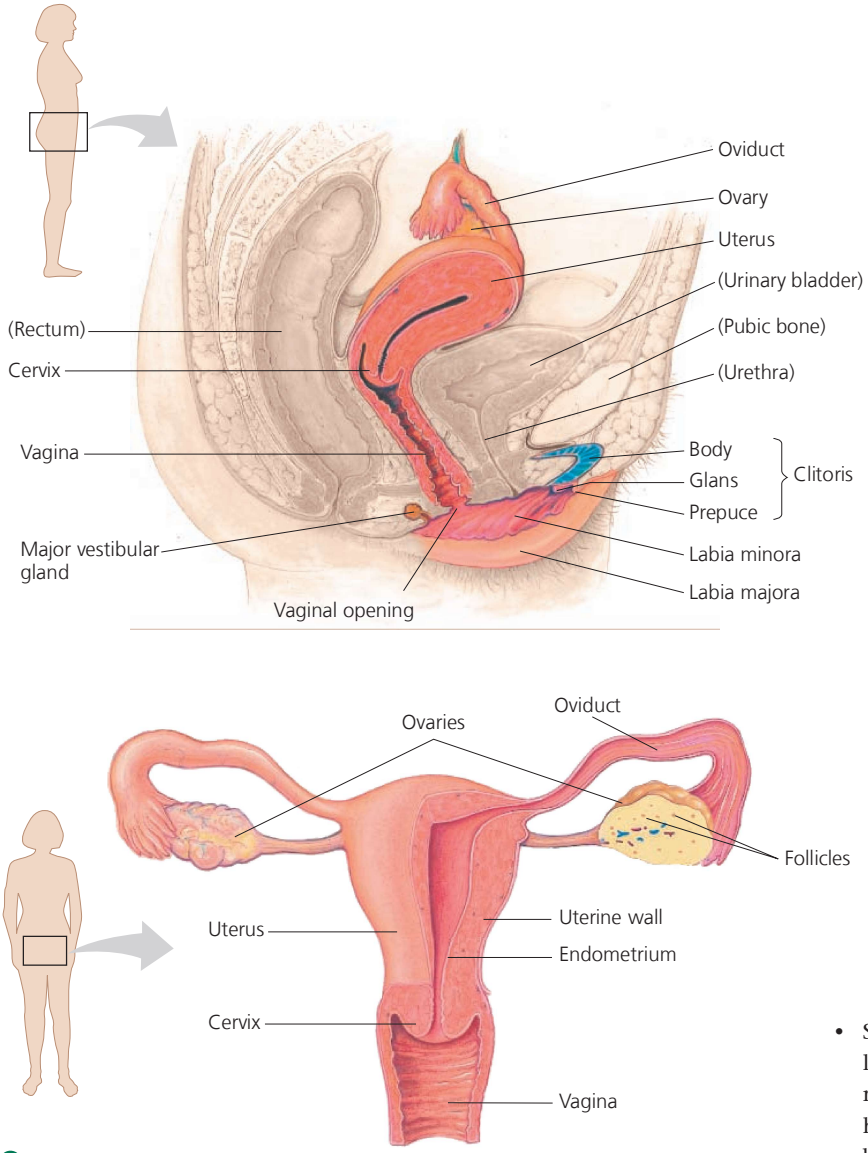
The **vagina** is a muscular but elastic chamber that is the site for insertion of the penis and deposition of sperm during copulation. The vagina, which also serves as the birth canal through which a baby is born, opens to the outside at the **vulva**, the collective term for the external female genitalia.

A pair of thick, fatty ridges called the **labia majora** enclose and protect 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, but becomes thinner over time and typically wears away through physical activity. 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

▼ **Figure 46.10 Reproductive anatomy of the human female.** Labels in parentheses identify nonreproductive structures shown for orientation purposes.



Mastering Biology **Animation: Reproductive System of the Human Female**

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.

Gametogenesis

With this overview of reproductive anatomy in mind, we turn now to **gametogenesis**, the production of gametes. In both males and females, there is a close relationship between the gonads' structure and their function. As shown in **Figure 46.11**, there are many parallels between **spermatogenesis**—the production of sperm—and **oogenesis**—the production of oocytes (eggs). Both processes generate haploid gametes via meiotic divisions of a set of dedicated diploid cells. In addition, support cells in the gonad play an essential role in both spermatogenesis and oogenesis. However, there are also several significant differences in gametogenesis between human males and females:

- Spermatogenesis is continuous in adult males. In producing hundreds of millions of sperm each day, cell division and maturation occur throughout the seminiferous tubules. For a single sperm, the process takes about seven weeks. In contrast, oogenesis 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.
- In spermatogenesis, the 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 known as polar bodies, degenerate.
- Spermatogenesis occurs throughout adolescence and adulthood. In contrast, the mitotic divisions that occur in 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 46.3

1. Why might frequent use of a hot tub make it harder for a couple to conceive a child?
2. The process of oogenesis is often described as the production of a haploid egg by meiosis, but in some animals, including humans, this description is not entirely accurate. Explain.
3. **WHAT IF?** If each vas deferens in a male were surgically sealed off, what changes would you expect in sexual response and ejaculate composition?

For suggested answers, see Appendix A.

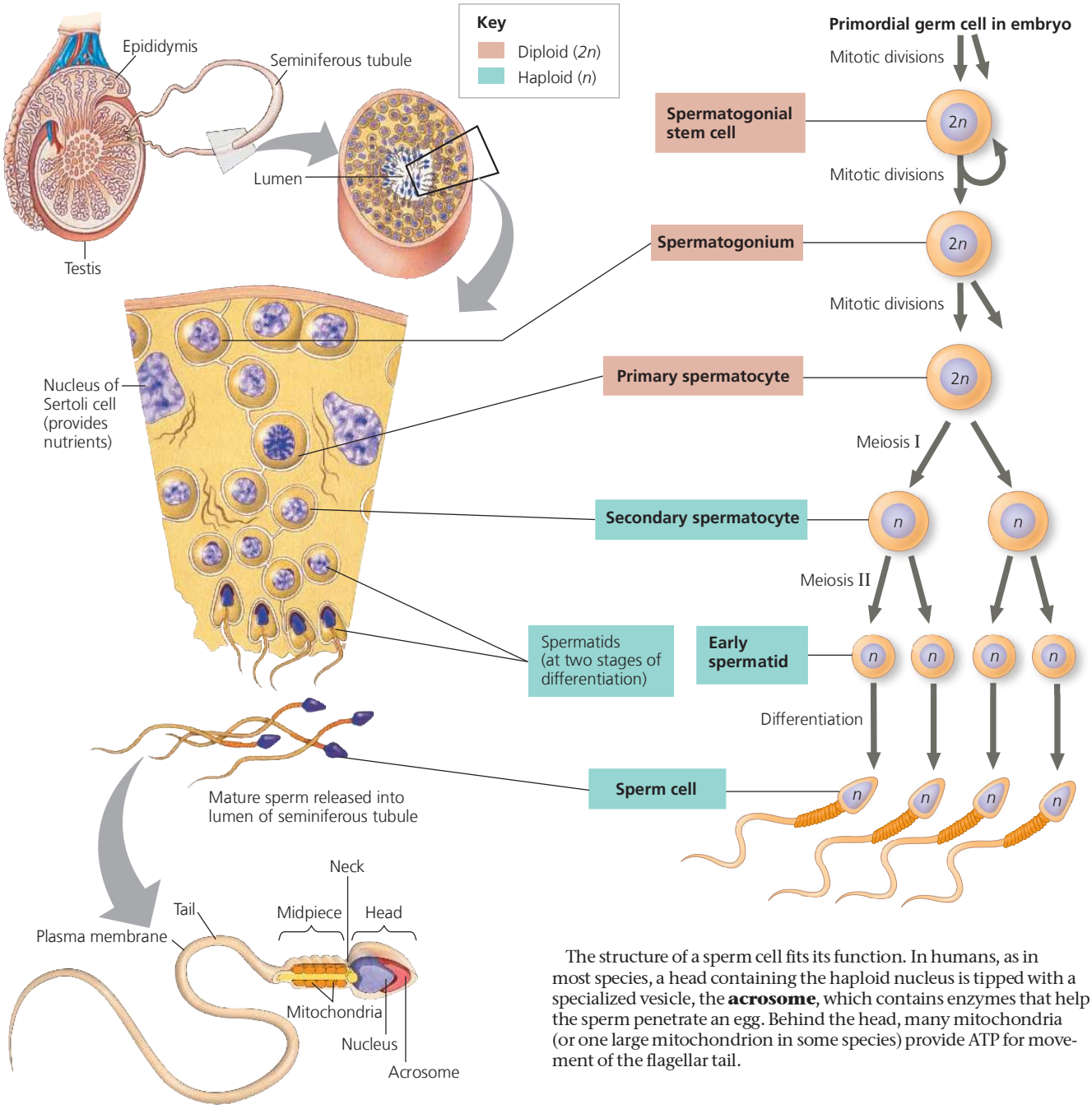
▼ Figure 46.11 Exploring Human Gametogenesis

Spermatogenesis

Stem cells that give rise to sperm are situated near the outer edge of the seminiferous tubules. Their progeny move inward as they pass through the spermatocyte and spermatid stages, and 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.

Mastering Biology Animation: Human Spermatogenesis

The stem cells arise from division and differentiation of primordial germ cells. In mature testes, the stem cells divide mitotically to form **spermatogonia**, which in turn generate spermatocytes 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 as they differentiate into sperm.

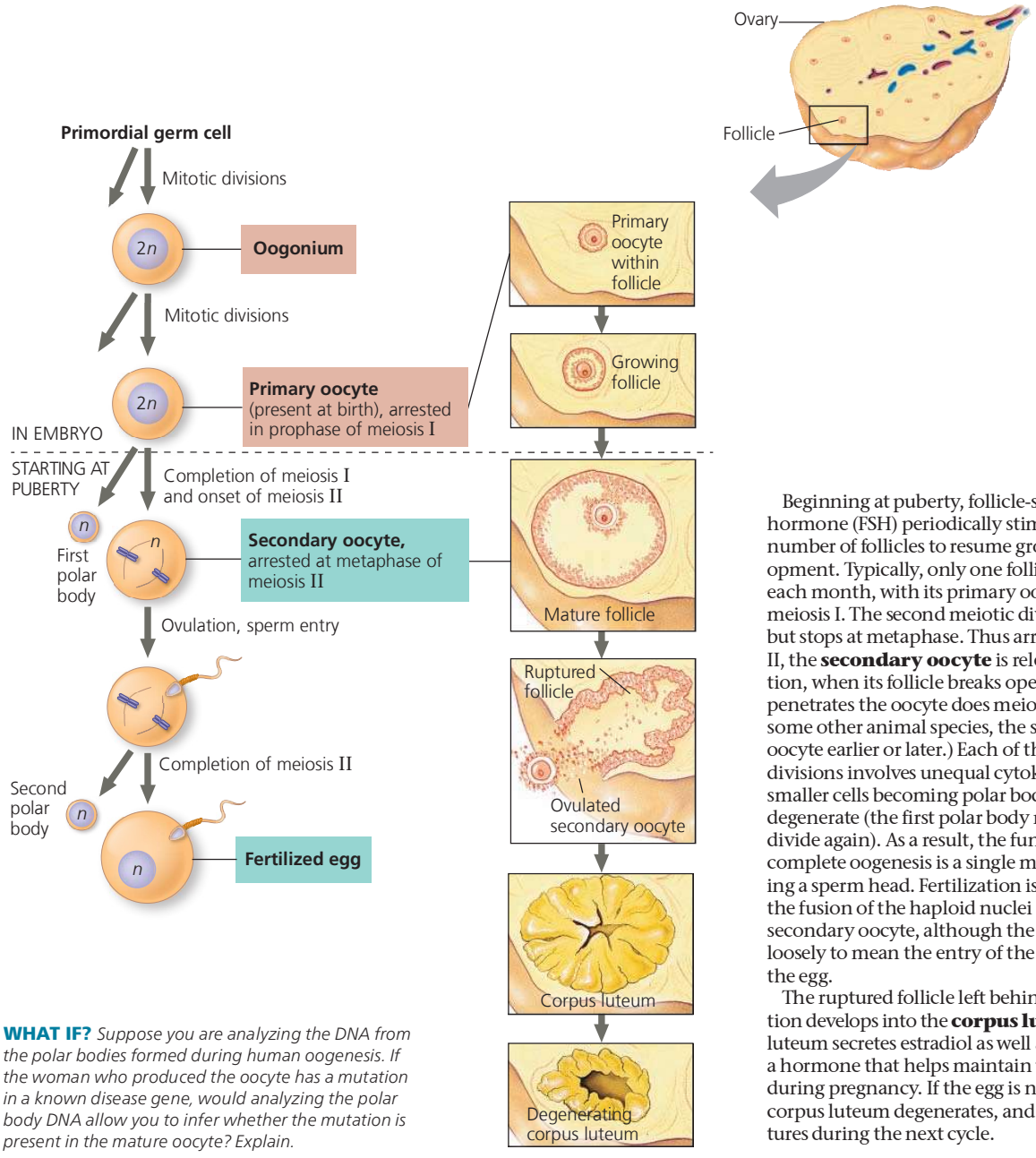


The structure of a sperm cell fits its function. In humans, as in most species, a head containing the haploid nucleus is tipped with a specialized vesicle, the **acrosome**, which contains enzymes that help the sperm penetrate an egg. Behind the head, many mitochondria (or one large mitochondrion in 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, which are **primary oocytes**, each reside within a small follicle, a cavity lined with protective cells. At birth, the ovaries together contain about 1–2 million primary oocytes, of which about 500 fully mature between puberty and menopause.

Mastering Biology Animation: Human Oogenesis



WHAT IF? *Suppose you are analyzing the DNA from the polar bodies formed during human oogenesis. If the woman who produced the oocyte 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.*

Beginning at puberty, follicle-stimulating hormone (FSH) periodically stimulates a small number of follicles to resume growth and development. 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 some other animal species, the sperm enters the oocyte 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). As a result, the functional product of complete oogenesis is a single mature egg containing a sperm head. Fertilization is defined strictly as the fusion of the haploid nuclei of the sperm and secondary oocyte, although the term is often used loosely to mean the entry of the sperm head into the egg.

The ruptured follicle left behind after ovulation develops into the **corpus luteum**. The corpus luteum secretes 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.

CONCEPT 46.4

The interplay of tropic and sex hormones regulates reproduction in mammals

Mammalian reproduction is governed by the coordinated actions of hormones from the hypothalamus, anterior pituitary, and gonads. Endocrine control of reproduction begins with the hypothalamus, which secretes *gonadotropin-releasing hormone* (*GnRH*). This hormone directs the anterior pituitary to secrete the gonadotropins **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** (see Figure 45.15). Both are tropic hormones, meaning that they regulate the activity of endocrine cells or glands. They are called *gonadotropins* because they act on the male and female gonads. FSH and LH support gametogenesis, in part by stimulating sex hormone production by the gonads.

The gonads produce and secrete three major types of steroid sex hormones: *androgens*, principally **testosterone**; *estrogens*, principally **estradiol**; and **progesterone**. All three hormones are found in both males and females, but at quite different concentrations. The concentration of testosterone in the blood is roughly ten times higher in males than in females. In contrast, the blood estradiol level is about ten times higher in females than in males; the peak blood progesterone level is also much higher in females. Although the gonads are the major source of sex hormones, the adrenal glands also secrete sex hormones in small amounts.

In mammals, sex hormone function in reproduction begins in the embryo. In particular, androgens produced in male embryos direct 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.

During sexual maturation, sex hormones in human males and females induce formation of secondary sex characteristics, the physical and behavioral differences between males and females that are not directly related to the reproductive system. Secondary sex characteristics often lead to sexual dimorphism, the difference in appearance between the male and female adults of a species **(Figure 46.12)**. When human males enter puberty, androgens cause the voice to deepen, facial and pubic hair to develop, and muscles to grow (by stimulating protein synthesis). Androgens also

Scientific Skills Exercise

Making Inferences and Designing an Experiment

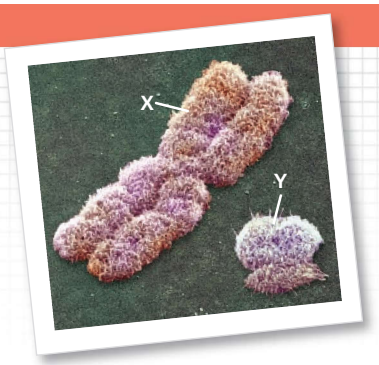
What Role Do Hormones Play in Making a Mammal Male or Female? In non-egg-laying mammals, females have two X chromosomes, whereas males have one X chromosome and one Y chromosome. In the 1940s, French physiologist Alfred Jost wondered whether development of mammalian embryos as female or male in accord 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

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).



▶ **Human sex chromosomes in metaphase (duplicated)**

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. **(a)** What normal process was blocked in Jost's experiment? **(b)** 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.

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

▼ Figure 46.12 Androgen-dependent male anatomy and behavior in a moose. The male and female in this mating pair of moose (*Alces alces*) differ in both anatomy and physiology. High levels of testosterone in the male are responsible for the appearance of secondary sex characteristics, such as antlers, and for male courtship and territorial behavior.

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.

Biological Sex, Gender Identity, and Sexual Orientation in Human Sexuality

A newborn baby is assigned a "biological sex" that typically reflects the genitals present at birth and the child's chromosomes. In mammals, the Y chromosome carries a gene called *SRY* that directs development of the gonad into a testis. In XX embryos, which lack the Y and hence lack *SRY*, the gonad becomes an ovary. Although most individuals are born male or female, roughly one in 100 is intersex, having both male and female biological characteristics. For example, intersex individuals may have a nonstandard chromosome set (such as XXY) or may differ in the hormone-directed pathways that control sexual development.

Though often confused with assigned sex, gender identity is distinct and refers to a person's internal sense of being male, female, some combination, or neither. The term *cisgender* describes a person having a gender identity in line with their assigned sex. In contrast, a *transgender* person experiences a mismatch between their gender identity and their assigned sex. Thus, for example, an individual may have an assigned sex of female, but a male gender identity.

Whereas gender identity is about a person's self, sexual orientation identifies the gender of people to whom an individual is attracted romantically, emotionally, and sexually. Members of a human population may have a sexual orientation that is heterosexual (straight), homosexual (lesbian or gay), bisexual, or asexual. As these descriptions make clear, human sexuality varies considerably.

Hormonal Control of the Male Reproductive System

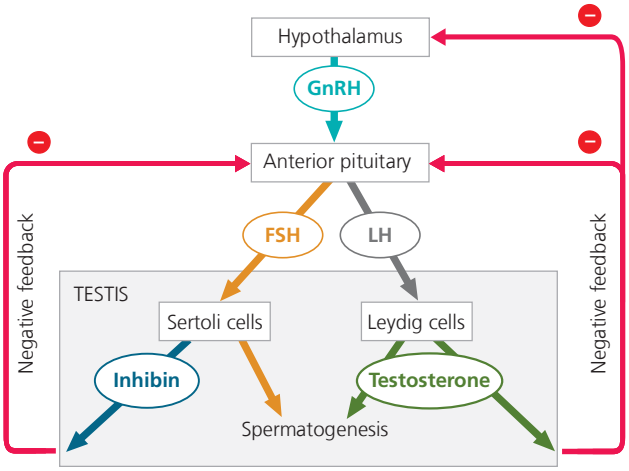
When mammals reach sexual maturity, the sex hormones and gonadotropins have essential roles in gametogenesis. In exploring this hormonal control of reproduction, we'll begin with the relatively simple system found in males.

In directing spermatogenesis, FSH and LH act on two types of cells in the testis **(Figure 46.13)**. FSH stimulates *Sertoli cells*, located within the seminiferous tubules, to nourish developing sperm (see Figure 46.11). LH causes *Leydig cells*, scattered in connective tissue between the tubules, to produce testosterone and other androgens, which promote spermatogenesis in the tubules.

Two negative-feedback mechanisms control sex hormone production in males (see Figure 46.13). Testosterone regulates the blood concentration 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 the level of androgen in the normal range.

Leydig cells have other roles besides producing testosterone. They in fact secrete small quantities of many other hormones and local regulators, including oxytocin, renin, angiotensin, corticotropin-releasing factor, growth factors, and prostaglandins. These signals coordinate the activity of reproduction with growth, metabolism, homeostasis, and behavior.

▼ Figure 46.13 Hormonal control of the testes.



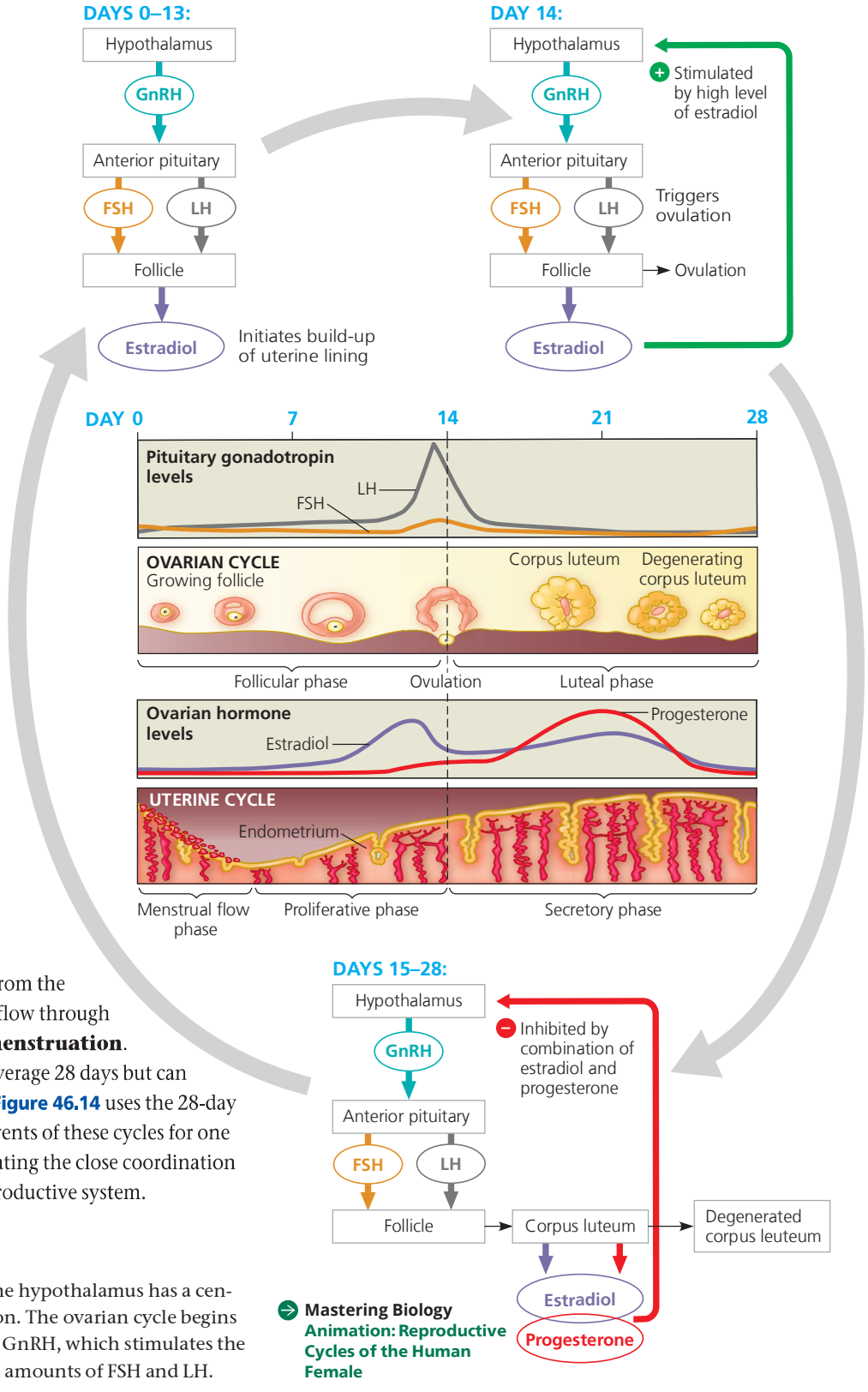
Hormonal Control of Female Reproductive Cycles

Whereas sperm are produced continuously in human males, there are two closely linked reproductive cycles in human females. Both are controlled by cyclic patterns of endocrine signaling.

Cyclic events in the ovaries define the **ovarian cycle**: Once per cycle a follicle matures and an oocyte is released. Changes in the uterus define the **uterine cycle**, which in humans and some other primates is a menstrual cycle. In each **menstrual cycle**, the endometrium (lining of the uterus) thickens and develops a rich blood supply before being shed through the cervix and vagina if pregnancy does not occur. By linking the ovarian and uterine cycles, hormone activity synchronizes ovulation with the establishment of a uterine lining that can support embryo implantation and development.

If an oocyte is not fertilized and pregnancy does not occur, the uterine lining is sloughed off, and another pair of ovarian and uterine cycles 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**. Menstrual (and ovarian) cycles average 28 days but can range from about 20 to 40 days. **Figure 46.14** uses the 28-day average to highlight the major events of these cycles for one ovarian and uterine cycle, illustrating the close coordination across different tissues of the reproductive system.

▼ **Figure 46.14 The reproductive cycles of the human female.** This figure shows how the ovarian cycle and the uterine (menstrual) cycle are regulated by changing hormone levels in the blood.



Mastering Biology
Animation: Reproductive Cycles of the Human Female

The Ovarian Cycle

In human females, as in males, the hypothalamus has a central role in regulating reproduction. The ovarian cycle begins when the hypothalamus releases GnRH, which stimulates the anterior pituitary to secrete small amounts of FSH and LH.

Follicle-stimulating hormone (as its name implies) stimulates follicle growth, aided by LH, and the cells of the growing follicles start to make estradiol. Estradiol concentration slowly rises during most of the *follicular phase* (days 0–14), 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.) A low concentration of estradiol inhibits secretion of pituitary hormones, keeping the concentration of FSH and LH relatively low. In this portion of the cycle, regulation of the reproductive hormones closely parallels the regulation in males.

When estradiol secretion by the follicle begins to rise steeply, the levels of FSH and LH increase markedly. Why? Whereas a low level of estradiol inhibits secretion of pituitary gonadotropins, a high concentration has the opposite effect: It stimulates gonadotropin secretion by causing the hypothalamus to increase output of GnRH. A high estradiol concentration also increases the GnRH sensitivity of LH-releasing cells in the pituitary, further increasing the LH level.

The maturing follicle, containing a fluid-filled cavity, enlarges to form a bulge at the surface of the ovary. The follicular phase ends at ovulation (day 14), about a day after the LH surge. In response to FSH and the peak in LH level, the follicle and adjacent wall of the ovary rupture, releasing the secondary oocyte. At or near the time of ovulation, women may feel a pain in the lower abdomen, on the same side as the ovary that released the oocyte.

The *luteal phase* (days 15–28) of the ovarian cycle follows ovulation. LH stimulates the remaining follicular tissue to form the corpus luteum, a glandular structure. Stimulated by LH, the corpus luteum secretes progesterone and estradiol, which in combination exert negative feedback on the hypothalamus and pituitary. This feedback greatly reduces LH and FSH secretion, preventing maturation of another egg when a pregnancy may be under way.

If pregnancy does not occur, the low gonadotropin concentration at the end of the luteal phase cause the corpus luteum to disintegrate, triggering a sharp decline in estradiol and progesterone concentrations. This decline liberates the hypothalamus and pituitary from negative feedback. The pituitary can then secrete enough FSH to stimulate the growth of new follicles, 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* (days 6–14) of the uterine cycle. After ovulation, the estradiol and progesterone secreted by the corpus luteum stimulate maintenance and further development of the uterine lining, 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 the *secretory phase* (days 15–28) of the uterine cycle.

Once the corpus luteum has disintegrated, the rapid drop in ovarian hormone concentration causes arteries in the endometrium to constrict. Deprived of its circulation, the uterine lining largely disintegrates, releasing blood that is shed along with endometrial tissue and fluid. The result is menstruation—the *menstrual flow phase* (days 1–5) of the uterine cycle. During this phase, which usually lasts a few days, a new set of ovarian follicles begin to grow. By convention, the first day of flow is designated day 1 of the new uterine (and ovarian) cycle.

About 7% of women of reproductive age suffer from a disorder called **endometriosis**, in which some cells of the uterine lining migrate to an abdominal location that is abnormal, or **ectopic** (from the Greek *ektopos*, away from a place). Having migrated to a location such as an oviduct, ovary, or large intestine, the ectopic tissue responds to hormones in the bloodstream. Like the uterine endometrium, the ectopic tissue swells and breaks down during each ovarian cycle, resulting in pelvic pain and bleeding into the abdomen. Researchers have not yet determined why endometriosis occurs, but hormonal therapy or surgery can be used to lessen discomfort.

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 can reproduce 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 chances for 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. In other mammals, both domesticated and wild, the uterus reabsorbs the endometrium in the absence of a pregnancy, and no extensive fluid flow occurs. For these animals, the cyclic changes in the uterus occur as part of an **estrous cycle** that also controls the sexual receptivity of females: 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, frequency, and nature of estrous cycles vary. Bears and wolves have one estrous cycle per year; elephants have several. Rats have estrous cycles throughout the year, each lasting just five days. The rat's nemesis, the household cat, ovulates only upon mating.

Human Sexual Response

In humans, the arousal of sexual interest is complex, involving a variety of psychological as well as physical factors. Although reproductive structures in the male and female differ in appearance, a number serve similar functions in arousal, reflecting their shared developmental origin. For example, the same embryonic tissues give rise to the scrotum and the labia majora, to the skin on the penis shaft and the labia minora, and to the glans of the penis and the clitoris. 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, as evident in nipple erection or tension of the limbs.

In the plateau phase, sexual 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 quickens 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 reaction to stimulation by the autonomic nervous system (see Figure 49.9).

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 normal size and color, and muscles relax. Most of these changes are completed within 5 minutes, but some may take as long as an hour. Following orgasm, the male typically enters a refractory period, lasting from a few minutes to hours, when 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 46.4

1. How are the functions of FSH and LH in females and males similar?
2. How does an estrous cycle differ from a menstrual cycle? In what animals are the two types of cycles found?
3. **WHAT IF?** If a human female begins taking estradiol and progesterone immediately after the start of a new menstrual cycle, how will ovulation be affected? Explain.
4. **MAKE CONNECTIONS** A coordination of events is characteristic of the reproductive cycle of a human female and the replicative cycle of an enveloped RNA virus (see Figure 19.8). What is the nature of the coordination in each of these cycles?

For suggested answers, see Appendix A.

CONCEPT 46.5

In placental mammals, an embryo develops fully within the mother's uterus

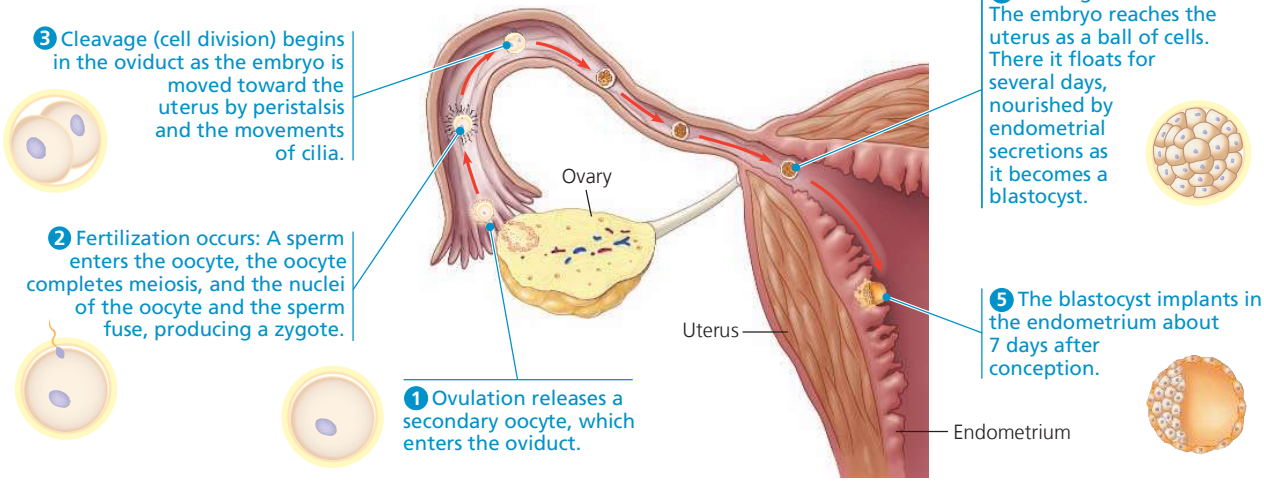
Having surveyed the ovarian and uterine cycles of human females, we turn now to reproduction itself, beginning with the events that transform an egg into a developing embryo.

Conception, Embryonic Development, and Birth

During human copulation, hundreds of millions of sperm are transferred in 2–5 mL of semen. When first ejaculated, the semen coagulates, which likely keeps the ejaculate in place until sperm reach the cervix. Soon after, anticoagulants liquefy the semen, and the sperm swim through the cervix and oviducts. Fertilization—also called **conception** in humans—occurs when a sperm fuses with an egg (mature oocyte) in an oviduct **(Figure 46.15)**.

The zygote begins a series of cell divisions called cleavage about 24 hours after fertilization and after an additional 4 days produces a **blastocyst**, a sphere of cells surrounding a central cavity. A few days later, the embryo implants into the endometrium of the uterus. 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

▼ **Figure 46.15 Formation of a human zygote and early postfertilization events.**



VISUAL SKILLS *If a woman's eggs need to be fertilized in vitro, they can be readily introduced into the uterus but not the extremely narrow oviduct. Based on this drawing, propose conditions for culturing a fertilized egg that you predict will optimize the chance of a successful pregnancy.*

rodents, 280 days in cows, and more than 600 days in elephants. The roughly nine months of human gestation are divided into three *trimesters* of equal length.

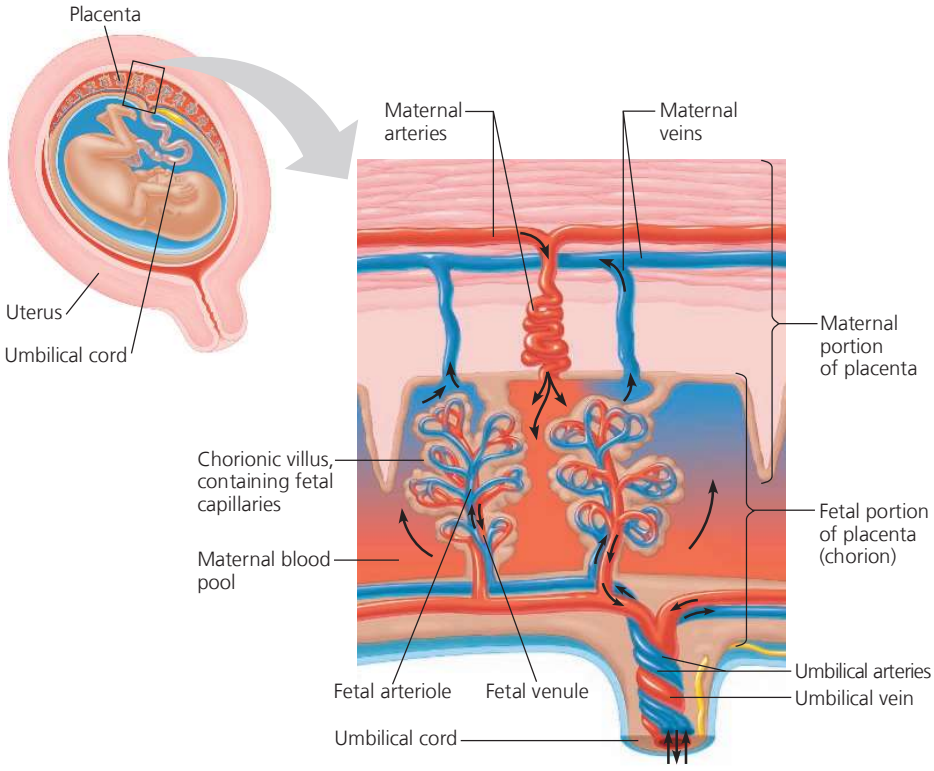
First Trimester

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 pituitary 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, where it can be detected by the most common early pregnancy tests.

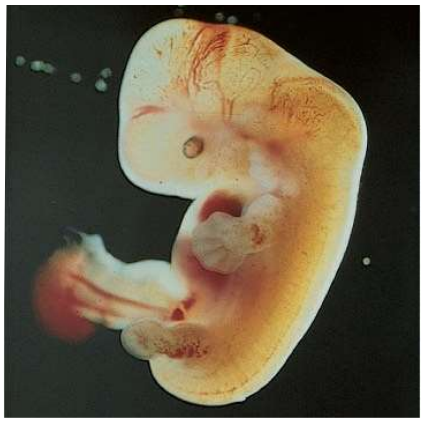
During its first 2–4 weeks of development, the embryo obtains nutrients directly from the endometrium. Meanwhile, the outer layer of the blastocyst, which is called the **trophoblast**, grows outward and mingles with the endometrium, eventually helping form the **placenta** (**Figure 46.16**).

► **Figure 46.16 Placental circulation.** Maternal blood enters the placenta in arteries, flows through blood pools in the endometrium, and leaves via veins. Embryonic or fetal blood, which remains in vessels, enters the placenta through arteries and passes through capillaries in finger-like chorionic villi, where oxygen and nutrients are acquired. Fetal blood leaves the placenta through veins leading back to the fetus.

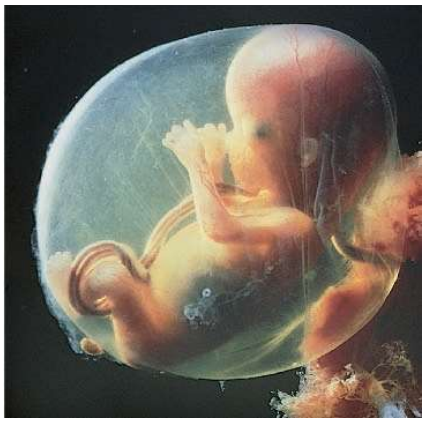
WHAT IF? *In a rare genetic disorder, the absence of a particular enzyme leads to increased testosterone production. When the fetus has this disorder, the mother develops a male-like pattern of body hair during the pregnancy. Explain why.*



▼ Figure 46.17 Some stages of human development during the first and second trimesters.



(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.

This disk-shaped organ contains both embryonic and maternal blood vessels. Exchange between the maternal and embryonic circulatory systems supplies nutrients, provides immune protection, exchanges respiratory gases, and disposes of metabolic wastes for the embryo. Blood from the embryo travels to the placenta through the arteries of the umbilical cord and returns via the umbilical vein.

Occasionally, an embryo splits during the first month of development, resulting in identical, or *monozygotic* (one-egg), twins. In contrast, fraternal, or *dizygotic*, twins arise when two follicles mature in a single cycle, followed by independent fertilization and implantation of two genetically distinct embryos.

The first trimester is the main period of **organogenesis**, the development of the body organs **(Figure 46.17a)**. 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 developmental and intellectual disabilities and other serious symptoms of fetal alcohol syndrome. The heart begins beating by the 4th week; a heartbeat can be detected at 8–10 weeks. At 8 weeks, all the major structures of the adult are present in rudimentary form, and the embryo is called a **fetus**.

At the end of the first trimester, the fetus is well differentiated, but only 5 cm long. Meanwhile, a high progesterone level brings about rapid changes in the mother: Mucus in the cervix forms a plug that protects against infection, the maternal part of the placenta grows, the mother's breasts and uterus get larger, and both ovulation and menstrual cycling stop. About three-fourths of all pregnant women experience nausea, misleadingly called "morning sickness," during the first trimester.

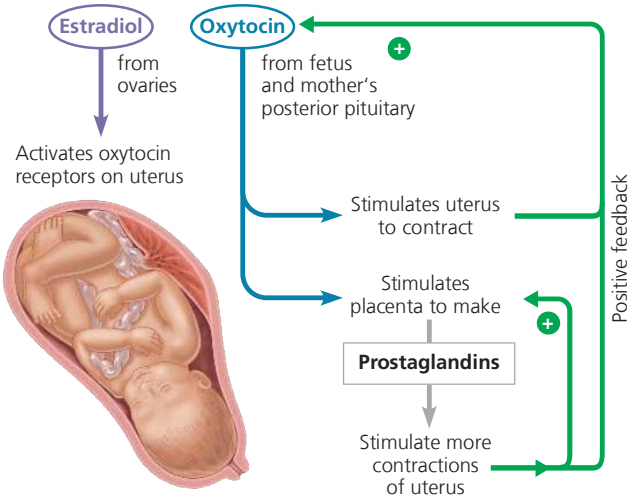
Second and Third Trimesters

During the second trimester, the fetus grows to about 30 cm in length. Development continues, including formation of fingernails, external sex organs, and outer ears **(Figure 46.17b)**. The mother may feel fetal movements as early as one month into the second trimester, and fetal activity is typically visible through the abdominal wall one to two months later. Hormone concentrations stabilize as hCG secretion declines; the corpus luteum deteriorates; and the placenta completely takes over the production of progesterone, the hormone that maintains the pregnancy.

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. As the fetus grows and the uterus expands around it, the mother's abdominal organs become compressed and displaced, leading to digestive blockages and a need for frequent urination.

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 **(Figure 46.18)**. Central

▼ Figure 46.18 Positive feedback in labor.

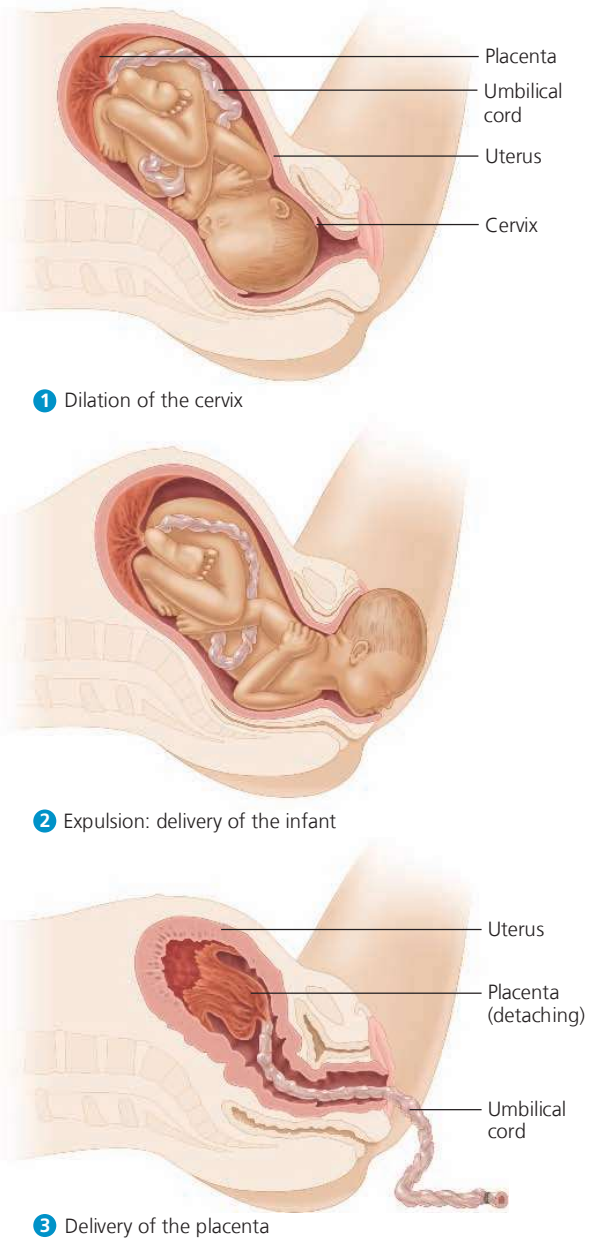


VISUAL SKILLS *Based on the feedback circuits shown, predict the effect of a single dose of oxytocin on a pregnant woman at the end of 39 weeks gestation.*

to this regulation is a positive-feedback loop (see Concept 45.2) in which uterine contractions stimulate secretion of oxytocin, which in turn stimulates further contractions.

Labor is typically described as having three stages **(Figure 46.19)**. The first stage is the thinning and opening up (dilation) of the cervix. The second stage is the expulsion, or delivery, of the baby. Continuous strong contractions force the fetus out of the uterus and through the vagina. The final stage of labor is the delivery of the placenta.

▼ Figure 46.19 The three stages of labor.



The newborn human or other mammal receives nourishment in the form of mother's milk. In response to suckling by the newborn and changes in estradiol concentration 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 release of milk from the mammary glands (see Figure 45.15).

Maternal Immune Tolerance of the Embryo and Fetus

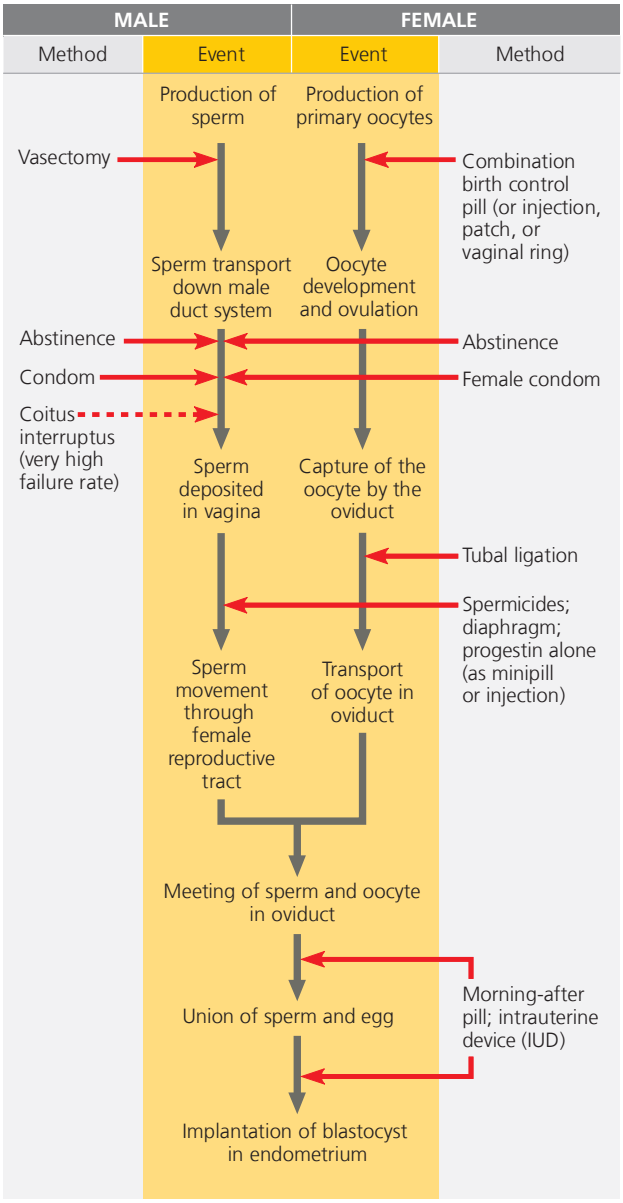
Pregnancy is an immunological puzzle. Because half of the embryo's genes are inherited from the father, many of the chemical markers present on the surface of the embryo are foreign to the mother. Why, then, does the mother not reject the embryo as a foreign body, as she would a tissue or organ graft from another person? One intriguing clue comes from the relationship between certain autoimmune disorders and pregnancy. For example, the symptoms of rheumatoid arthritis, an autoimmune disease of the joints, become less severe during pregnancy. Such observations suggest that the overall regulation of the immune system changes during pregnancy. Sorting out these changes and how they might protect the developing fetus is an active area of research for immunologists.

Contraception and Abortion

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 46.20** make no pretense of being a contraception manual.

Fertilization can be prevented by abstinence from sexual intercourse or by any of several kinds of barriers that keep live sperm from contacting the egg. Temporary abstinence, sometimes called *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 number of days before and after ovulation. Furthermore, because the timing of ovulation can vary significantly, the

▼ Figure 46.20 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 implantation of a developing embryo.



couple needs knowledge of physiological indicators associated with ovulation, such as changes in cervical mucus. Note also that a pregnancy rate of 10–20% is typical for couples practicing natural family planning. (In this context, pregnancy rate is the percentage of women who become pregnant in one year while using a particular pregnancy prevention method.)

As a method of preventing fertilization, *coitus interruptus*, or withdrawal (removal of the penis from the vagina before 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 methods of contraception that block 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 AIDS and other *sexually transmitted infections* (*STIs*), also known as *sexually transmitted diseases* (*STDs*). This protection is not absolute, however. Another common barrier device is the *diaphragm*, a dome-shaped rubber cap inserted into the upper portion of the vagina before intercourse. Both of these devices have lower pregnancy rates when used in conjunction with a spermicidal (sperm-killing) foam or jelly. Other barrier devices include the vaginal pouch, also called a "female condom."

Except for complete abstinence from sexual intercourse or sterilization (discussed later), the most effective means of birth control are the intrauterine device (IUD) and hormonal contraceptives. 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 contain a synthetic estrogen and a synthetic progesterone-like hormone called progestin. 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.

Another hormonal contraceptive with a very low pregnancy rate contains only progestin. Progestin causes thickening of a woman's cervical mucus 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. This contraceptive can be administered as injections that last for three months or as a tablet ("minipill") taken daily.

Hormonal contraceptives have both harmful and beneficial side effects. They increase the risk of some cardiovascular disorders slightly for nonsmokers and quite substantially (three- to tenfold) for women who smoke regularly. At the same time, oral contraceptives eliminate

the dangers of pregnancy; women on birth control pills have mortality rates about one-half those of pregnant women. Birth control pills also decrease the risk of ovarian and endometrial cancers. No hormonal contraceptives are available for men.

Sterilization is the permanent prevention of gamete production or release. For women, the most common method is **tubal ligation**, the sealing shut or tying off (ligating) of a section of each oviduct to prevent eggs from traveling into the uterus. Similarly, **vasectomy** in men is the cutting and tying off of each vas deferens to prevent sperm from entering the urethra. Sex hormone secretion and sexual function are unaffected by both procedures, with no change in menstrual cycles in females or ejaculate volume in males. Although tubal ligation and vasectomy are considered permanent, both procedures can in many cases be reversed by microsurgery.

The termination of a pregnancy in progress is called **abortion**. Spontaneous abortion, or *miscarriage*, is very common; it occurs in as many as one-third of all pregnancies, often before the woman is even aware she is pregnant. In addition, each year about 700,000 women in the United States choose to have an abortion performed by a physician.

A drug called mifepristone, or RU486, can terminate a pregnancy nonsurgically within the first 7 weeks. RU486 blocks progesterone receptors in the uterus, thus preventing progesterone from maintaining the pregnancy. It is taken with a small amount of prostaglandin to induce uterine contractions.

Modern Reproductive Technologies

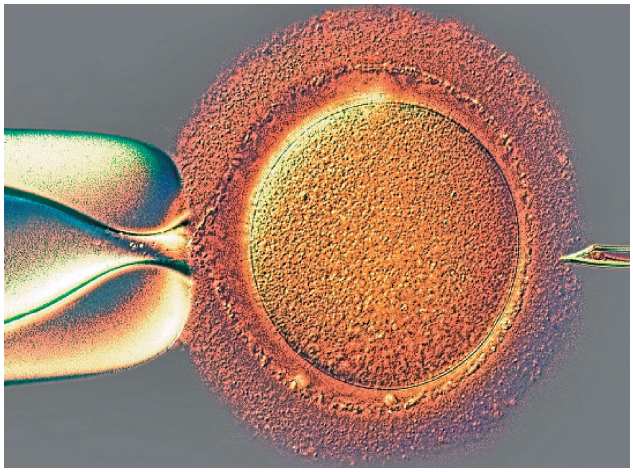
Recent scientific and technological advances have made it possible to address many reproductive problems, including genetic diseases and infertility.

Infertility and in Vitro *Fertilization*

Infertility—an inability to conceive offspring—is quite common, affecting about one in ten couples in the United States and worldwide. The likelihood of infertility is nearly the same for men and women and causes vary. For women, however, the risk of reproductive difficulties, as well as genetic abnormalities of the fetus, increases steadily past age 35. Evidence suggests that the prolonged period of time oocytes spend in meiosis is largely responsible for this increased risk.

Among preventable causes of infertility, sexually transmitted infections (STIs) are the most significant. In women 15–24 years old, approximately 830,000 cases of chlamydia and gonorrhea are reported annually in the United States. The actual number of women infected with the chlamydia or gonorrhea bacterium is considerably higher because most women with these infections have no symptoms and are therefore unaware of their infection.

▼ Figure 46.21 *In vitro* fertilization (IVF). In this form of IVF, a technician holds the egg in place with a pipette (left) and uses a very fine needle (right) to inject one sperm into the egg cytoplasm (colorized LM).



Up to 40% of women who remain untreated for either chlamydia or gonorrhea develop an inflammatory disorder that can scar the oviduct, substantially increasing the risk of a tubal, or ectopic, pregnancy. Rather than implanting in the uterus, the embryo becomes lodged in the oviduct (fallopian tube) where fertilization occurred. Such pregnancies cannot be sustained and may rupture the oviduct, resulting in serious internal bleeding.

Some forms of infertility are treatable. Hormone therapy can sometimes increase sperm or egg production, and surgery can often correct ducts that formed improperly or have become blocked. In some cases, doctors recommend ***in vitro* fertilization (IVF)**, which involves combining oocytes and sperm in the laboratory. Fertilized eggs are incubated until they form eight or more cells and are then transferred to the woman's uterus for implantation. If mature sperm are defective or low in number, a whole sperm or a spermatid nucleus may be injected directly into an oocyte **(Figure 46.21)**. Though costly and not always successful, IVF procedures have enabled more than a million couples to conceive children.

Detecting Disorders During Pregnancy

Many developmental problems and genetic diseases can now be diagnosed while the fetus is in the uterus. Ultrasound imaging, which generates images using sound frequencies above the normal hearing range, is commonly used to analyze the fetus's size and condition. In amniocentesis and chorionic villus sampling, a needle is used to obtain fetal cells from either fluid or tissue, respectively, surrounding the embryo; these cells then provide the basis for genetic analysis (see Figure 14.19).

A new reproductive technology makes use of a pregnant mother's blood to analyze the genome of her fetus. As discussed in Concept 14.4, a pregnant woman's blood contains

DNA from the growing embryo. How does it get there? The mother's blood reaches the embryo through the placenta. When cells produced by the embryo grow old, die, and break open within the placenta, the released DNA enters the mother's circulation. Although the blood also contains pieces of DNA from the mother, about 10–15% of the DNA circulating in the blood is from the fetus. Both the polymerase chain reaction (PCR) and high-throughput sequencing can convert the bits of fetal DNA into useful information.

Unfortunately, almost all detectable disorders remain untreatable in the uterus, and many cannot be corrected even after birth. Genetic testing may leave parents faced with difficult decisions about whether to terminate a pregnancy or to raise a child who may have profound developmental abnormalities and a short life expectancy. These are complex issues that demand careful, informed thought and competent genetic counseling.

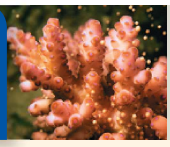
Parents will be receiving even more genetic information and confronting further questions in the near future. Indeed, in 2012 the first infant was born whose entire genome had been sequenced before the baby was born. Nevertheless, completing a genome sequence does not ensure complete information. Consider, for example, Klinefelter syndrome, in which males have an extra X chromosome. This disorder is quite common, affecting one in 1,000 men, and can cause reduced testosterone, a feminized appearance, and infertility. However, while some men with an extra X chromosome have a debilitating disorder, others have symptoms so mild that they are unaware of the condition. For other disorders, such as diabetes, heart disease, or cancer, a genome sequence may only indicate the degree of risk. How parents will use this and other information in having and raising children is a question with no clear answers.

CONCEPT CHECK 46.5

1. Why does testing for hCG (human chorionic gonadotropin) work as a pregnancy test early in pregnancy but not late in pregnancy? What is the function of hCG in pregnancy?
2. In what ways are tubal ligation and vasectomy similar?
3. **WHAT IF?** If a sperm nucleus is injected into an oocyte, what steps of gametogenesis and conception are bypassed?

For suggested answers, see Appendix A.

46 Chapter Review



Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 46.1

Both asexual and sexual reproduction occur in the animal kingdom *(pp. 1020–1022)*

- **Sexual reproduction** requires the fusion of male and female gametes, forming a diploid **zygote**. Examples of **asexual reproduction**—the production of offspring without gamete fusion—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.

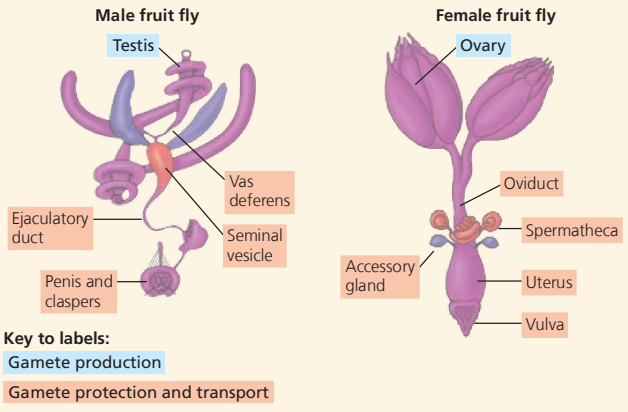
? *Would a pair of haploid offspring produced by parthenogenesis be genetically identical? Explain.*

CONCEPT 46.2

Fertilization depends on mechanisms that bring together sperm and eggs of the same species *(pp. 1022–1025)*

- **Fertilization** occurs externally, when sperm and eggs are both released outside the body, or internally, when sperm deposited by the male fertilize an egg in the female reproductive system. In either case, fertilization requires coordinated timing, which may be mediated by environmental cues, pheromones, or courtship behavior. Internal fertilization is often associated with relatively fewer offspring and greater protection of offspring by the parents.
- Systems for gamete production and delivery range from undifferentiated cells in the body cavity to complex systems that include **gonads**, which produce gametes, and accessory tubes and glands that protect or transport gametes and embryos. Although sexual reproduction involves a partnership, it also provides an opportunity for competition between individuals and between gametes.

Complex reproductive systems in fruit flies



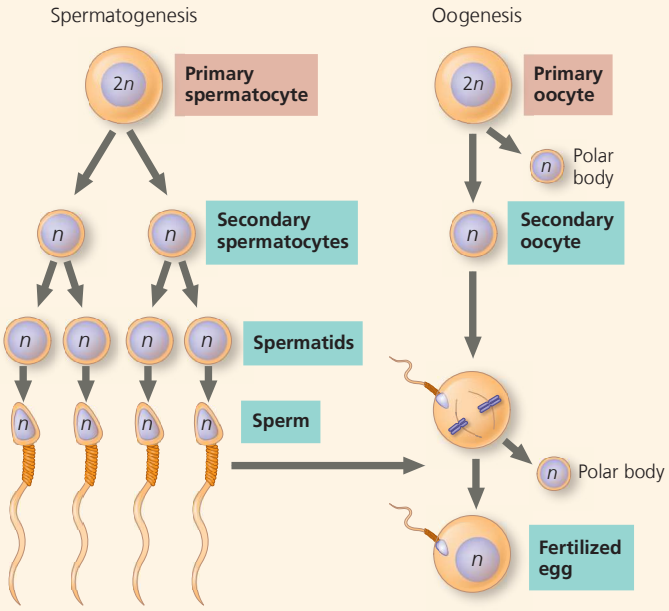
? *Identify which of the following, if any, are unique to mammals: a female uterus, a male vas deferens, extended internal development, and parental care of newborns.*

CONCEPT 46.3

Reproductive organs produce and transport gametes *(pp. 1025–1029)*

- 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 **labia** and the **glans** of the **clitoris** externally and the **vagina, uterus, oviducts**, and **ovaries** internally. **Eggs** are produced in the ovaries and upon fertilization develop in the uterus.
- **Gametogenesis**, or gamete production, consists of the processes of **spermatogenesis** in males and **oogenesis** in females. Human spermatogenesis is continuous and produces four sperm per meiosis. Human oogenesis is discontinuous and cyclic, generating one egg per meiosis.

Human gametogenesis

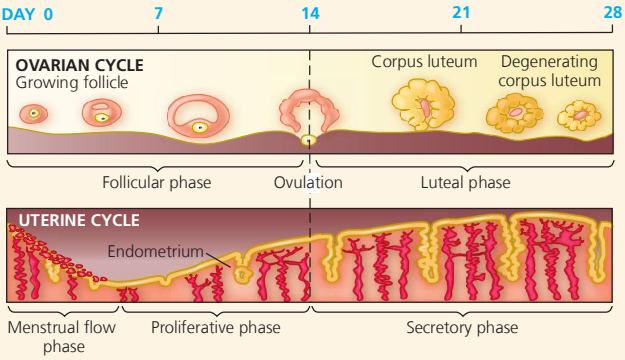


How does the difference in size and cellular contents between sperm and eggs relate to their specific functions in reproduction?

CONCEPT 46.4

The interplay of tropic and sex hormones regulates reproduction in mammals *(pp. 1030–1034)*

- Human sexuality, which includes biological sex, gender identity, and sexual orientation, exhibits considerable variation.
- In mammals, GnRH from the hypothalamus regulates the release of two hormones, **FSH** and **LH**, from the anterior pituitary. In males, FSH and LH control the secretion of androgens (chiefly **testosterone**) and sperm production. In females, cyclic secretion of FSH and LH orchestrates the **ovarian** and **uterine cycles** via estrogens (primarily **estradiol**) and **progesterone**. The developing **follicle** and the **corpus luteum** also secrete hormones, which help coordinate the uterine and ovarian cycles through positive and negative feedback.



- In **estrous cycles**, the lining of the **endometrium** is reabsorbed, and sexual receptivity is limited to a heat period. Reproductive structures with a shared origin in development underlie many features of human sexual arousal and orgasm common to males and females.

Why do anabolic steroids lead to reduced sperm counts?

CONCEPT 46.5

In placental mammals, an embryo develops fully within the mother's uterus *(pp. 1034–1040)*

- After fertilization and the completion of meiosis in the oviduct, the zygote undergoes a series of cell divisions and develops into a **blastocyst** before implantation in the endometrium. All major organs start developing by 8 weeks. A pregnant woman's acceptance of her "foreign" offspring likely reflects partial suppression of the maternal immune response.
- **Contraception** may prevent release of mature gametes from the gonads, fertilization, or embryo implantation. **Abortion** is the termination of a pregnancy in progress.
- Reproductive technologies can help detect problems before birth and can assist infertile couples. Infertility may be treated through hormone therapy or ***in vitro* fertilization**.

What route would oxygen in the mother's blood follow to arrive at a body cell of the fetus?

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

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.
2. In male mammals, excretory and reproductive systems share
   (A) the vas deferens.
   (B) the urethra.
   (C) the seminal vesicle.
   (D) the prostate.
3. Which of the following is properly paired?
   (A) seminiferous tubule—cervix
   (B) vas deferens—oviduct
   (C) corpus luteum—Sertoli cell
   (D) scrotum—clitoris

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 secretory phase of the uterine 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) during the blastocyst stage.

Levels 3-4: Applying/Analyzing

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) Ovulation occurs before the endometrium thickens in estrous cycles.

7. For which of the following is the number the same in human males and females?
   (A) interruptions in meiotic divisions
   (B) functional gametes produced by meiosis
   (C) meiotic divisions required to produce each gamete
   (D) different cell types produced by meiosis

8. Which statement about human reproduction is true?
   (A) Fertilization occurs in the vagina.
   (B) Spermatogenesis and oogenesis both require normal body temperature.
   (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.

Levels 5-6: Evaluating/Creating

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) Explain what would happen if stem cells divided like spermatogonia.

10. **EVOLUTION CONNECTION** Hermaphroditism is often found in animals that are fixed to a surface. Motile species are less often hermaphroditic. Explain why.

11. **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, explain how you would determine whether the worms can self-fertilize.

12. **WRITE ABOUT A THEME: ENERGY AND MATTER** In a short essay (100–150 words), discuss how different types of energy investment by females contribute to the reproductive success of a frog, a chicken, and a human.

13. **SYNTHESIZE YOUR KNOWLEDGE**

A female Komodo dragon (*Varanus komodoensis*) kept in isolation in a zoo had offspring. Each of the offspring had two identical copies of every gene in its genome. However, the offspring were not identical to one another. Based on your understanding of parthenogenesis and meiosis, propose a hypothesis to explain these observations.

For selected answers, see Appendix A.

47 Animal Development

KEY CONCEPTS

Study Tip

Use word roots to learn vocabulary: Word roots often provide clues to the meaning of biological terms. Study this list of word roots and their meanings to help you infer and remember the definitions of vocabulary words from this chapter and others.

Word root—meaning		
blast—group of immature cells	poly—many	endo—internal
tropho—change	derm—tissue	meso—middle
coel—cavity	genesis—origin	ecto—external
morpho—shape	diplo—two	
	triplo—three	

Term—definition
blastocoel—cavity in ball of immature cells
diploblast
triploblast
trophoblast
endoderm
morphogenesis

Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 47
- Video: Sea Urchin Fertilization and Cleavage
- HHMI Video: Differentiation and the Fate of Cells

For Instructors to Assign (in Item Library)
- Tutorial: Visualizing Gastrulation
- Experimental Inquiry: How Do Calcium Ions Help to Prevent Polyspermy During Egg Fertilization?

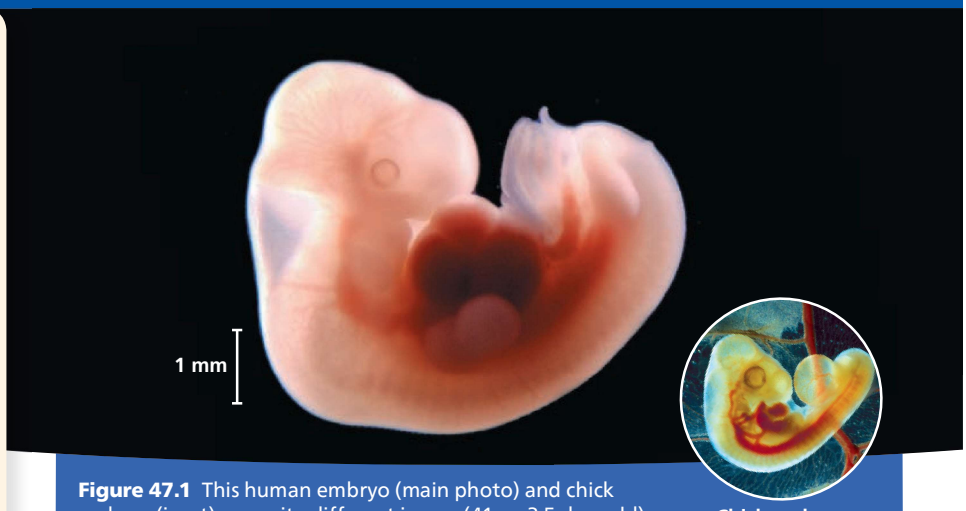
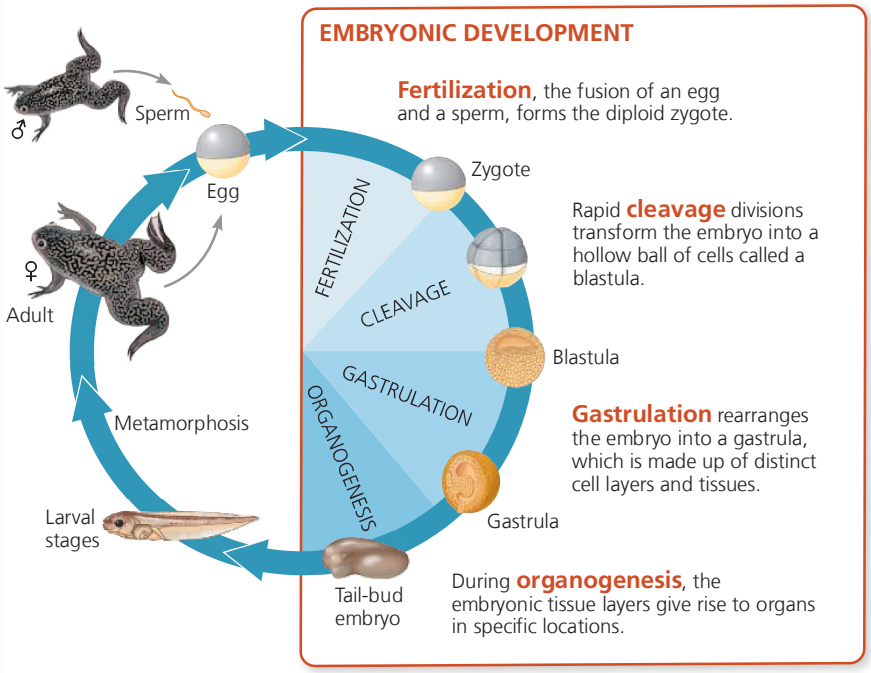


Figure 47.1 This human embryo (main photo) and chick embryo (inset) are quite different in age (41 vs. 3.5 days old), but remarkably alike in appearance. The developing eyes, heart, and digestive tract are recognizable. So too are the repeated blocks of tissue that will form the vertebrae. These similarities reflect the fact that the early stages of embryonic development are shared among many animals, giving rise to a basic body plan that is later transformed into distinct and specialized forms.

What processes transform an egg into an embryo with recognizable structures?



CONCEPT 47.1

Fertilization and cleavage initiate embryonic development

Development occurs at multiple points in the animal life cycle. In a frog, for example, the larva (tadpole) undergoes sweeping changes in anatomy in becoming an adult. Development occurs in adult animals too, as when stem cells in the gonads produce sperm and eggs (gametes). In this chapter, however, our focus is on development in the embryonic stage.

Embryonic development in many animal species involves common stages in a set order. The first is fertilization, the fusion of sperm and egg. Next is cleavage, a series of cell divisions that divide, or cleave, the embryo into many cells. These cleavage divisions, which typically are rapid and lack accompanying cell growth, generate a hollow ball of cells called a blastula. In gastrulation, this blastula folds in on itself, rearranging into a multilayered embryo, the gastrula. Then, during organogenesis, local changes in cell shape and large-scale changes in cell location generate the rudimentary organs.

Because embryonic development has many common features across the animal kingdom, lessons learned from studying one animal can often be applied quite broadly. For this reason, studying development lends itself well to the use of **model organisms**, species chosen for the ease with which they can be studied. For example, the sea urchin (phylum *Echinodermata*) is useful for studying cell-surface events that take place during fertilization. Sea urchin gametes are easy to collect and fertilization occurs outside the body. As a result, researchers can observe fertilization and development in the laboratory simply by combining eggs and sperm in seawater.

In this chapter, we will concentrate on the sea urchin and four other model organisms: the fruit fly, the frog, the chick, and the nematode (roundworm). We will also explore some aspects of human embryonic development. We'll begin with the events surrounding **fertilization**, the formation of a diploid zygote from a haploid egg and sperm.

Fertilization

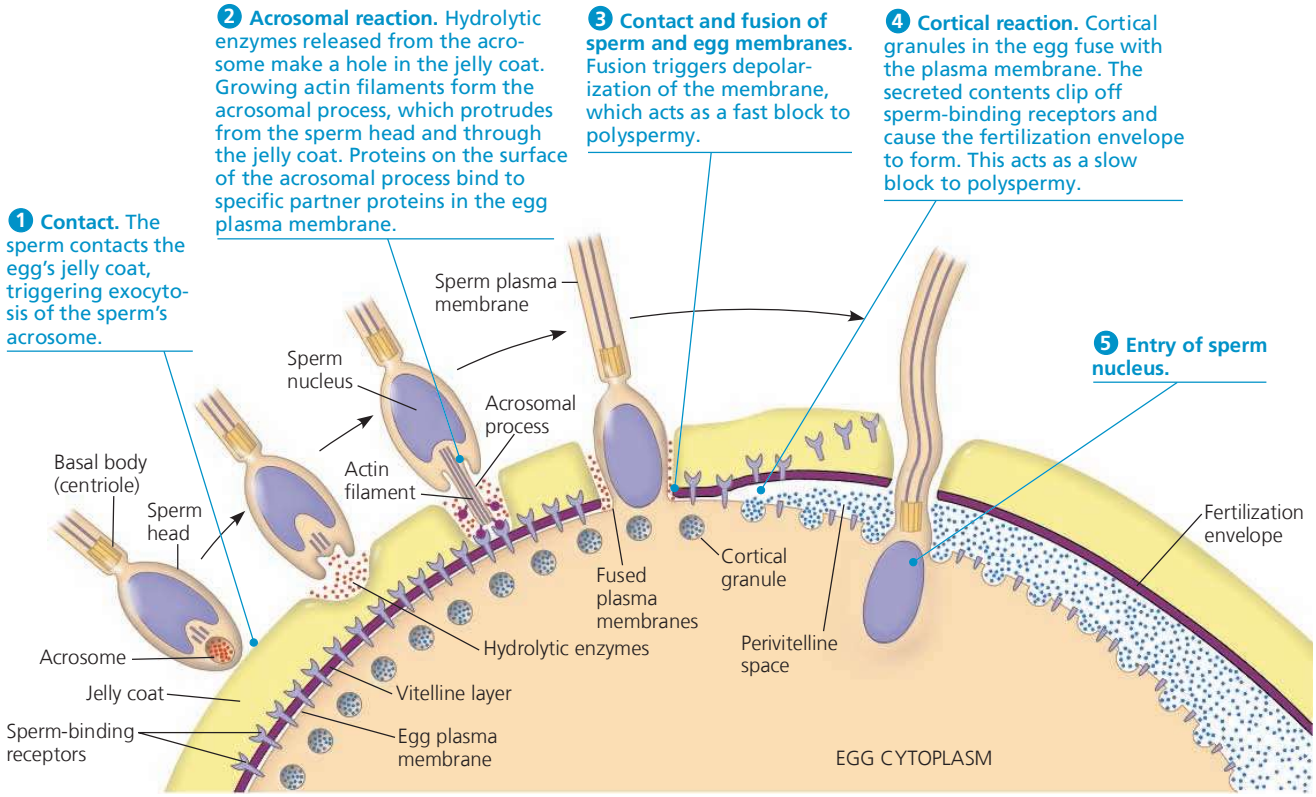
When sea urchins release their gametes into the water, the jelly coat of the egg exudes soluble molecules that attract the sperm, which swim toward the egg.

The Acrosomal Reaction

As detailed in **Figure 47.2**, the moment a sperm head contacts the egg surface, molecules in the jelly coat trigger

▼ Figure 47.2 The acrosomal and cortical reactions during sea urchin fertilization.

This icon is a simplified drawing of an adult sea urchin. Throughout the chapter, this icon and others of an adult frog, chicken, nematode, and human indicate the source of embryos in figures.



the **acrosomal reaction** in the sperm. This reaction begins with the discharge of hydrolytic enzymes from the **acrosome**, a specialized vesicle at the tip of the sperm. These enzymes partially digest the jelly coat, enabling a sperm structure called the *acrosomal process* to form, elongate, and penetrate the coat. Protein molecules on the tip of the acrosomal process bind to specific proteins in the egg plasma membrane. This "lock-and-key" recognition is especially important for sea urchins and other species with external fertilization because the water into which sperm and eggs are released may contain gametes of other species (see, for example, Figure 24.3h).

The recognition event between the sperm and egg triggers fusion of their plasma membranes. The sperm nucleus enters the egg cytoplasm as ion channels open in the egg's plasma membrane. Sodium ions diffuse into the egg and cause depolarization, a decrease in the charge difference, or potential, across the plasma membrane (see Concept 7.4).

Once depolarization takes place, additional sperm cannot fuse with the egg's plasma membrane. In this way, depolarization acts as a barrier to **polyspermy**, the entry of multiple sperm nuclei into the egg. If polyspermy were to occur, the resulting abnormal number of chromosomes would be lethal for the embryo. Because depolarization occurs 1–3 seconds after a sperm binds to an egg, depolarization acts as a *fast block to polyspermy*.

The Cortical Reaction

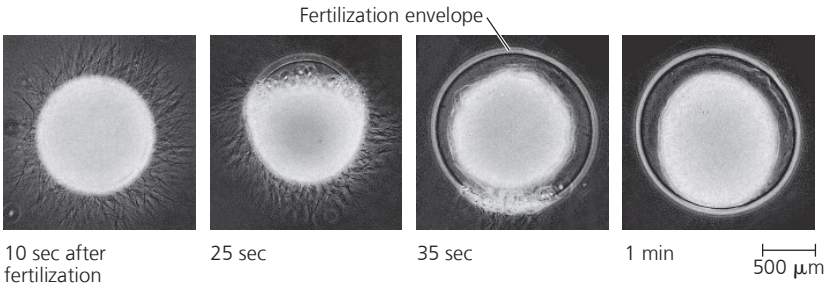
Although membrane depolarization in sea urchins lasts for only a minute or so, there is a longer-lasting change that also prevents polyspermy. This *slow block to polyspermy* is established by vesicles in the outer rim, or cortex, of the cytoplasm. Within seconds after a sperm binds to the egg, these vesicles, called cortical granules, fuse with the egg plasma membrane (see Figure 47.2). Contents of the cortical granules are released into the space between the plasma membrane and the surrounding vitelline layer, a structure formed by the egg's extracellular matrix. Enzymes and other granule contents then trigger a *cortical reaction*, which lifts the vitelline layer away from the egg and hardens the layer into a protective fertilization envelope.

Formation of the fertilization envelope requires a high concentration of calcium ions (Ca^{2+}) in the egg. As described in **Figure 47.3**, researchers wondered whether a change in the Ca^{2+} concentration triggers the cortical reaction. Using a

▼ Figure 47.3 Inquiry

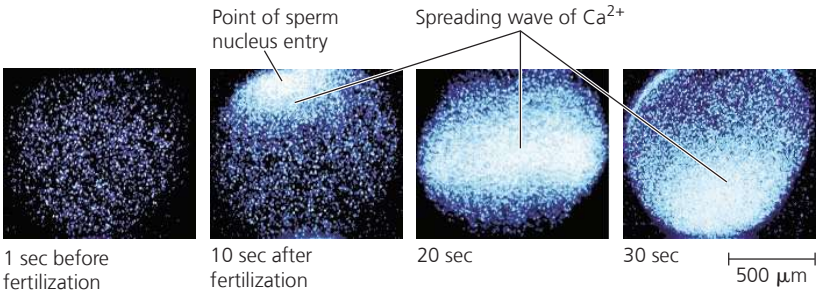
Does the distribution of Ca^{2+} in an egg correlate with formation of the fertilization envelope?

Experiment Investigators mixed sea urchin eggs with sperm, waited 10–60 seconds, and then added a chemical fixative, freezing cellular structures in place. When photomicrographs of each sample are ordered according to the time of fixation, they illustrate the stages in the formation of a fertilization membrane for a single egg.



Calcium ion (Ca^{2+}) signaling controls fusion of vesicles with the plasma membrane during neurotransmitter release, insulin secretion, and plant pollen tube formation. Researchers hypothesized that Ca^{2+} signaling plays a similar role in forming the fertilization envelope. To test this hypothesis, they tracked the release of free Ca^{2+} in sea urchin eggs after sperm binding. A fluorescent dye that glows when it binds free Ca^{2+} was injected into unfertilized eggs. The scientists then added sea urchin sperm and used fluorescence to produce the results shown here.

Results A rise in the concentration of Ca^{2+} in the cytosol began near where the sperm entered and spread in a wave. Soon after the wave passed, the fertilization envelope rose from the egg surface.



Conclusion Ca^{2+} release correlates with formation of the fertilization envelope, supporting the researchers' hypothesis that an increase in the Ca^{2+} level triggers cortical granule fusion.

Data from R. Steinhardt et al., Intracellular calcium release at fertilization in the sea urchin egg, *Developmental Biology* 58:185–197 (1977); M. Hafner et al., Wave of free calcium at fertilization in the sea urchin egg visualized with Fura-2, *Cell Motility and the Cytoskeleton* 9:271–277 (1988).

Instructors: A related Experimental Inquiry Tutorial can be assigned in **Mastering Biology**.

WHAT IF? *Suppose a particular molecule could enter the egg and bind to Ca^{2+}, blocking its function. How would you use this molecule to further test the hypothesis that a rise in the Ca^{2+} level triggers cortical granule fusion?*

calcium-sensitive dye, they assessed how Ca^{2+} is distributed in the egg before and during fertilization. They found that Ca^{2+} spread across the egg in a wave that correlated with the appearance of the fertilization envelope.

Further studies demonstrated that the binding of a sperm to the egg activates a signal transduction pathway that triggers release of Ca^{2+} into the cytosol from the endoplasmic reticulum. The resulting increase in Ca^{2+} level causes cortical granules to fuse with the plasma membrane. A cortical reaction triggered by Ca^{2+} also occurs in vertebrates such as fishes and mammals.

Egg Activation

Fertilization initiates and speeds up metabolic reactions that bring about the onset of embryonic development, "activating" the egg. For example, cellular respiration and protein synthesis in the egg markedly accelerate following the entry of the sperm nucleus. Soon thereafter, the egg and sperm nuclei fully fuse, and cycles of DNA synthesis and cell division begin.

What triggers activation of the egg? A major clue came from experiments demonstrating that the unfertilized eggs of sea urchins and many other species can be activated by an injection of Ca^{2+}. Based on this discovery, researchers concluded that the rise in Ca^{2+} concentration that causes the cortical reaction also causes egg activation. Further experiments revealed that artificial activation is possible even if the nucleus has been removed from the egg. This further finding indicates that the proteins and mRNAs required for activation are already present in the cytoplasm of the unfertilized egg.

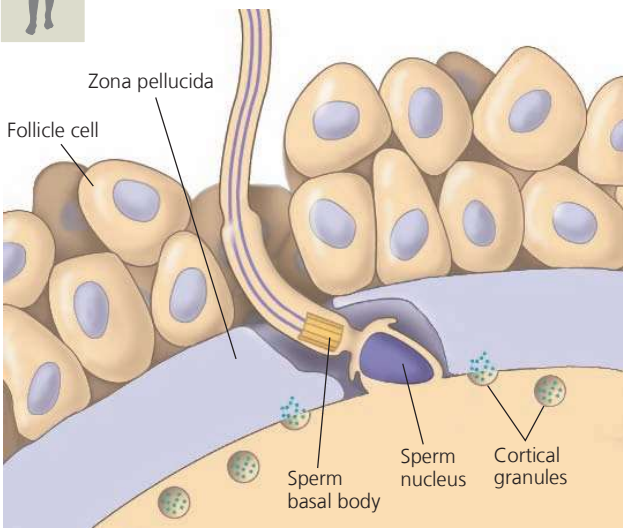
Not until about 20 minutes after the sperm nucleus enters the sea urchin egg do the sperm and egg nuclei fuse. DNA synthesis is then initiated. The first cell division, which occurs after about 90 minutes, marks the end of the fertilization stage.

Fertilization in other species shares many features with the process in sea urchins. However, there are differences, such as 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 many other species, eggs are arrested at a specific stage of meiosis and do not complete the meiotic divisions until a sperm head enters. Human eggs, for example, are arrested at metaphase of meiosis II until sperm entry (see Figure 46.11).

Fertilization in Mammals

Unlike sea urchins and most other marine invertebrates, terrestrial animals, including mammals, fertilize their eggs internally. Support cells of the developing follicle surround the mammalian egg before and after ovulation. As shown in **Figure 47.4**, a sperm must travel through this layer of follicle cells before it reaches the **zona pellucida**, the extracellular matrix of the egg. There, the binding of a sperm to a sperm receptor induces an acrosomal reaction, facilitating sperm entry.

▼ Figure 47.4 Fertilization in mammals. The sperm shown here has traveled through the follicle cells and zona pellucida and has fused with the egg. The cortical reaction has begun, initiating events that ensure that only one sperm nucleus enters the egg.



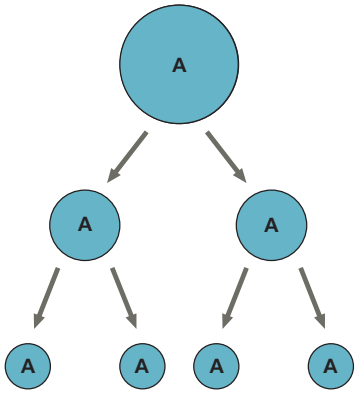
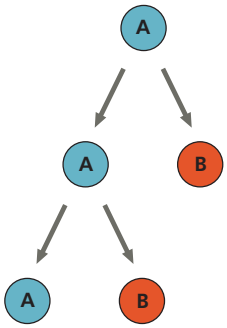
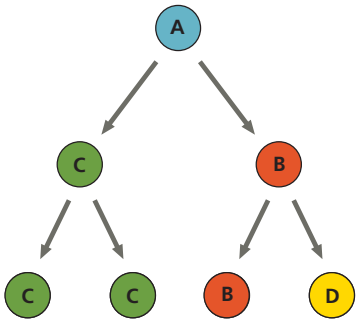
As in sea urchins, sperm binding triggers a cortical reaction, the release of enzymes from cortical granules to the outside of the cell. These enzymes catalyze changes in the zona pellucida, which then acts as the slow block to polyspermy. (No fast block to polyspermy is known in mammals.)

Overall, the process of fertilization is much slower in mammals than in sea urchins: The first cell division occurs within 12–36 hours after sperm binding in mammals, compared with about 1.5 hours in sea urchins. This cell division marks the end of fertilization and the beginning of the next stage of development, cleavage.

Cleavage

The single nucleus in a newly fertilized egg has too little DNA to produce the amount of mRNA required to meet the cell's need for new proteins. Instead, initial development is carried out by mRNA and proteins deposited in the egg during oogenesis. There is still a need, however, to restore a balance between the cell's size and its DNA content. The process that addresses this challenge is **cleavage**, a series of rapid cell divisions during early development **(Figure 47.5)**.

▼ Figure 47.5 Variation in mitotic cell division in embryonic development. Circles represent embryonic cells, with letters and colors indicating different cell types (fates).

(a) Cleavage divisions	(b) Stem cell divisions	(c) Patterning divisions
 Rapid mitotic divisions in early development: Cell number increases but cell size decreases, leaving embryo size unchanged.	 These divisions replenish cells that are needed continuously throughout life, such as blood cells.	 Daughter cells take on different fates based on positional information in the embryo.

During cleavage, the cell cycle consists primarily of the S (DNA synthesis) and M (mitosis) phases (see Figure 12.6 for a review of the cell cycle). The G_1 and G_2 (gap) phases are essentially skipped, and there is no increase in mass. Instead, cleavage partitions the cytoplasm of the large fertilized egg into many smaller cells called **blastomeres**. Because each blastomere is much smaller than the entire egg, its nucleus can make enough RNA to program further development.

The first five to seven cleavage divisions produce a hollow ball of cells, the **blastula**, surrounding a fluid-filled cavity called the **blastocoel**. In some species, including sea urchins and other echinoderms, the division pattern is uniform across the embryo **(Figure 47.6)**. In others, including frogs, the

▼ Figure 47.6 Cleavage in an echinoderm embryo. Cleavage is a series of mitotic cell divisions that transform the fertilized egg into a blastula, a hollow ball composed of cells called blastomeres. These light micrographs show the cleavage stages of a sand dollar embryo, which are virtually identical to those of a sea urchin. Each image is taken from above the embryo, with the focal plane, and hence the cells that are visible, at the equator.

(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. A cavity—the blastocoel—has begun to form in the center.

(d) Later blastula. A single layer of cells surrounds the blastocoel. Morphogenesis follows, after which the embryo hatches from the fertilization envelope and begins swimming.

VISUAL SKILLS *If the embryo in (c) or (d) were photographed at a focal plane midway from the equator to one of the poles, what visible features would change?*

Mastering Biology Video: Sea Urchin Fertilization and Cleavage

pattern is asymmetric, with regions of the embryo differing in both the number and size of newly formed cells.

Cleavage Pattern in Frogs

In the eggs of frogs (and many other animals), stored nutrients called **yolk** are concentrated toward one pole, called the **vegetal pole**, and away from the opposite or **animal pole**. This asymmetric distribution of yolk not only gives the two halves of the egg—the animal and vegetal hemispheres—different colors, but also influences the pattern of cleavage divisions, for reasons we will explore next.

When an animal cell divides, an indentation called a *cleavage furrow* forms in the cell surface as cytokinesis divides the cell in half **(Figure 47.7)**. In the frog embryo, the first two cleavage furrows form parallel to the line (or meridian) connecting the two poles. During these divisions, the dense yolk slows completion of cytokinesis. As a result, the first cleavage furrow is still dividing the yolky cytoplasm in the vegetal hemisphere when the second cell division begins. Eventually, four blastomeres of equal size extend from the animal pole to the vegetal pole.

During the third division, the yolk begins to affect the relative size of cells produced in the two hemispheres. This division is equatorial (perpendicular to the line connecting the poles) and produces an eight-cell embryo. However, as each of the four blastomeres begins this division, yolk near the vegetal pole displaces the mitotic apparatus and the cleavage furrow from the egg equator toward the animal pole. The result is a smaller blastomere size in the animal hemisphere than in the vegetal hemisphere. The displacing effect of the yolk persists in subsequent divisions, causing the blastocoel to form entirely in the animal hemisphere (see Figure 47.7).

Cleavage Patterns in Other Animals

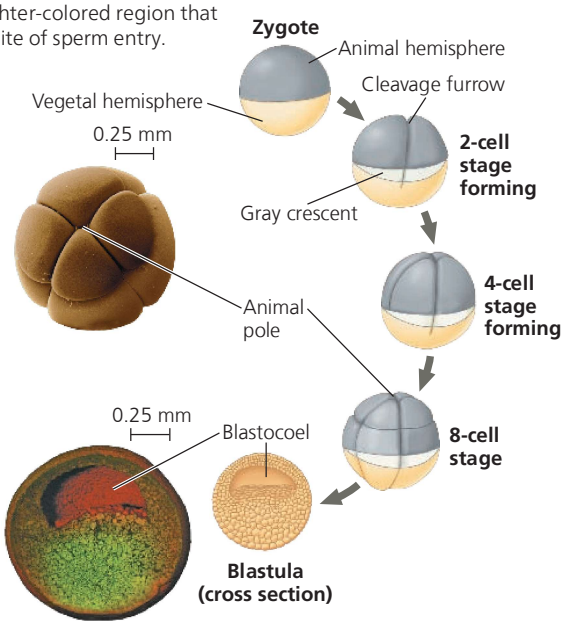
Although yolk affects where division occurs in the eggs of frogs and other amphibians, the cleavage furrow still passes entirely through the egg. Cleavage in amphibian development is therefore said to be *holoblastic* (from the Greek *holos*, complete). Holoblastic cleavage is also seen in many other groups of animals, including echinoderms, mammals, and annelids. In those animals whose eggs contain relatively little yolk, the blastocoel forms centrally and the blastomeres are often of similar size, particularly during the first few divisions of cleavage (see Figure 47.6). This is the case for humans.

Yolk is most plentiful and has its most pronounced effect on cleavage in the eggs of birds and other reptiles, many fishes, and insects. In these animals, the volume of yolk is so great that cleavage furrows cannot pass through it, and only the region of the egg lacking yolk undergoes cleavage. This incomplete cleavage of a yolk-rich egg is said to be *meroblastic* (from the Greek *meros*, partial).

For chickens and other birds, the part of the egg that we commonly call the yolk is actually the entire egg cell. Cell divisions are limited to a small whitish area at the animal pole. These divisions produce a cap of cells that sort into upper and lower layers. The cavity between these two layers is the avian version of the blastocoel.

In *Drosophila* and most other insects, yolk is found throughout the egg. Early in development, multiple rounds of mitosis occur without cytokinesis. In other words, no cell membranes form around the early nuclei. The first several hundred nuclei spread throughout the yolk and later migrate to the outer edge of the embryo. After several more rounds of mitosis, a plasma membrane forms around each nucleus, and the embryo, now the equivalent of a blastula, consists of a single layer of about 6,000 cells surrounding a mass of yolk (see Figure 18.22). Given that the number of cleavage divisions varies among animals, what determines the end of the cleavage stage? The **Scientific Skills Exercise** explores one of the landmark studies addressing this question.

▼ Figure 47.7 Cleavage in a frog embryo. The cleavage planes in the first and second divisions extend from the animal pole to the vegetal pole, but the third cleavage is perpendicular to the polar axis. In some species, the first division bisects the gray crescent, a lighter-colored region that appears opposite the site of sperm entry.



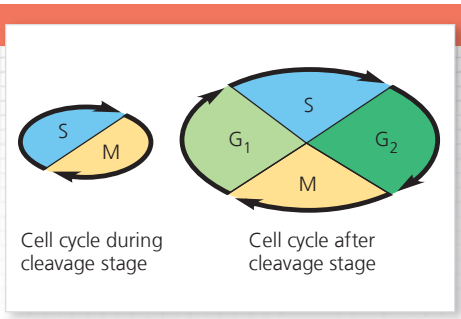
Eight-cell stage (viewed from the animal pole). The large amount of yolk displaces the third cleavage toward the animal pole, forming two tiers of cells. The four cells near the animal pole (closer, in this view) are smaller than the other four cells (colorized SEM).

Blastula (at least 128 cells). As cleavage continues, a fluid-filled cavity, the blastocoel, forms within the embryo. Because of unequal cell division, the blastocoel is located in the animal hemisphere. Both the drawing and the micrograph (assembled from fluorescence images) show cross sections of a blastula with about 4,000 cells.

Scientific Skills Exercise

Interpreting a Change in Slope

What Causes the End of Cleavage in a Frog Embryo? For a frog embryo in the cleavage stage, the cell cycle consists mainly of the S (DNA synthesis) and M (mitosis) phases. However, after the 12th cell division, G_1 and G_2 phases appear, and the cells grow, producing proteins and cytoplasmic organelles. What triggers this change?

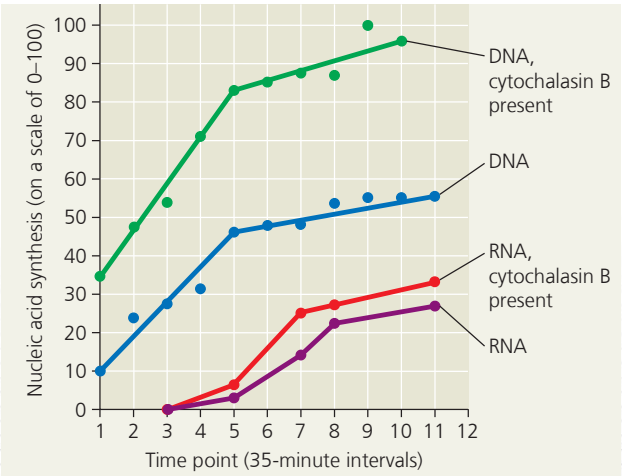


Cell cycle during cleavage stage

Cell cycle after cleavage stage

How the Experiments Were Done Researchers tested the hypothesis that a mechanism for counting cell divisions determines when cleavage ends. They let frog embryos take up radioactively labeled nucleosides, either thymidine (to measure DNA synthesis) or uridine (to measure RNA synthesis). They then repeated the experiments in the presence of cytochalasin B, a chemical that prevents cell division by blocking cleavage furrow formation and cytokinesis.

Data from the Experiments



INTERPRET THE DATA

1. How does the use of particular labeled nucleosides allow independent measurement of DNA and RNA synthesis?
2. Describe the changes in synthesis that occur at the end of cleavage (time point 5 corresponds to cell division 12).
3. Comparing the rate of DNA synthesis with and without cytochalasin B, the researchers hypothesized that the toxin increases diffusion of thymidine into the embryos. Explain their logic.
4. Do the data support the hypothesis that the timing of the end of cleavage depends on counting cell divisions? Explain.
5. In a separate experiment, researchers disrupted the block to polyspermy, generating embryos with seven to ten sperm nuclei. At the end of cleavage, these embryos had the same nucleus-to-cytoplasm ratio as the wild-type embryos, but cleavage ended at the 10th cell division rather than the 12th cell division. What do these results indicate about the timing of the end of cleavage?

Data from J. Newport and M. Kirschner, A major developmental transition in early Xenopus embryos: I. Characterization and timing of cellular changes at the mid-blastula stage, *Cell* 30:675–686 (1982).

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

CONCEPT CHECK 47.1

1. How does the fertilization envelope form in sea urchins? What is its function?
2. **WHAT IF?** Predict what would happen if Ca^{2+} was injected into an unfertilized sea urchin egg.
3. **MAKE CONNECTIONS** Review Figure 12.16 on cell cycle control. Would you expect MPF (maturation-promoting factor) activity to remain steady during cleavage? Explain.

For suggested answers, see Appendix A.

CONCEPT 47.2

Morphogenesis in animals involves specific changes in cell shape, position, and survival

The cellular and tissue-based processes that are called **morphogenesis** and by which the animal body takes shape occur over the last two stages of embryonic development.

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. Further transformation occurs during **organogenesis**, the formation of organs. We will discuss these two stages in turn.

Gastrulation

Gastrulation is a dramatic reorganization of the hollow blastula into a two-layered or three-layered embryo called a **gastrula**. Cells move during gastrulation, taking up new positions and often acquiring new neighbors. **Figure 47.8** will help you visualize these complex three-dimensional changes. The cell layers produced 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** forms the lining of the digestive tract. In a few radially symmetric animals, only these two germ layers form during gastrulation. Such animals are called

▼ Figure 47.8 VISUALIZING GASTRULATION

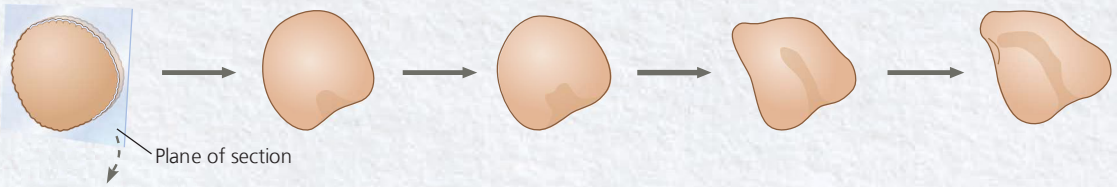
The embryos of all animals, and only animals, gastrulate. Cells change position: Some are brought inside the embryo, and others spread over the surface. The net result is an embryo with two, or more commonly three, cell layers. This figure will help you visualize the basic choreography of gastrulation before you explore the specific steps in different types of animals.

Instructors: Additional questions related to this Visualizing Figure can be assigned in **Mastering Biology**.

Reorganizing the animal embryo in three dimensions

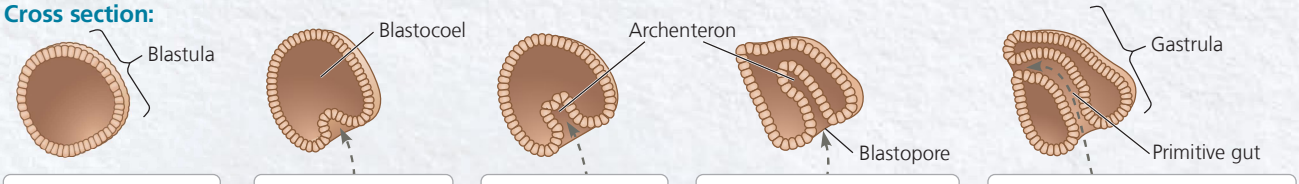
Gastrulation typically begins with invagination, the infolding of a sheet of cells, shown here in both surface view and cross section. The resulting changes to the epithelium covering the embryo resemble what happens if you push a finger into one end of a lightly inflated balloon.

Surface view:



1. ***In the gastrula, how many compartments are formed from the blastocoel?***

Cross section:



At the end of cleavage, a single sheet of cells covers the surface of the blastula.

A group of cells buckle into the blastocoel, forming a shallow depression.

Continued invagination forms a blind-ended tube, the **archenteron.**

The open end of the archenteron, the first opening formed in the embryo, is called the **blastopore.**

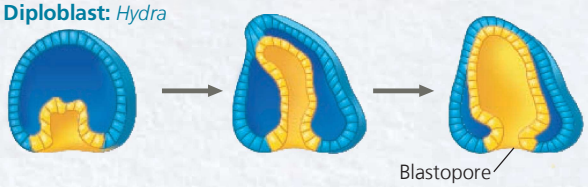
The tip of the archenteron reaches the embryo surface, completing formation of the primitive gut of the embryo, now a gastrula.

Forming the primary cell layers of the animal body

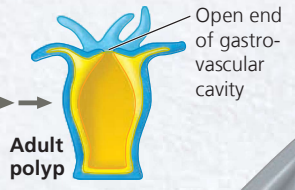
In diploblasts, gastrulation forms two germ layers: ectoderm and endoderm. Triploblasts—both protostomes and deuterostomes—gain a third layer: mesoderm. At the end of embryogenesis, each germ layer gives rise to specific tissues and organs. To visualize how this occurs, trace the fate of each germ layer in each row of drawings (all views are cross sections except the sea urchin larva, which is a transparent surface view).

Key
- Ectoderm
- Mesoderm
- Endoderm

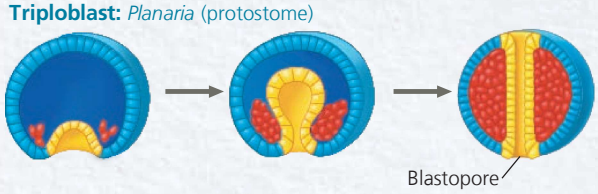
Diploblast: *Hydra*



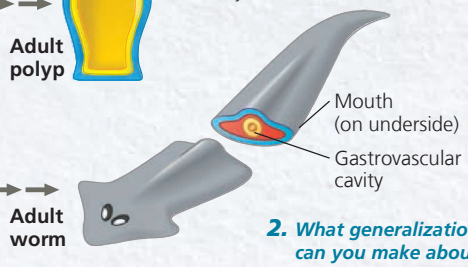
In diploblasts, the blastopore becomes the open end of the gastrovascular cavity.



Triploblast: *Planaria* (protostome)

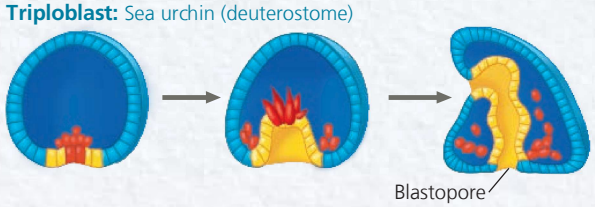


In protostomes, the mouth forms from the blastopore.

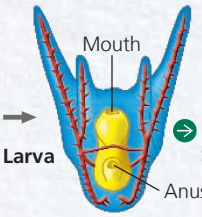


2. ***What generalizations can you make about the location of mesoderm, when it is present, during and after development?***

Triploblast: Sea urchin (deuterostome)



In deuterostomes, including all vertebrates as well as some invertebrates, the mouth forms *opposite* the blastopore.



Mastering Biology Video: Sea Urchin Gastrulation

diploblasts. In contrast, vertebrates and other bilaterally symmetric animals are triploblasts: In these animals, a third germ layer, the **mesoderm**, forms between the ectoderm and the endoderm.

Gastrulation in Frogs

Each embryonic germ layer contributes to a distinct set of structures in the adult animal, as shown in **Figure 47.9**. The embryonic organization of the germ layers is often reflected in the adult: The ectoderm forms the nervous system and outer body layer, the mesoderm gives rise to muscles and skeleton, and the endoderm lines many organs and ducts. There are, however, numerous exceptions.

Figure 47.10 details gastrulation in a frog. The blastula of frogs and other triploblasts has a dorsal (top) and ventral

▼ Figure 47.9 Major derivatives of the three embryonic germ layers in vertebrates.

ECTODERM (outer layer)	MESODERM (middle layer)	ENDODERM (inner layer)
• Epidermis of skin and its derivatives (including sweat glands, hair follicles) • Nervous and sensory systems • Pituitary gland, adrenal medulla • Jaws and teeth	• Skeletal and muscular systems • Circulatory and lymphatic systems • Excretory and reproductive systems (except germ cells) • Dermis of skin • Adrenal cortex	• Epithelial lining of digestive tract and associated organs • Epithelial lining of respiratory, excretory, and reproductive tracts and ducts • Thymus, thyroid, and parathyroid glands

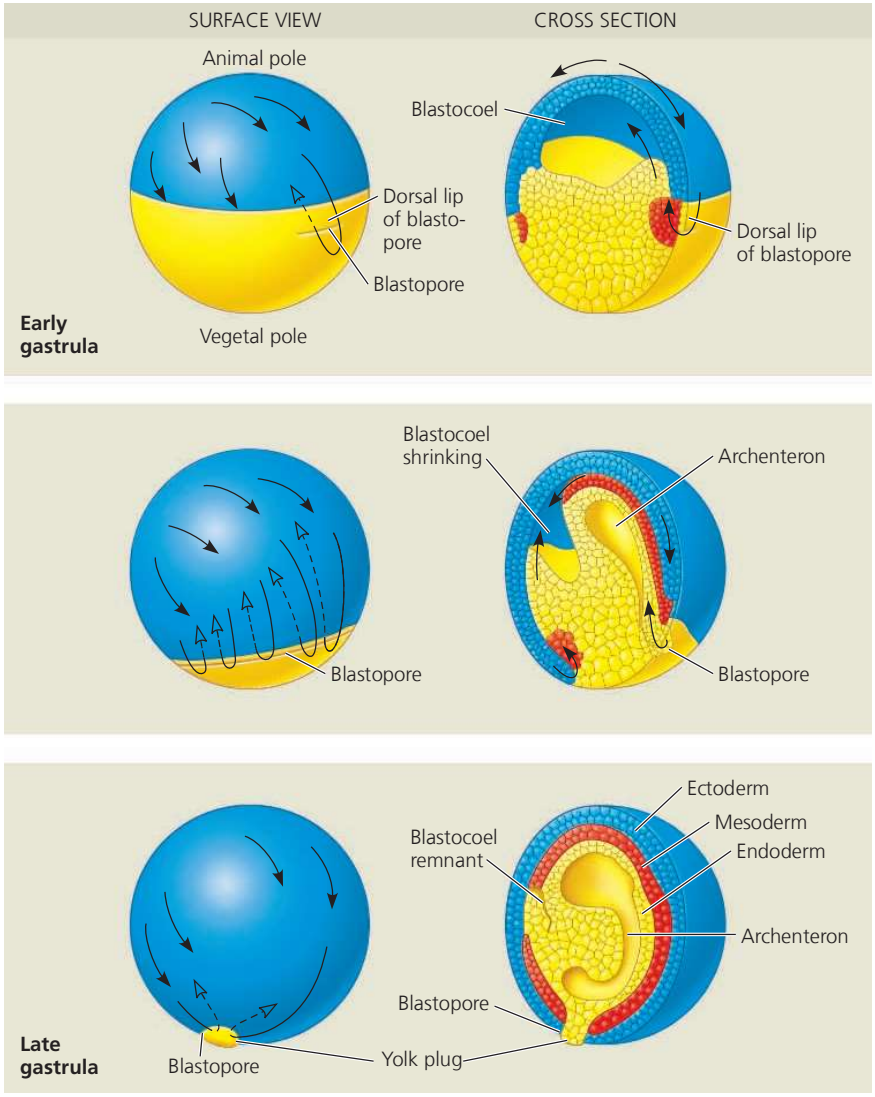
Mastering Biology HHMI Video: Differentiation and the Fate of Cells

▼ Figure 47.10 Gastrulation in a frog embryo. In the frog blastula, the blastocoel is displaced toward the animal pole and is surrounded by a wall several cells thick.

1. Gastrulation begins when cells on the dorsal side invaginate to form a small indented crease, the blastopore. The part above the crease is called the **dorsal lip**. As the blastopore is forming, a sheet of cells begins to spread out of the animal hemisphere, rolls inward over the dorsal lip (involution), and moves into the interior (shown by the dashed arrow). In the interior, these cells will form endoderm and mesoderm, with the endodermal layer on the inside. Meanwhile, cells at the animal pole change shape and begin spreading over the outer surface.

2. The blastopore extends around both sides of the embryo as more cells invaginate. When the ends meet, the blastopore forms a circle that becomes smaller as ectoderm spreads downward over the surface. Internally, continued involution expands the endoderm and mesoderm; an archenteron forms and grows as the blastocoel shrinks and eventually disappears.

3. Late in gastrulation, the cells remaining on the surface make up the ectoderm. The endoderm is the innermost layer, and the mesoderm lies between the ectoderm and endoderm. The circular blastopore surrounds a plug of yolk-filled cells.



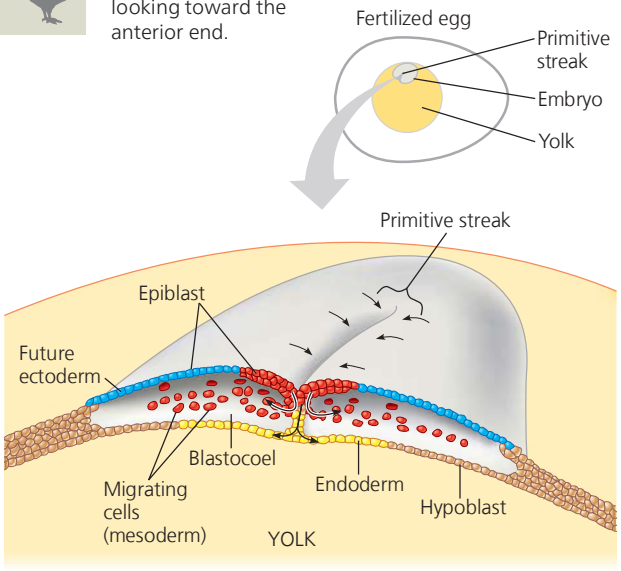
(bottom) side, a left and right side, and an anterior (front) and posterior (back) end. The cell movements that begin gastrulation occur on the dorsal side, opposite where the sperm entered the egg. The frog's anus develops from the blastopore, and the mouth eventually breaks through at the opposite end of the archenteron.

Gastrulation in Chicks

At the onset of gastrulation in chicks, an upper and a lower layer of cells—the *epiblast* and *hypoblast*—lie atop a yolk mass. All the cells that will form the embryo come from the epiblast. During gastrulation, some epiblast cells move toward the midline, detach, and move inward toward the yolk **(Figure 47.11)**. The pileup of cells moving inward at the midline produces a visible thickening called the *primitive streak*. Some of these cells move downward and form endoderm, pushing aside the hypoblast cells, while others migrate laterally (sideways) and form mesoderm. The cells left behind on the surface at the end of gastrulation will become ectoderm. The hypoblast cells later segregate from the endoderm and eventually form part of the sac that surrounds the yolk and also part of the stalk that connects the yolk mass to the embryo.

Although different terms describe gastrulation in different vertebrate species, the rearrangements and movements of cells exhibit a number of fundamental similarities. In particular, the primitive streak, shown in Figure 47.11 for the chick embryo, is the counterpart of the blastopore lip, shown in Figure 47.10 for the frog embryo. Formation of a primitive streak is also central to human embryo gastrulation, our next topic.

▼ Figure 47.11 Gastrulation in a chick embryo. This is a cross section of a gastrulating embryo, looking toward the anterior end.



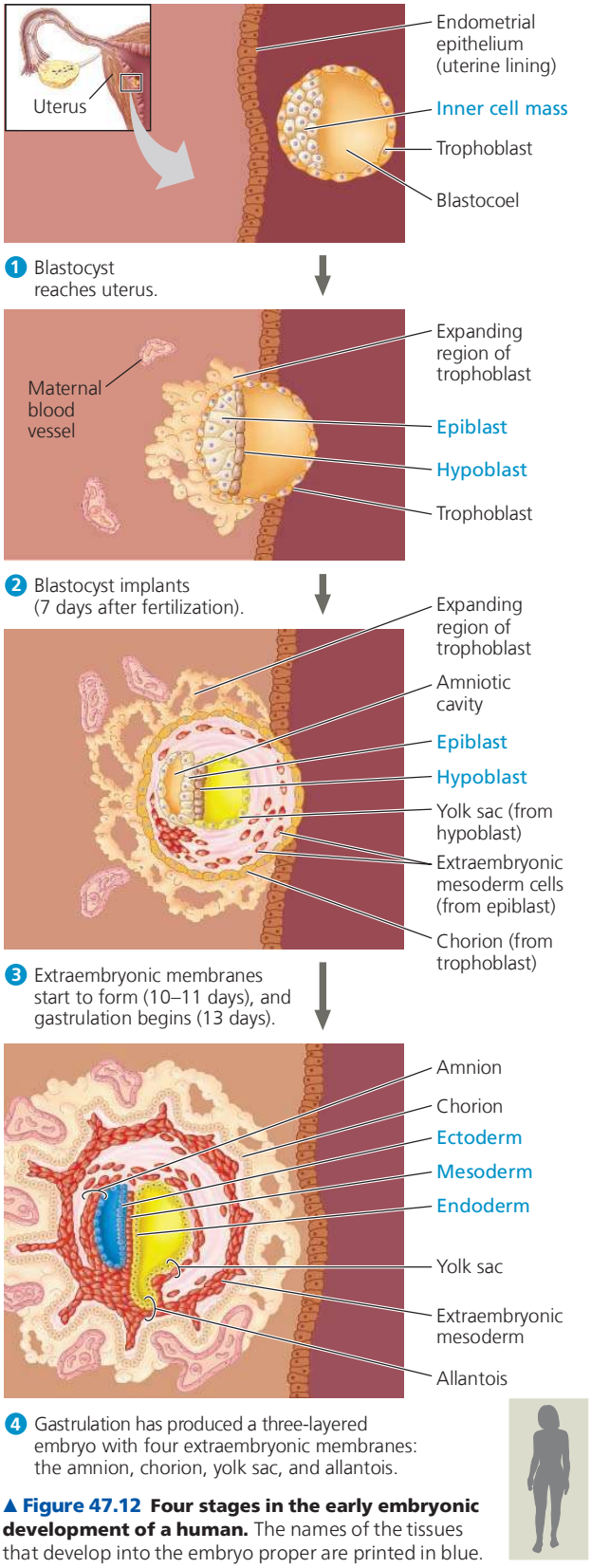
Gastrulation in Humans

Unlike the large, yolky eggs of many vertebrates, human eggs are quite small, storing little in the way of food reserves. Fertilization takes place in the oviduct, and development begins while the embryo completes its journey down the oviduct to the uterus (see Figure 46.15).

Figure 47.12 outlines the development of the human embryo, starting about 6 days after fertilization. This depiction is largely based on observations of embryos from other mammals, such as the mouse, and of very early human embryos following *in vitro* fertilization.

1. At the end of cleavage, the embryo has more than 100 cells arranged around a central cavity and has reached the uterus. At this stage, the embryo is called a **blastocyst**, the mammalian version of a blastula. Clustered at one end of the blastocyst cavity is a group of cells called the **inner cell mass**, which will develop into the embryo proper. It is the cells of the inner cell mass that are the source of embryonic stem cell lines (see Concept 20.3).
2. Implantation of the embryo is initiated by the **trophoblast**, the outer epithelium of the blastocyst. Enzymes secreted by the trophoblast during implantation break down molecules of the endometrium, the lining of the uterus, allowing invasion by the blastocyst. The trophoblast also extends finger-like projections that cause capillaries in the endometrium to spill out blood that can be captured by trophoblast tissues. Around the time the embryo undergoes implantation, the inner cell mass of the blastocyst forms a flat disk with an inner layer of cells, the *epiblast*, and an outer layer, the *hypoblast*. As is true for a bird embryo, the human embryo develops almost entirely from epiblast cells.
3. Following implantation, the trophoblast continues to expand into the endometrium, and four new membranes appear. Although these **extraembryonic membranes** arise from the embryo, they enclose specialized structures located outside the embryo. As implantation is completed, gastrulation begins. Some epiblast cells remain as ectoderm on the surface, while others move inward through a primitive streak and form mesoderm and endoderm, just as in the chick (see Figure 47.11).
4. By the end of gastrulation, the embryonic germ layers have formed. Extraembryonic mesoderm and four distinct extraembryonic membranes now surround the embryo. As development proceeds, cells of the invading trophoblast, the epiblast, and the adjacent endometrial tissue all contribute to the formation of the placenta. This vital organ mediates the exchange of nutrients, gases, and nitrogenous wastes between the developing embryo and the mother (see Figure 46.16).

Mastering Biology **HHMI Video: Human Embryonic Development**



▲ Figure 47.12 Four stages in the early embryonic development of a human. The names of the tissues that develop into the embryo proper are printed in blue.

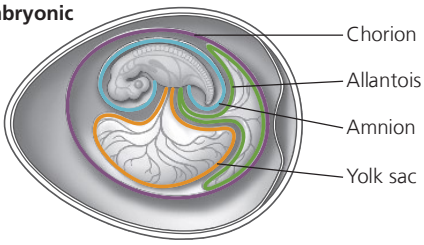
Developmental Adaptations of Amniotes

EVOLUTION During embryonic development, mammals and reptiles (including birds) form four extraembryonic membranes: the chorion, allantois, amnion, and yolk sac **(Figure 47.13)**. In all these groups, such membranes provide a "life-support system" for further development. Why did this adaptation appear in the evolutionary history of reptiles and mammals, but not other vertebrates, such as fishes and amphibians? We can formulate a reasonable hypothesis by considering a few basic facts about embryonic development. All vertebrate embryos require an aqueous environment for their development. The embryos of fishes and amphibians usually develop in the surrounding sea or pond and need no specialized water-filled enclosure. However, the extensive colonization of land by vertebrates was possible only after the evolution of structures that would allow reproduction in dry environments. Two such structures exist today: (1) the shelled egg of birds and other reptiles as well as a few mammals (the monotremes) and (2) the uterus of marsupial and eutherian mammals. Inside the shell or uterus, the embryos of these animals are surrounded by fluid within a sac formed by one of the extraembryonic membranes, the amnion. Mammals and reptiles, including birds, are therefore called **amniotes** (see Concept 34.5).

For the most part, the extraembryonic membranes have similar functions in mammals and reptiles, consistent with a common evolutionary origin (see Figure 34.25). The chorion is the site of gas exchange, and the fluid within the amnion physically protects the developing embryo. (This amniotic fluid is released from the vagina when a pregnant woman's

▼ Figure 47.13 The shelled egg of reptiles.

(a) The four extraembryonic membranes in a reptile egg



(b) A baby red-tailed racer snake (*Gonyosoma oxycephala*) hatching from its protective egg

"water breaks" before childbirth.) The allantois, which disposes of wastes in the reptilian egg, is incorporated into the umbilical cord in mammals. There, it forms blood vessels that transport oxygen and nutrients from the placenta to the embryo and rid the embryo of carbon dioxide and nitrogenous wastes. The fourth extraembryonic membrane, the yolk sac, encloses yolk in the eggs of reptiles. In mammals it is a site of early formation of blood cells, which later migrate into the embryo proper. Thus, the extraembryonic membranes common to reptiles and mammals exhibit adaptations specific to development within a shelled egg or a uterus.

After gastrulation is complete and any extraembryonic membranes are formed, the next stage of embryonic development begins: organogenesis, the formation of organs.

Organogenesis

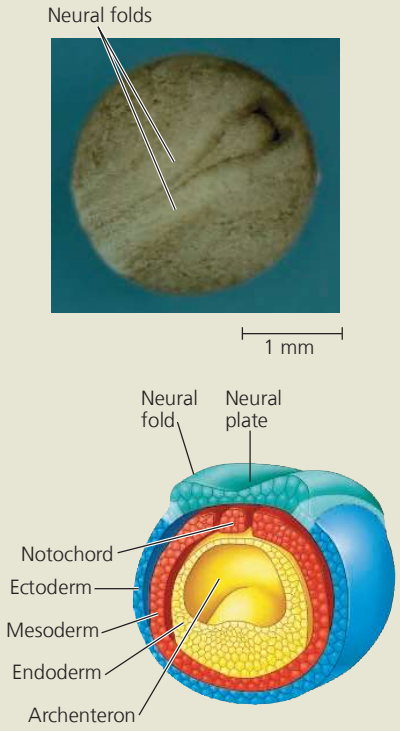
During organogenesis, regions of the three embryonic germ layers develop into the rudiments of organs. Often, cells from two or three germ layers participate in forming a single organ, with interactions between cells of different germ layers helping to specify cell fates. Adopting particular developmental fates may in turn cause cells to change shape or, in certain circumstances, migrate to another location in the body. To see how these processes contribute to organogenesis, we'll consider *neurulation*, the early steps in the formation of the brain and spinal cord in vertebrates.

Neurulation

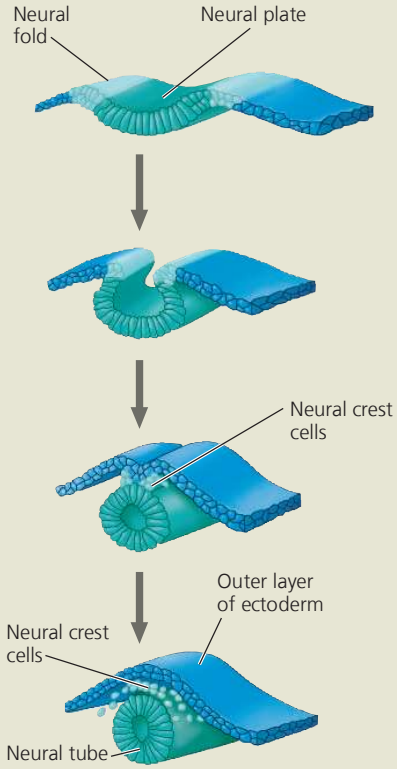
Neurulation begins as cells from the dorsal mesoderm form the **notochord**, a rod that extends along the dorsal side of the chordate embryo, as seen for the frog in **Figure 47.14a**. Signaling molecules secreted by these mesodermal cells and other tissues cause the ectoderm above the notochord to become the *neural plate*. Formation of the neural plate is thus an example of **induction**, a process in which a group of cells or tissues influences the development of another group through close-range interactions (see Figure 18.17b).

▼ Figure 47.14 Neurulation in a frog embryo.

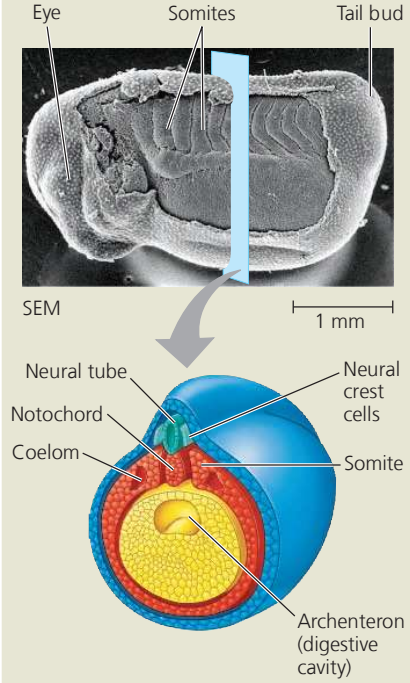
Mastering Biology Video: Frog Development



(a) Neural plate formation. By this stage, the notochord has developed from dorsal mesoderm, and the dorsal ectoderm has thickened, forming the neural plate. Two ridges called neural folds form the lateral edges of the neural plate and are visible in the micrograph (LM) of a whole embryo.



(b) Neural tube formation. Infolding and pinching off of the neural plate generates the neural tube.



(c) Somites. The SEM is a side view of the whole embryo at the tail-bud stage. Part of the ectoderm has been removed to reveal the somites, blocks of tissue that will give rise to segmental structures such as vertebrae. The drawing shows a similar-stage embryo as if cut and viewed in cross section. The somites, formed from mesoderm, flank the notochord.

After the neural plate is formed, its cells change shape, curving the structure inward. In this way, the neural plate rolls itself into the **neural tube**, which runs along the anterior-posterior axis of the embryo **(Figure 47.14b)**. The neural tube will become the brain in the head and the spinal cord along the rest of the body. In contrast, the notochord disappears before birth, although parts persist as the inner portions of the disks in the adult spine. (These are the disks that can herniate or rupture, causing back pain.)

Neurulation, like other stages of development, is sometimes imperfect. For example, *spina bifida*, the most common congenital disability in the United States, occurs when a portion of the neural tube fails to develop or close properly. The opening in the spinal column that remains causes nerve damage, resulting in varying degrees of leg paralysis. Although the opening can be surgically repaired shortly after birth, the nerve damage is permanent.

Cell Migration in Organogenesis

During organogenesis, some cells undergo long-range migration, including two sets of cells that develop near the vertebrate neural tube. The first set is called the **neural crest**, a set of cells that develops along the borders where the neural tube pinches off from the ectoderm (see Figure 47.14b). Neural crest cells subsequently migrate to many parts of the embryo, forming a variety of tissues that include peripheral nerves as well as parts of the teeth and skull bones.

A second set of migratory cells is formed when groups of mesodermal cells lateral to the notochord separate into blocks called **somites (Figure 47.14c)**. Somites play a significant role in organizing the segmented structure of the vertebrate body. Parts of the somites dissociate into mesenchyme cells. Some form the vertebrae; others form the muscles associated with the vertebral column and the ribs.

By contributing to the formation of vertebrae, ribs, and associated muscles, somites form repeated structures in the adult. Chordates, including ourselves, are thus segmented, although in the adult form the segmentation is much less obvious than in shrimp and other segmented invertebrates.

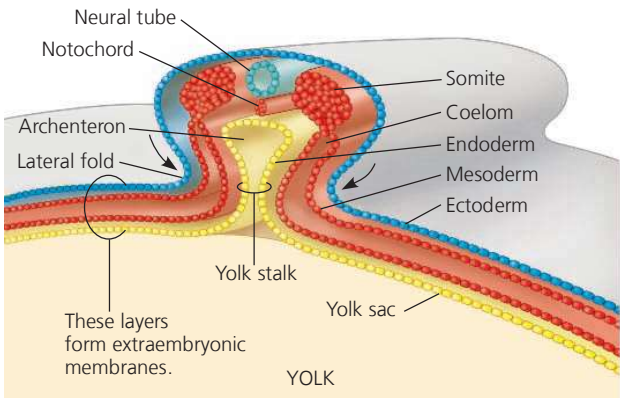
Organogenesis in Chicks and Insects

Early organogenesis in the chick is quite similar to that in the frog. For example, the borders of the chick blastoderm fold downward and come together, pinching the embryo into a three-layered tube joined under the middle of the body to the yolk **(Figure 47.15a)**. By the time the chick embryo is 56 hours old, rudiments of the major organs, including the brain, eyes, and heart, are readily apparent **(Figure 47.15b)**.

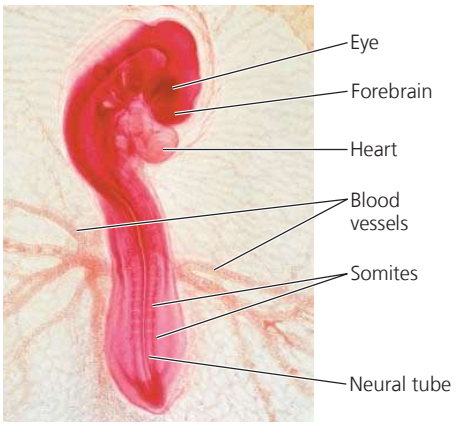
Comparing organogenesis in invertebrates with that in vertebrates often reveals fundamental similarities in mechanism that are masked by differences in pattern and appearance. For example, consider neurulation. In insects, tissues of the nervous system form on the ventral, not dorsal, side of the embryo. However, ectoderm along the anterior-posterior axis then rolls into a tube inside the embryo, just as in vertebrate neurulation. Furthermore, the molecular signaling pathways that bring about these similar events in different locations have many steps in common, underscoring a shared evolutionary history.

Like gastrulation, organogenesis in vertebrates and invertebrates relies substantially on changes in cell shape and location. We turn now to an exploration of how these changes take place.

▶ Figure 47.15 Organogenesis in a chick embryo.



(a) Early organogenesis. The archenteron forms when lateral folds pinch the embryo away from the yolk. The embryo remains open to the yolk, attached by the yolk stalk, as shown in this cross section.



(b) Late organogenesis. Rudiments of most major organs have already formed in this 56-hour-old chick embryo. Blood vessels extending from the embryo supply the extraembryonic membranes, as seen in this light micrograph (LM).

The Cytoskeleton in Morphogenesis

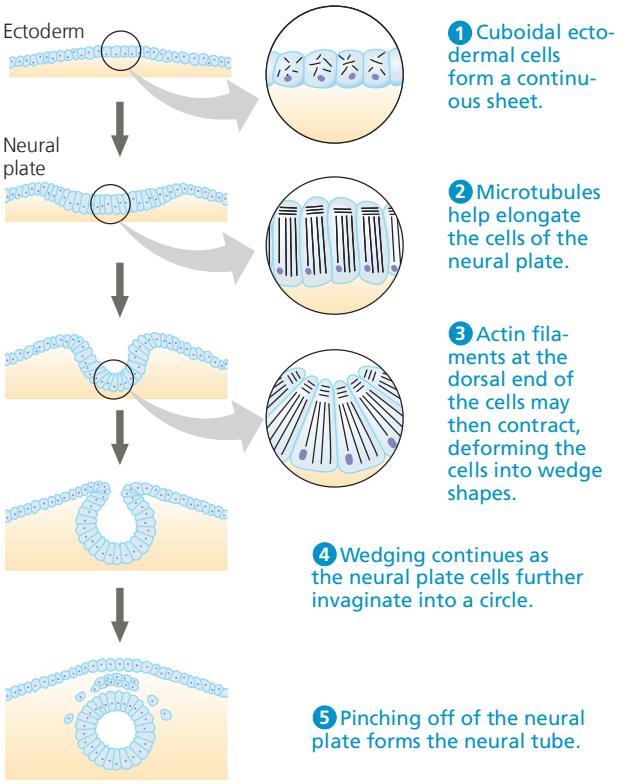
In animals, movement of parts of a cell can bring about changes in cell shape or enable a cell to migrate from one place to another within the embryo. One set of cellular components essential to these events is the collection of microtubules and microfilaments that make up the cytoskeleton (see Table 6.1).

Cell Shape Changes in Morphogenesis

Reorganization of the cytoskeleton is a major force in changing cell shape during development. As an example, let's return to the topic of neurulation. At the onset of neural tube formation, microtubules oriented from dorsal to ventral in a sheet of ectodermal cells help lengthen the cells along that axis **(Figure 47.16)**. At the apical end of each cell is a bundle of actin filaments (microfilaments) oriented crosswise. These actin filaments contract, giving the cells a wedge shape that bends the ectoderm layer inward.

The generation of wedge-shaped cells by apical constriction of actin filaments is a common mechanism in development for invaginating a cell layer. For instance, during gastrulation in the fruit fly *Drosophila melanogaster*, the formation of wedge-shaped cells along the ventral surface drives generation of the tube of cells that forms the mesoderm.

▼ Figure 47.16 Change in cell shape during morphogenesis. Reorganization of the cytoskeleton is associated with morphogenetic changes in embryonic tissues, as shown here.



The cytoskeleton also directs a morphogenetic movement called **convergent extension**, a rearrangement that causes a sheet of cells to become narrower (converge) while it becomes longer (extends). This type of lengthening and narrowing of cells occurs often in gastrulation, including formation of the primitive streak in the fertilized chick egg (see Figure 47.11) and elongation of the archenteron in the sea urchin embryo (see Figure 47.8). Convergent extension is also important during involution in the frog gastrula. There, convergent extension changes the gastrulating embryo from a spherical shape to the rounded rectangular shape seen in Figure 47.14c.

The cell movements during convergent extension are quite simple: The cells elongate, with their ends pointing in the direction they will move, and then wedge between each other, forming fewer columns of cells **(Figure 47.17)**. It's like a crowd of people about to enter a theater moving forward while also merging into a single-file line.

Cell Migration in Morphogenesis

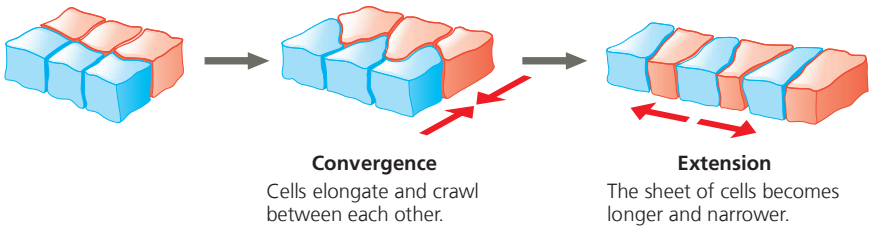
The cytoskeleton is responsible not only for cell shape changes but also for cell migration. During organogenesis in vertebrates, cells from the neural crest and from somites migrate to locations throughout the embryo. Cells "crawl" within the embryo by using cytoskeletal fibers to extend and retract cellular protrusions. This type of motility is akin to amoeboid movement (see Figure 6.26b). Transmembrane glycoproteins called *cell adhesion molecules* play a key role in cell migration by promoting interaction between pairs of cells. Cell migration also involves the *extracellular matrix* (*ECM*), the meshwork of secreted glycoproteins and other macromolecules lying outside the plasma membranes of cells (see Figure 6.28).

The ECM helps to guide cells in many types of movements, such as migration of individual cells and shape changes of cell sheets. Cells that line migration pathways regulate the movement of migrating cells by secreting specific molecules into the ECM. For these reasons, researchers are attempting to generate an artificial ECM that can serve as a scaffold for the repair or replacement of damaged tissues or organs. One promising approach involves the use of nanofiber fabrication to produce materials that mimic the essential properties of the natural ECM.

Programmed Cell Death

Just as certain cells of the embryo are programmed to change shape or location, others are programmed to die. At various times in development, individual cells, sets of cells, or whole tissues cease to develop, die, and are engulfed by neighboring cells. Thus, *programmed cell death*, also called **apoptosis**, is a common feature of animal development.

One circumstance for programmed cell death is when a structure functions only in a larval or other immature form of the organism. One familiar example is the tail of a tadpole, the free-swimming larval stage of a frog or toad. The tail forms during early development, enables locomotion during



▶ **Figure 47.17 Convergent extension of a sheet of cells.** In this simplified diagram, the cells elongate coordinately in a particular direction and crawl between each other (convergence) as the sheet becomes longer and narrower (extension).

larval growth, and is then eliminated during metamorphosis into the adult form (see Figure 45.22).

Apoptosis may also occur when a large set of cells is formed, but only a subset has the properties required for further function. Such is the case in both nervous and immune system development. In the vertebrate nervous system, for instance, many more neurons are produced during development than exist in the adult. Neurons that make functional connections with other neurons typically survive; many of the rest undergo apoptosis. Similarly, in the adaptive immune system, self-reactive cells—cells with the potential to attack the animal itself rather than invading pathogens—are often eliminated by apoptosis.

Some cells that undergo apoptosis don't seem to have any function. Why do such cells form? The answer can be found by considering the evolution of amphibians, birds, and mammals. When these groups began to diverge during evolution, the basic developmental program for making a vertebrate body was already in place. The differences in present-day body forms arose through modification of that common developmental program. For example, the shared developmental program generates webbing between the embryonic digits, but in many birds and mammals, including humans, the webbing is eliminated by apoptosis (see Figure 11.21). This is one reason why such different adult forms arise from early vertebrate embryos that look so much alike.

As you have seen, cell behavior and the molecular mechanisms underlying it are crucial to the morphogenesis of the embryo. In the next section, you'll learn some ways in which shared cellular and genetic processes ensure that particular types of cells each end up in the right place.

CONCEPT CHECK 47.2

1. In the frog embryo, convergent extension elongates the notochord. Explain how the words *convergent* and *extension* apply to this process.
2. **WHAT IF?** Predict what would happen if, just before neural tube formation, you treated frog embryos with a drug that enters all the cells of the embryo and blocks the function of microfilaments.
3. **MAKE CONNECTIONS** Unlike some other types of developmental abnormalities, neural tube defects are largely preventable. Explain (see Figure 41.4).

For suggested answers, see Appendix A.

CONCEPT 47.3

Cytoplasmic determinants and inductive signals regulate cell fate

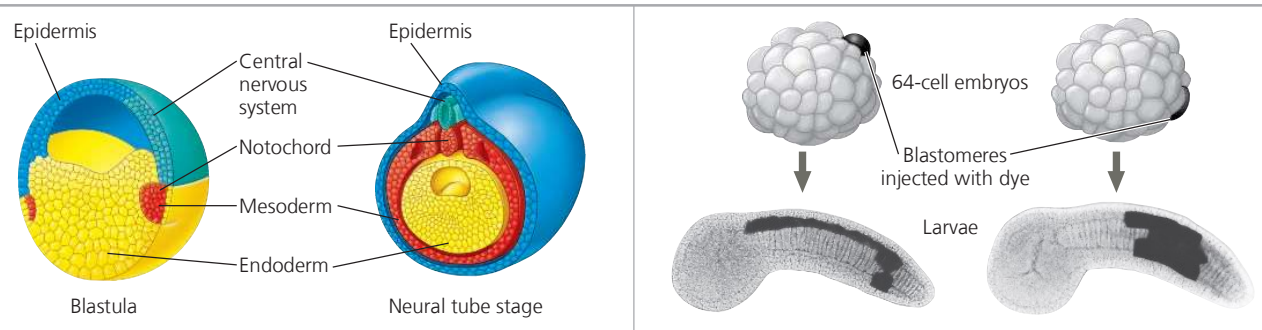
During embryonic development, cells arise by division, take up particular locations in the body, and become specialized in structure and function. Where a cell resides, how it appears, and what it does define its development *fate*. Developmental biologists use the terms **determination** to refer to the process by which a cell or group of cells becomes committed to a particular fate and **differentiation** to refer to the resulting specialization in structure and function. You may find it a useful analogy to think about determination being equivalent to declaring a major in college and differentiation being comparable to taking the courses required by your major.

Every diploid cell formed during an animal's development has the same genome. With the exception of certain mature immune cells, the collection of genes present in a given cell is the same throughout the cell's life. How, then, do cells acquire different fates? As discussed in Concept 18.4, particular tissues, and often cells within a tissue, differ from one another by expressing distinct sets of genes from their shared genome.

Even animals that display widely differing body plans share many basic mechanisms of development and often use a common set of regulatory genes. For example, the gene that specifies where eyes form in a vertebrate embryo has a close counterpart with a nearly identical function in the fruit fly *Drosophila melanogaster*. Indeed, when the gene from a mouse is experimentally introduced into a fly embryo, the mouse gene directs eye formation wherever it is expressed in the fly.

A major focus of developmental biology is to uncover the mechanisms that direct the differences in gene expression underlying developmental fates. As one step toward this goal, scientists often seek to trace tissues and cell types back to their origins in the early embryo.

▼ Figure 47.18 Fate mapping for two chordates.



(a) Fate map of a frog embryo. The fates of groups of cells in a frog blastula were determined in part by marking different regions of the blastula with nontoxic dyes and observing where the dye was found at later stages of development. The labeling of the two embryonic stages shown here represents the result of numerous such experiments.

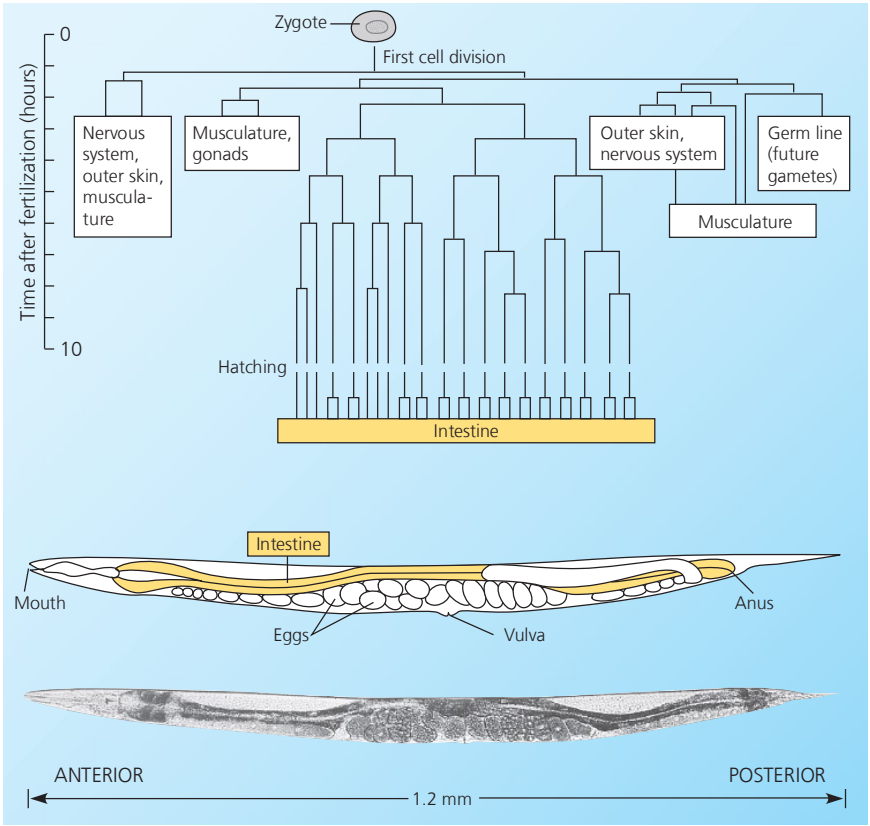
(b) Cell lineage analysis in a tunicate. In lineage analysis of this invertebrate chordate, an individual blastomere is injected with a dye during cleavage (top). The dark regions in the light micrographs of larvae (bottom) correspond to cells that developed from the two blastomeres indicated in the drawings.

Fate Mapping

One way to trace the ancestry of embryonic cells is direct observation through the microscope. Such studies produced the first **fate maps**, diagrams showing the structures arising from each region of an embryo. In the 1920s, German embryologist Walther Vogt used this approach to determine where groups of cells from the blastula end up in the gastrula **(Figure 47.18a)**. Later, researchers developed techniques that allowed them to mark an individual blastomere during cleavage and then follow the marker as it was distributed to all the mitotic descendants of that cell **(Figure 47.18b)**.

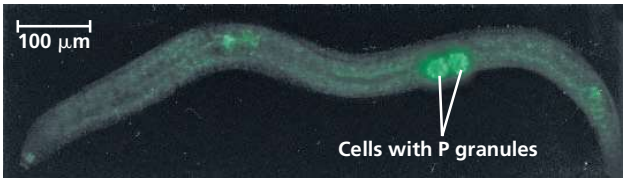
A much more comprehensive approach to fate mapping has been carried out on the soil-dwelling nematode *Caenorhabditis elegans*, as shown in **Figure 47.19**. This roundworm is about 1 mm long, has a simple, transparent body with only a few types of cells, and develops into a mature adult hermaphrodite worm in only 3.5 days in the laboratory. These attributes allowed Sydney Brenner, Robert Horvitz, and John Sulston to determine the complete developmental history, or *lineage*, of every cell in *C. elegans*. They found that every adult hermaphrodite worm has exactly 959 somatic cells, which arise

▼ Figure 47.19 Cell lineage in *Caenorhabditis elegans*. The *C. elegans* embryo is transparent, making it possible for researchers to trace the lineage of every cell, from the zygote to the adult worm (LM). The diagram shows a detailed lineage only for the intestine, which is derived exclusively from one of the first four cells formed from the zygote.



VISUAL SKILLS *The pattern of divisions is exactly the same in every* C. elegans *embryo. How many divisions of the fertilized egg give rise to the intestinal cell closest to the worm's mouth?*

▼ Figure 47.20 Determination of germ cell fate in *C. elegans*. Labeling with a fluorescent antibody that is specific for a *C. elegans* P granule protein (green) reveals the incorporation of P granules into four cells of the newly hatched larva (two of the four cells are visible in this view).



from the fertilized egg in virtually the same way for every individual. Careful microscopic observations of worms at all stages of development, coupled with experiments in which particular cells or groups of cells were destroyed by a laser beam or through mutations, resulted in the cell lineage diagram shown in Figure 47.19. Using this cell lineage diagram, you can identify all of the progeny of a single cell, just as you would use a family history to trace the descendants of, for example, one great-great-grandparent.

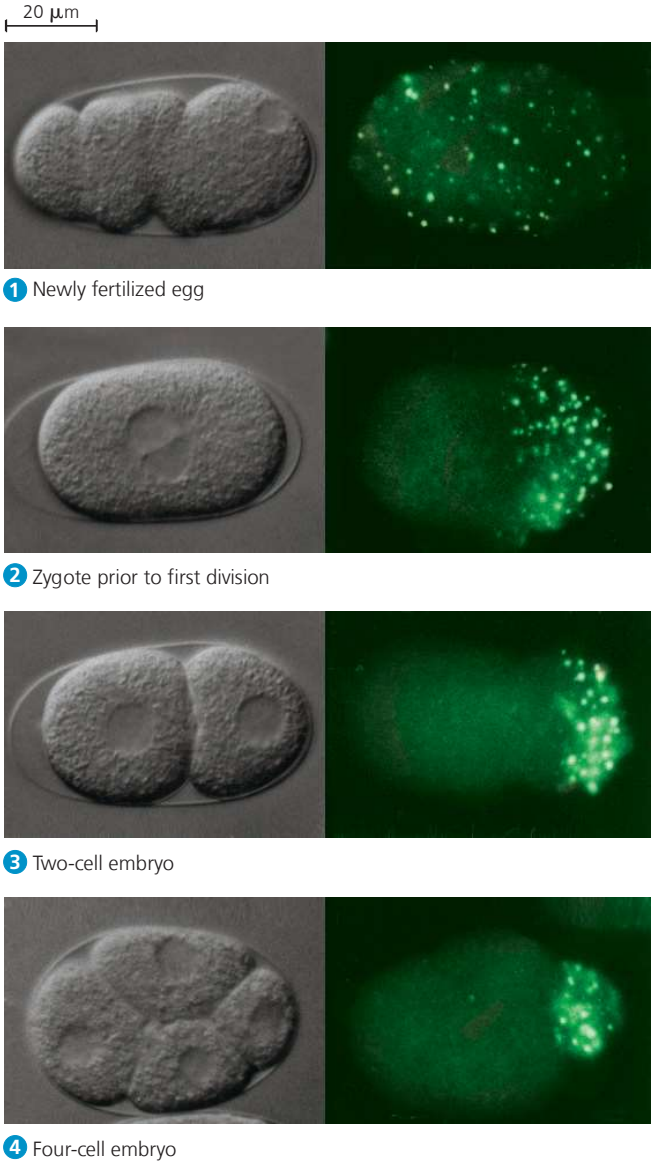
As an example of a particular cell fate, let's consider *germ cells*, the specialized cells that give rise to eggs or sperm. In all animals studied, complexes of RNA and protein direct particular cells to become germ cells. In *C. elegans*, such complexes, called *P granules*, can be detected in four cells of the newly hatched larva **(Figure 47.20)** and, later, in the cells of the adult gonad that produce sperm or eggs.

Tracing the position of the P granules provides a dramatic illustration of how cells acquire a specific fate, during development. As shown in **Figure 47.21**, the P granules are distributed throughout the newly fertilized egg but move to the posterior end of the zygote before the first cleavage division. As a result, only the posterior of the two cells formed by the first division contains P granules. The P granules continue to be asymmetrically partitioned during subsequent divisions. Thus, the P granules act as cytoplasmic determinants (see Concept 18.4), fixing germ cell fate at the earliest stage of *C. elegans* development.

Fate mapping in *C. elegans* paved the way for major discoveries about programmed cell death. Lineage analysis demonstrated that exactly 131 cells die during normal *C. elegans* development. In the 1980s, researchers found that a mutation inactivating a single gene allows all 131 cells to live. Further research revealed that this gene is part of a pathway that controls and carries out apoptosis in a wide range of animals, including humans. In 2002, Brenner, Horvitz, and Sulston shared a Nobel Prize for their use of the *C. elegans* fate map in studies of programmed cell death and organogenesis.

Having established fate maps for early development, scientists were positioned to answer questions about underlying

▼ Figure 47.21 Partitioning of P granules during *C. elegans* development. The differential interference contrast micrographs (left) highlight the boundaries of nuclei and cells through the first two cell divisions. The fluorescence micrographs (right) show identically staged embryos labeled with a fluorescent antibody specific for a P granule protein.



mechanisms, such as how the basic axes of the embryo are established, a process known as axis formation.

Axis Formation

A body plan with bilateral symmetry is found across a range of animals, including nematodes, echinoderms, and vertebrates (see Concept 32.4). This body plan exhibits asymmetry along the dorsal-ventral and anterior-posterior axes, as

shown for a frog tadpole in **Figure 47.22a**. The right-left axis is largely symmetrical, as the two sides are roughly mirror images. When and how are these three axes established? We'll begin answering this question by considering the frog.

Axis Formation in the Frog

In the frog, the future position of the anterior-posterior axis is determined during oogenesis. Asymmetry in the egg is apparent in the formation of two distinct hemispheres: Dark melanin granules are embedded in the cortex of the animal hemisphere, whereas a yellow yolk fills the vegetal hemisphere. This animal-vegetal asymmetry dictates where the anterior-posterior axis forms in the embryo. Note, however, that the anterior-posterior and animal-vegetal axes are not the same; that is, the head of the embryo does not coincide with the animal pole.

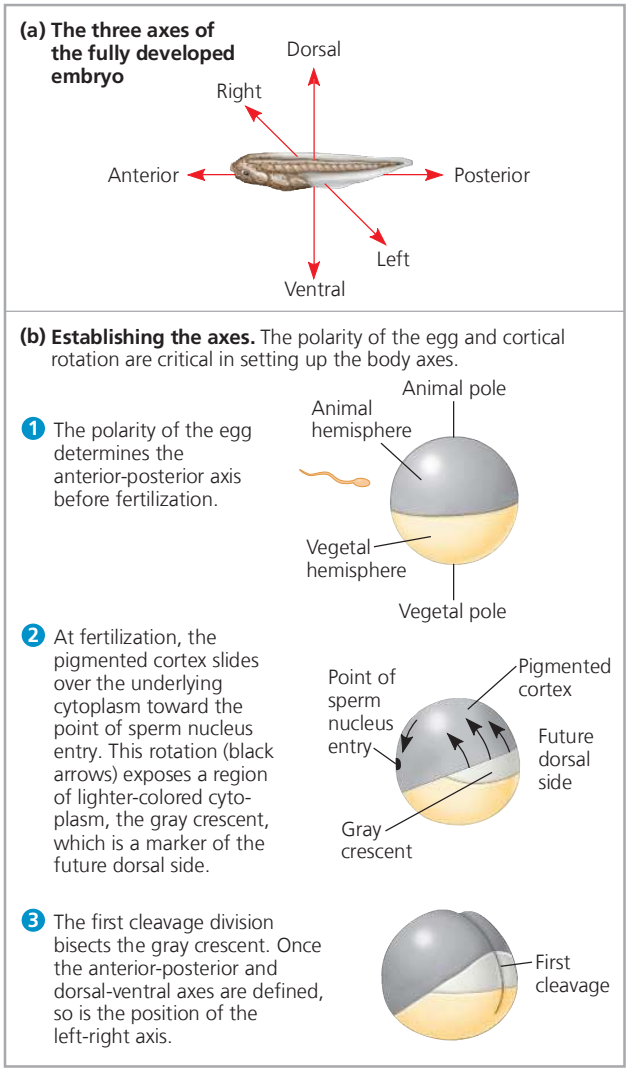
Surprisingly, the dorsal-ventral axis of the frog embryo is determined at random. Specifically, wherever the sperm enters in the animal hemisphere determines where the dorsal-ventral axis forms. Once the sperm and egg have fused, the egg surface—the plasma membrane and associated cortex—rotates with respect to the inner cytoplasm, a movement called *cortical rotation*. From the perspective of the animal pole, this rotation is always toward the point of sperm entry **(Figure 47.22b)**. The resulting interactions between molecules in the vegetal cortex and in the inner cytoplasm of the animal hemisphere activate regulatory proteins. Once activated, these proteins direct expression of one set of genes in dorsal regions and another set of genes in ventral regions.

Axis Formation in Birds, Mammals, and Insects

It turns out that there are many different processes by which animal embryos establish their body axes. In mammals, the sperm appears to contribute to axis formation, but not in the same manner as in frogs. In particular, the orientation of the egg and sperm nuclei before they fuse influences the location of the first cleavage plane. In chicks, the anterior-posterior axis is established by the pull of gravity during the time when the soon-to-be-laid egg is traveling down the hen's oviduct. In zebrafish, signals within the embryo gradually establish the anterior-posterior axis over the course of a day. Still other mechanisms occur in insects, where gradients of active transcription factors across the body establish both the anterior-posterior and dorsal-ventral axes (see Concept 18.4).

Once the anterior-posterior and dorsal-ventral axes are established, the position of the left-right axis is fixed. Nevertheless, specific molecular mechanisms must establish which side is left and which is right. In vertebrates, there are marked left-right differences in the location of internal organs as well as in the organization and structure of the heart and brain. Recent research has revealed a key role for cilia in setting up this left-right asymmetry, as we will discuss toward the end of this chapter.

▼ Figure 47.22 The body axes and their establishment in an amphibian. All three axes are established before the zygote begins to undergo cleavage.



WHAT IF? *When researchers allowed normal cortical rotation to occur and then forced the opposite rotation, the result was a two-headed embryo. How might you explain this finding, thinking about how cortical rotation influences body axis formation?*

Restricting Developmental Potential

Earlier we described determination in terms of commitment to a particular cell fate. The fertilized egg gives rise to all cell fates. How long during development do cells retain this ability? The German zoologist Hans Spemann addressed this question in 1938. By manipulating embryos to perturb normal development and then examining cell fate after the manipulation, he was able to assay a cell's *developmental potential*, the range of structures to which it can give rise

(Figure 47.23). The work of Spemann and others demonstrated that the first two blastomeres of the frog embryo are **totipotent**, meaning that they can each develop into all the different cell types of that species.

In mammals, embryonic cells remain totipotent through the eight-cell stage, much longer than in many other animals. Recent work, however, indicates that the very early cells (even the first two) are not actually equivalent in a normal embryo. Rather, their totipotency when isolated likely means that the cells can regulate their fate in response to their embryonic environment. Once the 16-cell stage is reached, mammalian cells are determined to form the trophoblast or the inner cell mass. Although the cells have a limited developmental potential from this point onward, their nuclei remain totipotent, as demonstrated in transplantation and cloning experiments (see Figures 20.17 and 20.18).

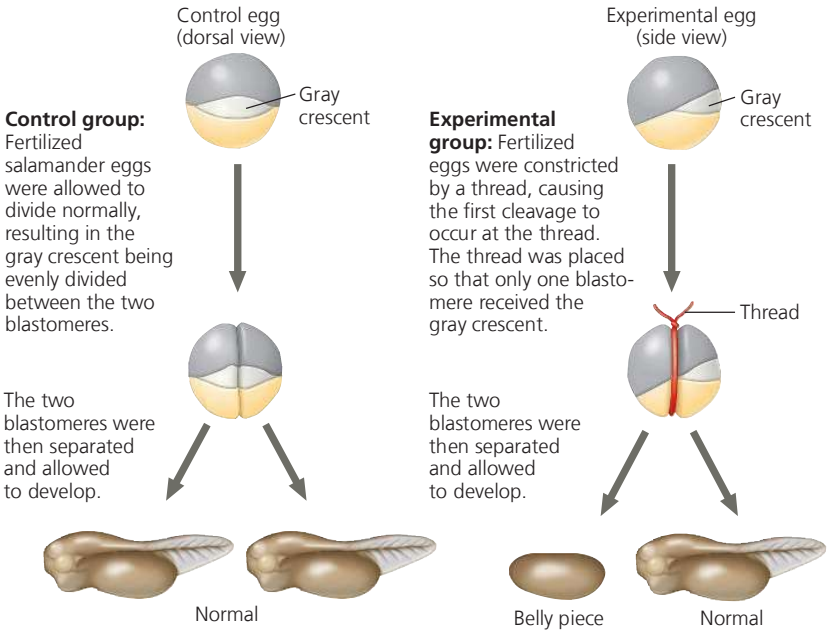
The totipotency of cells early in human embryogenesis is the reason why you or a classmate may have an identical twin. Identical (monozygotic) twins result when cells or groups of cells from a single embryo become separated. If the separation occurs before the trophoblast and inner cell mass become differentiated, two embryos grow, each with its own chorion and amnion. This is the case for about a third of identical twins. For the rest, the two embryos that develop share a chorion and, in very rare cases where separation is particularly late, an amnion as well.

Regardless of how uniform or varied early embryonic cells are in a particular species, the progressive restriction of developmental potential is a general feature of development in all animals. In general, the tissue-specific fates of cells are fixed in a late gastrula, but not always so in an early gastrula. For example, if the dorsal ectoderm of an early amphibian gastrula is experimentally replaced with ectoderm from some other location in the same gastrula, the transplanted tissue forms a neural plate. But if the same experiment is performed on a late-stage gastrula, the transplanted ectoderm does not respond to its new environment and does not form a neural plate.

▼ Figure 47.23 Inquiry

How does distribution of the gray crescent affect the developmental potential of the first two daughter cells?

Experiment Hans Spemann, at the University of Freiburg, Germany, carried out the following experiment in 1938 to test whether substances were located asymmetrically in the gray crescent.



Results Blastomeres that received half or all of the material in the gray crescent developed into normal embryos, but a blastomere that received none of the gray crescent gave rise to an abnormal embryo without dorsal structures. Spemann called it a "belly piece."

Conclusion The developmental potential of the two blastomeres normally formed during the first cleavage division depends on their acquisition of cytoplasmic determinants localized in the gray crescent.

Data from H. Spemann, *Embryonic Development and Induction*, Yale University Press, New Haven, CT (1938).

DRAW IT *Draw lines to show the plane of the first cell division that would occur in the fertilized eggs above if no manipulations were done.*

WHAT IF? *In a similar experiment 40 years earlier, embryologist Wilhelm Roux allowed the first cleavage to occur and then used a needle to kill just one blastomere. The embryo that developed from the remaining blastomere (plus remnants of the dead cell) was abnormal, resembling a half-embryo. How might the presence of molecules in the dead cell explain why Roux's result differed from the control result in Spemann's experiment?*

Cell Fate Determination and Pattern Formation by Inductive Signals

As embryonic development continues, cells influence each other's fates by induction. At the molecular level, the response to an inductive signal is usually to switch on a set of genes that make the receiving cells differentiate into a specific cell type or tissue. Here we will examine examples of this important developmental process in organizing the basic body plan of an embryo and in directing the three-dimensional development of a vertebrate limb.

The "Organizer" of Spemann and Mangold

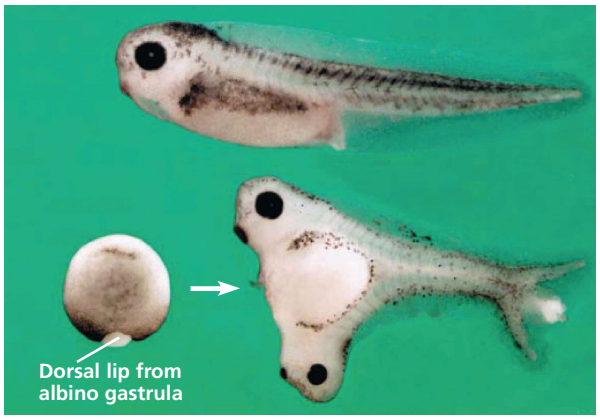
Before his studies of totipotency in the fertilized frog egg, Spemann had investigated cell fate determination during gastrulation. In these experiments, he and his student Hilde Mangold transplanted tissues between early gastrulas. In their most famous such experiment, summarized in **Figure 47.24**,

▼ Figure 47.24 Inquiry

Can the dorsal lip of the blastopore induce cells in another part of the amphibian embryo to change their developmental fate?

Experiment In 1924, Hans Spemann and Hilde Mangold, at the University of Freiburg, Germany, investigated the inductive ability of the dorsal lip of the gastrula. Using newts, they transplanted a piece of the dorsal lip from one gastrula to the ventral side of a second gastrula. Because the donor embryo was albino and thus lacked pigmentation, the researchers could visually follow how the transplanted material altered the fate of the recipient embryo.

Results The photograph in this figure documents a repeat of this classic experiment, using the frog *Xenopus laevis*. The tadpole at the top developed from a control gastrula. When an experimental gastrula received the transplant of a dorsal lip from an albino donor (lower left), the recipient embryo formed a second notochord and neural tube in the region of the transplant. Eventually most of a second embryo developed, producing a twinned tadpole (lower right).



Conclusion The transplanted dorsal lip was able to induce cells in a different region of the recipient to form structures different from their normal fate. In effect, the transplanted dorsal lip "organized" the later development of an entire extra embryo.

Data from H. Spemann and H. Mangold, Induction of embryonic primordia by implantation of organizers from a different species, Trans. V. Hamburger (1924). Reprinted in *International Journal of Developmental Biology* 45:13–38 (2001); and E. M. De Robertis and H. Kuroda, Dorsal-ventral patterning and neural induction in *Xenopus* embryos, *Annual Review of Cell and Developmental Biology* 20:285–308 (2004).

WHAT IF? *Because the transplant caused the recipient tissue to become something it would not have otherwise, a signal must have passed from the dorsal lip. If you identified a protein candidate for the signaling molecule, how would injecting it into ventral cells of a gastrula test its function?*

they made a remarkable discovery. Not only did a transplanted dorsal lip of the blastopore continue to be a blastopore lip, but it also triggered gastrulation of the surrounding tissue. They concluded that the dorsal lip of the blastopore in the early gastrula functions as an "organizer" of the embryo's body plan, inducing changes in surrounding tissue that direct formation of the notochord, the neural tube, and other organs.

Nearly a century later, developmental biologists are still studying the basis of induction by what is now called *Spemann's organizer*. An important clue has come from studies of a growth factor called bone morphogenetic protein 4 (BMP-4). One major function of the organizer seems to be to inactivate BMP-4 on the dorsal side of the embryo. Inactivating BMP-4 allows cells on the dorsal side to make dorsal structures, such as the notochord and neural tube. Proteins related to BMP-4 and its inhibitors are found as well in invertebrates such as the fruit fly, where they also function in regulating the dorsal-ventral axis.

Formation of the Vertebrate Limb

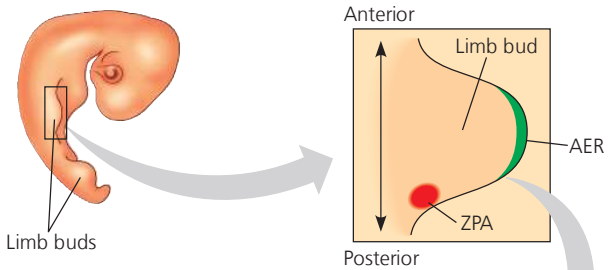
Inductive signals play a major role in **pattern formation**, the process governing the arrangement of organs and tissues in their characteristic places in three-dimensional space. The molecular cues that control pattern formation, called **positional information**, tell a cell where it is with respect to the animal's body axes and help to determine how the cell and its descendants will respond to molecular signaling during embryonic development.

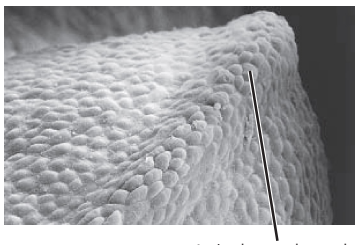
In Concept 18.4, we discussed pattern formation in the development of *Drosophila*. For the study of pattern formation in vertebrates, a classic model system has been limb development in the chick. The wings and legs of chicks, like all vertebrate limbs, begin as limb buds (see Figure 47.1). These bumps consist of mesodermal tissue covered by a layer of ectoderm (see Figure 47.1, inset). Each component of a chick limb, such as a specific bone or muscle, develops with a precise location and orientation relative to three axes: proximal-distal (shoulder to fingertip), anterior-posterior (thumb to little finger), and dorsal-ventral (knuckle to palm), as shown in **Figure 47.25**.

Two regions in a limb bud have profound effects on its development. One such region is the **apical ectodermal ridge (AER)**, a thickened area of ectoderm at the tip of the bud (see Figure 47.25a). Surgically removing the AER blocks outgrowth of the limb along the proximal-distal axis. Why? The AER secretes a protein signal called fibroblast growth factor (FGF) that promotes limb-bud outgrowth. If the AER is replaced with beads soaked with FGF, a nearly normal limb develops.

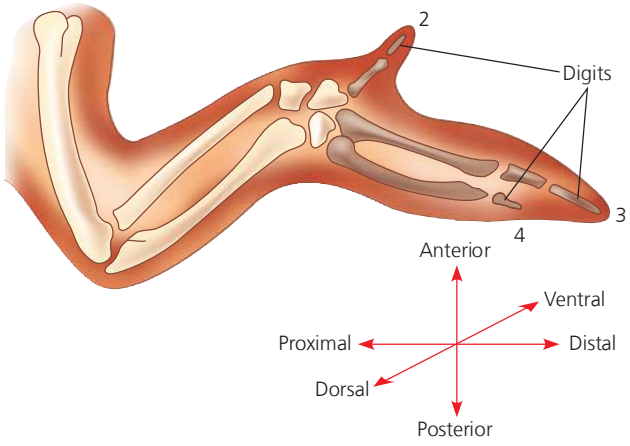
The second major limb-bud regulatory region is the **zone of polarizing activity (ZPA)**, a specialized block of mesodermal tissue (see Figure 47.25a). The ZPA regulates development along the anterior-posterior axis of the limb.

▼ Figure 47.25 Regulation of vertebrate limb development by organizer regions.





(a) Organizer regions. Vertebrate limbs develop from protrusions called limb buds. Two regions in each limb bud, the apical ectodermal ridge (AER, shown in this SEM) and the zone of polarizing activity (ZPA), play key roles as organizers in limb pattern formation.

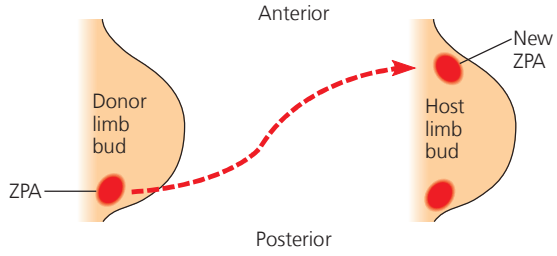


(b) Wing of chick embryo. Each embryonic cell receives positional information indicating location along the three axes of the limb. The AER and ZPA secrete molecules that help provide this information. (Numbers are assigned to the digits based on a convention established for vertebrate limbs. The chicken wing has only four digits; the first digit points backward and is not shown.)

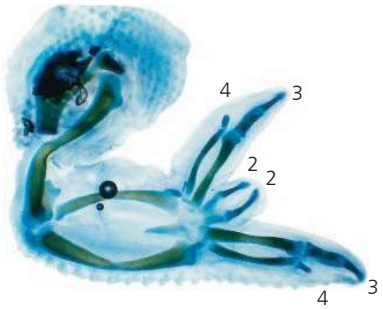
▼ Figure 47.26 Inquiry

What role does the zone of polarizing activity (ZPA) play in limb pattern formation in vertebrates?

Experiment In 1985, researchers were eager to investigate the nature of the zone of polarizing activity. They transplanted ZPA tissue from a donor chick embryo under the ectoderm in the anterior margin of a limb bud in another chick (the host).



Results The host limb bud developed extra digits from host tissue in a mirror-image arrangement to the normal digits, which also formed (compare with Figure 47.25b, which shows a normal chick wing).



Conclusion The mirror-image duplication observed in this experiment suggests that ZPA cells secrete a signal that diffuses from its source and conveys positional information indicating "posterior." As the distance from the ZPA increases, the signal concentration decreases, and hence more anterior digits develop.

Data from L. S. Honig and D. Summerbell, Maps of strength of positional signaling activity in the developing chick wing bud, *Journal of Embryology and Experimental Morphology* 87:163–174 (1985).

WHAT IF? *Suppose you learned that the ZPA forms after the AER, leading you to develop the hypothesis that the AER is necessary for formation of the ZPA. If you removed the AER and looked for expression of Sonic hedgehog, how would that test your hypothesis?*

Cells nearest the ZPA form posterior structures, such as the most posterior of the chick's digits (equivalent to our little finger); cells farthest from the ZPA form anterior structures, including the most anterior digit (like our thumb).

Like the AER, the ZPA influences development by secreting a protein signal. The signal secreted by the ZPA is called Sonic hedgehog, named after both a video game character and a similar protein in *Drosophila* that also regulates development. Implanting cells genetically engineered to produce Sonic hedgehog into the anterior region of a normal limb bud causes formation of a mirror-image limb—just as if a ZPA had been grafted there **(Figure 47.26)**. Furthermore, experiments with mice reveal that production of Sonic hedgehog in part of the limb bud where it is normally absent can result in extra toes.

The AER and ZPA regulate the axes of a limb bud, but what determines whether the bud develops into a forelimb or hind

limb? That information is provided by spatial patterns of *Hox* genes, which specify different developmental fates in particular body regions (see Figure 21.20).

BMP-4, FGF, Sonic hedgehog, and Hox proteins are examples of a much larger set of molecules that govern cell fates in animals. Having mapped out many of the basic functions of these molecules in embryonic development, researchers are now addressing their role in organogenesis, focusing in particular on the development of the brain.

Cilia and Cell Fate

Researchers have found that the cellular organelles known as cilia are essential for specifying cell fate in human embryos. Like other mammals, humans have stationary and motile cilia (see Figure 6.24). Stationary primary cilia, or *monocilia*, jut from the surface of nearly all cells, one per cell. In contrast, motile cilia are restricted to cells that propel fluid over their surface, such as the epithelial cells of airways, and sperm (as flagella that propel sperm movement). Both stationary and motile cilia have crucial roles in development.

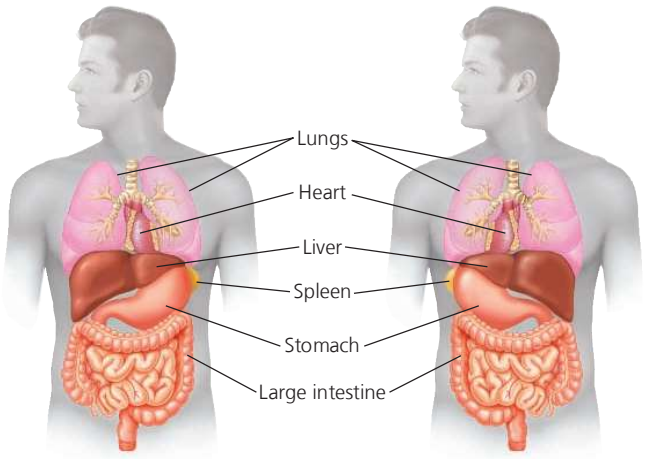
Genetic studies provided vital clues to the developmental role of monocilia. In 2003, researchers discovered that certain mutations disrupting development of the mouse nervous system affect genes that function in the assembly of monocilia. Other geneticists found that mutations responsible for a severe kidney disease in mice alter a gene important for the transport of materials up and down monocilia. In addition, mutations in humans that block the function of monocilia were linked to cystic kidney disease.

How do monocilia function in development? Evidence indicates that monocilia act as antennae on the cell surface, receiving signals from multiple signaling proteins, including Sonic hedgehog. Mechanisms that regulate which types of receptor proteins are present tune the cilium to particular signals. When the monocilia are defective, signaling is disrupted.

Insight into the role of motile cilia in development grew from studies of Kartagener's syndrome, a set of medical conditions that often appear together. These conditions include male infertility due to immotile sperm and infections of the nasal sinuses and bronchi in both males and females. A distinctive feature of Kartagener's syndrome is *situs inversus*, a reversal of the normal left-right asymmetry of the organs in the chest and abdomen **(Figure 47.27)**. The heart, for example, is on the right side rather than the left. (By itself, situs inversus causes no significant medical problems.)

Scientists studying Kartagener's syndrome came to realize that all of the associated conditions result from a defect that makes cilia immotile. Without motility, sperm tails cannot beat and airway cells cannot sweep mucus and microbes out of the airway. But what causes situs inversus in these individuals? The current model proposes that ciliary motion in a particular part of the embryo is essential for normal development. Evidence indicates that movement of the cilia generates a leftward fluid flow, breaking the symmetry between left and right sides. Without that flow, asymmetry along the left-right axis arises randomly, and half of the affected embryos develop situs inversus.

▼ Figure 47.27 Situs inversus, a reversal of normal left-right asymmetry in the chest and abdomen.



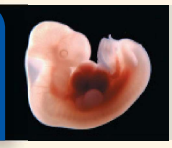
If we consider development as a whole, we see a sequence of events marked by cycles of signaling and differentiation. Initial cell asymmetries allow different types of cells to influence each other, resulting in the expression of specific sets of genes. The products of these genes then direct cells to differentiate into specific types. Through pattern formation and morphogenesis, differentiated cells ultimately produce a complex arrangement of tissues and organs, each functioning in its appropriate location and in coordination with other cells, tissues, and organs throughout the organism.

CONCEPT CHECK 47.3

1. How do axis formation and pattern formation differ?
2. **MAKE CONNECTIONS** How does a morphogen gradient differ from cytoplasmic determinants and inductive interactions with regard to the set of cells it affects (see Concept 18.4)?
3. **WHAT IF?** If the ventral cells of an early frog gastrula were experimentally induced to express large amounts of a protein that inhibits BMP-4, could a second embryo develop? Explain.
4. **WHAT IF?** If you removed the ZPA from a limb bud and then placed a bead soaked in Sonic hedgehog in the middle of the bud, what would be the most likely result?

For suggested answers, see Appendix A.

47 Chapter Review



Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

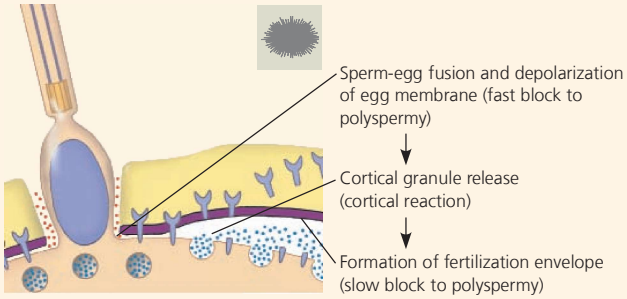
SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 47.1

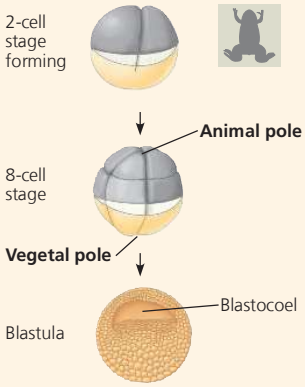
Fertilization and cleavage initiate embryonic development *(pp. 1044–1049)*

- **Fertilization** forms a diploid zygote and initiates embryonic development. The **acrosomal reaction** releases hydrolytic enzymes from the sperm head that digest material surrounding the egg.



In mammalian fertilization, the cortical reaction modifies the **zona pellucida** as a slow block to polyspermy.

- Fertilization is followed by **cleavage**, a period of rapid cell division without growth, producing a large number of cells called **blastomeres**. The amount and distribution of **yolk** strongly influence the pattern of cleavage. In many species, the completion of the cleavage stage generates a **blastula** containing a fluid-filled cavity, the **blastocoel**.

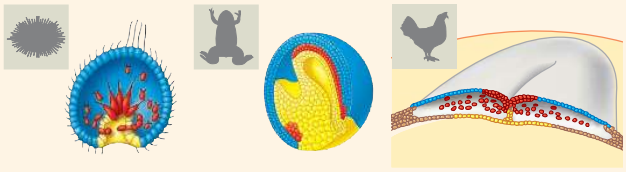


What cell-surface event would likely fail if a sperm contacted an egg of another species?

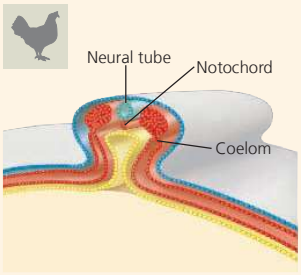
CONCEPT 47.2

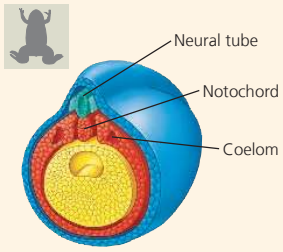
Morphogenesis in animals involves specific changes in cell shape, position, and survival *(pp. 1049–1057)*

- **Gastrulation** converts the blastula to a **gastrula**, which has a primitive digestive cavity and three **germ layers: ectoderm** (blue), which forms the outer layer of the embryo, **mesoderm** (red), which forms the middle layer, and **endoderm** (yellow), which gives rise to the innermost tissues.



- Gastrulation and organogenesis in mammals resemble the processes in reptiles, including birds. After fertilization and early cleavage in the oviduct, the **blastocyst** implants in the uterus. The **trophoblast** initiates formation of the fetal portion of the placenta, and the embryo proper develops from a cell layer, the epiblast, within the blastocyst.
- The embryos of birds, other reptiles, and mammals develop within a fluid-filled sac that is contained within a shell or the uterus. In these organisms, the three germ layers produce four **extraembryonic membranes**: the amnion, chorion, yolk sac, and allantois.
- The organs of the animal body develop from specific portions of the three embryonic germ layers. Early events in **organogenesis** in vertebrates include neurulation: formation of the **notochord** by cells of the dorsal mesoderm and development of the **neural tube** from infolding of the ectodermal neural plate.





- Cytoskeletal rearrangements cause changes in the shape of cells that underlie cell movements in gastrulation and organogenesis, including invaginations and **convergent extension**. The cytoskeleton is also involved in cell migration, which relies on cell adhesion molecules and the extracellular matrix to help cells reach specific destinations. Migratory cells arise both from the neural crest and from **somites**.
- Some processes in animal development require **apoptosis**, programmed cell death.

What are some functions of apoptosis in development?

CONCEPT 47.3

Cytoplasmic determinants and inductive signals regulate cell fate *(pp. 1057–1064)*

- Experimentally derived **fate maps** of embryos show that specific regions of the zygote or blastula develop into specific parts of older embryos. The complete cell lineage has been worked out for *C. elegans*, revealing that programmed cell death contributes to animal development. In all species, the developmental potential of cells becomes progressively more limited as embryonic development proceeds.
- Cells in a developing embryo receive and respond to **positional information** that varies with location. This information is often in the form of signaling molecules secreted by cells in specific regions of the embryo, such as the dorsal lip of the blastopore in the amphibian gastrula and the **apical ectodermal ridge** and **zone of polarizing activity** of the vertebrate limb bud.

Suppose you found two classes of mouse mutations, one that affected limb development only and one that affected both limb and kidney development. Which class would be more likely to alter the function of monocilia? Explain.

TEST YOUR UNDERSTANDING

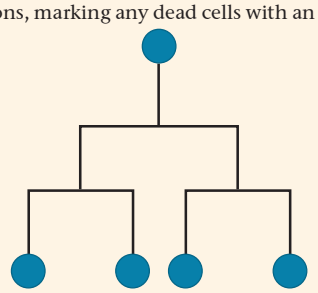
For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. 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 generation of an electrical impulse by the egg.
   (D) the fusion of egg and sperm nuclei.
2. Which of the following is common to the development of both birds and mammals?
   (A) holoblastic cleavage
   (B) epiblast and hypoblast
   (C) trophoblast
   (D) gray crescent
3. The archenteron develops into
   (A) the mesoderm.
   (B) the endoderm.
   (C) the placenta.
   (D) the lumen of the digestive tract.
4. What structural adaptation in chickens allows them to lay their eggs in arid environments rather than in water?
   (A) extraembryonic membranes
   (B) yolk
   (C) cleavage
   (D) gastrulation

Levels 3-4: Applying/Analyzing

5. If an egg cell were treated with EDTA, a chemical that binds calcium and magnesium ions,
   (A) the acrosomal reaction would be blocked.
   (B) the fusion of sperm and egg nuclei would be blocked.
   (C) the fast block to polyspermy would not occur.
   (D) the fertilization envelope would not form.
6. In humans, identical twins are possible because
   (A) extraembryonic cells interact with the zygote nucleus.
   (B) convergent extension occurs.
   (C) early blastomeres can form a complete embryo if isolated.
   (D) the gray crescent divides the dorsal-ventral axis into new cells.
7. Cells transplanted from the neural tube of a frog embryo to the ventral part of another embryo develop into nervous system tissues. This result indicates that the transplanted cells were
   (A) totipotent. (C) differentiated.
   (B) determined. (D) mesenchymal.
8. **DRAW IT** Each blue circle in the figure below represents a cell in a cell lineage. Draw two modified versions of the cell lineage so that each version produces three cells. Use apoptosis in one of the versions, marking any dead cells with an X.



Levels 5-6: Evaluating/Creating

9. **EVOLUTION CONNECTION** Evolution in insects and vertebrates has involved the repeated duplication of body segments, followed by fusion of some segments and specialization of their structure and function. In vertebrates, what anatomical features reflect segmentation?
10. **SCIENTIFIC INQUIRY** The "snout" region of a salamander has a mustache-shaped structure called a balancer, whereas that of a frog tadpole does not. When you transplant tissue from the side of a young salamander embryo to the snout of a frog embryo, the tadpole that develops has a balancer. If you use a slightly older salamander embryo as the donor, no balancer forms. Propose a hypothesis to explain these results and explain how you might test your hypothesis.
11. **SCIENCE, TECHNOLOGY, AND SOCIETY** Scientists can now make identical copies, or clones, of animals ranging from dairy cows to pet cats. Propose a few arguments for and against this application of discoveries about embryonic development.
12. **WRITE ABOUT A THEME: ORGANIZATION** In a short essay (100–150 words), describe how the emergent properties of the cells of the gastrula direct embryonic development.
13. **SYNTHESIZE YOUR KNOWLEDGE**

Occasionally, two-headed animals such as this turtle are born. Thinking about the occurrence of identical twins and the property of totipotency, explain how this might happen.

For selected answers, see Appendix A.

Explore Scientific Papers with Science in the Classroom AAAS
What is the molecular basis for limb regrowth in vertebrates?
Go to "Limb Regeneration: Fact or (Science) Fiction?"
at www.scienceintheclassroom.org.
Instructors: Questions can be assigned in Mastering Biology.

48 Neurons, Synapses, and Signaling

KEY CONCEPTS

Study Tip

Make a table: The term *potential* is central to understanding neuronal signaling, as it provides the driving force for both electrical and chemical signaling. Fill in a table like this one as you read to help you distinguish characteristics of a *resting potential, graded potential*, and *action potential*, as well as chemical potentials for sodium and potassium ion concentrations.

Membrane potentials of a neuron		Occurs in cell body?	Occurs in axon?	Variable strength?
Electrical	Resting	Yes	Yes	No
Electrical	Graded			
Electrical	Action			
Chemical	$[Na^+]$			
Chemical	$[K^+]$			

Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 48
- BioFlix® Animation: How Neurons Work
- BioFlix® Animation: How Synapses Work

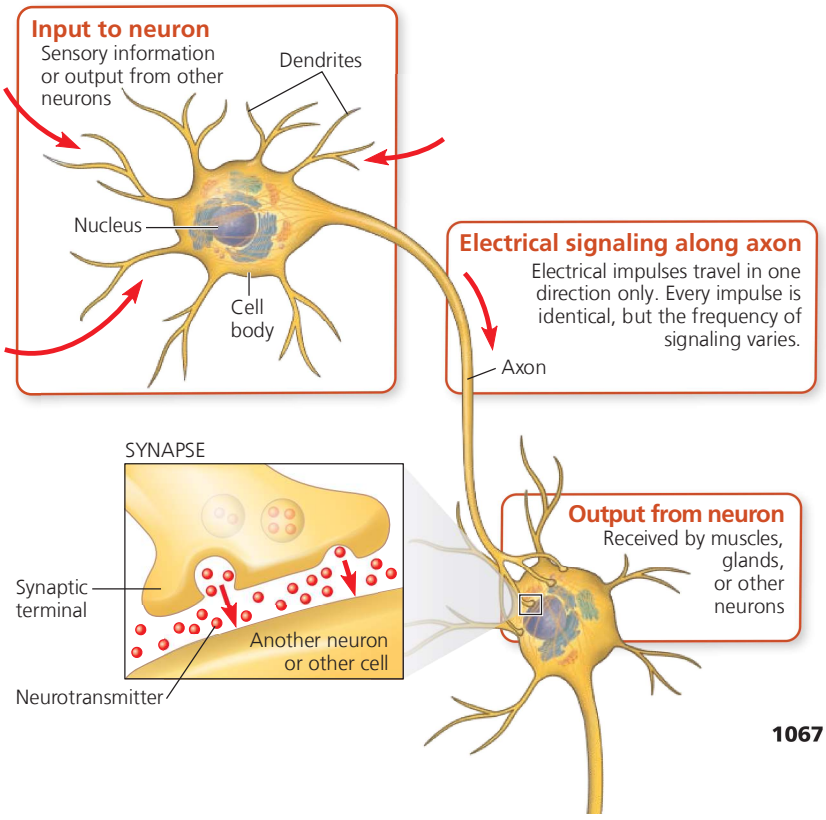
For Instructors to Assign (in Item Library)
- Scientific Skills Exercise: Interpreting Data Values Expressed in Scientific Notation

Ready-to-Go Teaching Module (in Instructor Resources)
- Resting and Action Potentials

Figure 48.1 This cone snail (*Conus geographus*) is slow-moving, but a dangerous hunter. Delivering venom with a hollow, harpoon-like tooth, it can paralyze a fish almost instantaneously. Scuba divers picking up a cone snail have died from a single injection. Underlying the fast-acting, lethal nature of the venom is an ability to block information transfer by neurons, specialized cells of the nervous system.

How does a neuron transmit information?

A neuron receives information, transmits it along an extension called an **axon**, and transmits the information to other cells via specialized junctions called **synapses**.



CONCEPT 48.1

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.

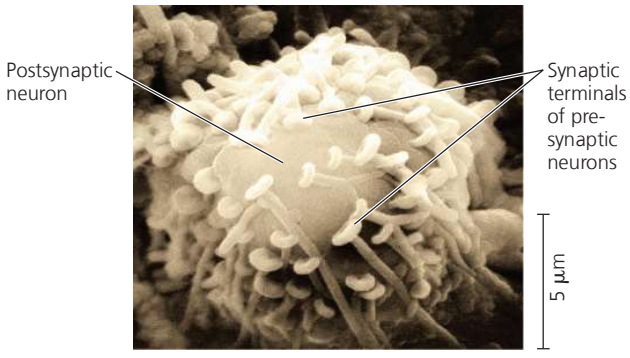
Neuron Structure and Function

The ability of a neuron to receive and transmit information is based on the highly specialized cellular organization shown in Figure 48.1. Most of a neuron's organelles, including its nucleus, are located in the **cell body**. In a typical neuron, the cell body is studded with numerous highly branched extensions called **dendrites** (from the Greek *dendron*, tree). Together with the cell body, the dendrites *receive* signals from other neurons.

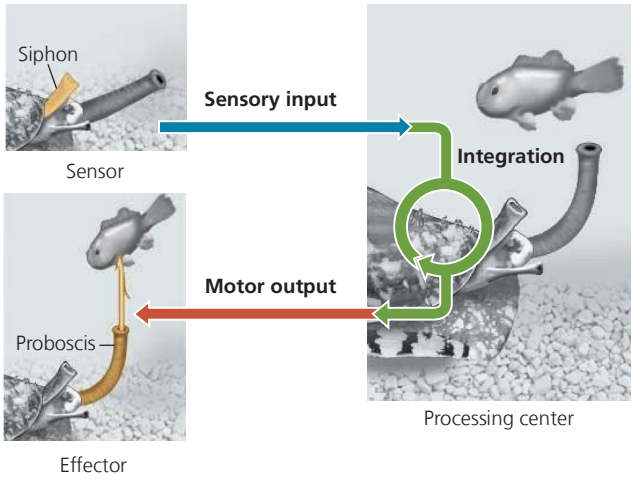
A typical neuron has a single **axon**, the extension that *transmits* signals to other cells. Axons are often much longer than dendrites, and some, such as those that reach from the spinal cord of a giraffe to the muscle cells in its feet, are over a meter long. The specialized structure of axons allows them to use pulses of electrical current to transmit information, even over long distances. 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.

Each branched end of an axon transmits information to another cell at a junction called a **synapse** (Figure 48.2). 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. Cone snail venom is particularly potent because it interferes not only with electrical signaling along axons but also with chemical signaling across synapses.

▼ Figure 48.2 Synaptic terminals on the cell body of a postsynaptic neuron. (colorized SEM)



▼ Figure 48.3 Summary of information processing. The cone snail's siphon acts as a sensor, transferring information to the neuronal circuits in the snail's head for processing. If prey is detected, these circuits issue motor commands—signals that control muscle activity. In this example, motor commands trigger release of a harpoon-like tooth from the proboscis, spearing the prey.



Mastering Biology
Interview with Baldomero Olivera: Developing drugs from research on cone snail venom

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 the cone snail, focusing on the steps involved in identifying and attacking its prey. To generate sensory input to the nervous system, the snail surveys its environment with sensors in its tubelike siphon, sampling scents that might reveal a nearby fish (Figure 48.3). During the integration stage, networks of neurons in the snail brain process this information to determine if a fish is in fact present and, if so, where the fish is located. Motor output from the processing center 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.

- **Sensory neurons**, like those in the snail's siphon, transmit information about external stimuli (such as light, touch, or smell), and internal conditions (such as blood pressure or muscle tension).
- **Interneurons** form the local circuits connecting neurons in the brain or ganglia. Interneurons are responsible for the integration (analysis and interpretation) of sensory input.
- **Motor neurons** transmit signals to muscle cells, causing them to contract. Additional neurons that extend out of the processing centers trigger gland activity.

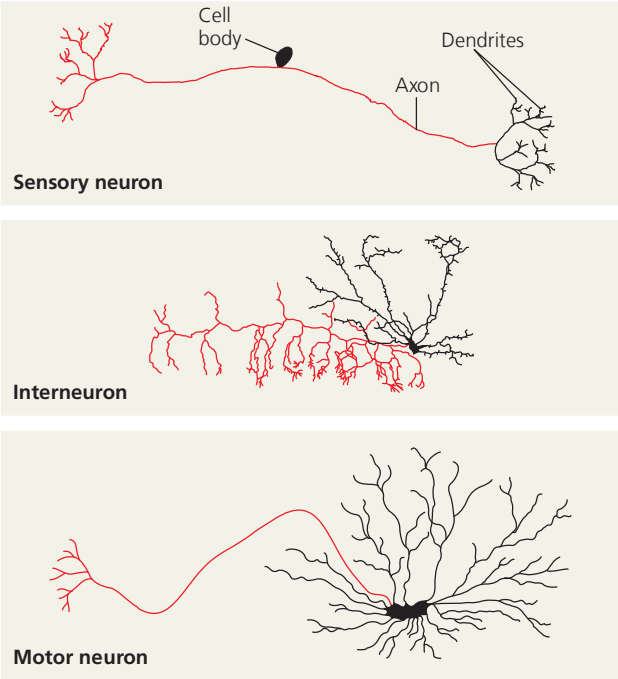
All neurons transmit electrical signals within the cell in an identical manner. Thus a neuron that detects an odor transmits

information along its length in the same way as a neuron that controls the movement of a body part. The particular connections made by the active neuron are what distinguish the type of information being transmitted. Interpreting nerve impulses therefore involves sorting neuronal paths and connections.

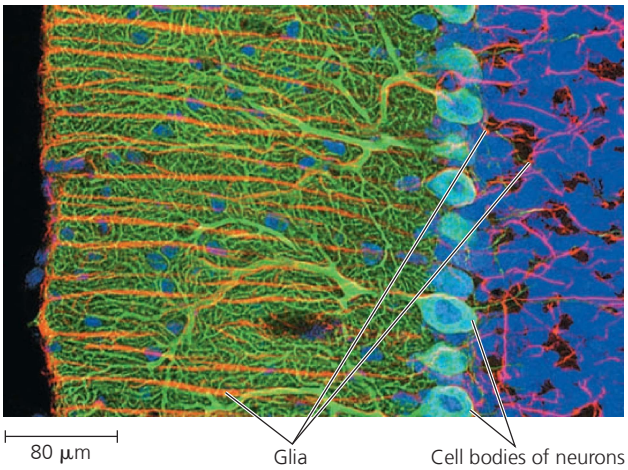
As shown in **Figure 48.4**, the shape of a neuron can vary from simple to quite complex, depending on its role in information processing. Neurons that have highly branched dendrites, such as some interneurons, can receive input through tens of thousands of synapses. Similarly, neurons that transmit information to many target cells do so through highly branched axons. When grouped together, the axons of neurons form the bundles we call **nerves**.

In many animals, the neurons that carry out sorting, processing, and integration are organized in a **central nervous system (CNS)**, which may include a **brain** or simpler clusters called **ganglia**. The neurons that carry information into and out of the CNS constitute the **peripheral nervous system (PNS)**. Neurons of both the CNS and PNS require supporting cells called glial cells, or **glia** (from a Greek word meaning "glue") **(Figure 48.5)**.

▼ Figure 48.4 Structural diversity of neurons. In these drawings of neurons, cell bodies and dendrites are black and axons are red.



▼ Figure 48.5 Glia in the mammalian brain. This fluorescently labeled laser confocal micrograph shows a region of the rat brain packed with glia and interneurons. The glia are labeled red, the DNA in nuclei is labeled blue, and the dendrites of neurons are labeled green.



CONCEPT CHECK 48.1

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 48.2

Ion pumps and ion channels establish the resting potential of a neuron

We turn now to the essential role of ions in neuronal signaling. In neurons, as in other cells, ions are unequally distributed between the interior of cells and the surrounding fluid (see Concept 7.4). As a result, the inside of a cell is negatively charged relative to the outside. This charge difference, or *voltage*, across the plasma membrane is called the **membrane potential**, reflecting the fact that the attraction of opposite charges across the plasma membrane is a source of potential energy. 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 millivolts (mV).

When a neuron receives a stimulus, the membrane potential changes. Rapid shifts in membrane potential are what enable us to see the intricate structure of a spiderweb, hear a song, or ride a bicycle. These changes, which are known as *action potentials*, will be discussed in Concept 48.3. To understand how they convey information, we need to explore the ways in which membrane potentials are formed, maintained, and altered.

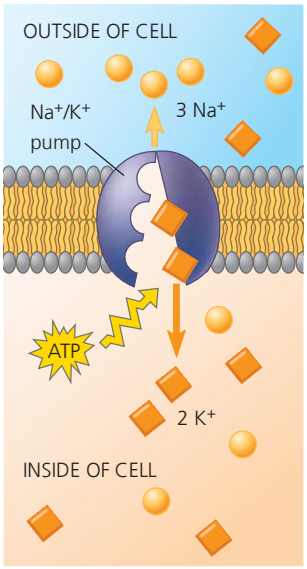
Formation of the Resting Potential

Potassium ions (K^+) and sodium ions (Na^+) play an essential role in the formation of the resting potential. These ions each have a concentration gradient across the plasma membrane of a neuron **(Table 48.1)**. In most neurons, the concentration of K^+ is higher inside the cell, while the concentration of Na^+ is higher outside. The Na^+ and K^+ concentration gradients are maintained by the **sodium-potassium pump**. This pump uses the energy of ATP hydrolysis to actively transport Na^+ out of the cell and K^+ into the cell. (There are also concentration gradients for chloride ions (Cl^-) and other anions, as shown in Table 48.1, but we can ignore these for now.)

Table 48.1 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^-), such as proteins, inside cell	100	Not applicable

The sodium-potassium pump transports three Na^+ out of the cell for every two K^+ that it transports in **(Figure 48.6)**. Although this pumping generates a net export of positive charge, the pump acts slowly. The resulting change in the membrane potential is therefore quite small—only a few millivolts. Why, then, is there a membrane potential 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. Furthermore, ions can move quite rapidly through ion channels. When this occurs, the resulting current—a *net* movement of positive or negative charge—generates a membrane potential, or voltage across the membrane.

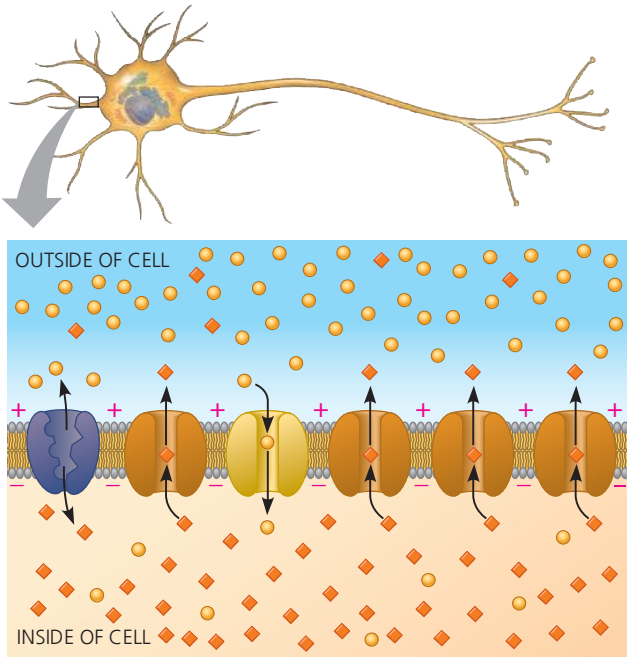


◀ Figure 48.6 Summary of active transport by the sodium-potassium pump. You can find a step-by-step description of the pump's activity in Figure 7.15.

Concentration gradients of ions across a plasma membrane represent a chemical form of potential energy that can be harnessed for cellular processes (see Figure 44.17). In neurons, the ion channels that convert this chemical potential energy to electrical potential energy can do so because they have *selective permeability*, allowing 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^+ or Cl^-.

Diffusion of K^+ through potassium channels that are always open (sometimes called *leak channels*) is critical for establishing the resting potential **(Figure 48.7)**. The K^+

▼ Figure 48.7 The basis of the membrane potential. The sodium-potassium pump generates and maintains the concentration gradients of Na^+ and K^+ shown in Table 48.1. The $[Na^+]$ gradient results in very little net diffusion of Na^+ in a resting neuron because very few sodium channels are open. In contrast, the many 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 potassium and sodium channels have the same rough overall structure, as shown. How must these proteins differ to allow passage of only a particular ion?*

Mastering Biology BioFlix® Animation: Resting Potential

concentration is 140 millimolar (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. 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. We can model this process by considering a pair of chambers separated by an artificial membrane. To begin, imagine that the membrane contains many open ion channels, all of which allow only K^+ to diffuse across **(Figure 48.8a)**. 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.

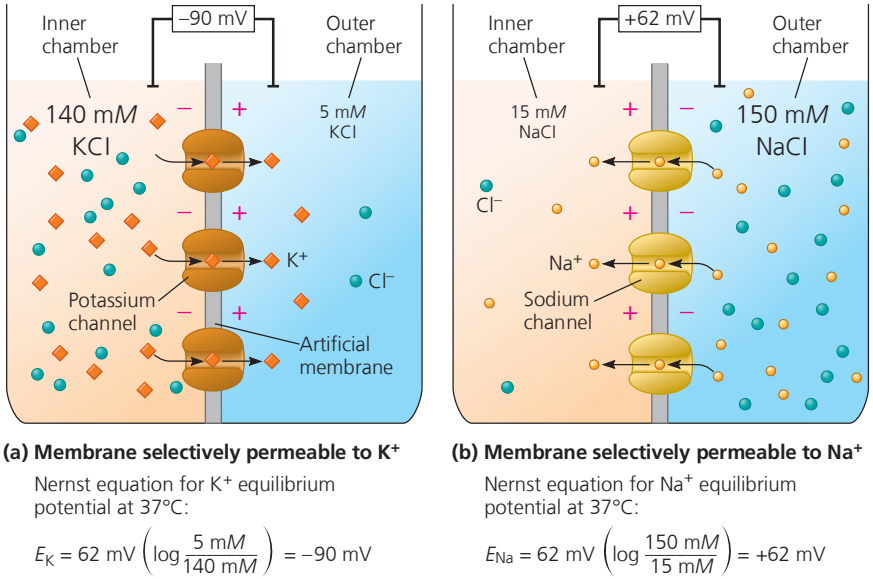
The magnitude of the membrane voltage at equilibrium for a particular ion is called that ion's **equilibrium potential (E_{ion})**. For a membrane permeable to a single type of ion, E_{ion} can be calculated using a formula called the *Nernst equation*. At human body temperature (37°C) and for an ion 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 the K^+ concentrations into the Nernst equation reveals that the equilibrium potential for K^+ (E_K) is −90 mV (see Figure 48.8a). 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 48.1). 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 48.8b)**. 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.

Because neither K^+ nor Na^+ is at equilibrium in a resting neuron, there is a net flow of each ion across the membrane. The resting potential remains steady, which means that these K^+ and Na^+ currents are equal and opposite. Ion



(a) Membrane selectively permeable to K^+

Nernst equation for K^+ equilibrium potential at 37°C:

$$E_K = 62\text{ mV}\left(\log\frac{5\text{ mM}}{140\text{ mM}}\right) = -90\text{ mV}$$

(b) Membrane selectively permeable to Na^+

Nernst equation for Na^+ equilibrium potential at 37°C:

$$E_{Na} = 62\text{ mV}\left(\log\frac{150\text{ mM}}{15\text{ mM}}\right) = +62\text{ mV}$$

▶ Figure 48.8 Modeling a mammalian neuron. In this model of the membrane potential of a resting neuron, an artificial membrane divides each container into two chambers. 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? *How would adding potassium or chloride channels to the membrane in (b) affect the membrane potential?*

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.

If Na^+ is allowed to cross the membrane more readily, the membrane potential will move toward E_{Na} and away from E_K. As you'll see, this happens in generation of a nerve impulse.

Mastering Biology **Animation: Membrane Potentials**

CONCEPT CHECK 48.2

1. Under what circumstances could ions flow through an ion channel from a region of lower ion 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** Review Figure 7.11, which illustrates the diffusion of dye molecules across a membrane. Could diffusion eliminate the concentration gradient of a dye that has a net charge? Explain.

For suggested answers, see Appendix A.

CONCEPT 48.3

Action potentials are the signals conducted by axons

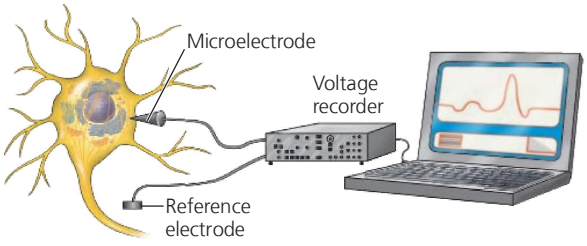
When a neuron responds to a stimulus, the membrane potential changes. Using intracellular recording, researchers can monitor these changes as a function of time **(Figure 48.9)**. As you will see, such recordings have been central to the study of information transfer by neurons.

▼ Figure 48.9 Research Method

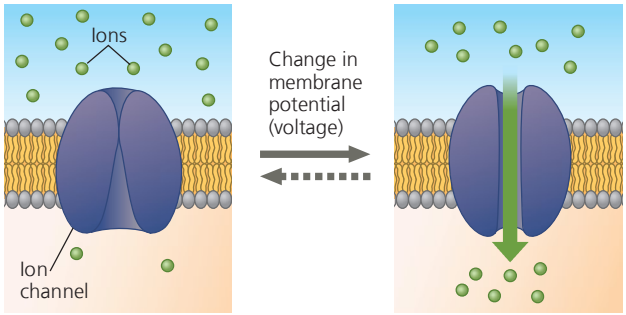
Intracellular Recording

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.



▼ Figure 48.10 Voltage-gated ion channel. A change in the membrane potential in one direction (solid arrow) opens the voltage-gated channel. The opposite change (dotted arrow) closes the channel.



Gate closed: No ions flow across membrane.

Gate open: Ions flow through channel.

VISUAL SKILLS *Gated ion channels allow ion flow in either direction. Using visual information in this figure, explain why there is net ion movement when the channel opens.*

How does a stimulus alter the membrane potential? Certain ion channels in a neuron, called **gated ion channels**, open or close in response to stimuli. When a gated ion channel opens or closes, it alters the membrane's permeability to particular ions **(Figure 48.10)**. The result is a rapid flow of ions across the membrane, altering the membrane potential.

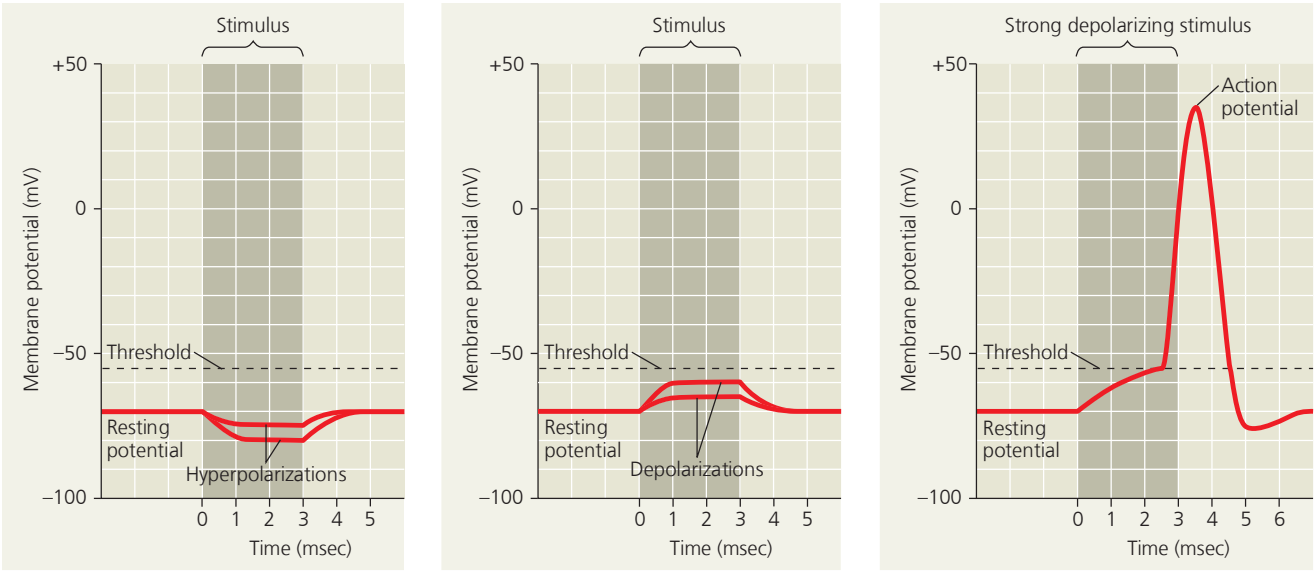
Particular types of gated channels respond to different stimuli. For example, Figure 48.10 illustrates a **voltage-gated ion channel**, a channel that opens or closes in response to a shift in the voltage across the plasma membrane of the neuron. Later in this chapter, we will discuss gated channels that are located in neurons and are regulated by chemical signals.

Hyperpolarization and Depolarization

Let's consider now what happens in a neuron when a stimulus causes closed voltage-gated ion channels to open. If gated potassium channels in a resting neuron open, the membrane's permeability to K^+ increases. As a result, 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 48.11a)**. 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 48.11b)**. A reduction in the

▼ Figure 48.11 Graded potentials and an action potential in a neuron.



(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.

DRAW IT *Redraw the graph in (c), extending the y-axis. Then label the positions of* E_K *and* E_{Na}.

magnitude of the membrane potential is a **depolarization**. In neurons, depolarization often involves gated sodium channels. If a stimulus causes gated sodium channels 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 the strength of the stimulus: A larger stimulus causes a greater change in the membrane potential (see Figure 48.11a and 48.11b). Graded potentials induce a small electrical current that dissipates as it flows along the membrane. Graded potentials thus decay with time and 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 (see Figure 48.10). If a depolarization increases the membrane potential to a level called **threshold**, the voltage-gated sodium channels open. 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 48.11c)**.

The positive-feedback loop of channel opening and depolarization triggers an action potential whenever the membrane potential reaches threshold, about −55 mV for many mammals. 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.

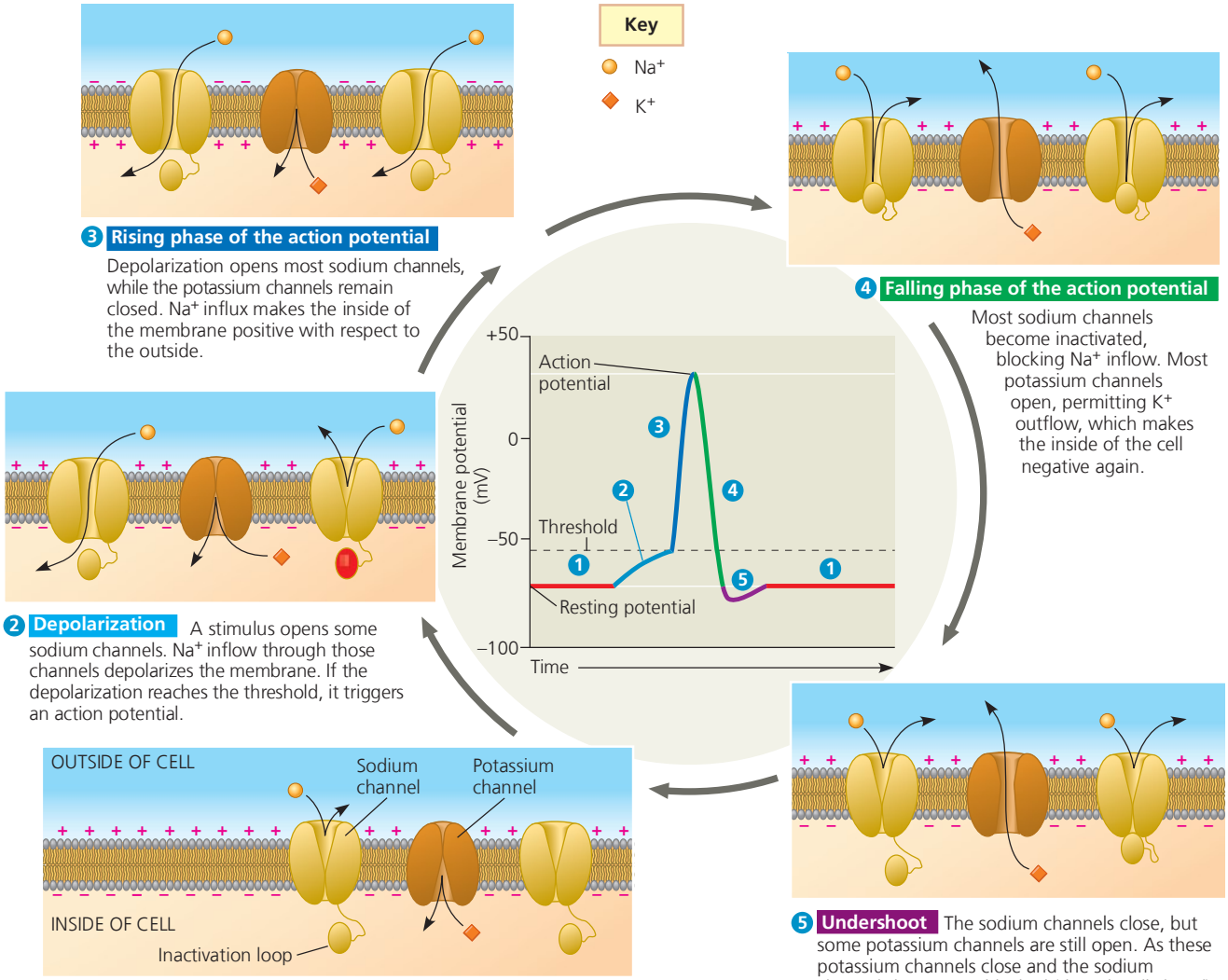
Generation of Action Potentials: *A Closer Look*

The characteristic shape of the action potential graph in Figure 48.11c reflects changes in membrane potential resulting from ion movement through voltage-gated sodium and potassium channels. 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, sodium channels remain open

but become *inactivated*: A portion of the channel protein called an inactivation loop blocks ion flow through the open channel. Sodium channels remain inactivated until after the membrane returns to the resting potential and the channels close. Potassium channels open more slowly than sodium channels, but remain open and functional until the end of the action potential.

To understand further how voltage-gated channels shape the action potential, consider the process as a series of stages, as depicted in **Figure 48.12**. (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. If the stimulus is sufficiently strong, the Na^+ inflow persists, causing further depolarization, which opens more gated sodium channels, allowing even more Na^+ to diffuse into the

▼ Figure 48.12 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.



DRAW IT *Draw a simple diagram showing how positive feedback underlies the rising phase of the action potential. Your diagram should include these three events: (1) a change in membrane potential; (2) ion flow; and (3) opening, closing, or inactivation of a channel.*

Mastering Biology BioFlix® Animation: Action Potential

cell. ❸ Once the threshold is crossed, the positive-feedback cycle then rapidly brings the membrane potential close to E_{Na}. This stage of the action potential is called the *rising phase*. ❹ Two events prevent the membrane potential from actually reaching E_{Na}: Voltage-gated sodium channels inactivate soon after opening, halting the flow of Na^+ into the cell, 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*. ❺ 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.

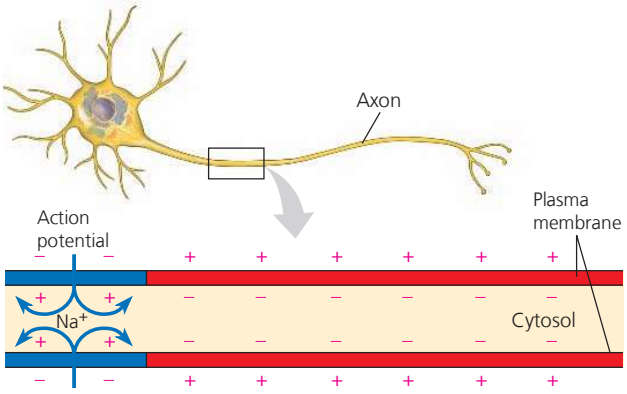
Why is inactivation of channels required during an action potential? Because they are voltage gated, the sodium channels open when the membrane potential reaches the threshold of −55 mV and don't close until the resting potential is restored. They are therefore open throughout the action potential. However, the resting potential cannot be restored unless the flow of Na^+ into the cell stops. This is accomplished by inactivation. The sodium channels remain in the "open" state, but sodium ions cease flowing once inactivation occurs. The end of Na^+ inflow allows K^+ outflow to repolarize the membrane.

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**. Note that the refractory period is due to the inactivation of sodium channels, not to a change in the ion concentration 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.

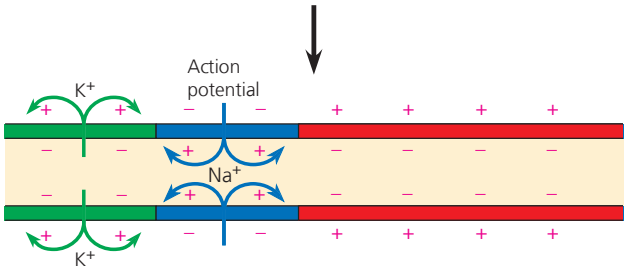
Conduction of Action Potentials

Having described the events of a single action potential, we'll explore next 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 48.13)**. 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.

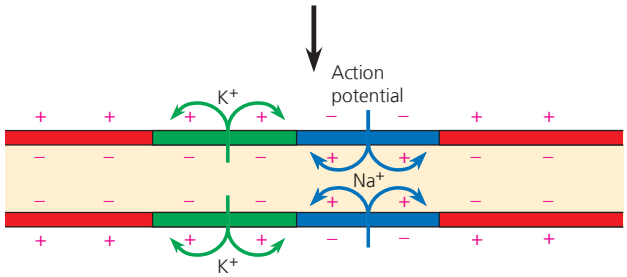
▼ Figure 48.13 Conduction of an action potential. This figure shows events at three successive times as an action potential passes from left to right. At each point along the axon, voltage-gated ion channels go through the sequence of changes shown in Figure 48.9. Membrane colors correspond to the action potential phases in that figure.



❶ An action potential is generated as Na^+ flows inward across the membrane in one region.



❷ 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.



❸ 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.

DRAW IT *For the axon segment shown, consider a point at the left end, a point in the middle, and a point at the right end. Draw a graph for each point showing the change in membrane potential over time at that point as a single nerve impulse moves from left to right across the segment.*

Mastering Biology BioFlix® Animation: Conduction of an Action Potential

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, the

sodium channels remain inactivated, making the membrane temporarily refractory (not responsive) to further input. Consequently, the inward current that depolarizes the axon membrane *ahead* of the action potential cannot produce another action potential *behind* it. This is why action potentials do not travel back toward the cell body.

After the refractory period is complete, depolarization of the axon hillock to threshold will trigger a new action potential. In many neurons, action potentials last less than 2 milliseconds (msec), and the firing rate can thus reach hundreds of action potentials per second.

The frequency of action potentials conveys information: The rate at which action potentials are produced in a particular neuron is proportional to input signal strength. In hearing, for example, louder sounds result in more frequent action potentials in neurons connecting the ear to the brain. Similarly, increased frequency of action potentials in a neuron that stimulates skeletal muscle tissue will increase the tension in the contracting muscle. 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 voltage-gated sodium channels in skeletal muscle cells can cause myotonia, a periodic spasming of those muscles. Mutations affecting sodium channels in the brain can cause epilepsy, in which groups of nerve cells fire simultaneously and excessively, producing seizures.

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. 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.

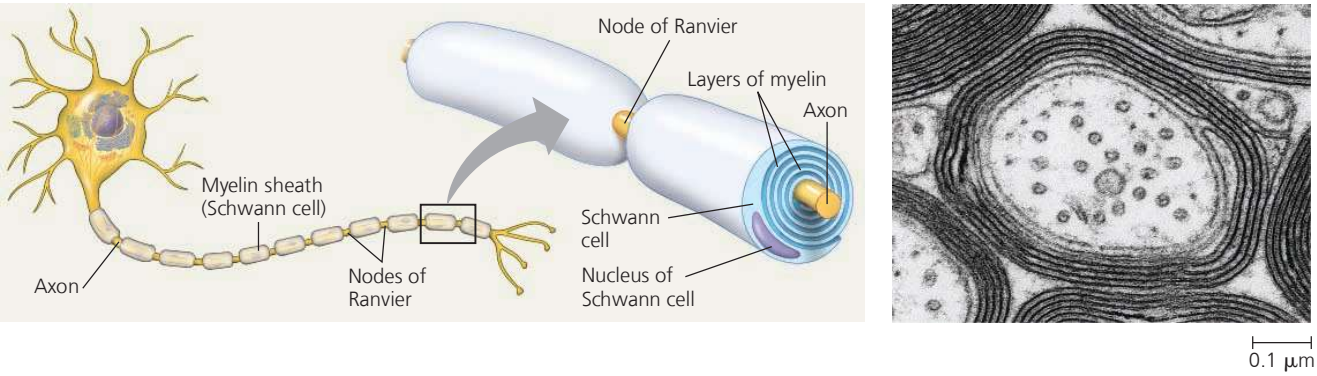
In invertebrates, conduction speed varies from several centimeters per second in very narrow axons to approximately 30 m/sec in the giant axons of some arthropods and molluscs. These giant axons (up to 1 mm in diameter) function in rapid behavioral responses, such as the muscle contraction that propels 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 travel farther along the axon interior, bringing more distant regions to the threshold sooner.

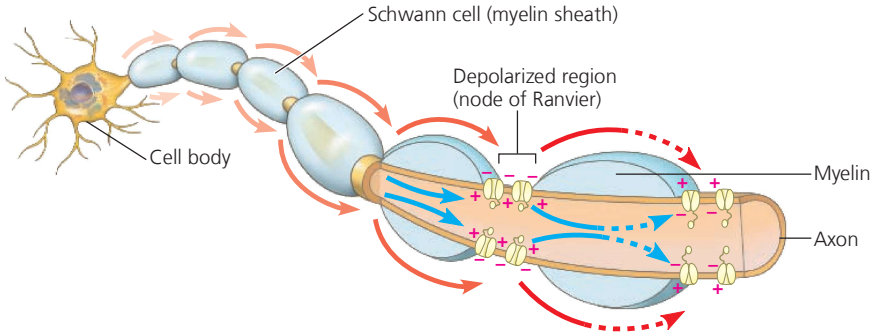
The electrical insulation that surrounds vertebrate axons is called a **myelin sheath** (Figure 48.14). Myelin sheaths are produced by glia: **oligodendrocytes** in the CNS and **Schwann cells** in the PNS. During development, these specialized glia wrap axons in many layers of membrane. The membranes forming these layers are mostly lipid, which is a poor conductor of electrical current and thus a good insulator.

In myelinated axons, voltage-gated sodium channels are restricted to gaps in the myelin sheath called **nodes of Ranvier** (see Figure 48.14). Furthermore, 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 within the axon all the way to the next node. There, the current

▼ Figure 48.14 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.



▼ Figure 48.15 Propagation of action potentials in myelinated axons. 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).



Mastering Biology **Animation: Propagation of an Action Potential in Unmyelinated and Myelinated Axons**

depolarizes the membrane and regenerates the action potential **(Figure 48.15)**.

Action potentials propagate more rapidly in myelinated axons because the time-consuming process of opening and closing of 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 from node to node along the axon.

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. Consequently, 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, our next topic.

CONCEPT CHECK 48.3

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. How do both negative and positive feedback contribute to the changes in membrane potential during an action potential?
4. **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 48.4

Neurons communicate with other cells at synapses

Transmission of information from neurons to other cells occurs at synapses. Synapses are either electrical or chemical.

Electrical synapses contain gap junctions (see Figure 6.30) that allow electrical current to flow directly from one neuron to another. Such synapses often play a role in synchronizing the activity of neurons that direct rapid, unvarying behaviors. For example, electrical synapses associated with the giant axons of squids and lobsters facilitate swift escapes from danger. Electrical synapses are also found in the vertebrate heart and brain.

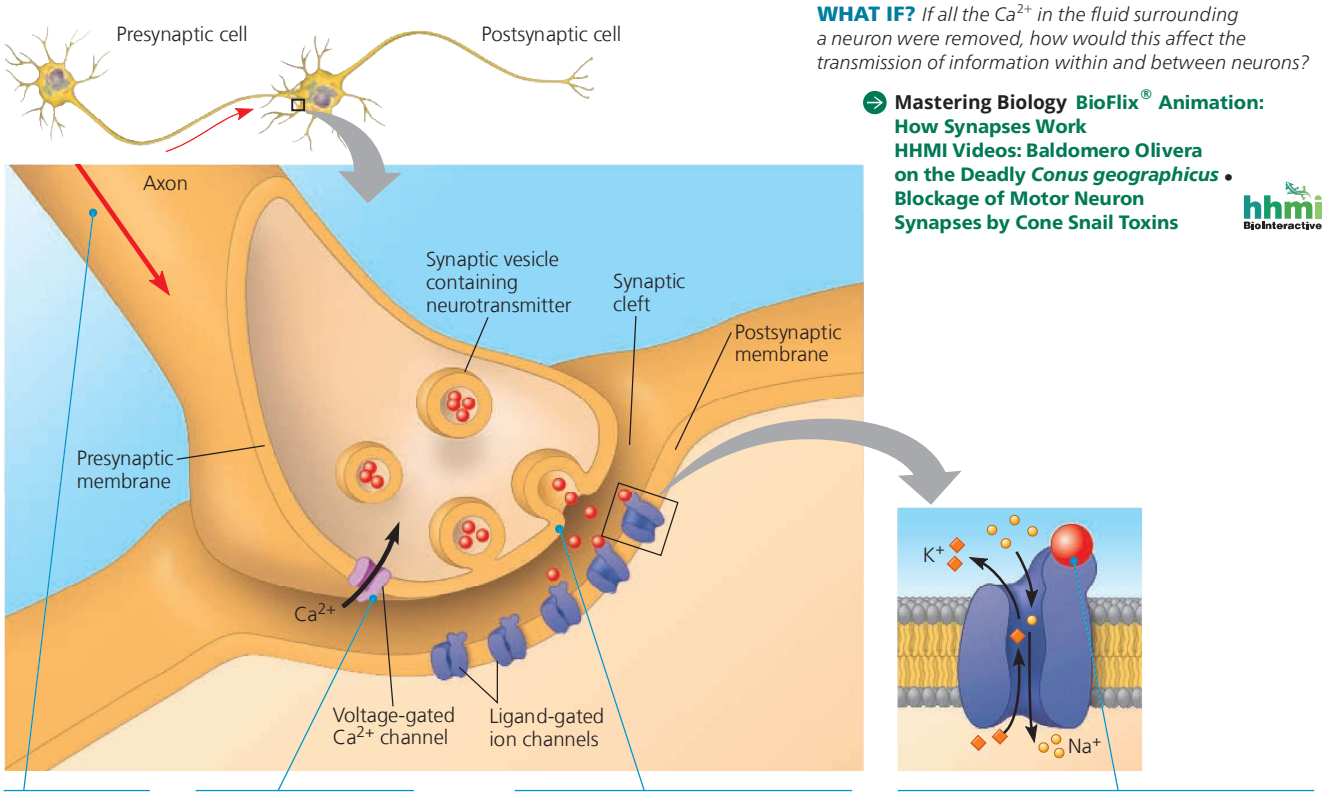
The majority of synapses are *chemical synapses*, which rely on the release of a chemical neurotransmitter by the presynaptic neuron to transfer information to the target cell. While at rest, the presynaptic neuron synthesizes the neurotransmitter at each synaptic terminal, packaging it in multiple membrane-enclosed compartments called *synaptic vesicles*. When an action potential arrives at a chemical synapse, it depolarizes the plasma membrane at the synaptic terminal, opening voltage-gated channels that allow Ca^{2+} to diffuse in. The Ca^{2+} concentration in the terminal rises, causing synaptic vesicles to fuse with the terminal membrane and release the neurotransmitter.

Neurotransmitter released from the synaptic terminus diffuses across the *synaptic cleft*, the gap that separates the presynaptic neuron 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. This series of events at the synapse is summarized in **Figure 48.16.**

▼ Figure 48.16 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?*

Mastering Biology BioFlix® Animation: How Synapses Work
HHMI Videos: Baldomero Olivera on the Deadly *Conus geographicus* • Blockage of Motor Neuron Synapses by Cone Snail Toxins



1 An action potential arrives, depolarizing the presynaptic membrane.

2 The depolarization opens voltage-gated channels, triggering an influx of Ca^{2+}.

3 The elevated Ca^{2+} concentration causes synaptic vesicles to fuse with the presynaptic membrane, releasing neurotransmitter into the synaptic cleft.

4 The neurotransmitter binds to ligand-gated ion channels in the postsynaptic membrane. In this example, binding triggers opening, allowing Na^+ and K^+ to diffuse through.

Information transfer at chemical synapses can be modified by altering either 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 also form the basis for learning and memory, as you will read in Concept 49.4.

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 chemical synapses, the ligand-gated ion channels are permeable to both K^+ and Na^+ (see Figure 48.16). When these channels open, 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 chemical synapses, the ligand-gated ion channels are selectively permeable for only K^+ or Cl^-. When such channels open, the postsynaptic membrane hyperpolarizes. A hyperpolarization produced in this manner is an **inhibitory postsynaptic potential (IPSP)** because it moves the membrane potential farther from threshold.

Summation of Postsynaptic Potentials

The interplay between multiple excitatory and inhibitory inputs is the essence of integration in the nervous system. The cell body and dendrites of a given postsynaptic neuron may receive inputs from chemical synapses formed with hundreds or even thousands of synaptic terminals (see Figure 48.2). How do so many synapses contribute to information transfer?

The input from an individual synapse is typically insufficient to trigger a response in a postsynaptic neuron. To see why, consider an EPSP arising at a single synapse. As a graded potential, the EPSP becomes smaller as it spreads from the synapse. Therefore, by the time a particular EPSP reaches the axon hillock, it is usually too small to trigger an action potential **(Figure 48.17a)**.

On some occasions, individual postsynaptic potentials combine to produce a larger postsynaptic potential, a process called **summation**. For instance, two EPSPs may occur at a single synapse in rapid succession. If the second EPSP arises before the postsynaptic membrane potential returns to its resting value, the EPSPs add together through *temporal summation*. If the summed postsynaptic potentials depolarize the membrane at the axon hillock to threshold, the result is an action potential **(Figure 48.17b)**. Summation can also involve multiple synapses on the same postsynaptic neuron. If such synapses are active at the same time, the resulting EPSPs can add together through *spatial summation* **(Figure 48.17c)**.

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 48.17d)**.

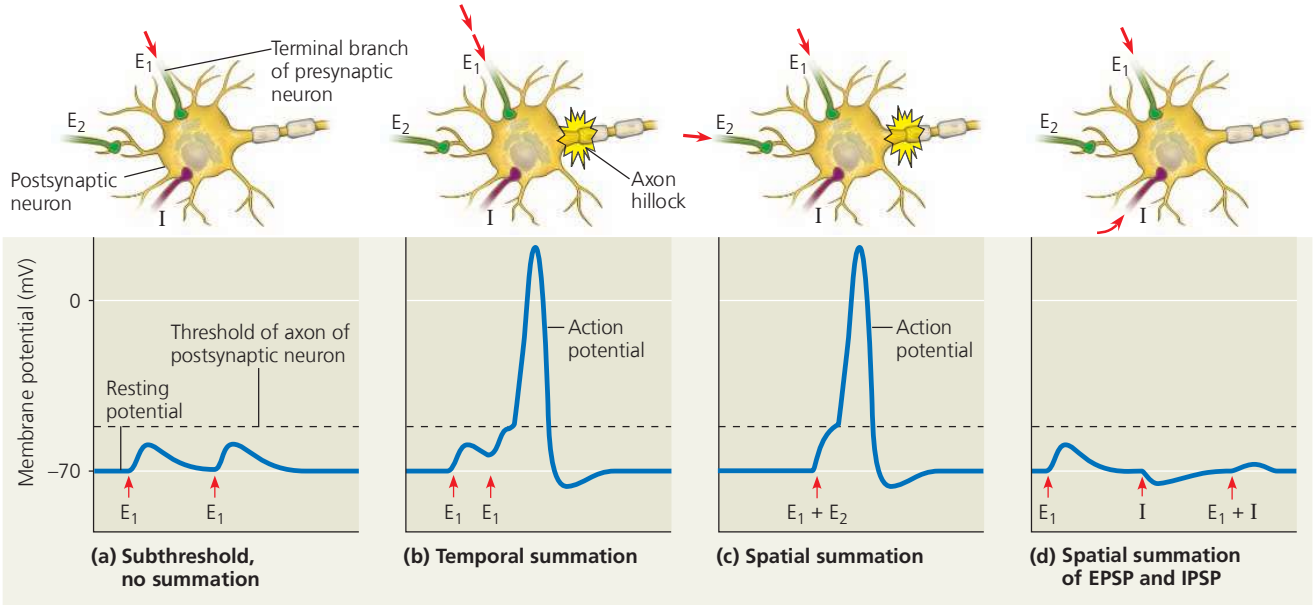
The axon hillock is the neuron's integrating center, the region where the membrane potential at any instant represents the summed effect of all EPSPs and IPSPs. Whenever the membrane potential at the axon hillock reaches threshold, an action potential is generated and travels along the axon to its synaptic terminals. After the refractory period, the neuron may produce another action potential, provided the membrane potential at the axon hillock once again reaches threshold.

Termination of Neurotransmitter Signaling

After a response is triggered, the chemical synapse returns to its resting state. How does this happen? The key step is clearing the neurotransmitter molecules from the synaptic cleft. Some neurotransmitters are inactivated by enzymatic

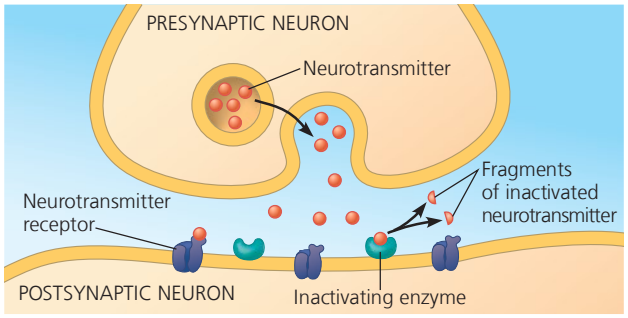
▼ Figure 48.17 Summation of postsynaptic potentials. These graphs trace changes in the membrane potential at a postsynaptic neuron's axon hillock. The red arrows indicate times when postsynaptic potentials occur at two excitatory synapses (E_1 and E_2, green in the diagrams above the graphs) and at one inhibitory synapse (I, purple). Like most EPSPs, those produced at E_1 or E_2 do not reach the threshold at the axon hillock without summation.

Mastering Biology
Animation: Action Potentials

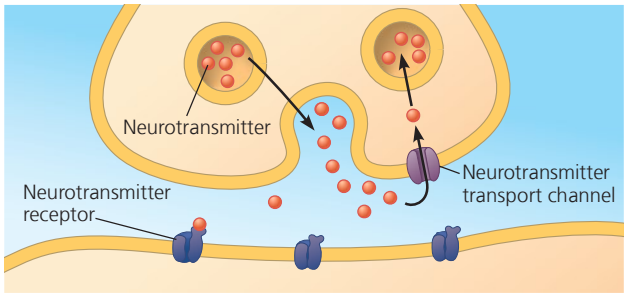


VISUAL SKILLS *Using these drawings, propose an argument for all summation being in some sense temporal.*

▼ Figure 48.18 Two mechanisms of terminating neurotransmission.



(a) Enzymatic breakdown of neurotransmitter in the synaptic cleft



(b) Reuptake of neurotransmitter by presynaptic neuron

hydrolysis **(Figure 48.18a)**. Other neurotransmitters are recaptured into the presynaptic neuron **(Figure 48.18b)**. After this reuptake occurs, neurotransmitters are repackaged in synaptic vesicles or transferred to glia for metabolism or recycling to neurons.

Clearing neurotransmitter from the synaptic cleft is an essential step in the transmission of information through the nervous system. Indeed, blocking this process can have severe consequences. For example, the nerve gas sarin triggers paralysis and death because it inhibits the enzyme that breaks down the neurotransmitter controlling skeletal muscles.

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 chemical synapses in which the receptor for the neurotransmitter is *not* part of an ion channel. At these synapses, the neurotransmitter binds to a G protein-coupled receptor, activating a signal transduction pathway in the postsynaptic cell involving a second messenger (see Concept 11.3). Because the resulting opening or closing of ion channels depends on one or more metabolic steps, these G protein-coupled receptors are also called *metabotropic receptors*.

G protein-coupled receptors modulate the responsiveness and activity of postsynaptic neurons in diverse ways. Consider, for example, the metabotropic receptor for the neurotransmitter norepinephrine. Binding of norepinephrine to its G protein-coupled receptor activates a G protein, which in turn activates adenylyl cyclase, the enzyme that converts ATP to cAMP (see Figure 11.11). 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 one norepinephrine molecule can trigger the opening or closing of many channels.

Many neurotransmitters have both ionotropic and metabotropic receptors. Compared with the postsynaptic potentials produced by ligand-gated channels, the effects of G protein pathways typically have a slower onset but last longer.

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. 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 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.

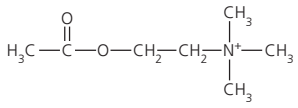
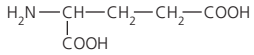
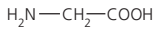
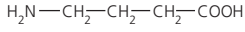
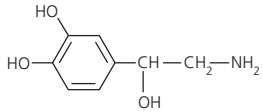
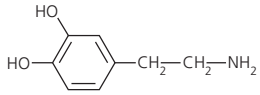
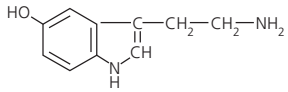
A G protein-coupled receptor for acetylcholine is found at locations that include the vertebrate CNS and heart. In heart muscle, acetylcholine released by neurons activates a signal transduction pathway. The G proteins in the pathway inhibit adenylyl cyclase and open potassium channels in the muscle 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.

Several chemicals with profound effects on the nervous system mimic or alter the function of acetylcholine. Nicotine, a chemical found in tobacco and tobacco smoke,

acts as a stimulant by binding to an ionotropic acetylcholine receptor in the CNS. As discussed earlier, the nerve gas sarin blocks enzymatic cleavage of acetylcholine. A third example is botulinum toxin, which inhibits presynaptic release of acetylcholine. The result is a form of food poisoning called botulism. Because muscles required for breathing fail to contract when acetylcholine release is blocked, untreated botulism is typically fatal. Today, injections of the botulinum toxin, known by the trade name Botox, are used cosmetically to minimize wrinkles around the eyes or mouth by inhibiting synaptic transmission to 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 48.2**, the rest fall into four classes: amino acids, biogenic amines, neuropeptides, and gases.

Table 48.2 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

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 you will see in Concept 49.4.

Two amino acids act as inhibitory neurotransmitters in the CNS. *Glycine* acts at inhibitory synapses in parts of the CNS that lie outside of the brain. Within the brain, the amino acid *gamma-aminobutyric acid (GABA)* is the neurotransmitter at most inhibitory synapses. 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, increasing the response to GABA.

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 Concept 45.3).

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 Concept 49.5). 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 it is released by presynaptic neurons.

Neuropeptides

Several **neuropeptides**, relatively short chains of amino acids, serve as neurotransmitters that operate via G protein-coupled 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.

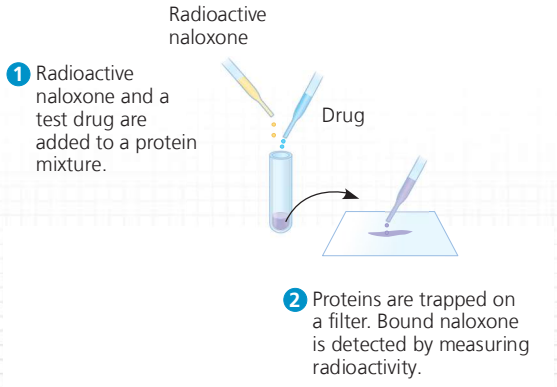
Endorphins are produced in the brain during times of physical or emotional stress, such as childbirth. In addition

Scientific Skills Exercise

Interpreting Data Values Expressed in Scientific Notation

Does the Brain Have Specific Protein Receptors for Opiates? 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 to test this hypothesis.

How the Experiment Was Done The researchers incubated radioactive naloxone with 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 $10^{-4}\ M$

Data from C. B. Pert and S. H. Snyder, Opiate receptor: demonstration in nervous tissue, *Science* 179:1011–1014 (1973).

INTERPRET THE DATA

1. The data above are expressed in 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, $10^{-1}\ M$ (molar) can also be written as 0.1 *M*. Write the concentrations in the table 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.
4. **(a)** Which drugs blocked naloxone binding in this experiment? **(b)** What do these results indicate about the brain receptors for naloxone?
5. When the researchers instead used tissue from intestinal muscles rather than brains, they found no naloxone binding. What does that suggest about opiate receptors in mammalian muscle?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

to relieving pain, they reduce urine output, decrease respiration, and produce euphoria as well as other emotional effects. Because opiates (drugs such as morphine and heroin) bind to the same receptor proteins as endorphins, opiates mimic endorphins and produce many of the same physiological effects (see Figure 2.16). In the **Scientific Skills Exercise**, you can interpret data from an experiment designed to search for opiate receptors in the brain.

Gases

Some vertebrate neurons release dissolved gases as neurotransmitters. In human males, for example, certain neurons release nitric oxide (NO) into the erectile tissue of the penis during sexual arousal. The resulting relaxation of smooth muscle in the blood vessel walls of the spongy erectile tissue allows the 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 the gas carbon monoxide (CO) is a deadly poison if inhaled, vertebrates produce small amounts of CO as a neurotransmitter. For example, CO synthesized

in the brain regulates the release of hormones from the hypothalamus.

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.

Mastering Biology The Visual Brain: Neural Conduction and Synaptic Transmission

CONCEPT CHECK 48.4

1. How is it possible for a particular neurotransmitter to produce opposite effects in different tissues?
2. Some pesticides inhibit acetylcholinesterase, the enzyme that breaks down acetylcholine. Explain how these toxins would affect EPSPs produced by acetylcholine.
3. **MAKE CONNECTIONS** Name one or more membrane activities that occur both in fertilization of an egg and in neurotransmission across a synapse (see Figure 47.3).

For suggested answers, see Appendix A.

48 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

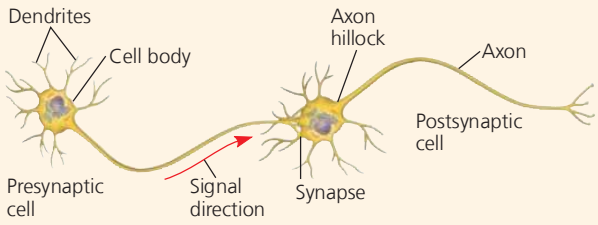
SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 48.1

Neuron structure and organization reflect function in information transfer *(pp. 1068–1069)*

- 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)** together 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 48.2

Ion pumps and ion channels establish the resting potential of a neuron *(pp. 1069–1072)*

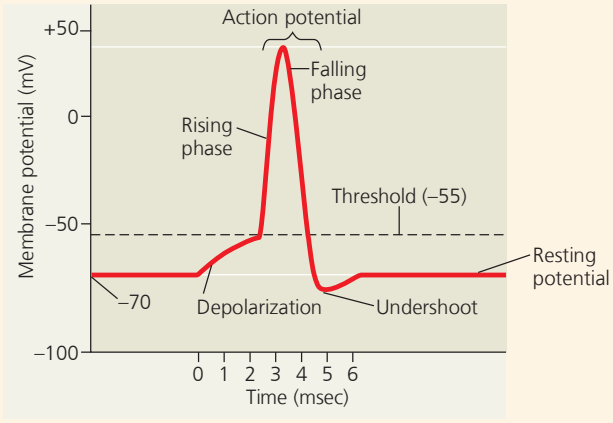
- Ion concentration gradients generate a voltage difference, or **membrane potential**, across the plasma membrane of cells. The concentration of Na^+ is higher outside than inside; the reverse is true for K^+. In resting neurons, the plasma membrane has many open potassium channels but few open sodium 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 Na^+. What change would you expect in the resting potential?*

CONCEPT 48.3

Action potentials are the signals conducted by axons *(pp. 1072–1077)*

- 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 are 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 appear to jump from one **node of Ranvier** to the next, a process called **saltatory conduction**.

INTERPRET THE DATA *Assuming a refractory period equal in length to the action potential (see graph above), what is the maximum frequency per unit time at which a neuron could fire action potentials?*

CONCEPT 48.4

Neurons communicate with other cells at synapses

(pp. 1077–1083)

- 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. A single neuron has many synapses on its dendrites and cell body. Temporal and spatial **summation** of EPSPs and IPSPs at the axon hillock determine 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

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

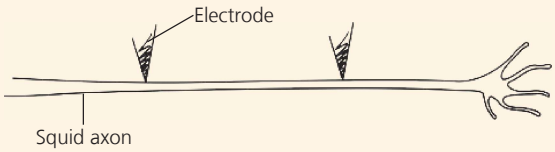
1. What happens when a resting neuron's membrane depolarizes?
   (A) There is a net diffusion of Na^+ out of the cell.
   (B) The equilibrium potential for K^+ (E_K) becomes more positive.
   (C) The neuron's membrane voltage becomes more positive.
   (D) The cell's inside becomes more negative than 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.
3. Where are neurotransmitter receptors located?
   (A) the nuclear membrane
   (B) the nodes of Ranvier
   (C) the postsynaptic membrane
   (D) synaptic vesicle membranes

Levels 3-4: Applying/Analyzing

4. Why are action potentials usually conducted in one direction?
   (A) Ions can flow along the axon in only 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) Voltage-gated channels for both Na^+ and K^+ open in only one direction.
5. Which of the following is the most *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) Ligand-gated channels open, allowing neurotransmitters to enter the synaptic cleft.
   (D) 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 for cell X is different from that for cell Y.
   (B) the axon of cell X is myelinated, but that of cell Y is not.
   (C) only cell Y produces an enzyme that terminates the activity of the neurotransmitter.
   (D) cells X and Y express different receptor molecules for this particular neurotransmitter.

Levels 5-6: Evaluating/Creating

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 electrodes at two 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. **EVOLUTION CONNECTION** 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. Imagine a nervous system in which the action potentials are graded, with the amplitude depending on the size of the stimulus. Describe what evolutionary advantage on/off signaling might have over this continuously variable kind of signaling.
11. **SCIENTIFIC INQUIRY** From what you know about action potentials and synapses, propose two hypotheses for how various anesthetics might block pain.
12. **WRITE ABOUT A THEME: 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.
13. **SYNTHESIZE YOUR KNOWLEDGE**

This diamond-back rattlesnake (*Crotalus atrox*) alerts enemies to its presence with a rattle—a set of modified scales at the tip of its tail. Describe the roles of gated ion channels in initiating and moving a signal along the nerve from the snake's head to its tail and then to the muscle that shakes the rattle.

For selected answers, see Appendix A.

49 Nervous Systems

KEY CONCEPTS

Study Tip

Think in pairs: Regional specialization involves many examples of paired structures or circuits. Fill in the complementary or reciprocal functions of these pairs to help you understand their roles in the brain or nervous system.

Structure A/*Function*	Structure B/*Function*
CNS (brain and spinal cord) *Integration of information*	PNS (ganglia and peripheral nerves) *Transfer of information to/from CNS*
Sympathetic division of autonomic nervous system	Parasympathetic division of autonomic nervous system
Left hemisphere of brain	Right hemisphere of brain
Hippocampus (role in memory)	Cerebral cortex (role in memory)

Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 49
- The Visual Brain: Nervous System
- HHMI Video: The Human Suprachiasmatic Nucleus

For Instructors to Assign (in Item Library)
- Scientific Skills Exercise: Designing an Experiment Using Genetic Mutants
- Tutorial: The Vertebrate Nervous System

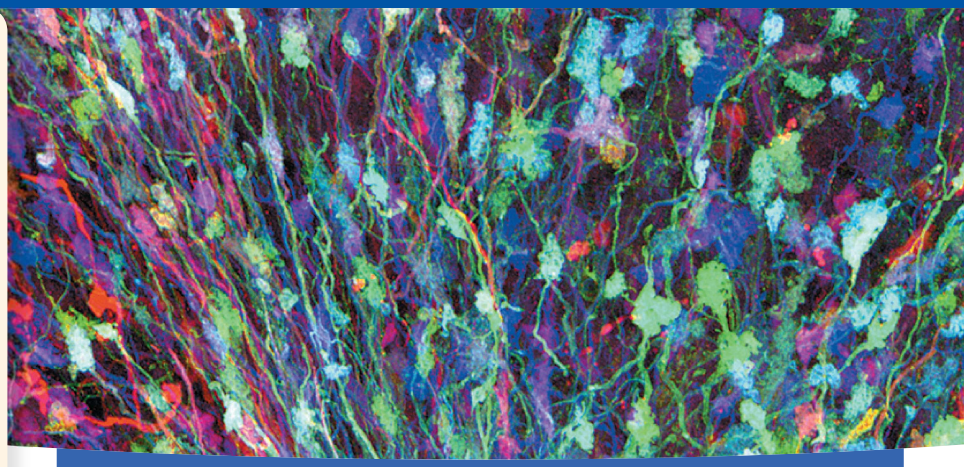
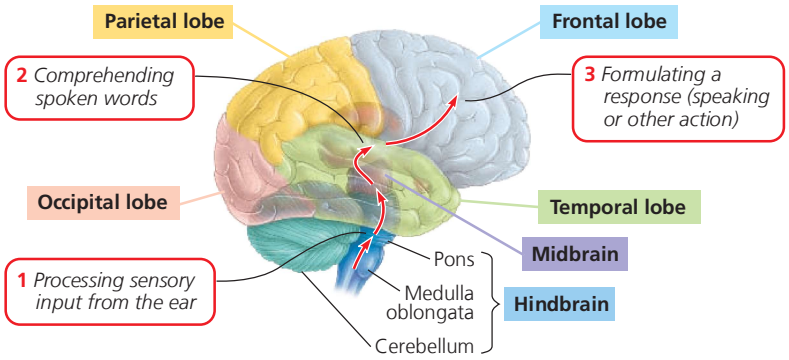


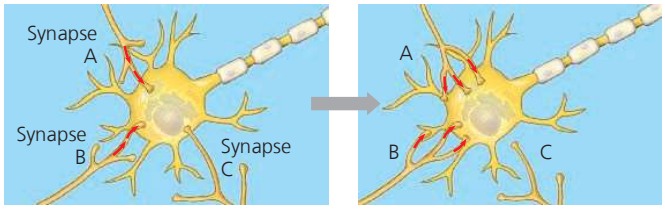
Figure 49.1 Neuroscientists engineered mice to express a random combination of four fluorescent proteins in each brain cell. The result, shown here, is a "brainbow," with each neuron displaying one of 90 different color combinations. This brainbow technology holds promise for studying particular pathways within the mouse brain. Ultimately, however, we want to understand our own brains, which contain an estimated 10^{11} (100 billion) neurons and 10^{14} (100 trillion) connections.

How are billions of neurons organized to perform complex tasks?

Regional specialization: Complex tasks, such as responding to a spoken question, involve the stepwise functions of different brain regions.



Memory formation: Information is stored by reinforcing patterns of active connections (synapses) among particular neurons.



Synapses that are active in synchrony (A and B) are strengthened. Synapses that are not part of an active circuit (C) are weakened or lost.

CONCEPT 49.1

Nervous systems consist of circuits of neurons and supporting cells

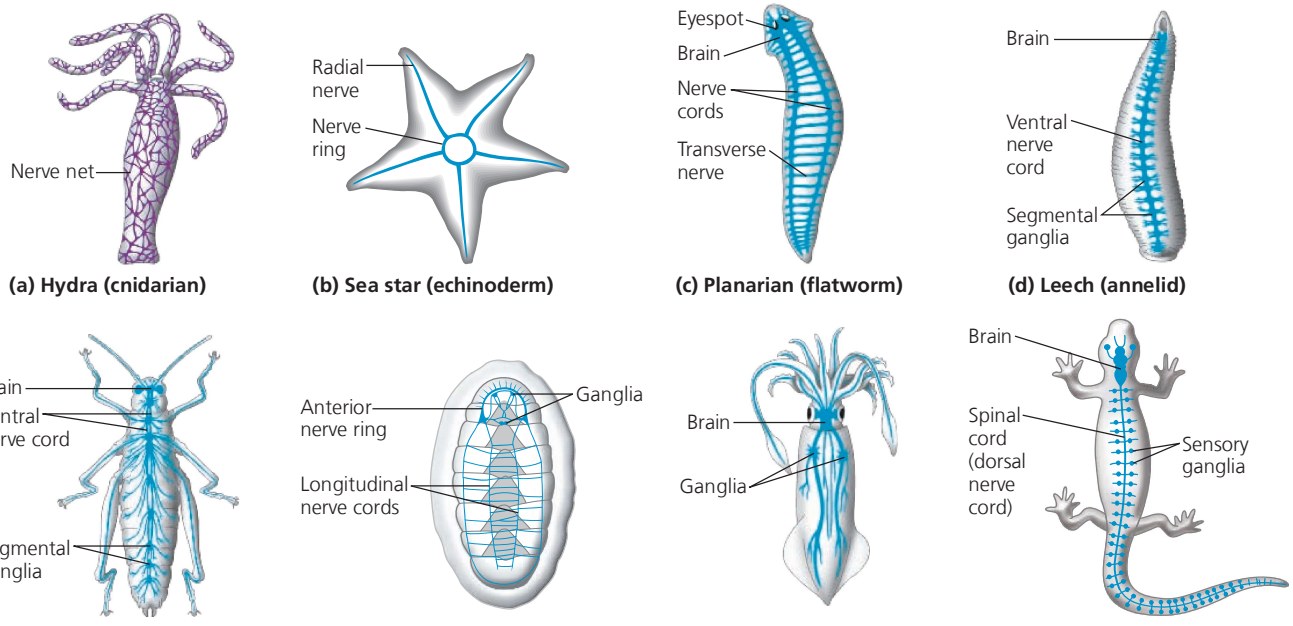
The ability to sense and react originated billions of years ago in prokaryotes, enhancing survival and reproductive success in changing environments. Later in evolution, modification of simple recognition and response processes provided a basis for communication between cells in an animal body. By the time of the Cambrian explosion, more than 500 million years ago (see Concept 32.2), specialized nervous systems had appeared that enable animals to sense their surroundings and respond rapidly.

Hydras, jellies, and other cnidarians are the simplest animals with nervous systems. In most cnidarians, interconnected neurons form a diffuse *nerve net* **(Figure 49.2a)**, which controls the contraction and expansion of the gastrovascular cavity. In more complex animals, the axons of multiple neurons are often bundled together, forming **nerves**. These fibrous structures channel information flow along specific routes through the nervous system. For example, sea stars have a set of radial nerves connecting to a central nerve ring **(Figure 49.2b)**. Within each arm of a sea star, the radial nerve is linked to a nerve net from which it receives input and to which it sends signals that control muscle contraction.

Animals with elongated, bilaterally symmetrical bodies have even more specialized nervous systems. In particular, they exhibit *cephalization*, an evolutionary trend toward a clustering of sensory neurons and interneurons at the anterior (front) end of the body. Nerves that extend toward the posterior (rear) end enable these anterior neurons to communicate with cells elsewhere in the body.

In many animals, neurons that carry out integration form a **central nervous system (CNS)**, and neurons that carry information into and out of the CNS form a **peripheral nervous system (PNS)**. In nonsegmented worms, such as the planarian in **Figure 49.2c**, a small brain and longitudinal nerve cords constitute the simplest clearly defined CNS. In certain nonsegmented worms, the entire nervous system is constructed from only a small number of cells, as in the case of the nematode *Caenorhabditis elegans*. In this species, an adult worm (hermaphrodite) has exactly 302 neurons, no more and no fewer. More complex invertebrates, such as segmented worms **(Figure 49.2d)** and arthropods **(Figure 49.2e)**, have many more neurons. Their behavior is regulated by more complicated brains and by ventral nerve cords containing **ganglia**, segmentally arranged clusters of neurons that act as relay points in transmitting information.

▼ Figure 49.2 Nervous system organization. (a) A hydra contains individual neurons (purple) organized in a diffuse nerve net. **(b–h)** Animals with more sophisticated nervous systems contain groups of neurons (blue) organized into nerves and often ganglia and a brain.



(a) Hydra (cnidarian) (b) Sea star (echinoderm) (c) Planarian (flatworm) (d) Leech (annelid)

(e) Insect (arthropod) (f) Chiton (mollusc) (g) Squid (mollusc) (h) Salamander (vertebrate)

Within an animal group, nervous system organization often correlates with lifestyle. Among the molluscs, for example, sessile and slow-moving species, such as clams and chitons, have relatively simple sense organs and little or no cephalization **(Figure 49.2f)**. In contrast, active predatory molluscs, such as octopuses and squids **(Figure 49.2g)**, have the most sophisticated nervous systems of any invertebrate. With their large, image-forming eyes and a brain containing millions of neurons, octopuses can learn to discriminate between visual patterns and to perform complex tasks, such as unscrewing a jar to feed on its contents.

In vertebrates such as a salamander **(Figure 49.2h)** or human **(Figure 49.3)**, the brain and the spinal cord form the CNS; nerves and ganglia are the key elements of the PNS. Regional specialization is a hallmark of both systems, as we will see throughout this chapter.

Organization of the Vertebrate Nervous System

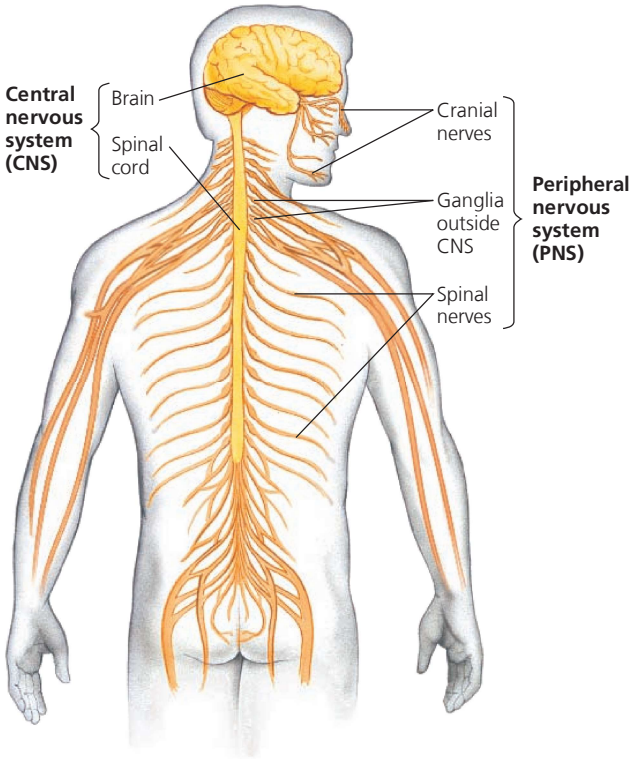
During embryonic development in vertebrates, the central nervous system develops from the hollow dorsal nerve cord—a hallmark of chordates (see Figure 34.3). The cavity of the nerve cord gives rise to the narrow *central canal* of the spinal cord as well as the *ventricles* of the brain. Both the canal and ventricles fill with *cerebrospinal fluid*, which is formed in the brain by filtering arterial blood **(Figure 49.4)**. The cerebrospinal fluid supplies the CNS with nutrients and hormones and carries away wastes, circulating through the ventricles and central canal before draining into the veins.

In addition to fluid-filled spaces, the brain and spinal cord have gray and white matter. **Gray matter** is primarily made up of neuron cell bodies. **White matter** consists of bundled axons. In the spinal cord, white matter forms the outer layer, reflecting its role in linking the CNS to sensory and motor neurons of the PNS. In the brain, white matter is predominantly in the interior, where signaling between neurons functions in learning, feeling emotions, processing sensory information, and generating commands.

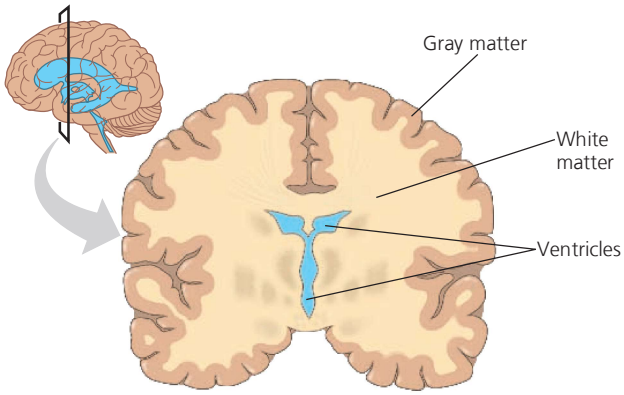
In vertebrates, the spinal cord runs lengthwise inside the vertebral column, known as the spine. The spinal cord conveys information to and from the brain and generates basic patterns of locomotion. It also acts independently of the brain as part of the simple nerve circuits that produce **reflexes**, the body's automatic responses to certain stimuli.

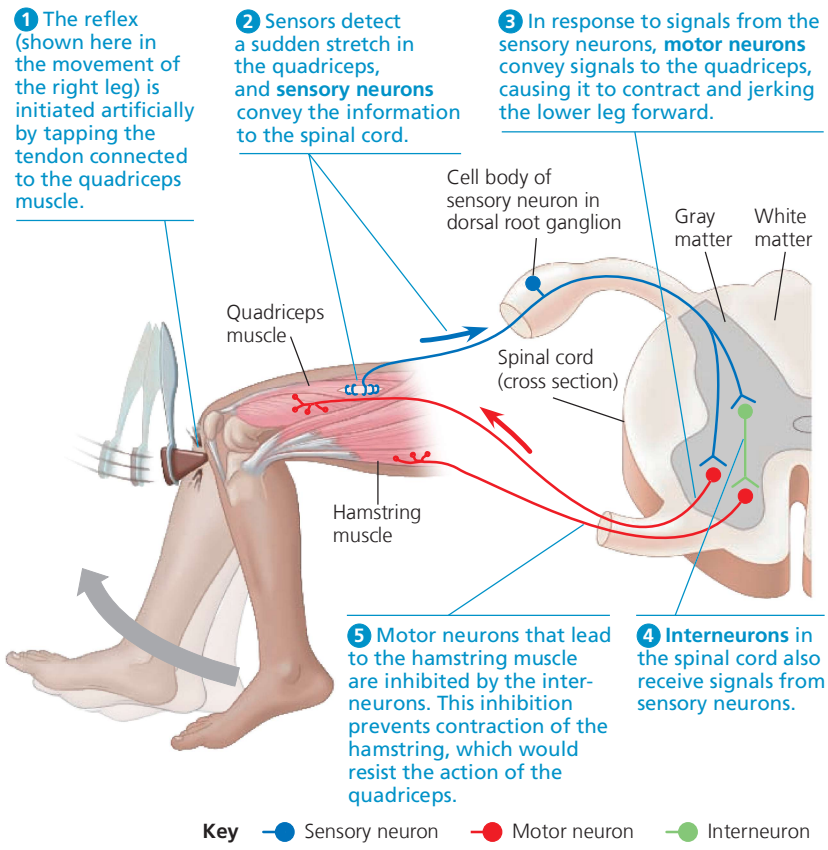
Reflexes protect the body by providing rapid, involuntary responses to particular stimuli. Reflexes are rapid because sensory information is used to activate motor neurons without the information first having to travel from the spinal cord to the brain and back. If you accidentally put your hand on a hot burner, a reflex jerks your hand back even before your brain processes pain. Similarly, the knee-jerk reflex provides an immediate protective response when you pick up an unexpectedly heavy object. If your legs buckle, the tension across your knees triggers contraction of your thigh muscle (quadriceps), helping you stay upright and support the load.

▼ Figure 49.3 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).



▼ Figure 49.4 Ventricles, gray matter, and white matter. Ventricles deep in the brain's interior contain cerebrospinal fluid. In the cerebrum, most of the gray matter is on the surface, surrounding the white matter.





▶ **Figure 49.5 The knee-jerk reflex.** Many neurons are involved in this reflex, but for simplicity only a few neurons are shown.

MAKE CONNECTIONS *Using the nerve signals to the hamstring and quadriceps in this reflex as an example, propose a model for regulation of smooth muscle activity in the esophagus during the swallowing reflex (see Figure 41.9).*

During a physical exam, your doctor may trigger the knee-jerk reflex with a triangular mallet to help assess nervous system function **(Figure 49.5)**.

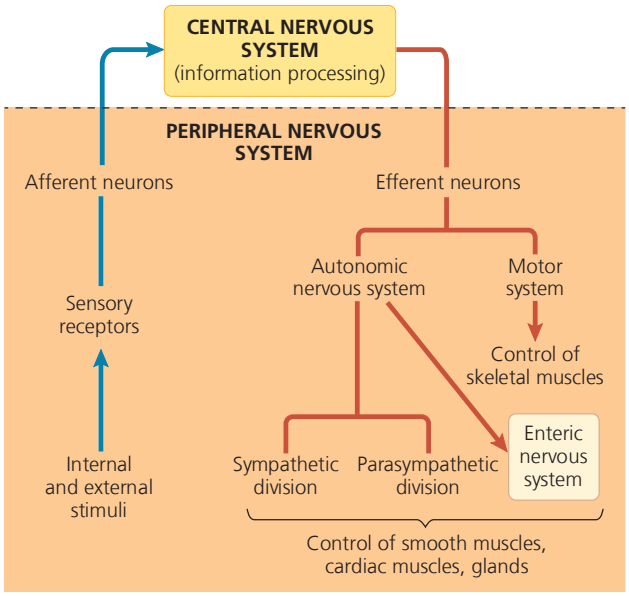
The Peripheral Nervous System

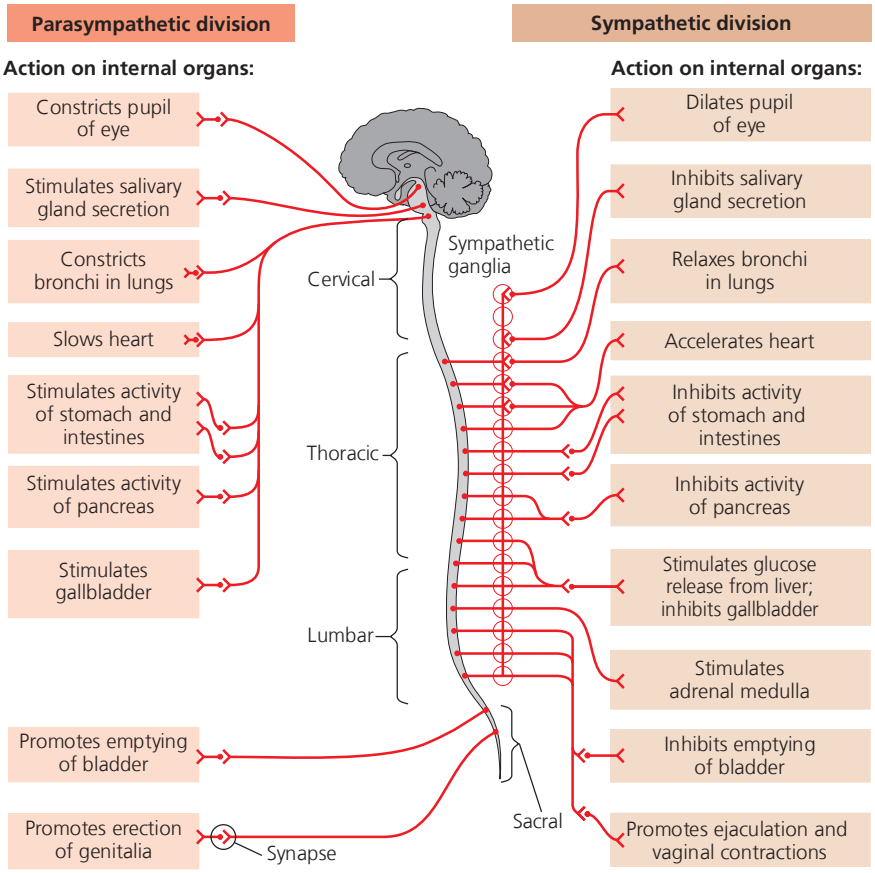
The PNS transmits information to and from the CNS and plays a large role in regulating an animal's movement and its internal environment **(Figure 49.6)**. Sensory information reaches the CNS along PNS neurons designated as *afferent* (from the Latin, meaning "to carry toward"). Following information processing within the CNS, instructions then travel to muscles, glands, and endocrine cells along PNS neurons designated as *efferent* (from the Latin, meaning "to carry away"). Note that most nerves are bundles of both afferent and efferent neurons.

The PNS has two efferent components: the motor system and the autonomic nervous system (see Figure 49.8). The neurons of the **motor system** carry signals to skeletal muscles. Motor control can be voluntary, as when you raise your hand to ask a question, or involuntary, as in the knee-jerk reflex controlled by the spinal cord. In contrast, regulation of smooth and cardiac muscles by the **autonomic nervous system** is generally involuntary. The sympathetic and parasympathetic divisions of the autonomic nervous system regulate organs of the cardiovascular, excretory, and endocrine systems. A distinct network of neurons now known as the **enteric nervous system** exerts direct and partially independent control over the digestive tract, pancreas, and gallbladder.

Homeostasis often relies on cooperation between the motor and autonomic nervous systems. In response to a

▼ **Figure 49.6 Functional hierarchy of the vertebrate peripheral nervous system.**





▶ Figure 49.7 The parasympathetic and sympathetic divisions of the autonomic nervous system. Most pathways in each division involve two neurons connecting the CNS to target organs. The axon of the first neuron extends from a cell body in the CNS to a set of PNS neurons whose cell bodies are clustered into a ganglion (plural, *ganglia*). The axons of these PNS neurons transmit instructions to internal organs, where they form synapses with smooth muscle, cardiac muscle, or gland cells.

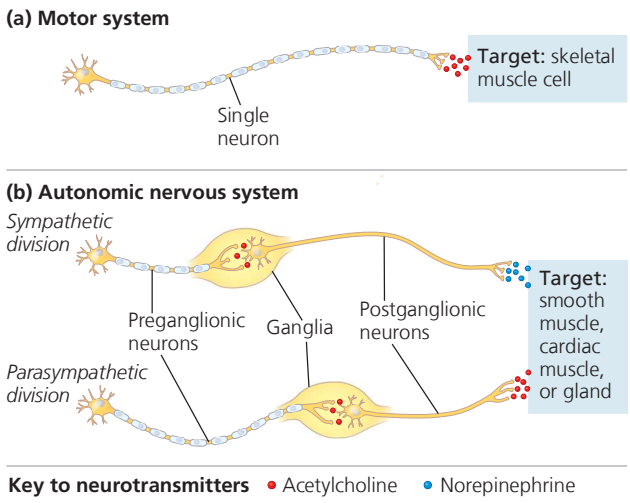
drop in body temperature, for example, the hypothalamus signals the motor system to cause shivering, which increases heat production. At the same time, the hypothalamus signals the autonomic nervous system to constrict surface blood vessels, reducing heat loss.

The sympathetic and parasympathetic divisions of the autonomic nervous system have largely antagonistic (opposite) functions in regulating organ function **(Figure 49.7)**. Activation of the **sympathetic division** corresponds to arousal and energy generation (the "fight-or-flight" response). For example, the heart beats faster, digestion is inhibited, the liver converts glycogen to glucose, and the adrenal medulla increases secretion of epinephrine (adrenaline). Activation of the **parasympathetic division** generally causes opposite responses that promote calming and a return to self-maintenance functions ("rest and digest"). Thus, heart rate decreases, digestion is enhanced, and glycogen production increases. However, in regulating reproductive activity, a function that is not homeostatic, the parasympathetic division complements rather than antagonizes the sympathetic division, as shown at the bottom of Figure 49.7.

The two divisions differ not only in overall function but also in organization and signals released. Parasympathetic nerves exit the CNS at the base of the brain or spinal cord and form synapses in ganglia near or within an internal organ. In contrast, sympathetic nerves typically exit the CNS midway along the spinal cord and form synapses in ganglia located just outside of the spinal cord.

In both the sympathetic and parasympathetic divisions, the pathway for information flow typically involves a preganglionic and a postganglionic neuron. The *preganglionic neurons* have cell bodies in the CNS and release acetylcholine as a neurotransmitter (see Concept 48.4). In the case of the *postganglionic neurons*, those of the parasympathetic division release acetylcholine, whereas nearly all their counterparts in the sympathetic division release norepinephrine. It is this difference in neurotransmitters that enables the sympathetic and parasympathetic divisions to bring about opposite effects in organs such as the lungs, heart, intestines, and bladder. A comparison of these pathways in the autonomic nervous system, along with a motor system pathway, is shown in **Figure 49.8**.

▼ Figure 49.8 Comparison of pathways in the motor and autonomic nervous systems.



Glia

The nervous systems of vertebrates and most invertebrates include not only neurons but also **glial cells**, or **glia**. The Schwann cells that myelinate axons in the PNS are an example of glia, as are oligodendrocytes, their counterparts in the CNS. **Figure 49.9** provides an overview of the major types of glia in the adult vertebrate and the ways in which they nourish, support, and regulate the functioning of neurons.

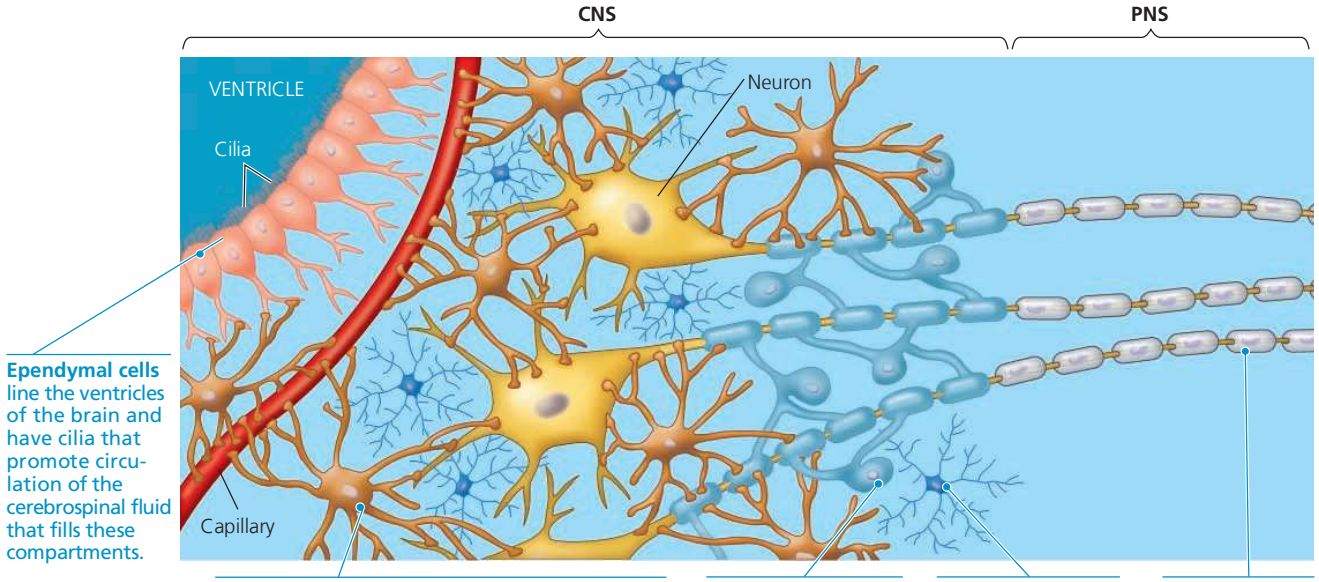
In embryos, two types of glia play essential roles in the development of the nervous system: radial glia and astrocytes. *Radial glia* form tracks along which newly formed neurons migrate from the neural tube, the structure that gives rise to the CNS (see Figure 47.14). Later, *astrocytes* that are adjacent to brain capillaries participate in the formation of the *blood-brain barrier*, a filtering mechanism that prevents many substances in the blood from entering the CNS. Both radial glia and astrocytes can also act as stem cells, which undergo unlimited cell divisions to self-renew and to form more specialized cells.

CONCEPT CHECK 49.1

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 your answer.
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?
3. **MAKE CONNECTIONS** Most tissues regulated by the autonomic nervous system receive both sympathetic and parasympathetic input from postganglionic neurons. Responses are typically local. In contrast, the adrenal medulla receives input only from the sympathetic division and only from preganglionic neurons, yet responses are observed throughout the body. Explain why (see Figure 45.19).

For suggested answers, see Appendix A.

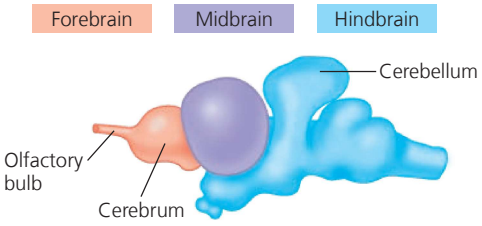
▼ Figure 49.9 Glia in the vertebrate nervous system.



CONCEPT 49.2

The vertebrate brain is regionally specialized

We turn now to the vertebrate brain, which has three major regions: the forebrain, midbrain, and hindbrain (shown here for a ray-finned fish).



Each region is specialized in function. The **forebrain**, which contains the *olfactory bulb* and *cerebrum*, has activities that include processing of olfactory input (smells), regulation of sleep, learning, and any complex processing. The **midbrain**, located centrally in the brain, coordinates routing of sensory input. The **hindbrain**, part of which forms the *cerebellum*, controls involuntary activities, such as blood circulation, and coordinates motor activities, such as locomotion.

EVOLUTION Comparing vertebrates across a phylogenetic tree, we see that the relative sizes of particular brain regions vary **(Figure 49.10)**. Furthermore, these size differences reflect differences in the importance of particular brain functions. Consider, for example, ray-finned fishes, which explore their environment using olfaction, vision, and a lateral line system that detects water currents, electrical stimuli, and body position. The olfactory bulb, which detects scents in the water, is relatively large in these fishes. So is the midbrain, which processes input from the visual and lateral line systems. In contrast, the cerebrum, required for complex processing and learning, is relatively small.

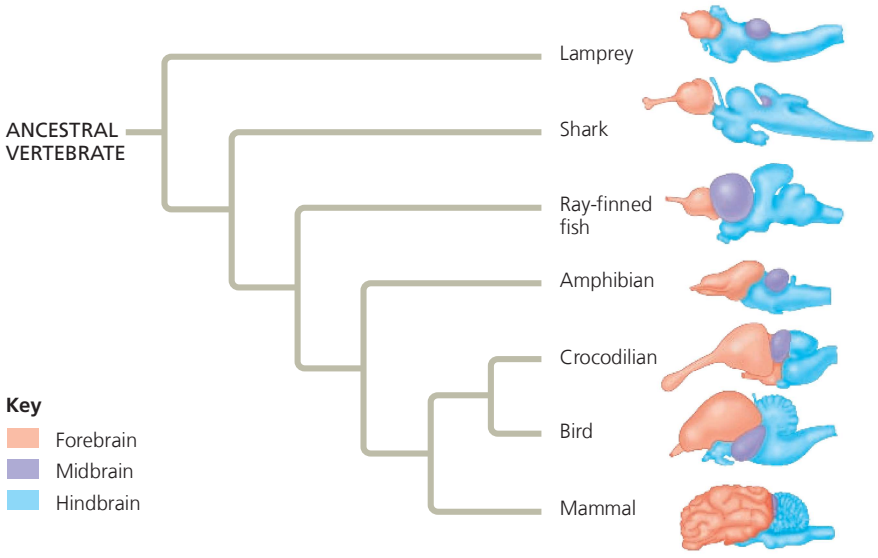
The correlation between the size and function of brain regions can also be observed by considering the cerebellum. Free swimming ray-finned fishes, such as the tuna, control movement in three dimensions in the open water and have a relatively large cerebellum. In comparison, the cerebellum is much smaller in species that don't swim actively, such as the lamprey. Evolution has thus resulted in a close match of structure to function, with the size of particular brain regions correlating with their importance for that species in nervous system function and, hence, species survival and reproduction.

If one compares birds and mammals with groups that diverged from the common vertebrate ancestor earlier in evolution, two trends are apparent. First, the forebrain of birds and mammals occupies a larger fraction of the brain than it does in amphibians, fishes, and other vertebrates. Second, birds and mammals have much larger brains relative to body size than do other groups. Indeed, the ratio of brain size to body weight for birds and mammals is ten times larger than that for their evolutionary ancestors. These differences in both overall brain size and the relative size of the forebrain reflect the greater capacity of birds and mammals for cognition and higher-order reasoning, traits we will return to later in this chapter.

In the case of humans, the 100 billion neurons in the brain make 100 trillion connections. How are so many cells and links organized into circuits and networks that can perform highly sophisticated information processing, storage, and retrieval? In addressing this question, let's begin with **Figure 49.11**, which explores the overall architecture of the human brain. You can 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.

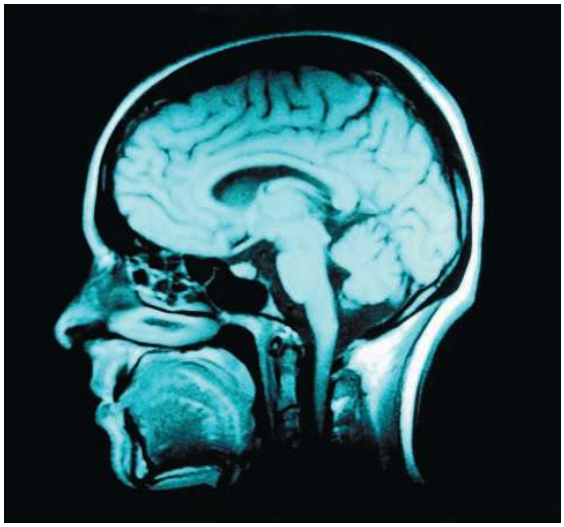
To learn more about how particular brain structure and brain organization overall relate to brain function in humans, we'll first consider activity cycles of the brain and the physiological basis of emotion. Then, in Concept 49.3, we'll shift our attention to regional specialization within the cerebrum.

▼ **Figure 49.10 Vertebrate brain structure and evolution.** These examples of vertebrate brains are drawn to the same overall dimensions to highlight differences in the relative size of major structures. These differences in relative size, which arose over the course of vertebrate evolution, correlate with the importance of particular brain functions for particular vertebrate groups.



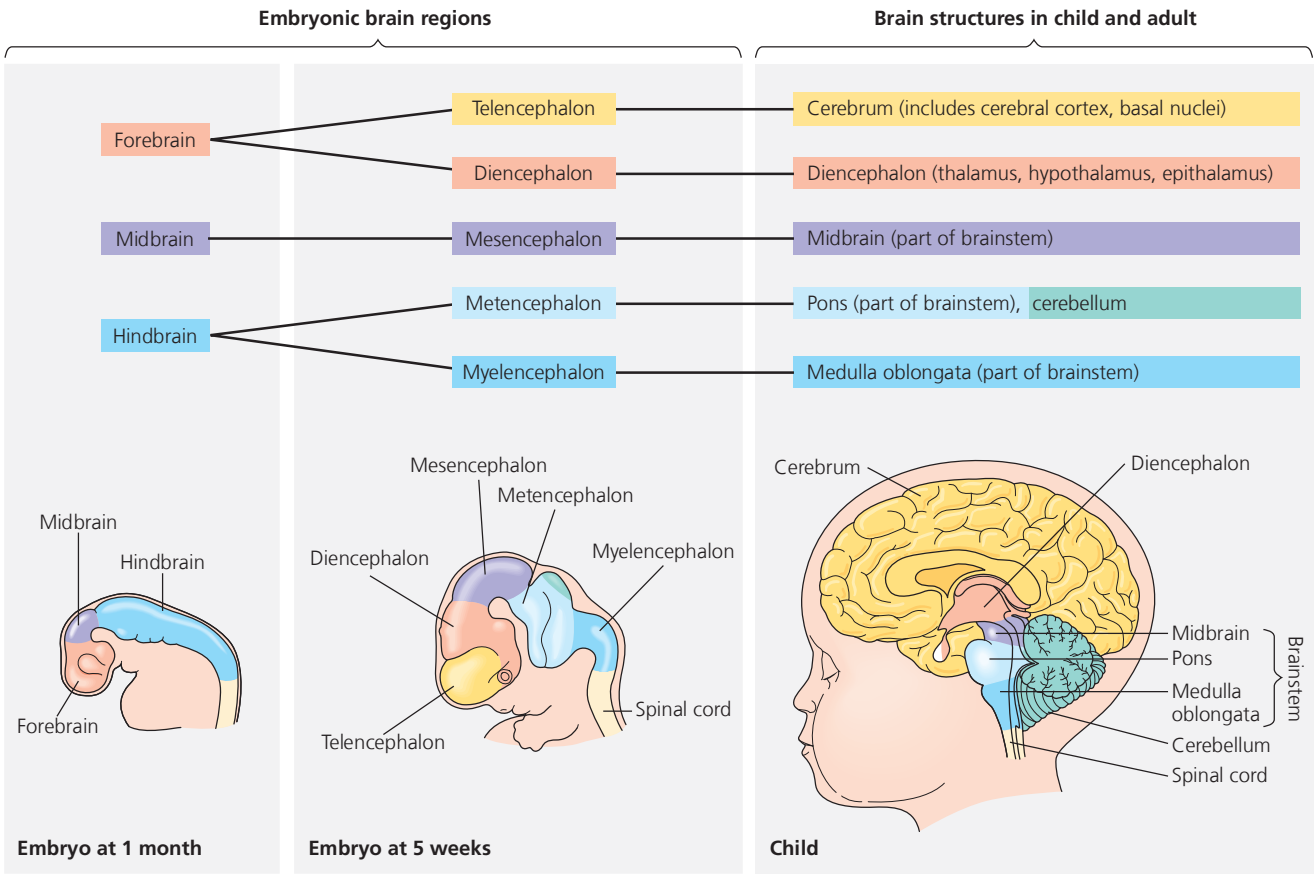
▼ Figure 49.11 Exploring the Organization of the Human Brain

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) of an adult's head shown at right. The diagram below traces the development of these structures in the embryo. Their major functions are explained in the main text of the chapter.



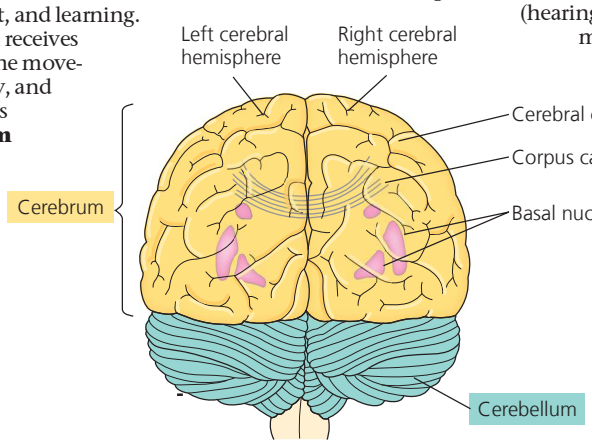
Human Brain Development

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. Meanwhile, 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 outer layer of the cerebrum is called the **cerebral cortex** and is vital for perception, voluntary movement, and learning. The left side of the cerebral cortex 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.



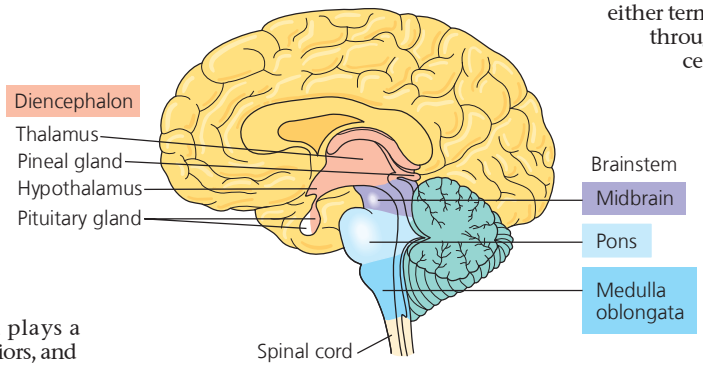
Adult brain viewed from the rear

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, as well as from the cerebral cortex, 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.



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 and sends it 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 as they pass through 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.

Mastering Biology The Visual Brain: Nervous System

Arousal and Sleep

If you've ever drifted off to sleep while listening to a lecture (or reading a book), 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, we can record patterns of electrical activity called brain waves in an electroencephalogram (EEG). These recordings reveal that brain wave frequencies change as the brain progresses through distinct stages of sleep.

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 is this possible? As in other mammals, the forebrain is physically and functionally 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 brain is asleep at a time. EEG recordings from each hemisphere of sleeping dolphins support this hypothesis **(Figure 49.12)**.

Although sleep is essential for survival, we still know very little about its function. One hypothesis is that sleep and dreams are involved in consolidating learning and memory. Evidence supporting this hypothesis includes the finding that test subjects who are kept awake for 36 hours have a reduced ability to remember when particular events occurred, even if they first "perk up" with caffeine. Other experiments show that regions of the brain that are activated during a learning task can become active again during sleep.

Arousal and sleep are controlled in part by the *reticular formation*, a diffuse network formed primarily by neurons in the midbrain and pons **(Figure 49.13)**. These neurons control the timing of sleep periods characterized by rapid eye movements (REMs) and by vivid dreams. Sleep is also regulated by the biological clock, discussed next, and by regions of the forebrain that regulate sleep intensity and duration.

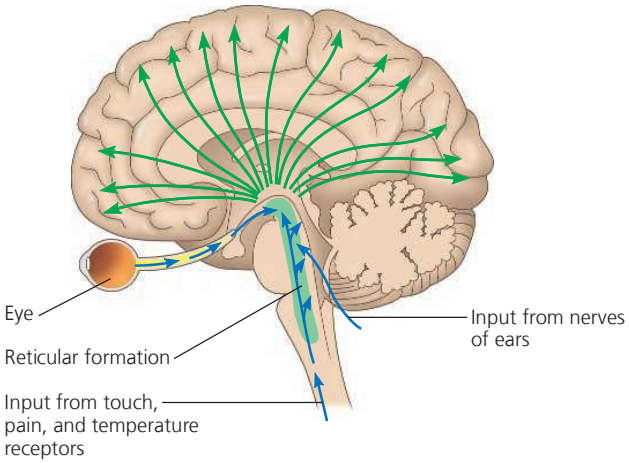
▼ Figure 49.12 Dolphins can be asleep and awake at the same time. EEG recordings were made separately for the two sides of a dolphin's brain. At each time point, low-frequency activity characteristic of sleep was recorded in one hemisphere while higher-frequency activity typical of being awake was recorded in the other hemisphere.

Location	Time: 0 hours	Time: 1 hour
Left hemisphere		
Right hemisphere		

Key

- Low-frequency waves characteristic of sleep
- High-frequency waves characteristic of wakefulness

▼ Figure 49.13 The reticular formation. Once thought to consist of a single diffuse network of neurons, the reticular formation is now recognized as many distinct clusters of neurons. These clusters function in part to filter sensory input (blue arrows), blocking familiar and repetitive information that constantly enters the nervous system before sending the filtered input to the cerebral cortex (green arrows).



Mastering Biology The Visual Brain: Sleep and Waking

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 (see Figure 40.9). For example, in a constant environment humans exhibit a sleep/wake cycle of 24.2 hours, with very little variation among individuals.

What normally links the biological clock to environmental cycles of light and dark in an animal's surroundings? In mammals, circadian rhythms are coordinated by clustered neurons in the hypothalamus (see Figure 49.11). These neurons form a structure called the **SCN**, which stands for **suprachiasmatic nucleus**. (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

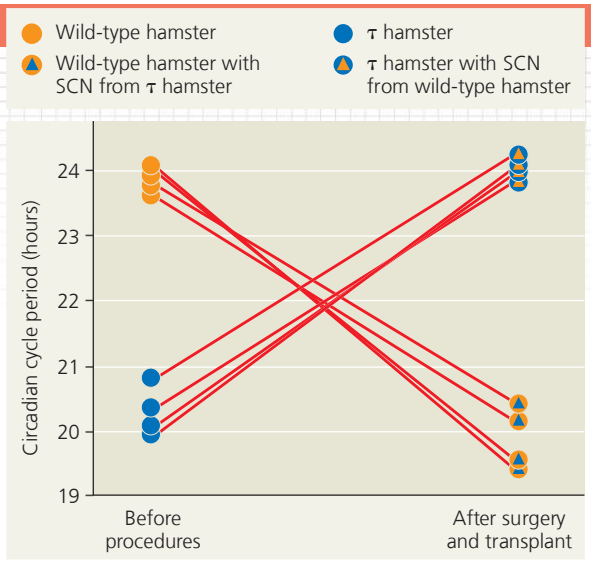
Scientific Skills Exercise

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. Those experiments did not, however, 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 wild-type hamsters have a circadian cycle lasting about 24 hours in the absence of external cues, hamsters that are homozygous for the τ (tau) mutation have a cycle 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. To determine the periodicity of rhythmic activity for the hamsters before the surgery and after the transplants, the researchers measured activity levels over a three-week period. They plotted the data collected for each day in the manner shown in Figure 40.9a and then calculated the circadian cycle period.

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 period is graphed at the upper right. Each red line connects the two data points for an individual hamster.



Data from M. R. Ralph et al., Transplanted suprachiasmatic nucleus determines circadian period, *Science* 247:975–978 (1990).

INTERPRET THE DATA

1. In a controlled experiment, researchers manipulate one variable at a time. **(a)** What was the variable manipulated in this study? **(b)** Why did the researchers use more than one hamster for each procedure? **(c)** What traits of the individual hamsters would likely have been held constant among the treatment groups?
2. For the wild-type hamsters that received τ SCN transplants, what would have been an appropriate experimental control?
3. **(a)** What general trends does the graph above reveal about the circadian cycle period of the transplant recipients? **(b)** 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 of the circadian rhythm?
4. **(a)** In 20% of the hamsters, there was no restoration of rhythmic activity following the SCN transplant. What are some possible reasons for this finding? **(b)** How confident are you in your conclusion about the role of the SCN based on data from 80% of the hamsters?
5. Suppose that researchers identified a mutant hamster that lacked rhythmic activity; that is, its circadian activity 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(b).

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

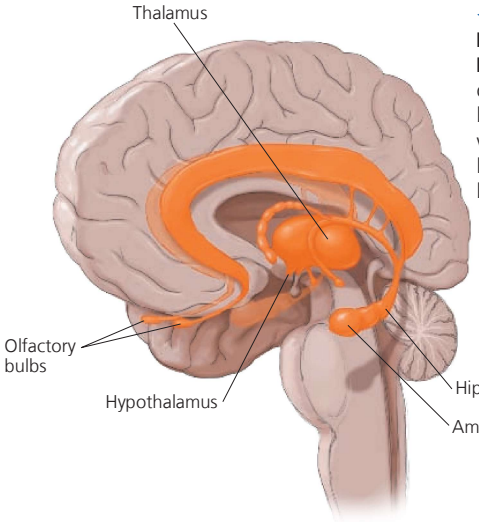
data from an experiment and propose experiments to test the role of the SCN in hamster circadian rhythms.

Mastering Biology **HHMI Video: The Human Suprachiasmatic Nucleus**

Emotions

Whereas a single structure in the brain controls the biological clock, the generation and experience of emotions depend on many brain structures, including the amygdala, hippocampus, and parts of the thalamus. As shown in **Figure 49.14**, these structures border the brainstem in mammals and are therefore called the *limbic system* (from the Latin *limbus*, border).

One way the limbic system contributes to our emotions is by storing emotional experiences as memories that can be recalled by similar circumstances. This is why, for example, a situation that causes you to remember a frightening event



◀ Figure 49.14 The limbic system of the human brain. This diagram shows the brain and brainstem, with the left cerebral hemisphere of the brain removed.

can trigger a faster heart rate, sweating, or fear, even if there is currently nothing scary or threatening in your surroundings. Such storage and recall of emotional memory are especially dependent on function of the **amygdala**, an almond-shaped brain structure near the base of the cerebrum.

Often, generating emotion and experiencing emotion require interactions between different regions of the brain. For example, both laughing and crying 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.

To study the function of the human amygdala, researchers sometimes present adult subjects with an image followed by an unpleasant experience, such as a mild electrical shock. After several trials, study participants experience *autonomic arousal*—as measured by increased heart rate or sweating—if they see the image again. Subjects with brain damage confined to the amygdala can recall the image because their explicit memory is intact. However, they do not exhibit autonomic arousal, indicating that damage to the amygdala has resulted in a reduced capacity for emotional memory.

Functional Imaging of the Brain

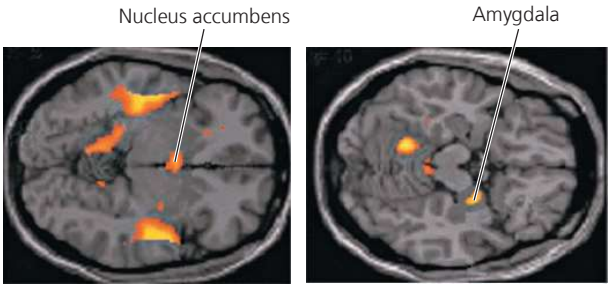
In recent years, scientists have begun studying the amygdala and other brain structures with functional imaging techniques. By scanning the brain while the subject performs a particular function, such as forming a mental image of a person's face, researchers are able to match particular functions with activity in specific brain areas.

Several approaches are available for functional imaging. The first widely used technique was positron-emission tomography (PET), in which injection of radioactive glucose enables a display of metabolic activity. Today, the most commonly used approach is 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 is detected by an increase in the flow of oxygen-rich blood into a particular region.

In one experiment using fMRI, researchers mapped brain activity while subjects listened to music that they described as sad or happy **(Figure 49.15)**. The findings were striking: Different regions of the brain were associated with the experience of each of these contrasting emotions. Subjects who heard sad music had increased activity in the amygdala. In contrast, listening to happy music led to increased activity in the *nucleus accumbens*, a brain structure important for the perception of pleasure.

Functional imaging has an ever-increasing number of applications. Hospitals use fMRI to, for example, monitor recovery from stroke, map abnormalities in migraine headaches, and increase the effectiveness of brain surgery.

▼ Figure 49.15 Functional imaging in the working brain. These images resulted from using fMRI to reveal brain activity associated with music that listeners described as happy or sad. (Each view shows activity in a single plane of the brain, as seen from above.)



VISUAL SKILLS *The two images reveal activity in different horizontal planes through the brain. How can you tell this from the two photographs? What can you conclude about the location of the nucleus accumbens and the amygdala?*

CONCEPT CHECK 49.2

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. Which brain region does this observation indicate is one of those 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 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.

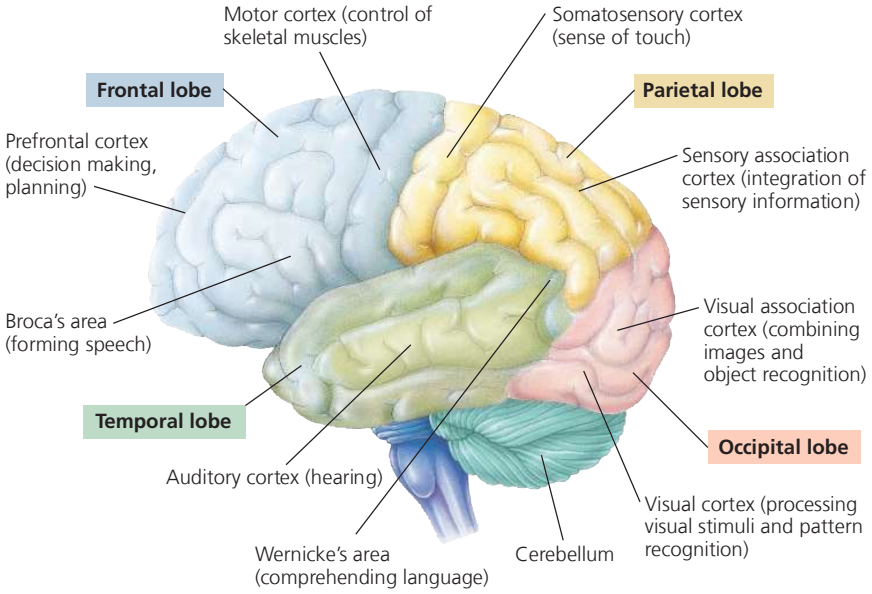
CONCEPT 49.3

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. As shown in Figure 49.11, the cerebrum is the largest structure in the human brain. Like the brain overall, it exhibits regional specialization. For the most part, cognitive functions reside in the cortex, the outer layer of the cerebrum. Within this 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 location of particular functions in the cerebral cortex, neurobiologists often use four regions, or *lobes*, as physical landmarks. Each lobe—frontal, temporal, occipital, and parietal—is named for a nearby bone of the skull, and each is the focus of specific brain activities **(Figure 49.16)**.

▼ Figure 49.16 The human cerebral cortex. Each of the four lobes of the cerebral cortex 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).



Information Processing

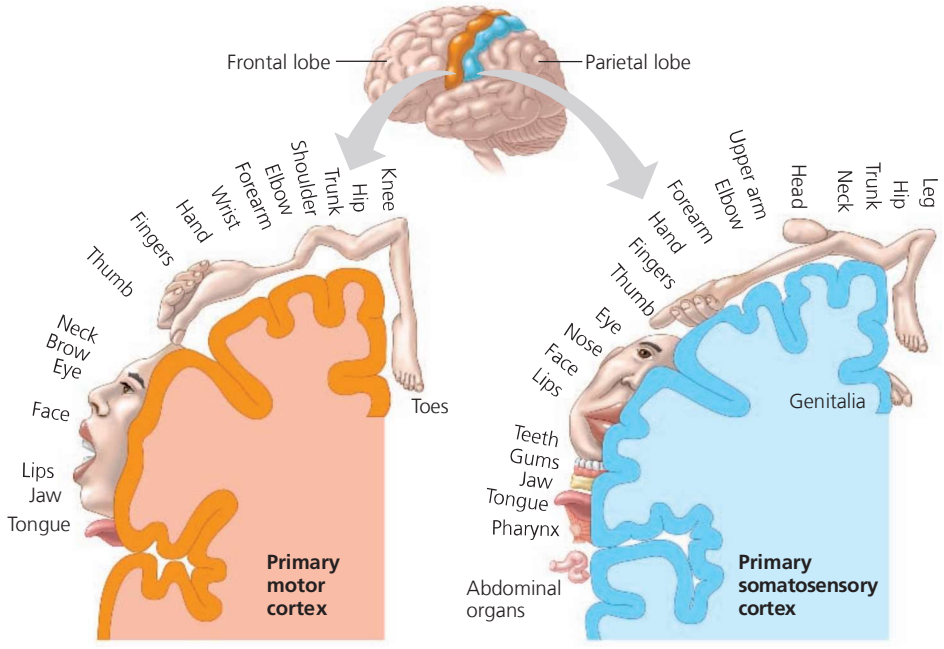
Broadly speaking, the human cerebral cortex receives sensory information from two sources. Some sensory input originates in individual receptors in the hands, scalp, and elsewhere in the body. These somatic sensory, or *somatosensory*, receptors (from the Greek *soma*, body) provide information about touch, pain, pressure, temperature, and the position of muscles and limbs. Other sensory input comes from groups of receptors clustered in dedicated sensory organs, such as the eyes and nose.

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. In the visual association area, information related to such features is combined in a region dedicated to recognizing complex images, such as faces.

Once processed, sensory information passes to the prefrontal cortex, which helps plan actions and movement. The cerebral cortex may then generate motor commands that cause particular behaviors—moving a limb or saying hello, for example. These commands consist of action potentials produced by neurons in the motor cortex, which lies at the rear of the frontal lobe (see Figure 49.16). The action potentials travel along axons to the brainstem and spinal cord, where they excite motor neurons, which in turn excite skeletal muscle cells.

In the somatosensory cortex and motor cortex, neurons are arranged according to the part of the body that generates the sensory input or receives the motor commands **(Figure 49.17)**. For example, neurons that process sensory information from the legs and feet lie in the region of the somatosensory cortex closest to the midline. Neurons that control muscles in the legs and feet are located in the corresponding region of the motor cortex. Notice in Figure 49.17 that the cortical surface area

▼ Figure 49.17 Body part representation in the primary motor and primary somatosensory cortices. In these cross-sectional maps of the cortices, the cortical surface area devoted to each body part is represented by the relative size of that part in the cartoons.



VISUAL SKILLS *Why is the hand larger than the forearm in both parts of this figure?*

devoted to each body part is not proportional to the size of the part. Instead, surface area correlates with the extent of neuronal control needed (for the motor cortex) or with the number of sensory neurons that extend axons to that part (for the somatosensory cortex). Thus, the surface area of the motor cortex devoted to the face is proportionately quite large, reflecting the extensive involvement of facial muscles in communication.

Language and Speech

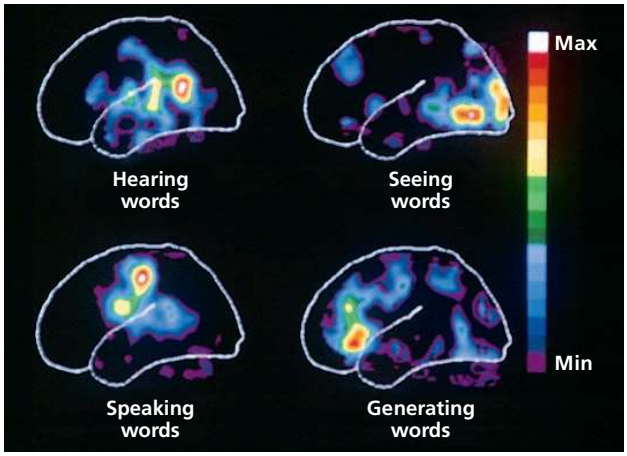
The mapping of cognitive functions within the cortex began in the 1800s when physicians studied the effects of damage to particular regions of the cortex by injuries, strokes, or tumors. Pierre Broca conducted postmortem (after death) examinations of patients who had been able to understand language 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*. 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. PET studies have now confirmed activity in Broca's area during speech generation and Wernicke's area when speech is heard **(Figure 49.18)**.

Lateralization of Cortical Function

Both Broca's area and Wernicke's area are located in the left cerebral hemisphere, reflecting a greater role in 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 dominate in the recognition of faces and patterns, spatial relations, and nonverbal thinking. This difference in function between the right and left hemispheres is called **lateralization**.

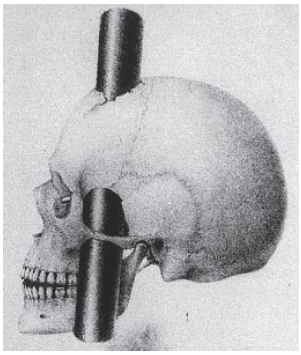
The two cerebral hemispheres normally exchange information through the fibers of the corpus callosum (see Figure 49.11). Severing this connection (a treatment of last resort for the most extreme forms of epilepsy, a seizure disorder) results in a "split-brain" effect. In such patients, the two hemispheres function independently. For example, they cannot read even a familiar word that appears only in their left field of vision: The sensory information travels from the left field of vision to the right hemisphere, but cannot then reach the language centers in the left hemisphere.

▼ Figure 49.18 Mapping language areas in the cerebral cortex. These PET images show activity levels on the left side of one person's brain during four activities, all related to speech. Increases in activity are seen in Wernicke's area when hearing words, Broca's area when speaking words, the visual cortex when seeing words, and the prefrontal cortex when generating words (without reading them).



Frontal Lobe Function

▼ Figure 49.19 Phineas Gage's skull injury.



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 **(Figure 49.19)**. Gage recovered, but his personality changed dramatically. He became emotionally detached, impatient, and erratic in his behavior, providing evidence of the role of the prefrontal cortex in temperament and decision making.

Two further sets of observations support the hypothesis that Gage's brain injury and personality change inform us about frontal lobe function. First, frontal lobe tumors cause similar symptoms: Intellect and memory seem intact, but decision making is flawed and emotional responses are diminished. Second, the same problems arise when the connection between the prefrontal cortex and the limbic system is surgically severed. (This procedure, called a frontal lobotomy, was once a common treatment for severe behavioral disorders but is no longer in use.) Together, these observations provide evidence that the frontal lobes have a substantial influence on what are called "executive functions."

Evolution of Cognition in Vertebrates

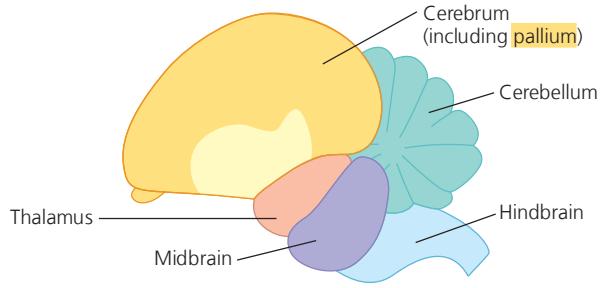
EVOLUTION In nearly all vertebrates, the brain has the same basic structures (see Figure 49.10). Given this uniform organization, how did a capacity for advanced cognition, the perception and reasoning that constitute knowledge,

evolve in certain species? For many years researchers favored the hypothesis that higher-order reasoning in vertebrates required evolution of an extensively convoluted cerebral cortex, as is found in humans, other primates, and cetaceans (whales, dolphins, and porpoises). In humans, for example, the cerebral cortex accounts for about 80% of total brain mass.

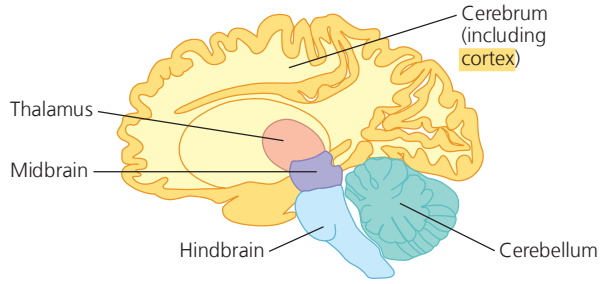
Birds lack a convoluted cerebral cortex and were long thought to have much lower intellectual capacity than primates and cetaceans. However, recent experiments have refuted this idea: Western scrub jays (*Aphelocoma californica*) can remember which food items they hid first. New Caledonian crows (*Corvus moneduloides*) are highly skilled at making and using tools, an ability otherwise well documented only for humans and some other apes. African grey parrots (*Psittacus erithacus*) understand numerical and abstract concepts, such as "same" and "different" and "none."

What brain structures enable some birds to have such sophisticated information processing? The answer appears to be a nuclear (clustered) organization of neurons within the *pallium*, the top or outer portion of the brain **(Figure 49.20a)**. Note that this arrangement is different from that in the human cerebral cortex **(Figure 49.20b)**, where six parallel layers of neurons are arranged tangential to the surface. Thus, vertebrate evolution has resulted in two different types of outer brain organization that can support complex and flexible function.

▼ Figure 49.20 Comparison of regions for higher cognition in avian and human brains. Although structurally different, the **(a)** pallium of a songbird brain and the **(b)** cerebral cortex of the human brain play similar roles in higher cognitive activities and make many similar connections with other brain structures.



(a) Songbird brain (cross section)



(b) Human brain (cross section)

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 clustered 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 to the cerebral cortex in mammals.

Sophisticated information processing depends not only on the overall organization of a brain but also on the very small-scale changes that enable learning and encode memory. We'll turn to these changes in the context of humans in the next section.

Mastering Biology
Interview with Erich Jarvis: Studying how songbirds learn melodies

CONCEPT CHECK 49.3

1. How can studying individuals with damage to a particular brain region provide insight into the normal function of that region?
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 49.4

Changes in synaptic connections underlie memory and learning

Formation of the nervous system occurs stepwise. First, regulated gene expression and signal transduction determine where neurons form in the developing embryo. Next, neurons compete for survival. Every neuron requires growth-supporting factors, which are produced in limited quantities by tissues that direct neuron growth. Neurons that don't reach the proper locations fail to receive such factors and undergo programmed cell death. The net effect is the preferential survival of neurons that are in a proper location. The competition is so severe that half of the neurons formed in the embryo are eliminated.

In the final phase of organizing the nervous system, synapse elimination takes place. During development, each neuron forms numerous synapses, more than are required for its proper function. Once a neuron begins to function, its activity stabilizes some synapses and destabilizes others. By the time the embryo completes development, more than half of all synapses have been eliminated. In humans, this elimination of unnecessary connections, a process called synaptic pruning, continues after birth and throughout childhood.

Together, neuron development, neuron death, and synapse elimination establish the basic network of cells and connections within the nervous system required throughout life.

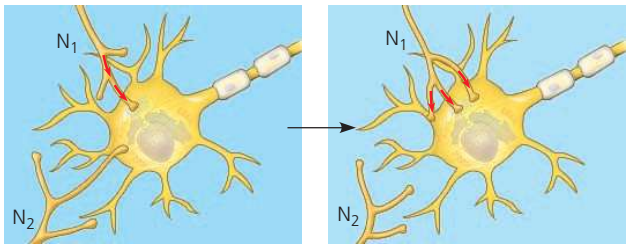
Neuronal Plasticity

Although the overall organization of the CNS is established during embryonic development, the connections between neurons can be modified. This capacity for the nervous system to be remodeled, especially in response to its own activity, is called **neuronal plasticity**.

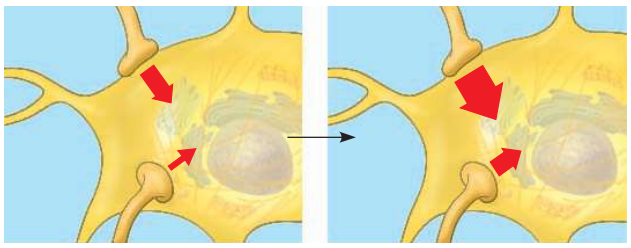
Much of the reshaping of the nervous system occurs at synapses. Synapses belonging to circuits that link information in useful ways are maintained, whereas those that convey bits of information lacking any context may be lost. Specifically, when the activity of a synapse coincides with that of other synapses, changes may occur that reinforce that synaptic connection. Conversely, when the activity of a synapse fails to coincide with that of other synapses, the synaptic connection sometimes becomes weaker.

Figure 49.21a illustrates how activity-dependent events can trigger the gain 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. Signaling at a synapse can also be strengthen or weakened, as shown in **Figure 49.21b**. In our traffic analogy, this would be equivalent to widening or narrowing an entrance ramp.

▼ **Figure 49.21 Neuronal plasticity.** Synaptic connections can change over time, strengthening or weakening in response to the level of activity at the synapse.



(a) High-level activity at the synapse of neuron N_1 with the postsynaptic neuron leads to recruitment of additional axon terminals from that neuron. Lack of activity at the synapse with neuron N_2 leads to loss of functional connections with that neuron.



(b) If two synapses on a postsynaptic cell are often active at the same time, the strength of both responses may increase.

A defect in neuronal plasticity may underlie *autism spectrum disorder*, which results in impaired communication and social interaction, as well as stereotyped and repetitive behaviors beginning in early childhood. There is now growing evidence that autism spectrum disorder involves a disruption of activity-dependent remodeling at synapses. At the same time, extensive research has ruled out any link to vaccine preservatives, once proposed as a potential risk factor based on fraudulent data.

Although the underlying causes of autism are unknown, there is a strong genetic contribution to this and related disorders. Further understanding of the autism-associated disruption in synaptic plasticity may help efforts to better understand and treat this disorder.

Memory and Learning

Neuronal 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.

Short-term and long-term memory both 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 memories are made long-term, the links in the hippocampus are replaced by connections within the cerebral cortex itself. As discussed earlier, some of this consolidation of memory 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.

According to our current understanding of memory, the hippocampus is essential for acquiring new long-term memories but not for maintaining them. This hypothesis readily explains the symptoms of some individuals who suffer damage to the hippocampus: They cannot form any new lasting memories but can freely recall events from before their injury. In effect, their lack of normal hippocampal function traps them in their past. Hippocampal damage and memory loss are common in the early stages of Alzheimer's disease (see Concept 49.5).

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.

Motor skills, such as tying your shoes or writing, are usually learned by repetition. You can perform these skills without consciously recalling the individual steps required to do these tasks correctly. Learning skills and procedures, such as those required to ride a bicycle, appears to involve cellular mechanisms very similar to those responsible for brain growth and development. In such cases, neurons actually make new connections. In contrast, memorizing phone numbers, facts, and places—which can be very rapid and may require only one exposure to the relevant item—may rely mainly on changes in the strength of existing neuronal connections. Next we will consider one way that such changes in strength can take place.

Long-Term Potentiation

In searching for the physiological basis of memory, researchers have concentrated their attention on processes that can alter a synaptic connection, making the flow of communication either more efficient or less efficient. We will focus here on **long-term potentiation (LTP)**, a lasting increase in the strength of synaptic transmission. Data indicate that LTP represents a fundamental process for memory storage and learning.

First characterized in tissue slices from the hippocampus, LTP involves a presynaptic neuron that releases the excitatory neurotransmitter glutamate. LTP involves two types of glutamate receptors, each named for a molecule—NMDA or AMPA—that can be used to artificially activate that particular receptor. As shown in **Figure 49.22**, the set of receptors present on the postsynaptic membrane changes when two conditions are met: a rapid series of action potentials at the presynaptic neuron and a depolarizing stimulus elsewhere on the postsynaptic cell. The result is LTP—a stable increase in the size of the postsynaptic potentials at a synapse whose activity coincides with that of another input.

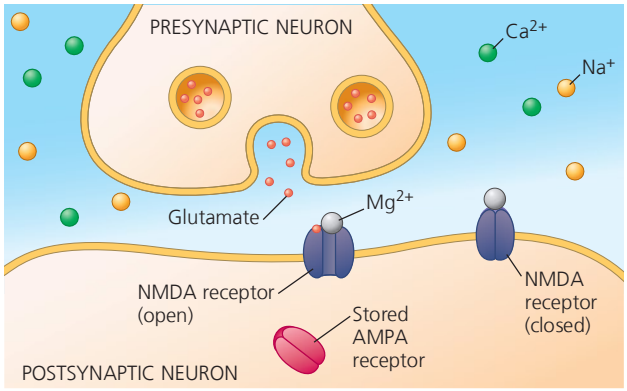
Mastering Biology The Visual Brain: Learning and Memory

CONCEPT CHECK 49.4

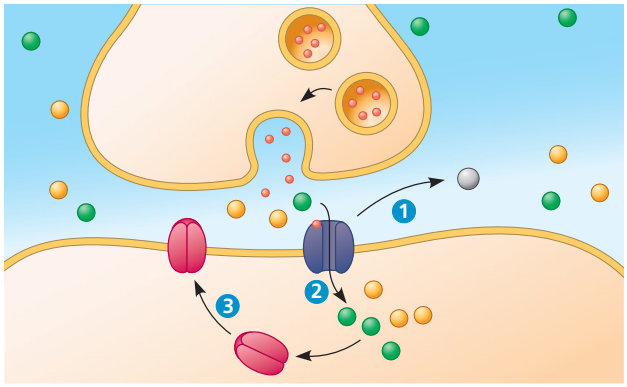
1. Outline two mechanisms by which information flow between two neurons in an adult can increase.
2. Individuals with localized brain damage have been very useful in the study of many brain functions. Why is this unlikely to be true for consciousness?
3. **WHAT IF?** Suppose that a person with damage to the hippocampus is unable to acquire new long-term memories. Why might the acquisition of short-term memories also be impaired?

For suggested answers, see Appendix A.

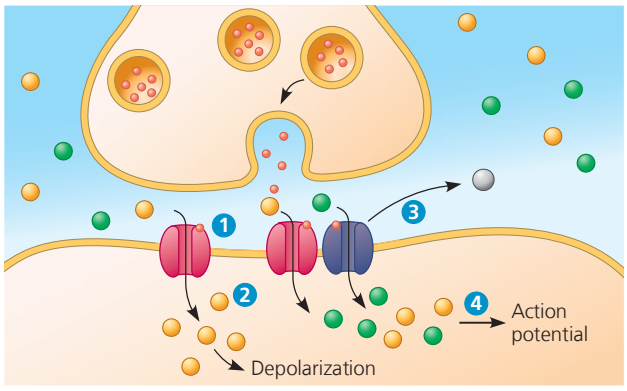
▼ Figure 49.22 Long-term potentiation in the brain.



(a) Synapse prior to long-term potentiation (LTP). The NMDA glutamate receptors open in response to glutamate but are blocked by Mg^{2+}.



(b) Establishing LTP. Activity at nearby synapses (not shown) depolarizes the postsynaptic membrane, causing 1 Mg^{2+} release from NMDA receptors. The unblocked receptors respond to glutamate by allowing 2 an influx of Na^+ and Ca^{2+}. The Ca^{2+} influx triggers 3 insertion of stored AMPA glutamate receptors into the postsynaptic membrane.



(c) Synapse exhibiting LTP. Glutamate release activates 1 AMPA receptors that trigger 2 depolarization. The depolarization unblocks 3 NMDA receptors. Together, the AMPA and NMDA receptors trigger postsynaptic potentials strong enough to initiate 4 action potentials without input from other synapses. Additional mechanisms (not shown) contribute to LTP, including receptor modification by protein kinases.

CONCEPT 49.5

Many nervous system disorders can now be explained in molecular terms

Disorders of the nervous system, including schizophrenia, depression, drug addiction, Alzheimer's disease, and Parkinson's disease, are a major public health problem. Together, they result in more hospitalizations in the United States than do heart disease or cancer. Until recently, hospitalization was typically the only available treatment, and many affected individuals were institutionalized for the rest of their lives. Today, many disorders that alter mood or behavior can be treated with medication, reducing average hospital stays for these disorders to only a few weeks. Nevertheless, many challenges remain with regard to preventing or treating nervous system disorders, especially Alzheimer's disease and other disorders that lead to nervous system degeneration.

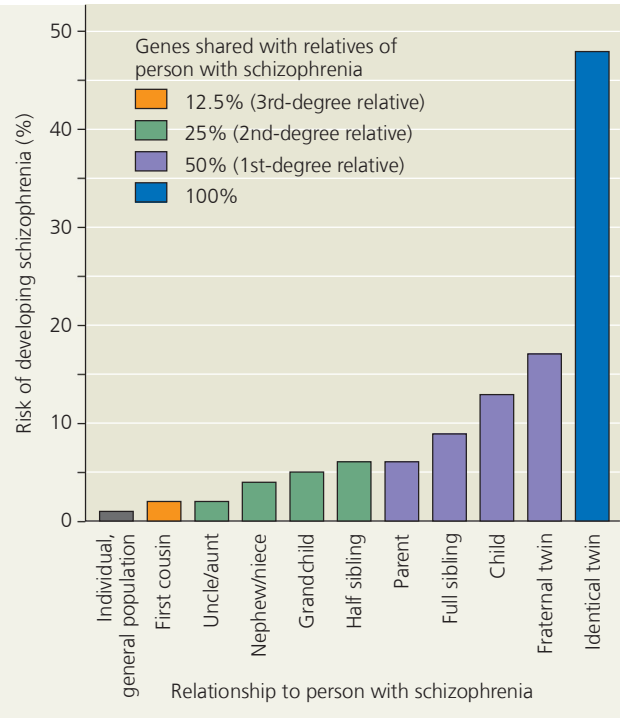
Major research efforts are under way to identify genes that cause or contribute to disorders of the nervous system. Identifying such genes offers hope for identifying causes, predicting outcomes, and developing effective treatments. For most nervous system disorders, however, genetic contributions only partially account for which individuals are affected. The other significant contribution to disease comes from environmental factors. Unfortunately, such environmental contributions are typically very difficult to identify.

To distinguish between genetic and environmental variables, scientists often carry out family studies. In these studies, researchers track how family members are related genetically, which individuals are affected, and which family members grew up in the same household. These studies are especially informative when one of the affected individuals has either an adopted sibling who is genetically unrelated or an identical twin, as we'll see for the disorder schizophrenia, our next topic.

Schizophrenia

Approximately 1% of the world's population suffers from **schizophrenia**, a severe mental disturbance characterized by psychotic episodes in which patients have a distorted perception of reality. People with schizophrenia typically experience hallucinations (such as "voices" that only they can hear) and delusions (for example, the idea that others are plotting to harm them). Family studies have revealed a very strong genetic component for schizophrenia. However, as shown in **Figure 49.23**, the disease is also subject to environmental influences, since an individual who shares 100% of his or her genes with a twin with schizophrenia has only a 48% chance of developing the disorder. Despite the commonly held notion, schizophrenia does not necessarily result in multiple personalities. Rather, the name *schizophrenia* (from the Greek *schizo*, split, and *phren*, mind) refers to the fragmentation of what are normally integrated brain functions.

▼ **Figure 49.23 Genetic contribution to schizophrenia.** First cousins, uncles, and aunts of a person with schizophrenia have twice the risk of unrelated members of the population of developing the disease. The risks for closer relatives are many times greater.



INTERPRET THE DATA *What is the likelihood of a person developing schizophrenia if the disorder affects his or her fraternal twin? How would the likelihood change if DNA sequencing revealed that the twins shared the genetic variants that contribute to the disorder?*

One current hypothesis is that neuronal pathways that use dopamine as a neurotransmitter are disrupted in schizophrenia. Supporting evidence comes from the fact that many drugs that alleviate the symptoms of schizophrenia block dopamine receptors. In addition, the drug amphetamine ("speed"), which stimulates dopamine release, can produce the same set of symptoms as schizophrenia. Recent genetic studies suggest a link between schizophrenia and particular forms of the complement protein C4, an immune system component.

Depression

Depression is a disorder characterized by depressed mood, as well as abnormalities in sleep, appetite, and energy level. Two broad forms of depressive illness are known: major depressive disorder and bipolar disorder. Individuals affected by **major depressive disorder** undergo periods—often lasting many months—during which once enjoyable activities provide no pleasure and provoke no interest. One of the most common nervous system disorders, major depression affects about one in every seven adults at some point, and twice as many women as men.

Bipolar disorder, or manic-depressive disorder, involves extreme swings of mood and affects about 1% of the world's population. The manic phase is characterized by high self-esteem, increased energy, a flow of ideas, overtalkativeness, and increased risk taking. In its milder forms, this phase is sometimes associated with great creativity, and some well-known artists, musicians, and literary figures (Vincent van Gogh, Robert Schumann, Virginia Woolf, and Ernest Hemingway, to name a few) have had productive periods during manic phases. The depressive phase comes with lessened motivation, sense of worth, and ability to feel pleasure, as well as sleep disturbances. These symptoms can be so severe that affected individuals attempt suicide.

Major depressive and bipolar disorders are among the nervous system disorders for which therapies are available. Many drugs used to treat depressive illness, including fluoxetine (Prozac), increase activity of biogenic amines in the brain.

The Brain's Reward System and Drug Addiction

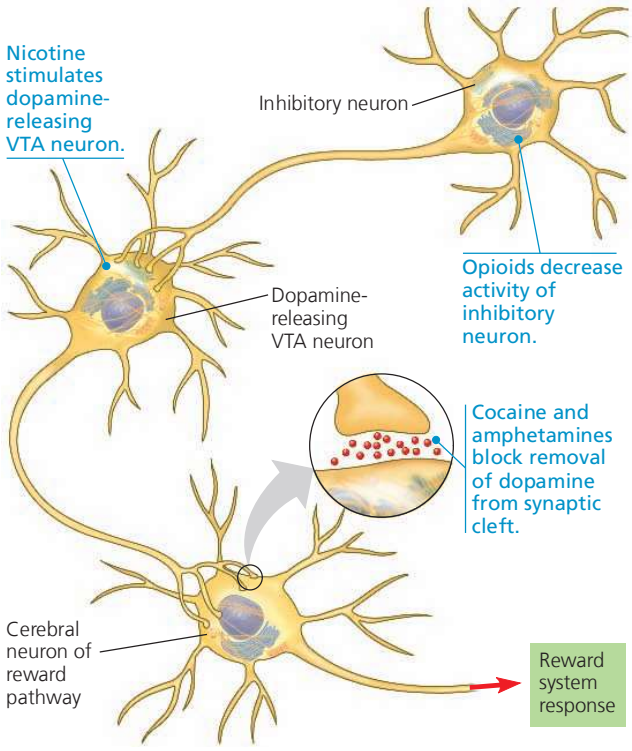
Emotions are strongly influenced by a neuronal circuit in the brain called the *reward system*. The reward system provides motivation for activities that enhance survival and reproduction, such as eating in response to hunger, drinking when thirsty, and engaging in sexual activity when aroused. Inputs to the reward system are received by neurons in the *ventral tegmental area* (*VTA*), a region located within the midbrain (see Figure 49.11). When activated, these neurons release the neurotransmitter dopamine from their synaptic terminals **(Figure 49.24)**. Targets of this dopamine signaling include the nucleus accumbens and the prefrontal cortex.

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 range from sedatives to stimulants and include alcohol, cocaine, and nicotine, as well as opioids, such as heroin, fentanyl and oxycodone. All enhance the activity of the dopamine pathway (see Figure 49.24). 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 consumption. In 2018, the Centers for Disease Control and Prevention reported that an average of 130 Americans died from opioid overdose every day.

Laboratory animals are highly valuable in modeling and studying addiction. Rats, for example, will provide themselves with heroin, cocaine, or amphetamine when given a dispensing system linked to a lever in their cage. Furthermore, they exhibit addictive behavior, continuing to self-administer the drug rather than seek food, even to the point of starvation.

As scientists expand their knowledge about the brain's reward system and the various forms of addiction, there is hope that the insights will lead to more effective prevention and treatment.

▼ Figure 49.24 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), a region located near the base of the brain.



MAKE CONNECTIONS *Review depolarization in Concept 48.3. What effect would you expect if you depolarized the neurons in the VTA? Explain.*

Mastering Biology
Interview with Ulrike Heberlein: Research with drunk flies

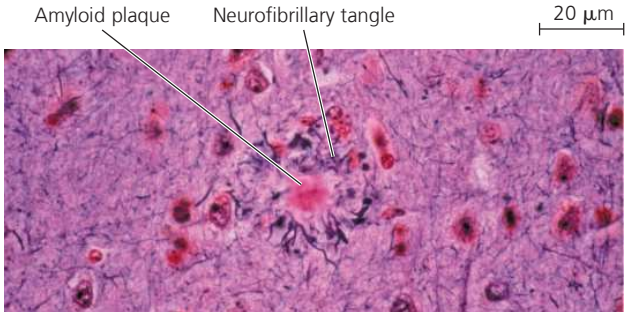
Alzheimer's Disease

The condition now known as **Alzheimer's disease** is a mental deterioration, or dementia, characterized by confusion and memory loss. Its incidence is age related, rising from about 10% at age 65 to about 35% at age 85. Overall, Alzheimer's disease accounts for about two of every three cases of dementia. It is also the sixth most common cause of death among adults in the United States, affecting individuals including former President Ronald Reagan, author E.B. White, and civil rights heroine Rosa Parks.

Alzheimer's disease is progressive; patients gradually become less able to function and eventually need to be dressed, bathed, and fed by others. Individuals with Alzheimer's disease often lose their ability to recognize people and may treat even immediate family members with suspicion and hostility.

Examining the brains of individuals who have died of Alzheimer's disease reveals two characteristic

▼ Figure 49.25 Microscopic signs of Alzheimer's disease. A hallmark of Alzheimer's disease is the presence in brain tissue of neurofibrillary tangles surrounding plaques made of β-amyloid (LM).



Mastering Biology **BBC Video: Searching for a Cure for Alzheimer's**

features: amyloid plaques and neurofibrillary tangles, as shown in **Figure 49.25**. There is also often massive shrinkage of brain tissue, reflecting the death of neurons in many areas of the brain, including the hippocampus and cerebral cortex.

The plaques are aggregates of β-amyloid, an insoluble peptide that is cleaved from the extracellular portion of a membrane protein found in neurons. Membrane enzymes, called secretases, catalyze the cleavage, causing β-amyloid to accumulate in plaques outside the neurons. It is these plaques that appear to trigger the death of surrounding neurons.

The neurofibrillary tangles observed in Alzheimer's disease are primarily made up of the tau protein. (This protein is unrelated to the tau mutation that affects circadian rhythm in hamsters.) The tau protein normally helps assemble and maintain microtubules that transport nutrients along axons. In Alzheimer's disease, tau undergoes changes that cause it to bind to itself, resulting in neurofibrillary tangles. There is evidence that changes in tau are associated with the appearance of early-onset Alzheimer's disease, a much less common disorder that affects relatively young individuals. At present, there are no treatments available that block the progression of Alzheimer's disease.

Tau protein accumulation is also characteristic of a degenerative brain disease found in athletes, military veterans, and others with a history of concussion or other repetitive brain trauma. (A concussion is a brain injury caused by a blow or jolt to the head or a hit to the body that shakes the brain.) Known as *chronic traumatic encephalopathy (CTE)*, this disease was first described in the early 2000s and has now been detected in postmortem diagnosis of more than 100 men who had played professional football in the National Football League, among others.

Parkinson's Disease

Symptoms of **Parkinson's disease**, a motor disorder, include muscle tremors, poor balance, a flexed posture, and a shuffling gait. Facial muscles become rigid, limiting the ability of patients to vary their expressions. Cognitive defects may also develop. Like Alzheimer's disease, Parkinson's disease is a progressive brain illness and is more common with advancing age. The incidence of Parkinson's disease is about 1% at age 65 and about 5% at age 85. In the United States population, approximately 1 million people have Parkinson's disease.

Parkinson's disease involves the death of neurons in the midbrain that normally release dopamine at synapses in the basal nuclei. As with Alzheimer's disease, protein aggregates accumulate. Most cases of Parkinson's disease lack an identifiable cause; however, a rare form of the disease that appears in relatively young adults has a clear genetic basis. Molecular studies of mutations linked to this early-onset Parkinson's disease reveal disruption of genes required for certain mitochondrial functions. Researchers are investigating whether mitochondrial defects also contribute to the more common, later-onset form of the disease.

At present, Parkinson's disease can be treated, but not cured. Approaches used to manage the symptoms include brain surgery, deep-brain stimulation, and a dopamine-related drug, L-dopa. Unlike dopamine, L-dopa crosses the blood-brain barrier. Within the brain, the enzyme dopa decarboxylase converts the drug to dopamine, reducing the severity of Parkinson's disease symptoms:

Future Directions in Brain Research

In 2014, the United States government launched a bold 12-year project, the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. The aim is to develop innovative technologies and drive scientific advances, similar to the major projects that accomplished landing a person on the moon and mapping the human genome. Specific BRAIN goals are to map brain circuits, measure activity within those circuits, and discover how this activity is translated into thought and behavior.

CONCEPT CHECK 49.5

1. Compare Alzheimer's disease and Parkinson's disease.
2. How is dopamine activity related to schizophrenia, drug addiction, and Parkinson's disease?
3. **WHAT IF?** If you could detect early-stage Alzheimer's disease, would you expect to see brain changes that were similar to, although less extensive than, those seen in patients who have died of this disease? Explain.

For suggested answers, see Appendix A.

49 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

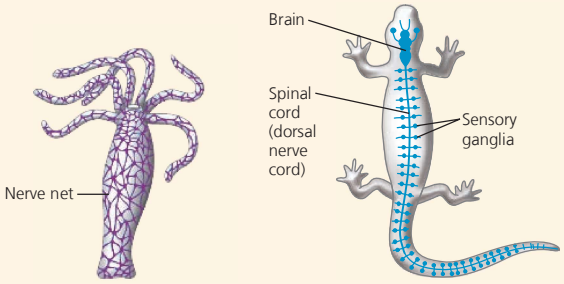
SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 49.1

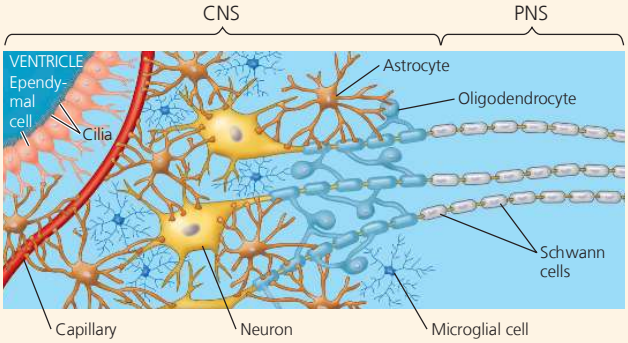
Nervous systems consist of circuits of neurons and supporting cells *(pp. 1086–1090)*

- Invertebrate nervous systems range in complexity from simple nerve nets to highly centralized nervous systems having complicated brains and ventral nerve cords.



Hydra (cnidarian) Salamander (vertebrate)

- 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 control **reflex** responses, in which sensory input is linked to motor output without involvement of the brain.

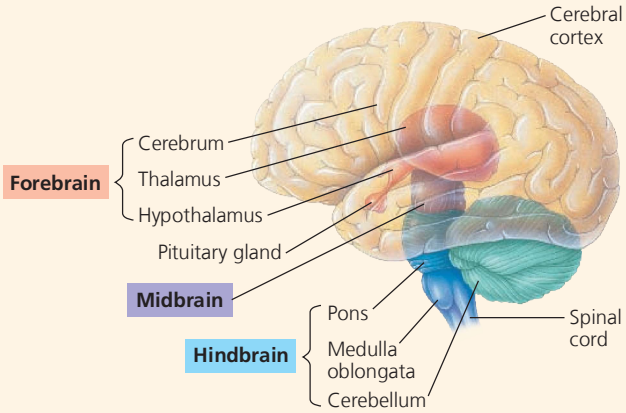


- Afferent neurons carry sensory signals to the CNS. Efferent neurons function in either the **motor system**, which carries signals to skeletal muscles, or the **autonomic nervous system**, which regulates smooth and cardiac muscles. The **sympathetic** and **parasympathetic divisions** of the autonomic nervous system have antagonistic effects on a diverse set of target organs, while the **enteric nervous system** controls the activity of many digestive organs.
- Vertebrate neurons are supported by **glia**, including astrocytes, oligodendrocytes, and Schwann cells. Some glia serve as stem cells that can differentiate into mature neurons.

? *How does the circuitry of a reflex facilitate a rapid response?*

CONCEPT 49.2

The vertebrate brain is regionally specialized *(pp. 1091–1096)*



- 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 reticular formation, a network of neurons within the **brainstem**, regulates 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, a group of neurons called 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 49.3

The cerebral cortex controls voluntary movement and cognitive functions *(pp. 1096–1099)*

- Each side of the **cerebral cortex** has four lobes—frontal, temporal, occipital, and parietal—that contain primary sensory areas and association areas. Association areas integrate information from different sensory areas. Broca's area and Wernicke's area are essential for generating and understanding language. These functions are concentrated in the left cerebral hemisphere, as are math and logic operations. The right hemisphere appears to be stronger at pattern recognition and nonverbal thinking.
- In the somatosensory cortex and the motor cortex, neurons are distributed according to the part of the body that generates sensory input or receives motor commands.
- Primates and cetaceans, which are capable of higher cognition, have an extensively convoluted cerebral cortex. 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. Some birds can solve problems and understand abstractions in a manner indicative of higher cognition.

? *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 49.4

Changes in synaptic connections underlie memory and learning *(pp. 1099–1101)*

- During development, more neurons and synapses form than will exist in the adult. The programmed death of neurons and elimination of synapses in embryos establish the basic structure of the nervous system. In the adult, 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 **neuronal plasticity.** Our **short-term memory** relies on temporary links in the hippocampus. In **long-term memory**, these links are replaced by connections within the cerebral cortex.

? *Learning multiple languages is typically easier early in childhood than later in life. How does this fit with our understanding of neural development?*

CONCEPT 49.5

Many nervous system disorders can now be explained in molecular terms *(pp. 1102–1104)*

- **Schizophrenia**, which is characterized by hallucinations, delusions, and other symptoms, affects neuronal pathways that use dopamine as a neurotransmitter. Drugs that increase the activity of biogenic amines in the brain can be used to treat **bipolar disorder** and **major depressive disorder**. The compulsive drug use that characterizes addiction reflects altered activity of the brain's reward system, which normally provides motivation for actions that enhance survival or reproduction.
- **Alzheimer's disease** and **Parkinson's disease** are neurodegenerative and typically age related. Alzheimer's disease is a dementia in which neurofibrillary tangles and amyloid plaques form in the brain. Parkinson's disease is a motor disorder caused by the death of dopamine-secreting neurons and associated with the presence of protein aggregates.

? *The fact that both amphetamine and PCP have effects similar to the symptoms of schizophrenia suggests a potentially complex basis for this disease. Explain.*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. Activation of the parasympathetic branch of the autonomic nervous system
   (A) increases heart rate.
   (B) enhances digestion.
   (C) triggers release of epinephrine.
   (D) causes conversion of glycogen to glucose.
2. Which of the following structures or regions is correctly paired with its function?
   (A) limbic system—motor control of speech
   (B) medulla oblongata—homeostatic control
   (C) cerebrum—coordination of movement and balance
   (D) amygdala—short-term memory
3. Patients with damage to Wernicke's area have difficulty
   (A) coordinating limb movement.
   (B) generating speech.
   (C) recognizing faces.
   (D) understanding language.
4. The cerebral cortex plays a major role in
   (A) emotional memory.
   (B) hand-eye coordination.
   (C) circadian rhythm.
   (D) breath holding.

Levels 3-4: Applying/Analyzing

5. After suffering a stroke, a patient can see objects anywhere in front of him but pays attention only to objects in his right field of vision. When asked to describe these objects, he has difficulty judging their size and distance. What part of the brain was likely damaged by the stroke?
   (A) the left frontal lobe
   (B) the right frontal lobe
   (C) the right parietal lobe
   (D) the corpus callosum
6. Injury localized to the hypothalamus would most likely disrupt
   (A) regulation of body temperature.
   (B) short-term memory.
   (C) executive functions, such as decision making.
   (D) sorting of sensory information.
7. **DRAW IT** The reflex that pulls your hand away when you prick your finger on a sharp object relies on a neuronal circuit with two synapses in the spinal cord. (a) Using a circle to represent a cross section of the spinal cord, draw the circuit. Label the types of neurons, the direction of information flow in each, and the locations of synapses. (b) Draw a simple diagram of the brain indicating where pain would eventually be perceived.

Levels 5-6: Evaluating/Creating

8. **EVOLUTION CONNECTION** 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. Identify problems you see in defining intelligence in these ways.
9. **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 that sign language but could not readily generate sign language that represented his thoughts. Propose *two* hypotheses that could explain this finding. How might you distinguish between them?
10. **SCIENCE, TECHNOLOGY, AND SOCIETY** With increasingly sophisticated methods for scanning brain activity, scientists are developing the ability to detect an individual's particular emotions and thought processes from outside the body. What benefits and problems do you envision when such technology becomes readily available? Explain.
11. **WRITE ABOUT A THEME: INFORMATION** In a short essay (100–150 words), explain how specification of the adult nervous system by the genome is incomplete.
12. **SYNTHESIZE YOUR KNOWLEDGE**

Imagine you are standing at a microphone in front of a crowd. Checking your notes, you begin speaking. Using the information in this chapter, describe the series of events in particular regions of the brain that enabled you to say the very first word.

For selected answers, see Appendix A.

Explore Scientific Papers with Science in the Classroom AAAS
How does a neuron develop different functions than those of similar neighboring neurons?
Go to "New Neurons Stand Out from the Crowd" at www.scienceintheclassroom.org.
Instructors: Questions can be assigned in Mastering Biology.

50 Sensory and Motor Mechanisms

KEY CONCEPTS

50.1 Sensory receptors transduce stimulus energy and transmit signals to the central nervous system *p. 1108*

50.2 In hearing and equilibrium, mechanoreceptors detect moving fluid or settling particles *p. 1112*

50.3 The diverse visual receptors of animals depend on light-absorbing pigments *p. 1117*

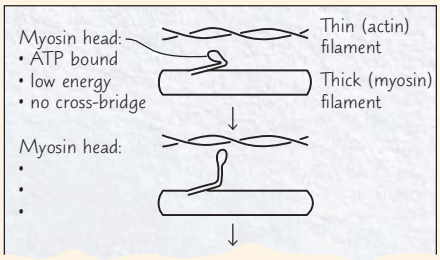
50.4 The senses of taste and smell rely on similar sets of sensory receptors *p. 1123*

50.5 The physical interaction of protein filaments is required for muscle function *p. 1125*

50.6 Skeletal systems transform muscle contraction into locomotion *p. 1132*

Study Tip

Diagram a process: To help you understand the sliding-filament mechanism of muscle contraction, fill in the remaining steps of the process. For each step, draw the position of the myosin head and list 1) the form of ATP or its components bound; 2) the energy state (low/high); and 3) whether a cross-bridge forms at that step.



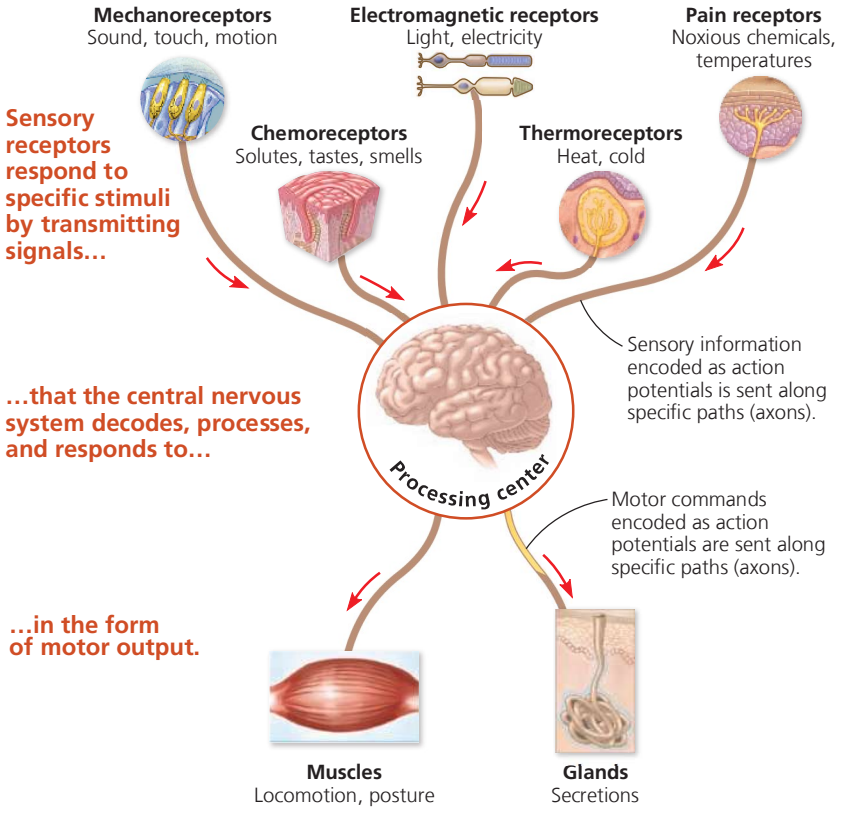
Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 50
- Figure 50.18 Walkthrough: Response of a Photoreceptor Cell to Light
- BioFlix® Animation: Muscle Contraction

For Instructors to Assign (in Item Library)
- Activity: Structure and Function of the Eye
- Tutorial: Energy Costs of Locomotion

Figure 50.1 Tunneling beneath North American wetlands, the star-nosed mole (*Condylura cristata*) finds its prey in almost total darkness. To do so, the mole relies on a star-shaped cluster of appendages, each with 25,000 touch-sensitive receptors. Relaying signals to the mole's brain, the receptors initiate information processing that enables the animal to capture and eat its prey in a fraction of a second.

What steps link sensory stimuli to animal activity?



CONCEPT 50.1

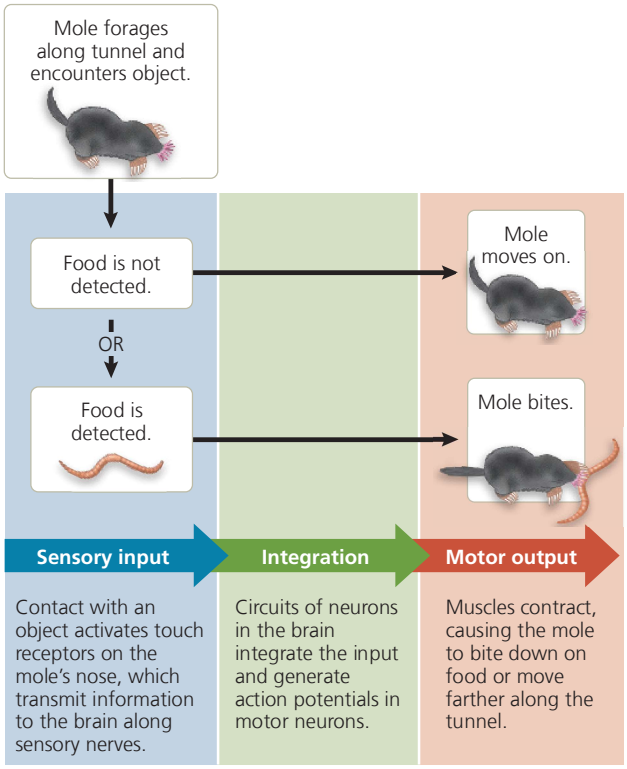
Sensory receptors transduce stimulus energy and transmit signals to the central nervous system

All sensory processes begin with stimuli, and all stimuli represent forms of energy. A sensory receptor converts stimulus energy to a change in membrane potential, thereby regulating the output of action potentials to the central nervous system (CNS). Decoding of this information within the CNS results in sensation.

When a stimulus is received and processed by the nervous system, a motor response may be generated. One of the simplest stimulus-response circuits is a reflex, such as the knee-jerk reflex shown in Figure 49.5. For many other behaviors, sensory input undergoes more elaborate processing. As an example, consider how the star-nosed mole in Figure 50.1 searches for food, or forages, in a tunnel. When the mole's nose contacts an object, touch receptors in the nose are activated **(Figure 50.2)**. These receptors transmit sensory information about the object, such as whether the object is moving, to the mole's brain. Circuits in the brain integrate the input and initiate one of two response pathways. If prey or other food is detected, the brain sends motor output commands to skeletal muscles that cause the jaws to bite down. If no food is detected, the brain sends instructions to skeletal muscles to continue movement along the tunnel.

With this overview in mind, let's examine the general organization and activity of animal sensory systems. We'll focus on four basic functions common to sensory pathways: sensory reception, transduction, transmission, and perception.

▼ Figure 50.2 A simple response pathway: foraging by a star-nosed mole.



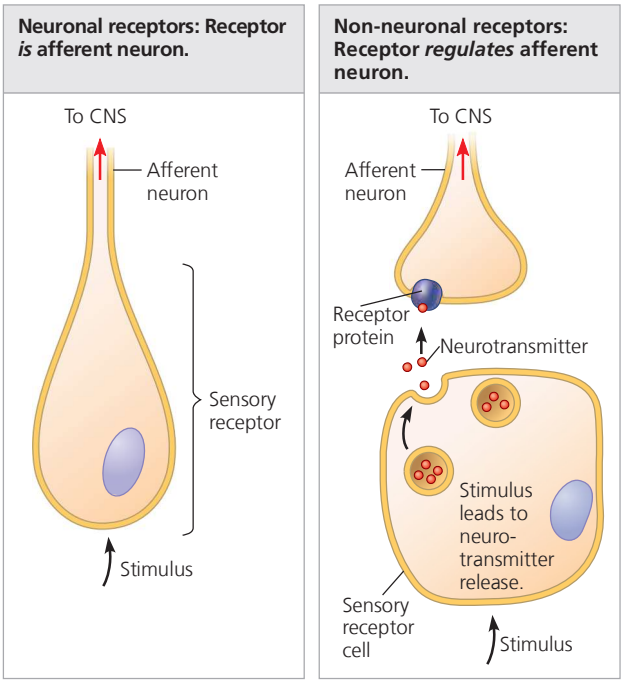
Sensory Reception and Transduction

A sensory pathway begins with **sensory reception**, the detection of a stimulus by specialized sensory cells. Each sensory cell is either a neuron or a cell that regulates a neuron **(Figure 50.3)**. Some sensory cells exist singly; others are collected in sensory organs, such as the star-shaped nose of the mole in Figure 50.1.

The term **sensory receptor** describes a sensory cell or organ, as well as the subcellular structure that detects stimuli. Some sensory receptors respond to stimuli from within the body, such as blood pressure and body position. Other receptors detect stimuli from outside the body, such as heat, light, pressure, or chemicals. Some of these receptors are sensitive to the smallest possible unit of stimulus. Most light receptors, for example, can detect a single quantum (photon) of light.

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. The resulting change in the flow of ions across

▼ Figure 50.3 Neuronal and non-neuronal sensory receptors.



the membrane alters the membrane potential. The change in membrane potential is called a **receptor potential**, and conversion of the stimulus to a receptor potential is known as **sensory transduction**. Note that receptor potentials are graded potentials: Their magnitude varies with the strength of the stimulus.

Transmission

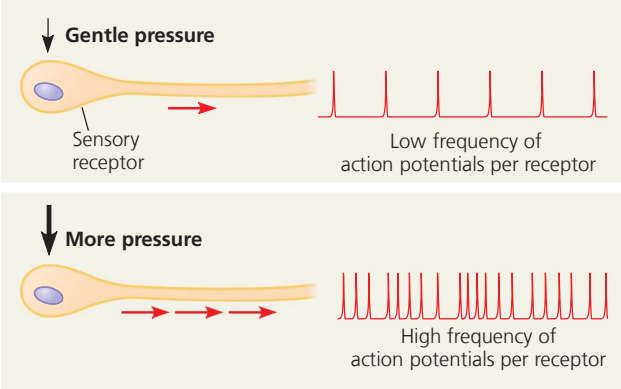
Sensory information travels through the nervous system as action potentials. A sensory receptor that is also a neuron generates action potentials that travel along an axon extending into the CNS (see Figure 50.3). In contrast, a nonneuronal sensory receptor does not itself generate action potentials, but instead conveys information to an afferent neuron via a chemical synapse. Because this chemical signaling alters the rate at which the afferent neurons produce action potentials, the sensory information generated also enters the CNS in the form of action potentials.

The size of a receptor potential increases with the intensity of the stimulus. If the receptor is a sensory neuron, a larger receptor potential results in more frequent action potentials **(Figure 50.4)**. If the receptor is not a sensory neuron, a larger receptor potential usually causes the receptor to release more neurotransmitter.

Many sensory neurons spontaneously generate action potentials at a low rate. In these neurons, a stimulus does not switch the production of action potentials on or off, but instead changes *how often* an action potential is produced, alerting the nervous system to changes in stimulus intensity.

Processing of sensory information can occur before, during, and after transmission of action potentials to the CNS. In many cases, the *integration* of sensory information begins as soon as the information is received. Receptor potentials produced by stimuli delivered to different parts of a sensory receptor cell are integrated through summation, as are postsynaptic potentials in neurons that receive input from multiple sensory receptors. As you'll see shortly, sensory structures such as eyes also provide higher levels of integration, and the brain further processes all incoming signals.

▼ Figure 50.4 Coding of stimulus intensity by a single sensory receptor.



Perception

When action potentials reach the brain via afferent neurons, circuits of neurons process this input, generating the **perception** of the stimulus. 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 and sound solely by the path along which the action potentials have arrived.

Perceptions—such as colors, smells, sounds, and tastes—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 if sound is defined as a perception, then there is no sound unless an animal senses the waves and its brain perceives them.

Amplification and Adaptation

The transduction of stimuli by sensory receptors is subject to two types of modification—amplification and adaptation. **Amplification** refers to the strengthening of a sensory signal during transduction. The effect of amplification 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 that involves enzyme-catalyzed reactions (see Concept 11.3). Because a single enzyme molecule catalyzes the formation of many product molecules, these pathways amplify signal strength considerably. Amplification may also take place in accessory structures of a sense organ. For example, the lever system formed by three small bones in the ear enhances the pressure associated with sound waves more than 20-fold before the stimulus reaches receptors in the innermost part of the ear.

Upon continued stimulation, many receptors undergo a decrease in responsiveness known as **sensory adaptation** (not to be confused with the evolutionary term *adaptation*). Sensory adaptation has very important roles in our perception of ourselves and our surroundings. Without it, you

would feel each beat of your heart and be constantly aware of every bit of clothing on your body. Furthermore, adaptation is essential for you to see, hear, and smell changes in external stimuli that vary widely in intensity.

Types of Sensory Receptors

Sensory receptors fall into five categories based on the nature of the stimuli they transduce: mechanoreceptors, chemoreceptors, electromagnetic receptors, thermoreceptors, and pain receptors.

Mechanoreceptors

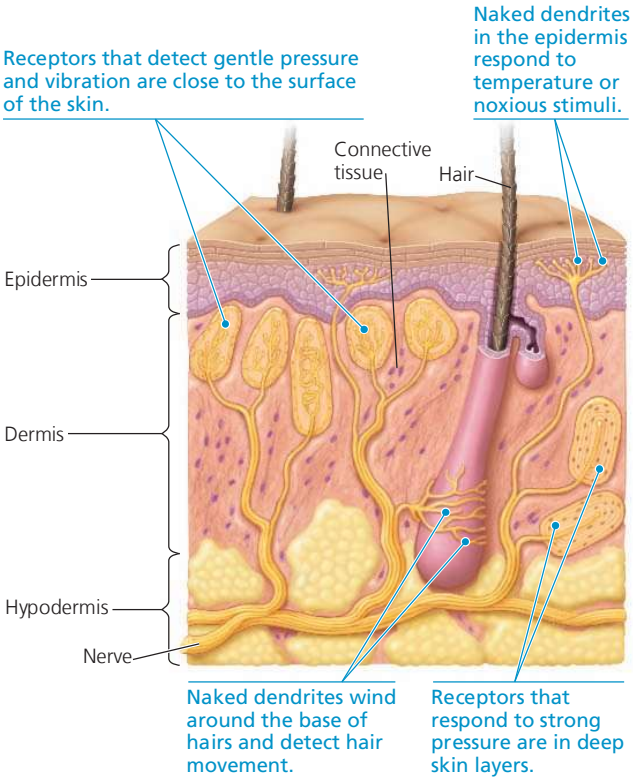
Our senses of hearing and balance, as well as our responses to pressure, touch, stretch, and motion, rely on sensory receptors called **mechanoreceptors**, which sense physical deformation caused by forms of mechanical energy. Mechanoreceptors typically consist of ion channels that are linked to structures that extend outside the cell, such as "hairs" (cilia), and also anchored to internal cell structures, such as the cytoskeleton. Bending or stretching of the external structure generates tension that alters ion channel permeability. This change in turn alters the membrane potential, resulting in a receptor potential—a depolarization or hyperpolarization.

The vertebrate stretch receptor, a mechanoreceptor that detects muscle movement, triggers the familiar knee-jerk reflex (see Figure 49.5). Stretch receptors in vertebrates are dendrites of sensory neurons that spiral around the middle of certain small skeletal muscle fibers. When the muscle fibers are stretched, the sensory neurons depolarize, triggering nerve impulses that reach the spinal cord, activate motor neurons, and generate a reflex response.

Mechanoreceptors that are the dendrites of sensory neurons are also responsible for the mammalian sense of touch. Touch receptors are often embedded in layers of connective tissue. The structure of the connective tissue and the location of the receptors dramatically affect the type of mechanical energy (light touch, vibration, or strong pressure) that best stimulates them **(Figure 50.5)**. Receptors that detect a light touch or vibration are close to the surface of the skin; they transduce very slight inputs of mechanical energy into receptor potentials. Receptors that respond to stronger pressure and vibrations are in deep skin layers.

Some animals use mechanoreceptors to literally get a feel for their environment. For example, cats and many rodents have extremely sensitive mechanoreceptors at the base of their whiskers. Like the appendages on the face of the star-nosed mole, whiskers act as touch organs. Deflection of different whiskers triggers action potentials that reach different cells in the brain. As a result, an animal's whiskers enable the brain to assemble a "touch map" detailing the location of nearby objects such as food or obstacles.

▼ Figure 50.5 Sensory receptors in human skin. Most receptors in the dermis are encapsulated by connective tissue. Receptors in the epidermis are naked dendrites, as are hair movement receptors that wind around the base of hairs in the dermis.



Chemoreceptors

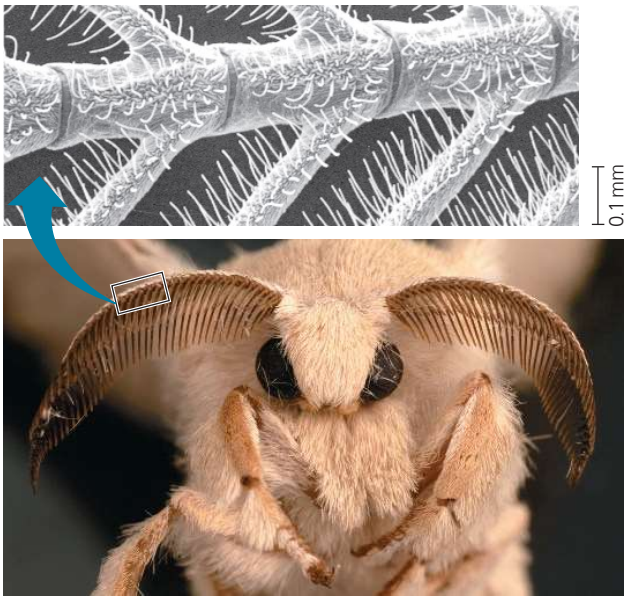
Chemoreceptors that monitor the internal environment fall into two broad categories. Some transmit information about overall solute concentration. For example, osmoreceptors in the mammalian brain detect changes in the total solute concentration of the blood and stimulate thirst when osmolarity increases (see Figure 44.19). Other chemoreceptors respond to specific molecules in body fluids, including glucose, oxygen, carbon dioxide, and amino acids.

Animals also use chemoreceptors to detect stimuli in their diet and in the environment they occupy. The antennae of the male silkworm moth contain two of the most sensitive and specific chemoreceptors known **(Figure 50.6)**; these receptors can detect components of the sex pheromone released by a female moth several kilometers away. For pheromones and other molecules detected by chemoreceptors, the stimulus molecule binds to the specific receptor on the membrane of the sensory cell and initiates changes in ion permeability.

Electromagnetic Receptors

An **electromagnetic receptor** detects a form of electromagnetic energy, such as light, electricity, and magnetism. For instance, the platypus has electroreceptors on its bill

▼ Figure 50.6 Chemoreceptors in an insect. The antennae of the male silkworm moth *Bombyx mori* are covered with sensory hairs, visible in the SEM enlargement. The hairs have chemoreceptors that are highly sensitive to the sex pheromone released by the female.



that can detect the electric field generated by the muscles of crustaceans, small fishes, 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 or other objects that disturb those currents.

Many animals can use Earth's magnetic field lines to orient themselves as they migrate **(Figure 50.7a)**. In 2015, researchers identified a pair of proteins that appear to act as a sensor for the Earth's magnetic field in many animals that can orient to it, including monarch butterflies, pigeons, and minke whales. One of these proteins binds iron; the other is a receptor that is sensitive to electromagnetic radiation.

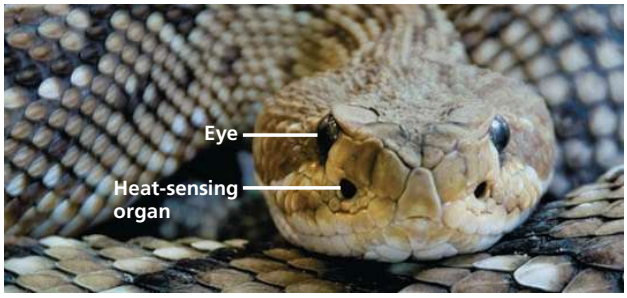
Thermoreceptors

Thermoreceptors detect heat and cold. For example, certain venomous snakes rely on thermoreceptors to detect the infrared radiation emitted by warm prey. These thermoreceptors are located in a pair of pit organs on the snake's head **(Figure 50.7b)**. In humans, thermoreceptors are located in the skin and in the anterior hypothalamus.

Recently, our understanding of thermoreception has increased substantially, thanks to scientists with an appreciation for fiery foods. Jalapeno and cayenne peppers that we describe as "hot" contain a substance called capsaicin. Applying capsaicin to a sensory neuron causes an influx of calcium ions. When scientists identified the receptor protein in neurons 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.

▼ Figure 50.7 Examples of electromagnetic reception and thermoreception.

(a) Some migrating animals, such as these beluga whales, apparently sense Earth's magnetic field and use the information, along with other cues, for orientation.



(b) This rattlesnake and other pit vipers have a pair of heat-sensing pit organs, one anterior to and just below each eye. These organs are sensitive enough to detect the infrared radiation emitted by a warm prey a meter away. The snake moves its head from side to side until the radiation is detected equally by the two pit organs, indicating that the prey is straight ahead.

Mammals have a variety of thermoreceptors, each specific for a particular temperature range. The capsaicin receptor and at least five other types of thermoreceptors belong to the TRP (transient receptor potential) family of ion channel proteins. Just as the TRP-type receptor specific for high temperature is sensitive to capsaicin, the receptor for low temperatures (below 28°C) can be 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 (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. The capsaicin receptor of mammals can detect dangerously high temperatures, so it also functions as a pain receptor.

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 (see Concept 45.1). Prostaglandins worsen pain by increasing nociceptor sensitivity to noxious stimuli. Aspirin and ibuprofen reduce pain by inhibiting the synthesis of prostaglandins.

Next we'll turn our focus to sensory systems, beginning with systems for maintaining balance and detecting sound.

CONCEPT CHECK 50.1

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 electrically, how would that stimulation be perceived?

For suggested answers, see Appendix A.

CONCEPT 50.2

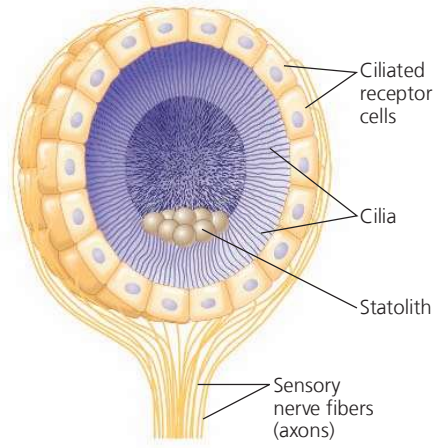
In hearing and equilibrium, mechanoreceptors detect moving fluid or settling particles

For most animals, the sense of hearing is closely related to the sense of balance, the perception of body equilibrium. For both senses, mechanoreceptor cells produce receptor potentials in response to deflection of cell-surface structures by settling particles or moving fluid.

Sensing of Gravity and Sound in Invertebrates

To sense gravity and maintain equilibrium, most invertebrates rely on mechanoreceptors located in organs called **statocysts** (Figure 50.8). In a typical statocyst, **statoliths**, granules formed by grains of sand or other dense materials, sit freely in a chamber lined with ciliated cells. Each time an animal repositions itself, the statoliths resettle, stimulating mechanoreceptors at the low point in the chamber.

▼ **Figure 50.8 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.

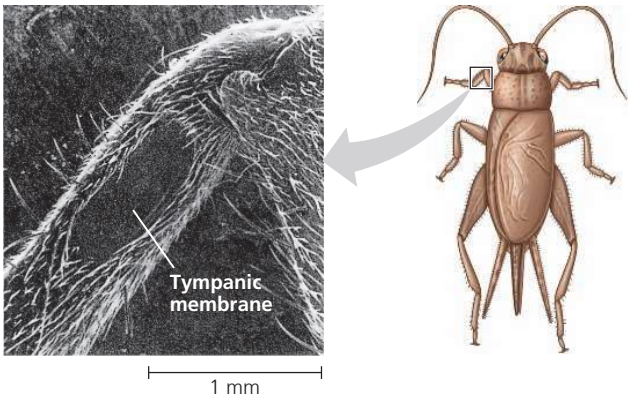


How did researchers test the hypothesis that resettling of statoliths provides information about body position relative to Earth's gravity? In one key experiment, statoliths were replaced with metal shavings. Researchers then "tricked" crayfish into swimming upside down by using magnets to pull the shavings to the upper end of statocysts at the base of their antennae.

Many (perhaps most) insects have body hairs that vibrate in response to sound waves. Hairs differing in stiffness and length vibrate at different frequencies. For example, fine hairs on the antennae of a male mosquito vibrate in a specific way in response to the hum produced by the beating wings of flying females. The importance of this sensory system in attracting males to a potential mate can be readily demonstrated: A tuning fork vibrating at the same frequency as that of a female's wings by itself attracts males.

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 (Figure 50.9). Cockroaches lack such a tympanic membrane, but instead have vibration-sensitive organs that sense air movement, such as that caused by a descending human foot.

▼ **Figure 50.9 An insect's "ear"—on its leg.** The tympanic membrane, visible in this SEM of a cricket's front leg, vibrates in response to sound waves. The vibrations stimulate mechanoreceptors attached to the inside of the tympanic membrane.



Hearing and Equilibrium in Mammals

In mammals, as in most other terrestrial vertebrates, the sensory organs for hearing and equilibrium are closely associated. Figure 50.10 explores the structure and function of these organs in the human ear.

▼ Figure 50.10 Exploring the Structure of the Human Ear

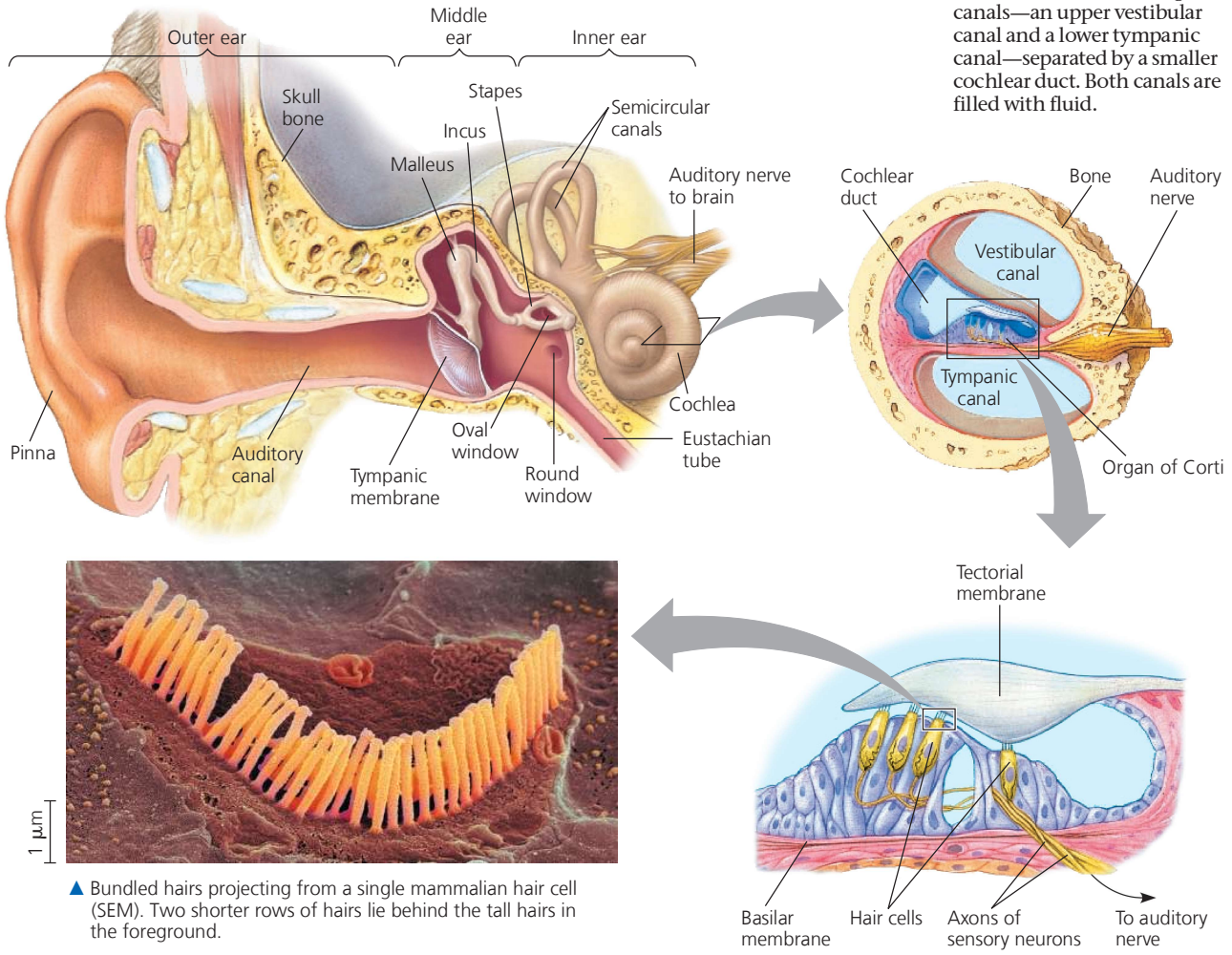
1 Overview of Ear Structure

The **outer ear** consists of the external pinna and the auditory canal, which collect sound waves and channel them to the **tympanic membrane** (eardrum), a thin tissue that 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**, a passage that 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.

Mastering Biology **Animation: The Human Ear**

2 The Cochlea

The cochlea, shown here in cross section, 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

Within the bundle of hairs projecting from each hair cell lies 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. Displacing the hairs causes a change in the membrane potential of the hair cell.

3 The Organ of Corti

The floor of the cochlear duct, the basilar membrane, is the base of the **organ of Corti**, which contains the mechanoreceptors of the ear—hair cells with bundles of rod-shaped "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.

Hearing

Vibrating objects, such as a plucked guitar string or the vocal cords of a person who is speaking, 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 cells with hairlike projections that detect motion.

Before vibration waves reach hair cells, they are amplified and transformed by accessory structures. The first steps involve structures in the ear that convert the vibrations of moving air to pressure waves in fluid. Moving air that reaches the outer ear causes the tympanic membrane to vibrate. The three bones of the middle ear transmit these 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 inside the cochlea.

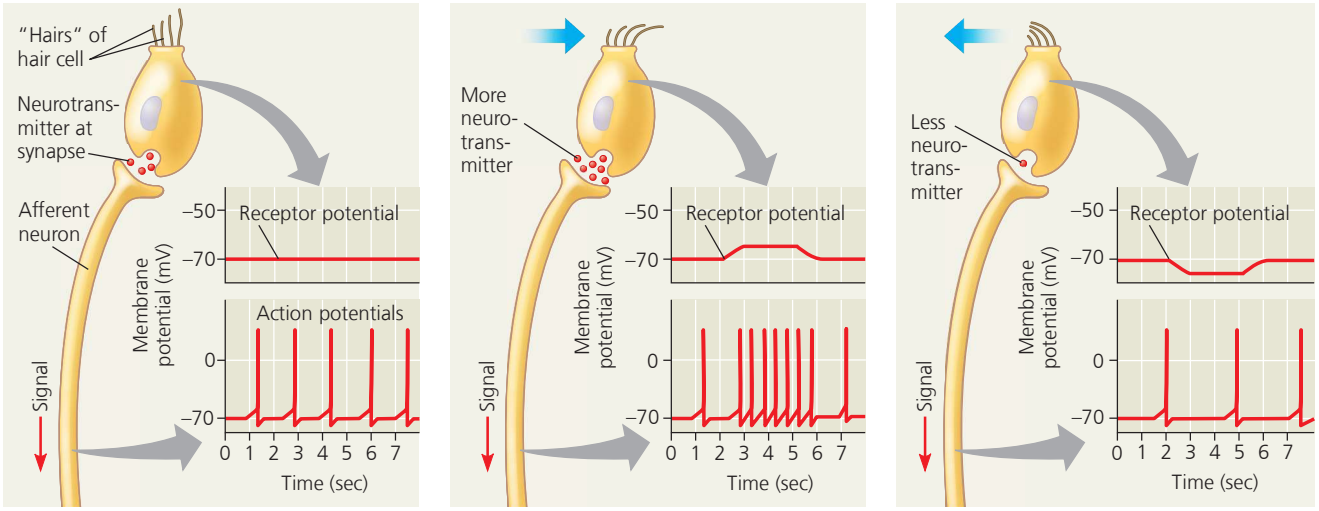
Upon entering the vestibular canal, fluid pressure waves push down on the cochlear duct and basilar membrane. In response, the basilar membrane and attached hair cells vibrate up and down. The hairs projecting from the hair cells are deflected by the fixed tectorial membrane, which lies above (see Figure 50.10). 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. Bending in one direction depolarizes hair cells, increasing neurotransmitter release and the frequency of action potentials directed to the brain along the auditory nerve **(Figure 50.11)**. Bending the hairs in the other direction hyperpolarizes hair cells, reducing neurotransmitter release and the frequency of auditory nerve sensations.

What prevents pressure waves from reverberating within the ear and causing prolonged sensation? After propagating through the vestibular canal, pressure waves pass around the apex (tip) of the cochlea and dissipate as they strike the **round window (Figure 50.12a)**. This damping of sound waves resets the apparatus for the next vibrations that arrive.

The ear captures 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 afferent neurons that transmit information to the brain. *Pitch* is determined by a sound wave's frequency, the number of vibrations per unit time. The detection of sound wave frequency takes place in the cochlea and relies on the asymmetric structure of that organ.

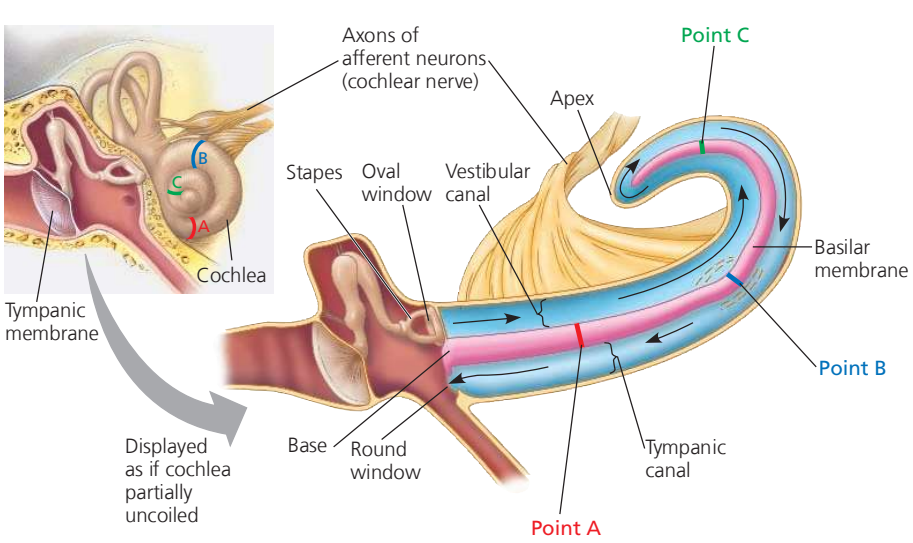
The cochlea can distinguish pitch because the basilar membrane is not uniform along its length: It is relatively narrow and stiff near the oval window and wider and more flexible at the apex at the base of the cochlea. Each region of the basilar membrane is tuned to a different vibration frequency **(Figure 50.12b)**. Furthermore, each region is connected by axons to a different location in the cerebral cortex. Consequently, when a sound wave causes vibration of a particular region of the basilar membrane, nerve impulses are transduced to a specific site in our cortex and we perceive sound of a particular pitch.

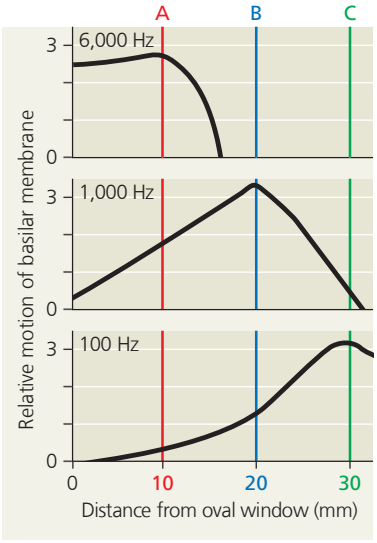
▼ Figure 50.11 Sensory reception by hair cells. In hearing or balance, each hair cell forms a synapse with an afferent neuron that conducts action potentials to the CNS. Bending of the hairs of the hair cell in one direction depolarizes the cell. Depolarization increases release of excitatory neurotransmitter, resulting in more frequent action potentials in the afferent neuron. Bending the hairs in the other direction decreases neurotransmitter release, reducing action potential frequency in the afferent neuron.



(a) No bending of hairs **(b) Bending of hairs in one direction** **(c) Bending of hairs in other direction**

▼ Figure 50.12 Sensory transduction in the cochlea.





(a) Vibrations of the stapes against the oval window produce pressure waves (black arrows) in the fluid (perilymph; blue) of the cochlea. (For purposes of illustration, the cochlea on the right is drawn partially uncoiled.) The waves travel to the apex via the vestibular canal and back towards the base via the tympanic canal. The energy in the waves causes the basilar membrane (pink) to vibrate, stimulating hair cells (not shown). Because the basilar membrane varies in stiffness along its length, each point along the membrane vibrates maximally in response to waves of a particular frequency.

(b) These graphs show the patterns of vibration along the basilar membrane for three different frequencies, high (top), medium (middle), and low (bottom). The higher the frequency, the closer the vibration to the oval window.

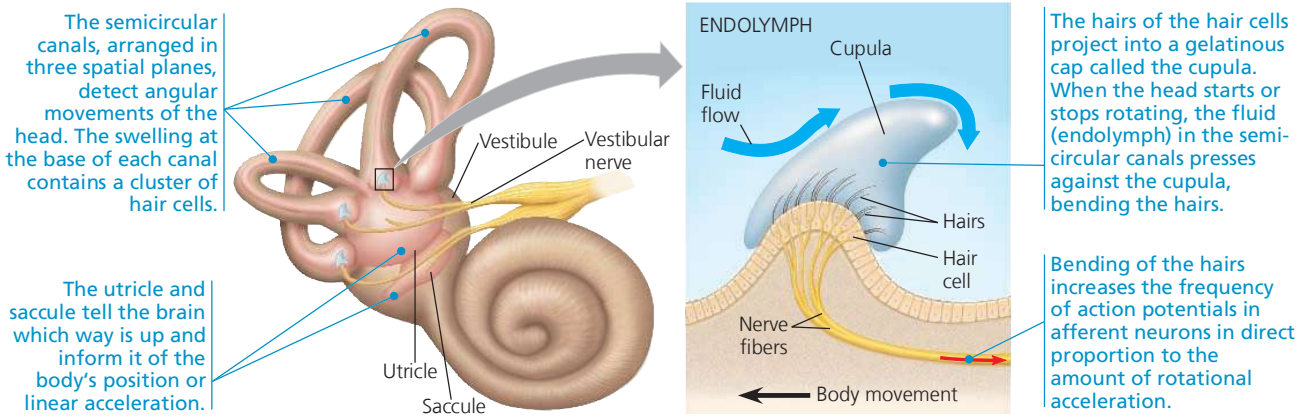
INTERPRET THE DATA *A musical chord consists of several notes, each formed by a sound wave of different frequency. If a chord had notes with frequencies of 100, 1,000, and 6,000 Hz, what would happen to the basilar membrane? How would this result in your hearing a chord?*

Mastering Biology Animation: Detecting Pitch

Equilibrium

Several organs in the inner ear of humans and most other mammals detect body movement, position, and equilibrium. For example, the chambers called the *utricle* and *saccule* allow us to perceive position with respect to gravity as well as linear movement **(Figure 50.13)**. Situated in a vestibule behind the oval window, each of these chambers 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 shift position, contacting a different set of hairs protruding into the gel. The hair cell receptors transform this deflection into a change in neurotransmitter output. This alters the activity of afferent neurons, signaling the brain that your head is at an angle. The otoliths are also responsible for your ability to perceive acceleration, such as when a stationary car in which you are sitting moves forward.

▼ Figure 50.13 Organs of equilibrium in the inner ear.



Three fluid-filled semicircular canals connected to the utricle detect turning of the head and other rotational acceleration. Within each canal, the hair cells form a cluster, with the hairs projecting into a gelatinous cap called a cupula (see Figure 50.13). Because the three canals are arranged in the three spatial planes, they can 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, triggering the false sensation of angular motion that we call dizziness.

Hearing and Equilibrium in Other Vertebrates

Fishes rely on several systems for detecting movement and vibrations in their aquatic environment. One system involves a pair of inner ears that contain otoliths and hair cells. Unlike the ears of mammals, these ears have no eardrum, cochlea, or opening to the outside of the body. Instead, the vibrations of the water caused by sound waves are conducted to the inner ear through the skeleton of the head. Some fishes also have a series of bones that conduct vibrations from the swim bladder to the inner ear.

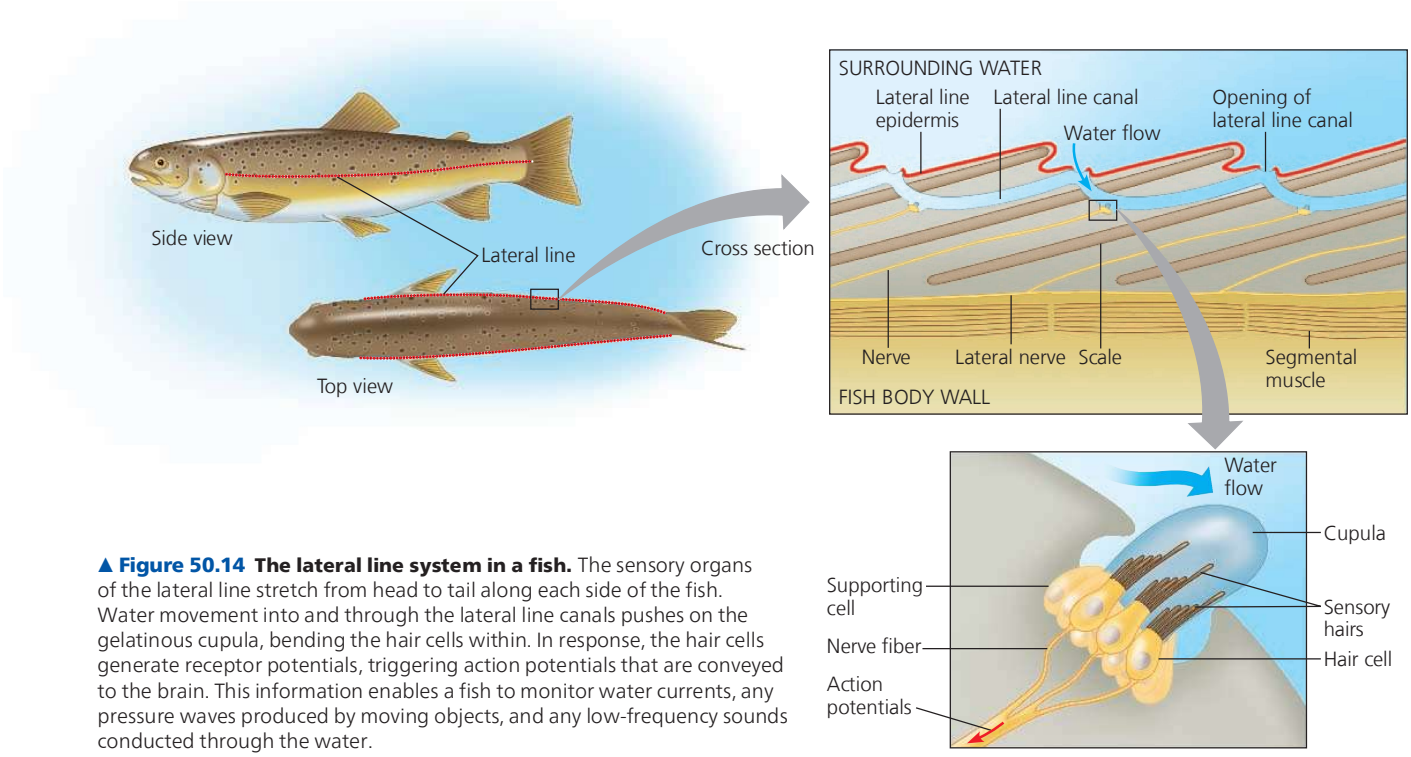
Most fishes and aquatic amphibians are able to detect low-frequency waves by means of a **lateral line system** along each side of their body **(Figure 50.14)**. As in our semicircular canals, receptors are formed from a cluster of hair cells whose hairs are embedded in a cupula. Water entering the lateral line system through numerous pores bends the cupula, leading to depolarization of the hair cells and production of action potentials. In this way, the fish perceives its movement through water or the direction and velocity of water currents flowing over its body. The lateral line system also detects water movements or vibrations generated by prey, predators, and other moving objects.

In the ear of a frog or toad, sound vibrations in the air are conducted to the inner ear by a tympanic membrane on the body surface and a single middle ear bone. The same is true in birds and other reptiles, although they, like mammals, have a cochlea.

CONCEPT CHECK 50.2

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.
4. **MAKE CONNECTIONS** Plants use statoliths to detect gravity (see Figure 39.22). How do plants and animals differ with regard to the type of compartment in which statoliths are found and the physiological mechanism for detecting their response to gravity?

For suggested answers, see Appendix A.



▲ Figure 50.14 The lateral line system in a fish. The sensory organs of the lateral line stretch from head to tail along each side of the fish. Water movement into and through the lateral line canals pushes on the gelatinous cupula, bending the hair cells within. In response, the hair cells generate receptor potentials, triggering action potentials that are conveyed to the brain. This information enables a fish to monitor water currents, any pressure waves produced by moving objects, and any low-frequency sounds conducted through the water.

CONCEPT 50.3

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 the animal kingdom 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**, sensory 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.

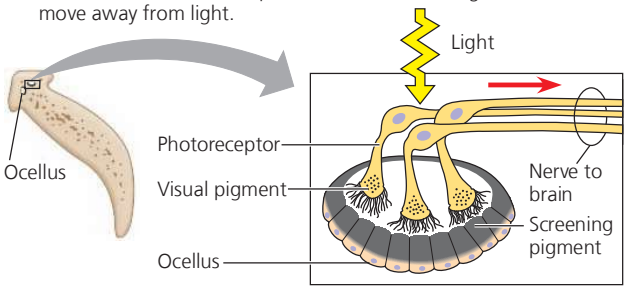
Mastering Biology BBC Video: How Did Eyes Evolve?

Light-Detecting Organs

Most invertebrates have some kind of light-detecting organ. One of the simplest is that of planarians **(Figure 50.15)**.

▼ Figure 50.15 Ocelli and orientation behavior of a planarian.

(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, enabling the light avoidance behavior.

A pair of ocelli (singular, *ocellus*), 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 rate of action potentials coming from the two ocelli, the planarian can move away from a light source until it reaches a shaded location, where the object providing the shade may hide it from predators.

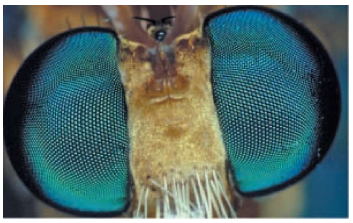
Compound Eyes

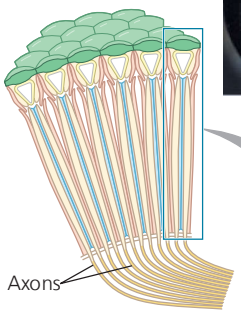
Insects, crustaceans, and some polychaete worms have **compound eyes**, each consisting of up to several thousand light detectors called **ommatidia (Figure 50.16)**. Each of these "facets" of the eye has its own light-focusing lens that captures light from a tiny portion of the visual field (the total 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. Many compound eyes, including those of the fly in Figure 50.16, offer a very wide field of view.

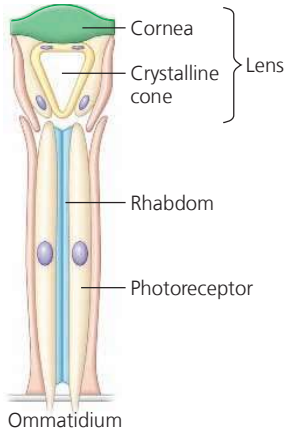
Insects have excellent color vision, and some, such as bees, can see into the ultraviolet (UV) range of the electromagnetic spectrum. Because UV light is invisible to humans, we don't see differences in the environment that bees and

▼ Figure 50.16 Compound eyes.

(a) The faceted eyes on the head of a fly form a repeating pattern visible in this photomicrograph.







(b) The cornea and crystalline cone of each ommatidium together function as a lens that focuses light on the rhabdom, an organelle formed by and extending inward from a circle of photoreceptors. The rhabdom traps light, serving as the photosensitive part of the ommatidium. Information gathered from different intensities of light entering the many ommatidia from different angles is used to form a visual image.

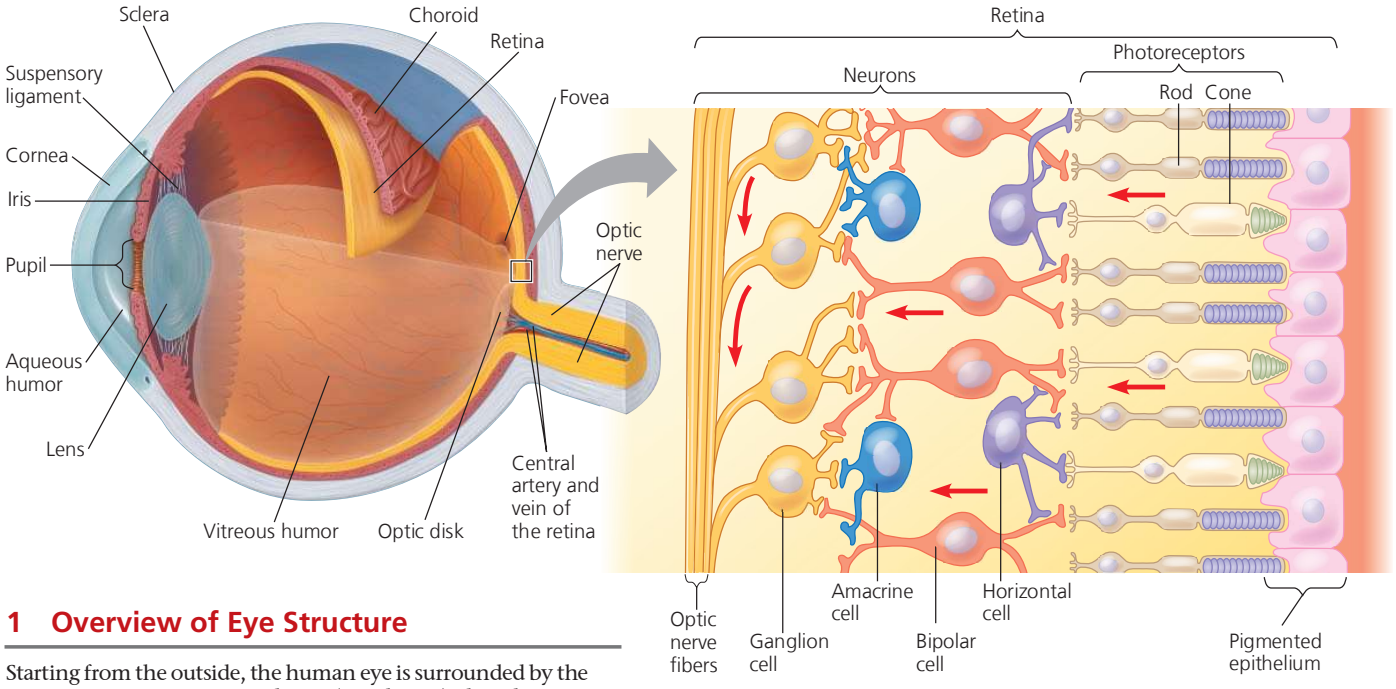
other insects detect. In studying animal behavior, we cannot simply extrapolate our sensory world to other species; different animals have different sensitivities and different brain organizations.

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 or less light. Behind the pupil, a single lens directs 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.

▼ Figure 50.17 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 the left in this diagram) 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 photo receptors 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.

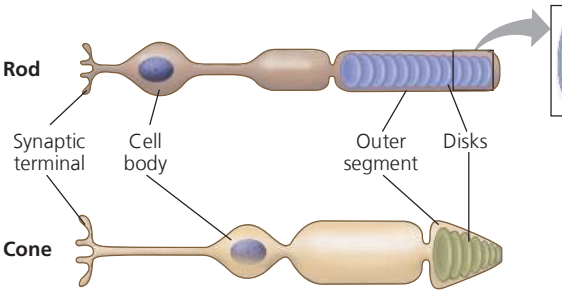
The optic disk, where the optic nerve exits the retina, lacks photoreceptors. As a result, this region forms a "blind spot" where light is not detected.

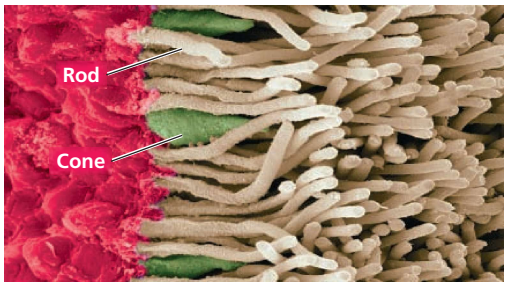
The eyes of all vertebrates have a single lens. In fishes, focusing occurs as in invertebrates, with the lens moving forward or backward. In other species, including mammals, focusing is achieved by changing the shape of the lens.

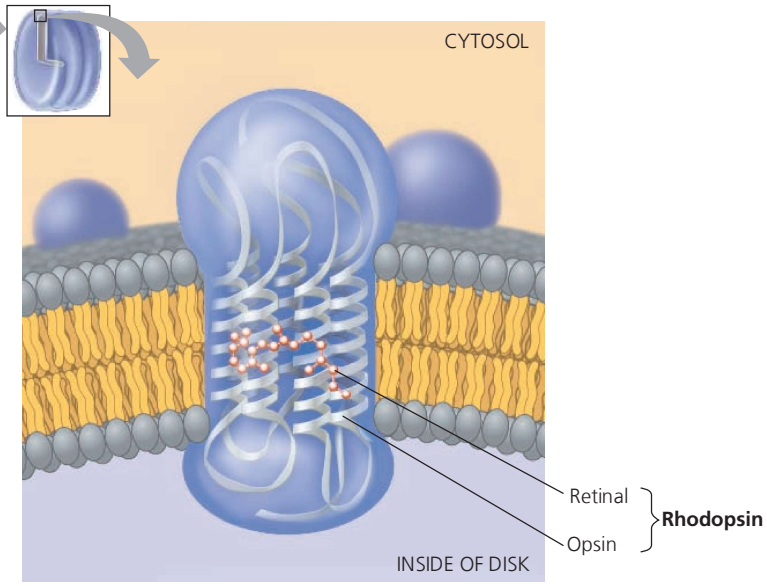
The Vertebrate Visual System

The human eye will serve as our model of vision in vertebrates. As described in **Figure 50.17**, vision begins when photons of light enter the eye and strike the rods and cones. There the energy of each photon is captured in retinal, the light-absorbing molecule in the visual pigment rhodopsin.

Although light detection in the eye is the first stage in vision, remember that it is actually the brain that "sees." Thus, to understand vision, we must examine how the capture of light by retinal changes the production of action potentials and then follow these signals to the visual centers of the brain, where images are perceived.







3 Photoreceptor Cells

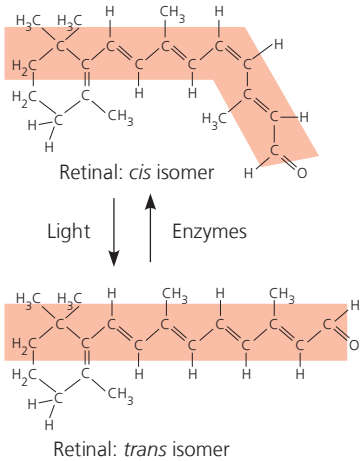
Humans have two main types of photoreceptor cells: rods and cones. Within the outer segment of a rod or cone is a stack of membranous disks in which *visual pigments* are embedded. **Rods** are more sensitive to light than cones are, but they do not distinguish colors; rods enable us to see at night, 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 (red) 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 activates the opsin protein to which retinal is bound.



Mastering Biology **Animations: Structure and Function of the Eye • Function of the Retina • Photoreception**

VISUAL SKILLS *The isomers of retinal have the same number of atoms and bonds but differ in the spatial arrangement at one carbon-carbon double bond (C═C). In each isomer, circle that (C═C). Looking at the atoms around that bond, to what atoms do the terms cis (same side) and trans (opposite side) refer?*

Sensory Transduction in the Eye

The transduction of visual information to the nervous system begins with the light-induced conversion of *cis*-retinal to *trans*-retinal in rods and cones. Like other *cis-trans* pairs, these isomers of retinal differ only in the spatial arrangement of atoms at a carbon-carbon double bond (see Figure 4.7).

As shown in Figure 50.17, *trans*-retinal and *cis*-retinal differ in shape. This shift in shape activates the visual pigment (in rods, rhodopsin), which activates a G protein, which in turn activates the enzyme phosphodiesterase. The substrate for this enzyme in rods and cones is cyclic GMP (cGMP), which in the dark binds to sodium ion (Na^+) channels and keeps them open **(Figure 50.18a)**. When the enzyme hydrolyzes cGMP, Na^+ channels close, and the cell becomes hyperpolarized **(Figure 50.18b)**. The signal transduction pathway then shuts off as enzymes convert retinal back to the *cis* form, inactivating the visual pigment.

In bright light, rhodopsin remains active, and the response in the rods becomes saturated. If the amount of light entering the eyes abruptly decreases, the rods do not regain full responsiveness for several minutes. This is why you are briefly blinded if you pass quickly from bright sunshine into a dark movie theater. (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.")

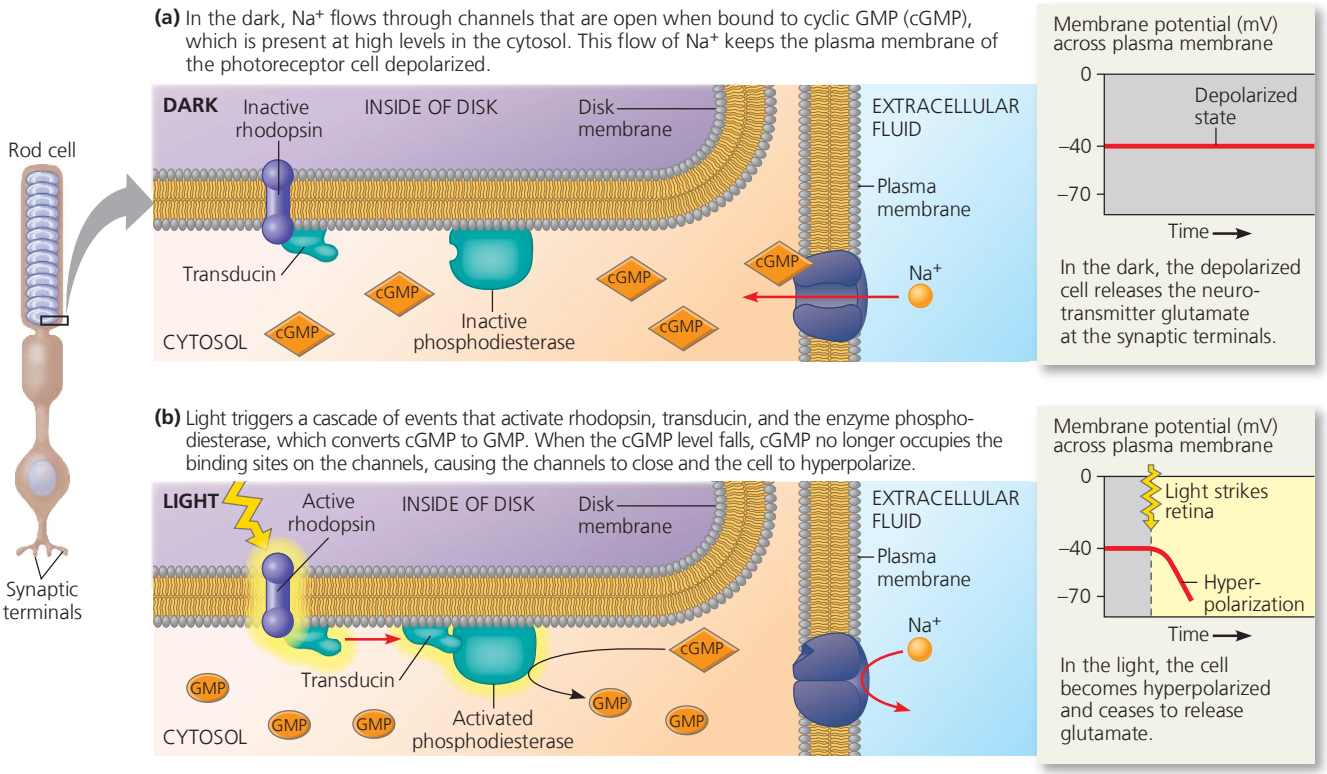
Processing of Visual Information in the Retina

The processing of visual information begins in the retina itself, where both rods and cones form synapses with bipolar cells (see Figure 50.17). In the dark, rods and cones are depolarized and continually release the neurotransmitter glutamate at these synapses **(Figure 50.19)**. When light strikes the rods and cones, they hyperpolarize, shutting off their release of glutamate. This decrease triggers a change in the membrane potential of the bipolar cells, altering their regulation of action potential transmission to the brain.

Processing of signals from rods and cones occurs via 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.

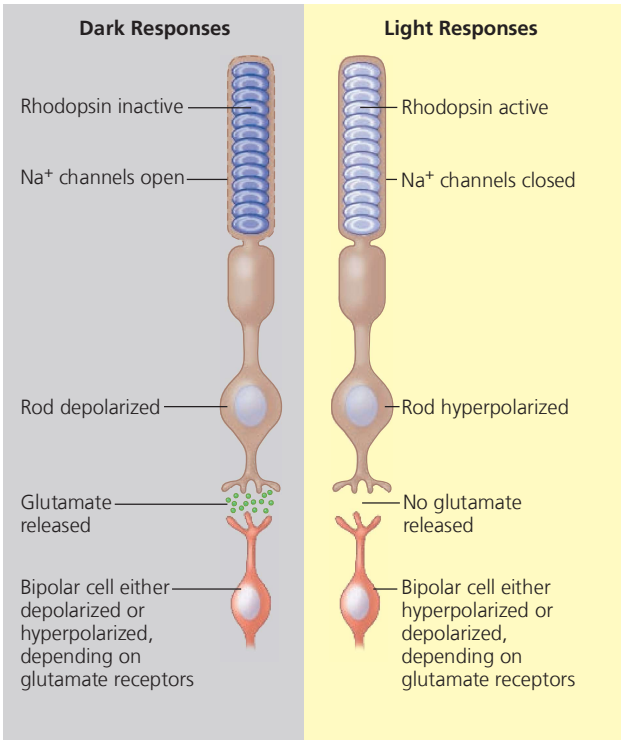
How is it adaptive for visual information to follow several paths? We'll consider one example. When an illuminated rod or cone stimulates a horizontal cell, the horizontal cell inhibits more distant photoreceptors and bipolar cells that are not illuminated. The result is that the region receiving light appears lighter and the dark surroundings even darker. This form of integration, called *lateral inhibition*, sharpens edges and enhances contrast in the image. An essential part of visual processing, lateral inhibition occurs in the brain as well as the retina.

▼ Figure 50.18 Response of a photoreceptor cell to light. Light triggers a receptor potential in a rod (shown here) or cone. Note that for photoreceptors, this change in membrane potential is a hyperpolarization.



Mastering Biology **Figure Walkthrough**

▼ Figure 50.19 Synaptic activity of rod cells in light and dark.



? *Like rods, cone cells are depolarized when their opsin molecules are inactive. In the case of a cone, why might it be misleading to call this a dark response?*

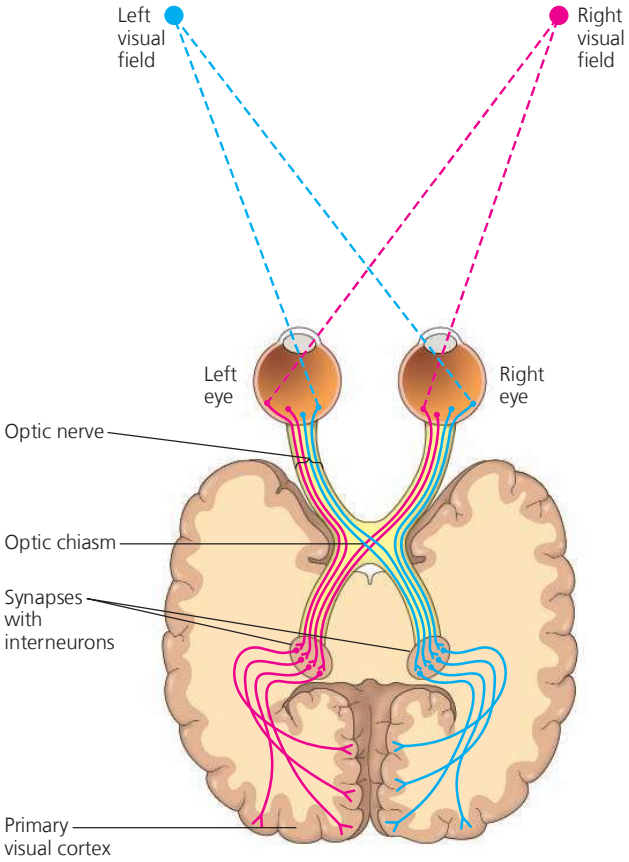
A single ganglion cell receives information from an array of rods and cones, each of which responds to light coming from a particular location. Together, the rods and cones that are feeding information to one ganglion cell define a *receptive field*—the part of the visual field to which that ganglion cell can respond. The fewer rods or cones that supply a single ganglion cell, the smaller the receptive field. 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 action potentials from the eyes to the brain **(Figure 50.20)**. The two optic nerves meet at the *optic chiasm* near the center of 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 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.)

Within the brain, most ganglion cell axons lead to the *lateral geniculate nuclei*, which have axons that reach the *primary visual cortex* in the cerebrum. Additional neurons carry the information to higher-order visual processing and

▼ Figure 50.20 Neural pathways for vision. Each optic nerve contains about a million axons that synapse with interneurons in the brain. The nuclei relay sensations to the primary visual cortex, one of many brain centers that cooperate in constructing visual perceptions.



integrating centers elsewhere in the cortex. 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. For cats and other mammals that are most active at night, a high proportion of rods in the retina is an adaptation that provides keen night vision. Color vision among these nocturnal animals is limited, and they 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

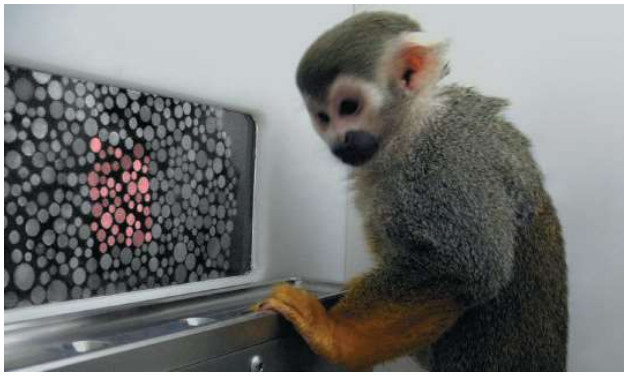
from the binding of retinal to three distinct opsin proteins. Slight differences in the opsin proteins cause each photopsin to absorb light optimally at a different wavelength. Although the visual pigments are designated as red, green, and blue, their absorption spectra in fact overlap. For this reason, the brain's perception of intermediate hues depends on the differential stimulation of two or more classes of cones. For example, if both red and green cones are stimulated, we see either yellow or orange, depending on which class of cones is more strongly stimulated.

Abnormal color vision typically results from mutations in the genes for one or more photopsin proteins. In humans, color blindness nearly always affects perception of red or green and is far more common in one gender than the other: 5–8% of males, fewer than 1% of females. Why? The human genes for both the red and green pigments are X-linked. Thus, males are affected by a single mutation, whereas females are color-blind only if both copies are mutant. (The human gene for the blue pigment is on chromosome 7.)

Experiments on color vision in the squirrel monkey (*Saimiri sciureus*) enabled an early breakthrough in the field of gene therapy. These monkeys have only two opsin genes, one sensitive to blue light and the other sensitive to either red or green light, depending on the allele. Because the red/green opsin gene is X-linked, all males have only the red- or green-sensitive version and are red-green color-blind. When researchers injected a virus containing the gene for the missing version into the retina of adult male monkeys, evidence of full color vision was apparent after 20 weeks **(Figure 50.21)**.

The squirrel monkey gene therapy studies demonstrate that the neural circuits required to process visual information can be generated or activated even in adults, making it possible to treat a range of vision disorders. Indeed, gene therapy has been used to treat Leber's congenital amaurosis (LCA), an inherited retinal degenerative disease that causes severe loss of vision. After using gene therapy to restore vision in dogs and mice with LCA, researchers successfully treated the disease in humans by injecting the functional LCA gene in a viral vector (see Figure 20.22).

▼ Figure 50.21 Gene therapy for vision. Once color-blind, this adult male monkey treated with gene therapy demonstrates his ability to distinguish red from green.



MAKE CONNECTIONS *Red-green color blindness is X-linked in squirrel monkeys and in humans (see Figure 15.7). Why is the inheritance pattern in humans not apparent in squirrel monkeys?*

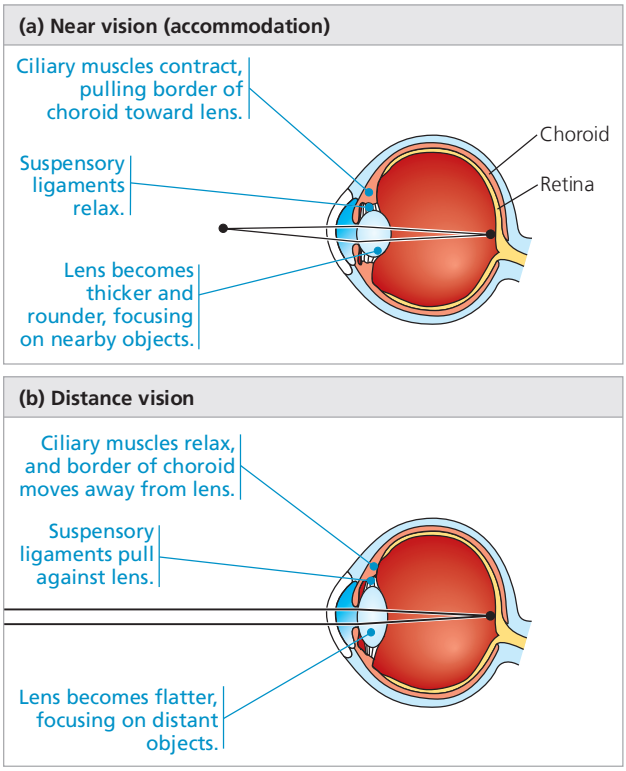
Mastering Biology HHMI Video: Genes as Medicine

The Visual Field

The brain not only processes visual information but also controls what information is captured. One important control is focusing, which in humans occurs by changing the shape of the lens, as noted earlier and illustrated in **Figure 50.22**. 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 6 million cones. At the **fovea**, the center of the visual field, there are no rods but a very high density of

▼ Figure 50.22 Focusing in the mammalian eye. Ciliary smooth muscles control the shape of the lens, which bends light and focuses it on the retina. The thicker the lens, the more sharply the light is bent.



Mastering Biology Animation: Near and Distance Vision

cones—about 150,000 cones per square millimeter. The ratio of cones to rods falls 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 absent from the fovea. For this reason, you see a dim star best by focusing on a point just to one side of it.

CONCEPT CHECK 50.3

1. Contrast the light-detecting organs of planarians and flies. How is each organ adaptive for the lifestyle of the animal?
2. In a condition called presbyopia, the eyes' lenses lose much of their elasticity and maintain a flat shape. How would you expect this condition to affect a person's vision?
3. **WHAT IF?** Our 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.
4. **MAKE CONNECTIONS** Compare the function of retinal in the eye with that of the pigment chlorophyll in a plant photosystem (see Concept 10.2).

For suggested answers, see Appendix A.

CONCEPT 50.4

The senses of taste and smell rely on similar sets of sensory receptors

Animals use their chemical senses for a wide range of purposes, including finding mates, recognizing marked territories, and helping navigate during migration. In addition, animals such as ants and bees that live in large social groups rely extensively on chemical "conversation."

In all animals, chemical senses are important for feeding behavior. The perceptions of **gustation** (taste) and **olfaction** (smell) both depend on chemoreceptors. In the case of terrestrial animals, taste is the detection of chemicals called **tastants** that are present in a solution, and smell is the detection of **odorants** that are carried through the air. There is no distinction between taste and smell in aquatic animals.

In insects, taste receptors are located within sensory hairs located on the feet and in mouthparts, where they are used to select food. A tasting hair contains several chemoreceptors, each especially responsive to a particular class of tastant, such as sugar or salt. Insects are also capable of smelling airborne odorants using olfactory hairs, usually located on their antennae (see Figure 50.6). The chemical DEET (*N,N*-diethyl-meta-toluamide), marketed as an insect "repellant," actually protects against bites by blocking the olfactory receptor in mosquitoes that detects human scent.

Taste in Mammals

Humans and other mammals perceive five tastes: sweet, sour, salty, bitter, and umami. Umami (which means "pleasant savory taste" in Japanese) is elicited by the amino acid glutamate. Sometimes used as a flavor enhancer in the form of monosodium glutamate, or MSG, glutamate occurs naturally in meat, aged cheese, and other foods, to which it imparts a "savory" quality.

For decades, many researchers assumed that a taste cell could have more than one type of receptor. An alternative idea is that each taste cell has a single receptor type, programming the cell to recognize only one of the five tastes. To test this hypothesis, scientists used a cloned bitter taste receptor to genetically reprogram gustation in a mouse **(Figure 50.23)**. This reprogramming experiment, together with follow-up studies, revealed that an individual taste cell does in fact express a single receptor type and detects tastants representing only one of the five tastes.

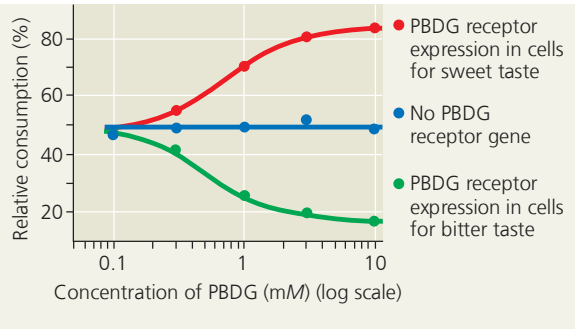
▼ Figure 50.23 Inquiry

How do mammals detect different tastes?

Experiment To investigate the basis of mammalian taste perception, researchers used a chemical called phenyl-β-D-glucopyranoside (PBDG). Humans find PBDG extremely bitter. Mice, however, lack a receptor for PBDG. Mice avoid drinking water containing other bitter tastants but show no aversion to water that contains PBDG.

Using a molecular cloning strategy, the researchers generated mice that made the human PBDG receptor in cells that normally make either a sweet receptor or a bitter receptor. The mice were given a choice of two bottles, one filled with pure water and one filled with water containing PBDG at varying concentrations. The researchers then observed whether the mice had an attraction or an aversion to PBDG.

Results



Conclusion The researchers found that the presence of a bitter receptor in sweet taste cells is sufficient to cause mice to be attracted to a bitter chemical. They concluded that the mammalian brain must therefore perceive sweet or bitter taste solely on the basis of which afferent neurons are activated.

Data from K. L. Mueller et al., The receptors and coding logic for bitter taste, *Nature* 434:225–229 (2005).

WHAT IF? *Suppose that instead of the PBDG receptor, the researchers had used a receptor specific for a sweetener that humans crave but mice ignore. How would the results of the experiment have differed?*

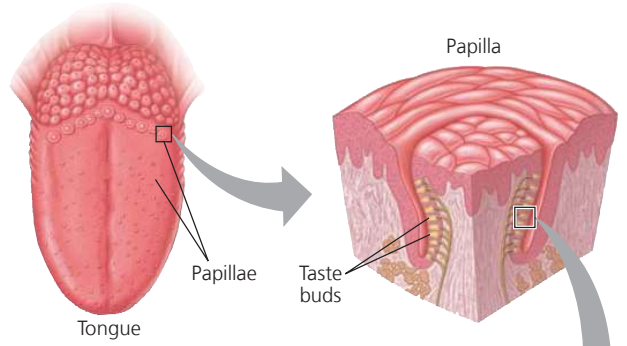
The receptor cells for taste in mammals are modified epithelial cells organized into **taste buds**, which are scattered in several areas of the tongue and mouth **(Figure 50.24)**. Most taste buds on the tongue are associated with nipple-shaped projections called papillae. Any region of the tongue with taste buds can detect any of the five types of taste. (The frequently reproduced "taste maps" of the tongue are thus not accurate.)

Researchers have identified the receptor proteins for all five tastes. The sensations of sweet, umami, and bitter tastes each require one or more genes encoding a G protein-coupled receptor, or GPCR (see Figures 11.7 and 11.8). Humans have one type of sweet receptor and one type of umami receptor, each assembled from a different pair of GPCR proteins. In contrast, humans have more than 30 different receptors for bitter taste, and each receptor is able to recognize multiple bitter tastants. GPCR proteins are also critical for the sense of smell, as will be discussed shortly.

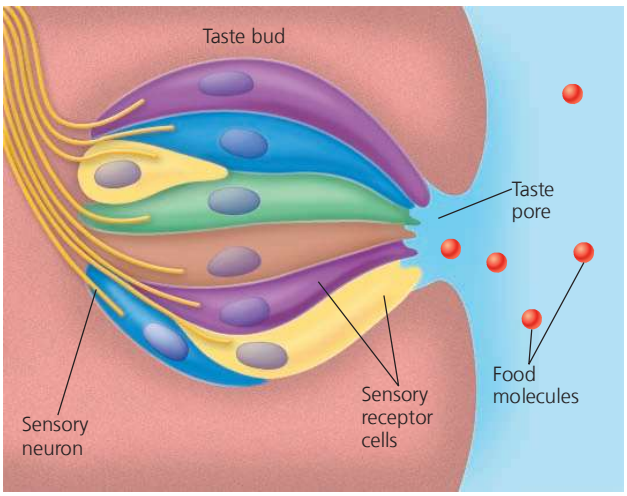
The receptor for sour tastants belongs to the TRP family and is similar to the capsaicin receptor and other thermoreceptor proteins. In taste buds, the TRP proteins of the sour receptor assemble into an ion channel in the plasma membrane of the taste cell. Binding of an acid or other sour-tasting substance to the receptor triggers a change in the ion channel. Depolarization occurs, activating an afferent neuron that relays information to the CNS, triggering the perception of a sour taste.

The taste receptor for salt turns out to be a sodium channel. Not surprisingly, it specifically detects sodium salts, such as the NaCl that we use in cooking and flavoring.

▼ Figure 50.24 Human taste receptors.



(a) The tongue. Small raised structures called papillae cover the tongue surface. The enlarged cross section shows the side walls of a papilla lined with taste buds.



Key

Sweet, Bitter, Umami, Salty, Sour

(b) A taste bud. Taste buds in all regions of the tongue contain sensory receptor cells specific for each of the five taste types.

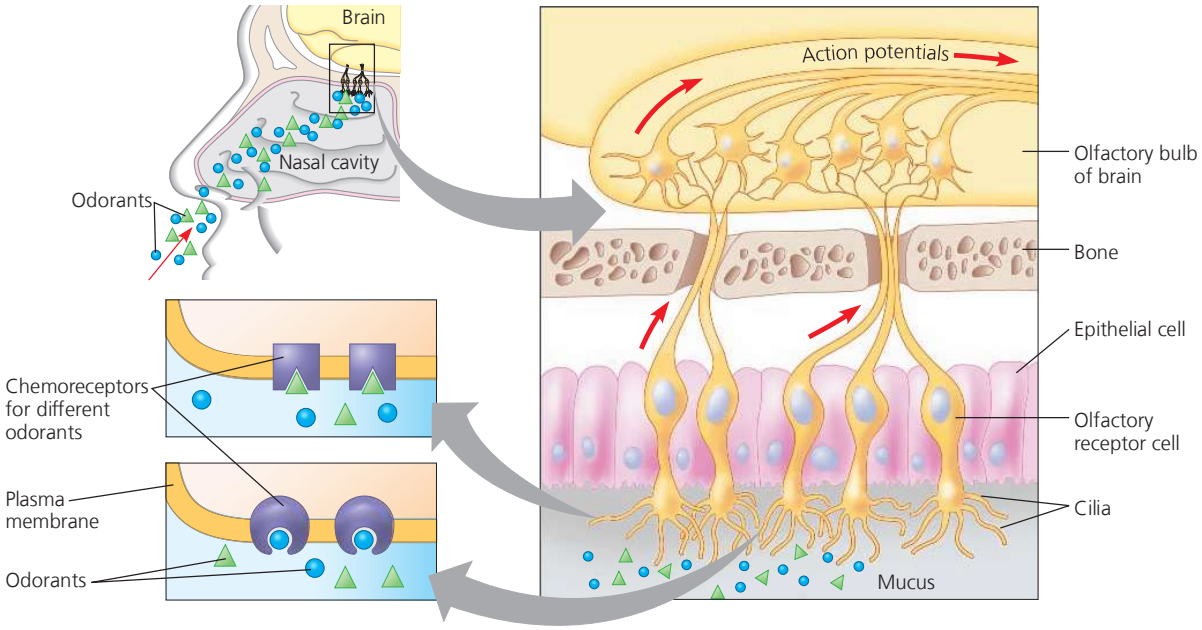
Smell in Humans

In olfaction, unlike gustation, the sensory cells are neurons. Olfactory receptor cells line the upper portion of the nasal cavity and send impulses along their axons to the olfactory bulb of the brain **(Figure 50.25)**. The receptive ends of the cells contain cilia that extend into the layer of mucus coating the nasal cavity. When an odorant diffuses into this region, it binds to a specific GPCR protein called an olfactory receptor (OR) on the plasma membrane of the olfactory cilia. These events trigger signal transduction leading to the production of cyclic AMP. In olfactory cells, cyclic AMP opens channels in the plasma membrane that are permeable to both Na^+ and Ca^{2+}. The flow of these ions into the receptor cell leads to depolarization of the membrane, generating action potentials.

Mammals can distinguish thousands of different odors, each caused by a structurally distinct odorant. How is this remarkable sensory discrimination possible? American researchers Linda Buck and Richard Axel found the answer—a very large gene family. Working with mice, Buck and Axel discovered 1,200 different OR genes—and were honored with a Nobel Prize in 2004. Humans have just 380 OR genes, far fewer than mice, but still nearly 2% of all the genes in our genome. Identification of particular odors relies on two basic properties of the olfactory system. First, each olfactory receptor cell expresses one OR gene. Second, those cells that express the same OR gene transmit action potentials to the same small region of the olfactory bulb.

After odorants are detected, information from olfactory receptors is collected and integrated. Genetic studies on mice, worms, and flies have shown that signals from the nervous system regulate this process, dialing the response to particular odorants up or down. As a result, animals can detect the location of food sources even if the concentration of a key odorant is particularly low or high.

▼ Figure 50.25 Smell in humans. Odorant molecules bind to specific chemoreceptor proteins in the plasma membrane of olfactory receptor cells, triggering action potentials. Each olfactory receptor cell has just one type of chemoreceptor. As shown, cells that express different chemoreceptors detect different odorants.



WHAT IF? *If you spray an air freshener in a musty room, would you be affecting detection, transmission, or perception of the odorants responsible for the musty smell?*

Studies of model organisms also reveal that complex mixtures of odorants are not processed as the simple sum of each input. Rather, the brain integrates olfactory information from different receptors into single sensations. These sensations contribute to the perception of the environment in the present and to the memory of events and emotions.

Although the receptors and neuronal pathways for taste and smell are independent, the two senses do interact. Indeed, much of the complex flavor humans experience when eating is due to our sense of smell. If the olfactory system is blocked, as occurs when you have a head cold, the perception of flavor is sharply reduced.

CONCEPT CHECK 50.4

1. Explain why some taste receptor cells and all olfactory receptor cells use G protein-coupled receptors, yet only olfactory receptor cells produce action potentials.
2. Pathways involving G proteins provide an opportunity for an increase in signal strength in the course of signal transduction, a change referred to as amplification. How might this be beneficial in olfaction?
3. **WHAT IF?** If you discovered a mutation in mice that disrupted the ability to taste sweet, bitter, and umami but not sour or salty, what might you predict about where this mutation acts in the signaling pathways used by these receptors?

For suggested answers, see Appendix A.

CONCEPT 50.5

The physical interaction of protein filaments is required for muscle function

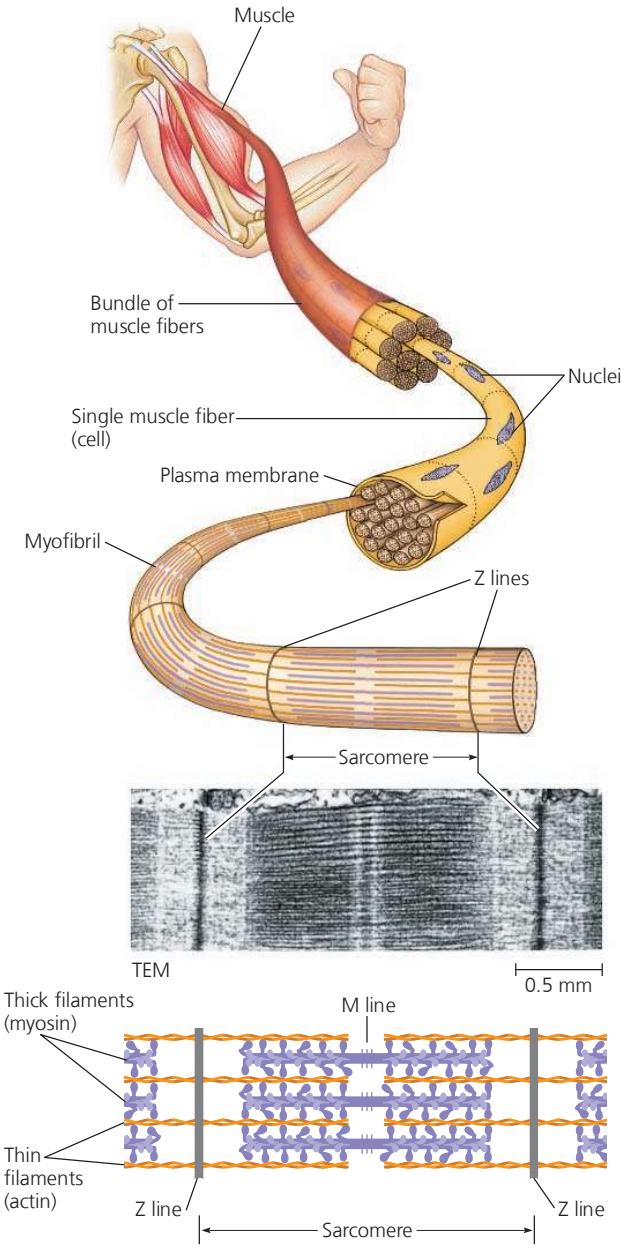
In discussing sensory mechanisms, we have seen how sensory inputs to the nervous system can result in specific behaviors: the touch-guided foraging of a star-nosed mole, the upside-down swimming of a crayfish with manipulated statocysts, and the light-avoiding maneuvers of planarians. Underlying these diverse behaviors are common fundamental mechanisms: Feeding, swimming, and crawling all require muscle activity in response to nervous system motor output.

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. The **thick filaments** are staggered arrays of myosin molecules. Muscle contraction is the result of filament movement powered by chemical energy; muscle extension occurs only passively. To understand how filaments bring about muscle contraction, we will begin by examining the skeletal muscle of vertebrates.

Vertebrate Skeletal Muscle

Vertebrate **skeletal muscle**, which moves bones and body, has a hierarchy of smaller and smaller units **(Figure 50.26)**. Within a typical skeletal muscle is a bundle of long fibers running along the length of the muscle. Each individual fiber is a single cell. Within are multiple nuclei, each derived from one of the embryonic cells that fused to form the fiber.

▼ Figure 50.26 The structure of skeletal muscle.



VISUAL SKILLS *Looking at this figure, would you say that there are multiple sarcomeres per myofibril or multiple myofibrils per sarcomere? Explain.*

Surrounding these nuclei are longitudinal **myofibrils**, which consist of bundles of 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 sarcomere line up in adjacent myofibrils, forming a pattern of light and dark bands (striations) visible with a light microscope. For this reason, skeletal muscle is also called *striated muscle*. Thin filaments attach at the Z lines at the sarcomere ends, while thick filaments are anchored in the middle of the sarcomere (M line).

In a resting (relaxed) myofibril, 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 partially overlapping arrangement is the key to how the sarcomere, and hence the whole muscle, contracts.

The Sliding-Filament Model 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 50.27**, the filaments slide past each other, much like the segments of a telescoping support pole. According to the well-accepted **sliding-filament model**, the thin and thick filaments ratchet past each other, powered by myosin molecules.

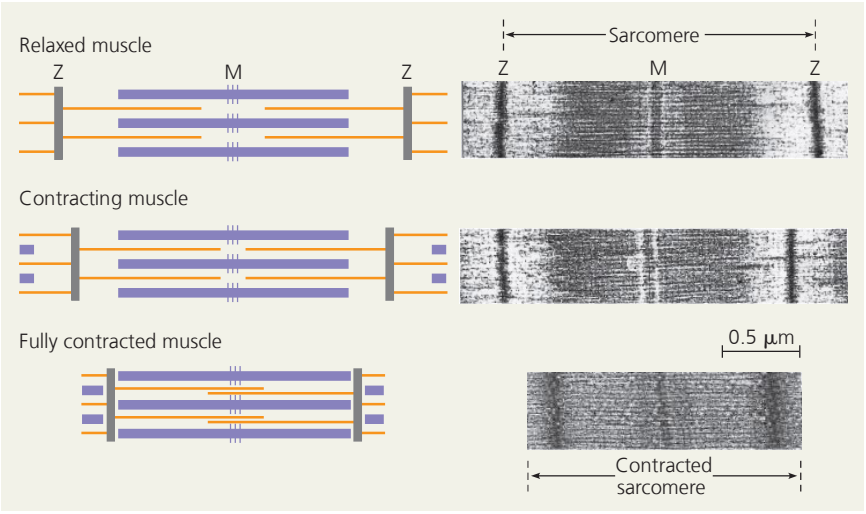
Figure 50.28 illustrates the cycles of change in the myosin molecule that convert the chemical energy of ATP into the longitudinal sliding of thick and thin filaments.

As shown in the figure, each myosin molecule has a long "tail" region and a globular "head" region. The tail adheres to the tails of other myosin molecules, binding together the thick filament. The head, jutting to the side, can bind ATP. Hydrolysis of bound ATP converts myosin to a high-energy form that binds to actin, forming a cross-bridge between the myosin and the thin filament. The myosin head then returns to its low-energy form as it helps to pull the thin filament toward the center of the sarcomere. When a new ATP molecule binds to the myosin head, the cross-bridge is disrupted, releasing the myosin head from the actin filament.

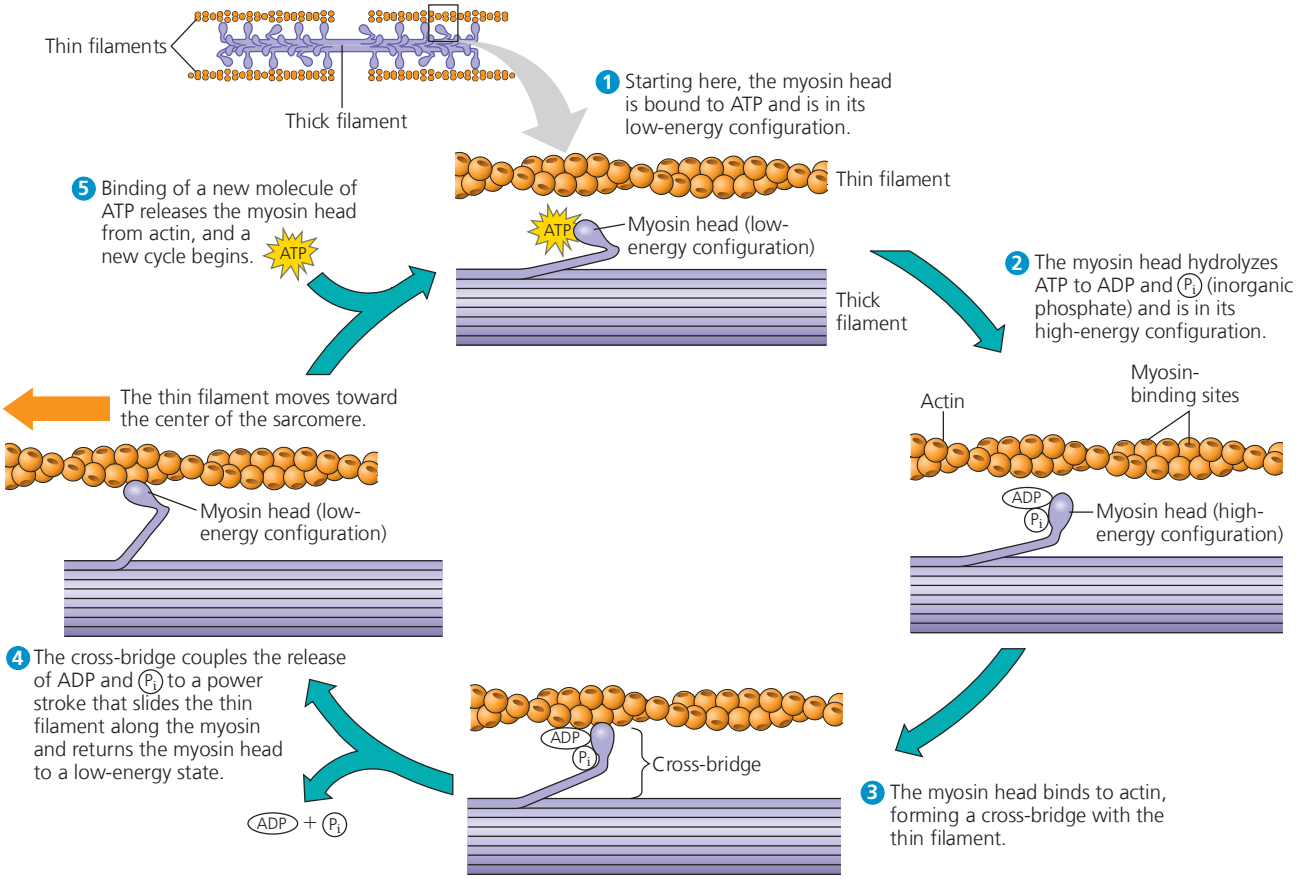
Muscle contraction requires repeated cycles of binding and release. During each cycle of each myosin head, the head is freed from a cross-bridge, cleaves the newly bound ATP, and binds again to actin. Because the thin filament moves toward the center of the sarcomere in each cycle, the myosin head now attaches to a binding site farther along the thin filament than in the previous cycle. Each end of a thick filament contains approximately 300 heads, each of which forms and re-forms about five cross-bridges per second, driving the thick and thin filaments past each other.

▶ Figure 50.27 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.

Mastering Biology BioFlix® Animation: From Muscle Cells to Movement



▼ Figure 50.28 Myosin-actin interactions underlying muscle fiber contraction.



? *When ATP binds the myosin head, what prevents the filaments from sliding back into their original positions?*

Mastering Biology BioFlix® Animation: Sliding-Filament Model of Muscle Contraction

At rest, most muscle fibers contain only enough ATP for a few contractions. Powering repetitive contractions requires two other storage compounds: creatine phosphate and glycogen. The transfer of 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. During light or moderate muscle activity, this glucose is metabolized by aerobic respiration. This highly efficient metabolic process yields enough power to sustain contractions for nearly an hour. During intense muscle activity, oxygen becomes limiting and ATP is instead generated by lactic acid fermentation (see Concept 9.5). This anaerobic pathway, although very rapid, generates much less ATP per glucose molecule and can sustain contraction for only about 1 minute.

The Role of Calcium and Regulatory Proteins

Proteins bound to actin play crucial roles in controlling muscle contraction. In a muscle fiber at rest, **tropomyosin**, a regulatory protein, and the **troponin complex**, a set of additional regulatory proteins, are bound to the actin strands of thin filaments. Tropomyosin covers the myosin-binding sites along the thin filament, preventing actin and myosin from interacting **(Figure 50.29a)**.

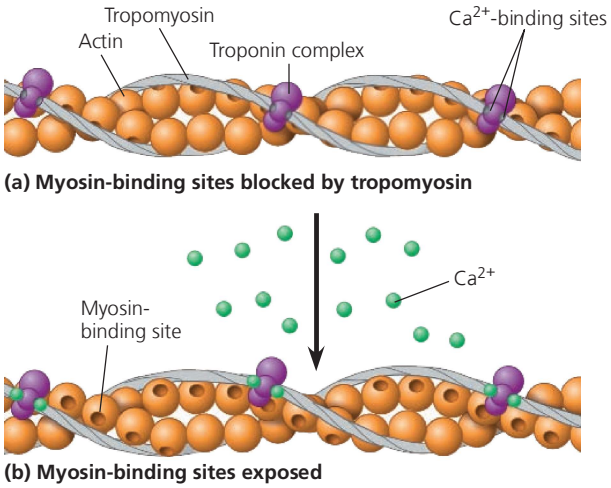
Motor neurons enable actin and myosin to interact by triggering a release of calcium ions (Ca^{2+}) into the cytosol. Once in the cytosol, Ca^{2+} binds to the troponin complex, causing the myosin-binding sites on actin to be exposed **(Figure 50.29b)**. Note that the effect of Ca^{2+} is indirect: Binding to Ca^{2+} causes the troponin complex to change shape, dislodging tropomyosin from the myosin-binding sites.

When the Ca^{2+} concentration rises in the cytosol, the cycle of cross-bridge formation begins, the thin and thick filaments slide past each, and the muscle fiber contracts. When the Ca^{2+} concentration falls, the binding sites are covered, and contraction stops.

Motor neurons cause muscle contraction through a multistep process triggering the movement of Ca^{2+} into the cytosol of muscle cells. This process is summarized in **Figure 50.30** and detailed step by step in **Figure 50.31**. First, the arrival of an action potential at the synaptic terminal of a motor neuron (1) causes release of the neurotransmitter acetylcholine. Binding of acetylcholine to receptors on the muscle fiber leads to a depolarization that initiates 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**. (2) 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 (3). Calcium ions stored in the interior of the SR flow through open channels into the cytosol (4) and bind to the troponin complex, (5) initiating the muscle fiber contraction.

When motor neuron input stops, the filaments slide back to their starting position as the muscle relaxes. Relaxation

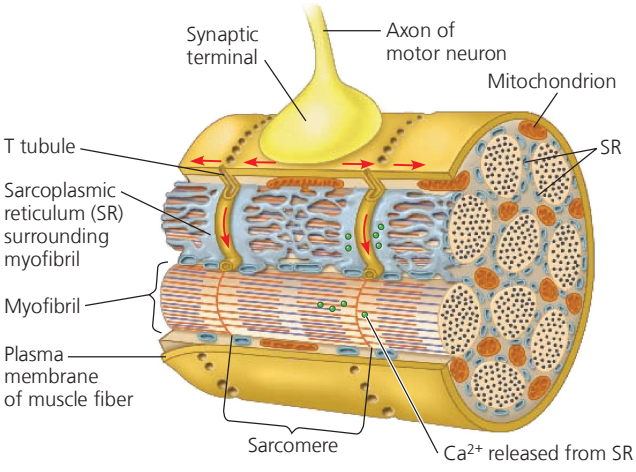
▼ Figure 50.29 The role of regulatory proteins and calcium in muscle fiber contraction. Each thin filament consists of two strands of actin and associated regulatory proteins: two long molecules of tropomyosin and multiple copies of the troponin complex.



(a) Myosin-binding sites blocked by tropomyosin

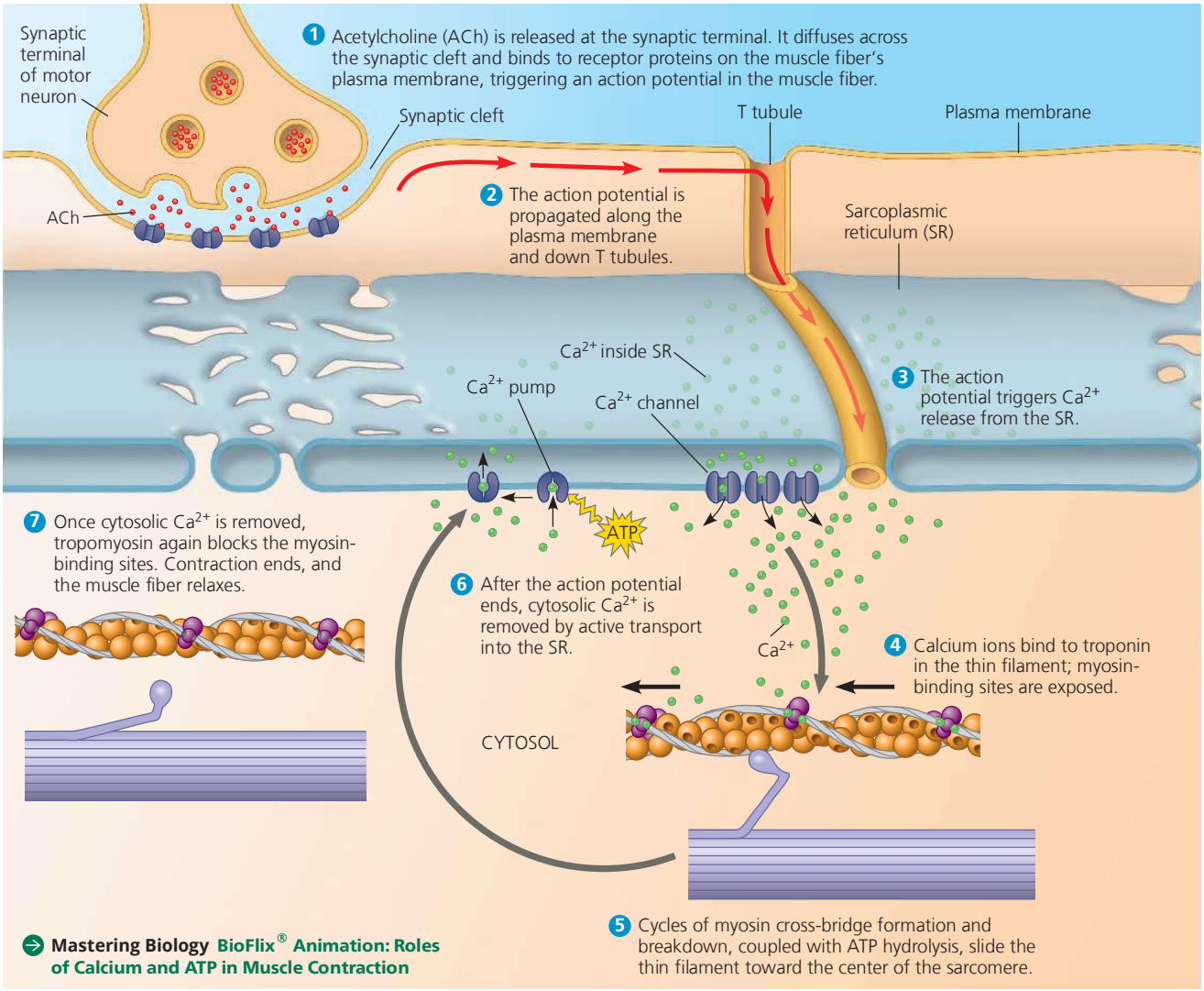
(b) Myosin-binding sites exposed

▼ Figure 50.30 The roles of the sarcoplasmic reticulum and T tubules in muscle fiber contraction. The synaptic terminal of a motor neuron releases acetylcholine, which depolarizes the plasma membrane of the muscle fiber. The depolarization causes action potentials (red arrows) to sweep across the muscle fiber and deep into it along the transverse (T) tubules. The action potentials trigger the release of calcium (green dots) from the sarcoplasmic reticulum into the cytosol. Calcium initiates the sliding of filaments by allowing myosin to bind to actin.



Mastering Biology BioFlix® Animation: Muscle Structure

▼ Figure 50.31 Summary of contraction in a skeletal muscle fiber.



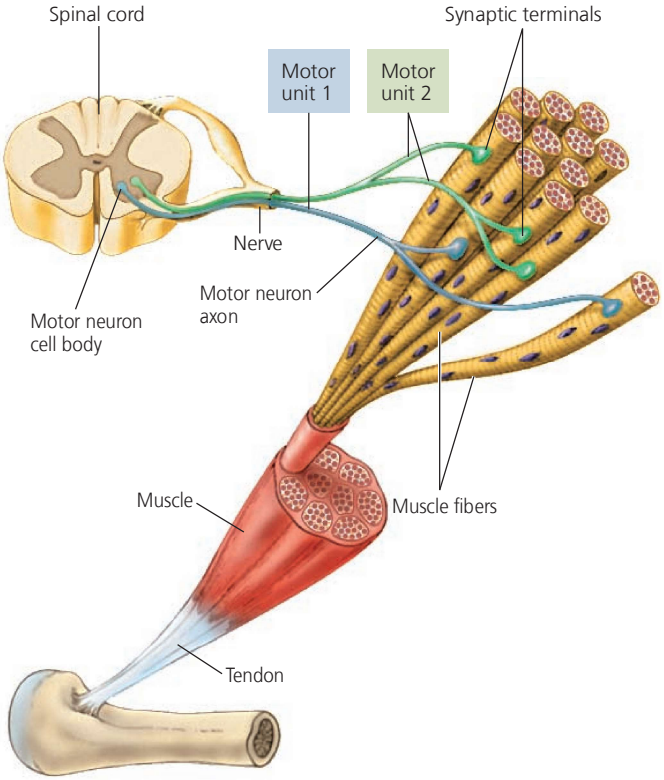
begins as proteins in the SR pump Ca^{2+} back into the SR 6 from the cytosol. When the Ca^{2+} concentration in the cytosol drops to a low level, the regulatory proteins bound to the thin filament shift back to their starting position, 7 once again blocking the myosin-binding sites. At the same time, the Ca^{2+} pumped from the cytosol accumulates in the SR, providing the stores needed to respond to the next action potential.

Several diseases cause paralysis by interfering with the excitation of skeletal muscle fibers by motor neurons. In amyotrophic lateral sclerosis (ALS), 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, a person produces antibodies to the acetylcholine receptors of skeletal muscle. As the disease progresses and the number of receptors decreases, transmission between motor neurons and 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 contraction of a single skeletal muscle fiber 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. The nervous system produces graded contractions of whole muscles by varying (1) the number of muscle fibers that contract and (2) the rate at which muscle fibers are stimulated. Let's consider each mechanism in turn.

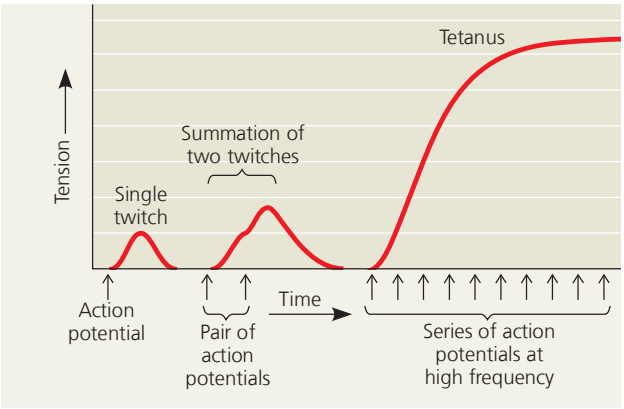
▼ Figure 50.32 Motor units in a vertebrate skeletal muscle. Each muscle fiber (cell) forms synapses with only one motor neuron, but each motor neuron typically synapses with many muscle fibers. A motor neuron and all the muscle fibers it controls constitute a motor unit.



In vertebrates, each branched motor neuron may form synapses 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 50.32)**. 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. As more and more of the corresponding motor neurons are activated, a process called *recruitment*, the force (tension) developed by a muscle progressively increases. 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 activation among the motor units, reducing the length of time any one set of fibers is contracted.

▼ Figure 50.33 Summation of twitches. This graph illustrates how the number of action potentials during 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 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 milliseconds 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 50.33)**. 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**. (Note that 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. We 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 50.1)**.

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

Table 50.1 Types of Skeletal Muscle Fibers

	Slow-Twitch	Fast-Twitch	
	Oxidative	Oxidative	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)

as their primary source of ATP and fatigue more readily than oxidative fibers. These two fiber types are readily apparent in the muscle of poultry and fish: The dark meat (red muscle) is made up of oxidative fibers rich in myoglobin, and the light meat (white muscle) is composed of glycolytic fibers.

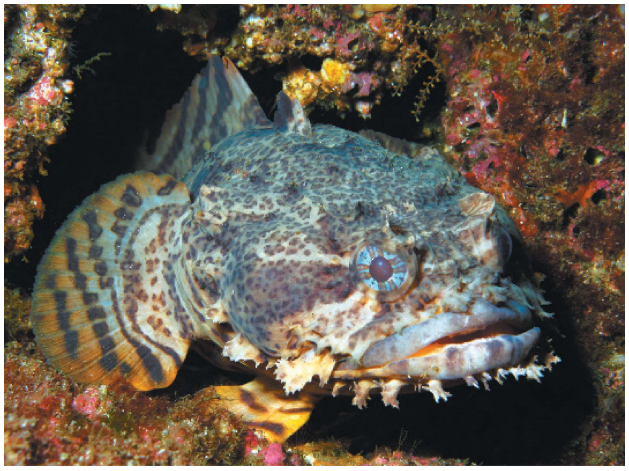
Fast-Twitch and Slow-Twitch Fibers Muscle fibers vary in the speed with which they contract: **Fast-twitch fibers** develop tension two to three times faster than **slow-twitch fibers**. Fast fibers enable brief, rapid, powerful contractions. Compared with a fast fiber, a slow fiber has less sarcoplasmic reticulum and pumps Ca^{2+} more slowly. 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.

Most human skeletal muscles contain both fast-twitch 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.

Some vertebrates have skeletal muscle fibers that twitch at rates far faster than any human muscle. For example, superfast muscles produce a rattlesnake's rattle and a dove's coo. Even faster are the muscles surrounding the gas-filled swim bladder of the male oyster toadfish **(Figure 50.34)**. In producing its "boat whistle" mating call, the toadfish can contract and relax these muscles more than 200 times per second!

▼ Figure 50.34 Specialization of skeletal muscles. The male oyster toadfish (*Opsanus tau*) uses superfast muscles to produce its mating call.



Other Types of Muscle

Although all muscles share the same fundamental mechanism of contraction—actin and myosin filaments sliding past each other—there are many different types of muscle. Vertebrates, for example, have cardiac muscle and smooth muscle in addition to skeletal muscle (see Figure 40.5).

Vertebrate **cardiac muscle** is found only in the heart and, like skeletal muscle, is striated. Unlike the cells of skeletal muscle fibers, some cardiac muscle cells can initiate rhythmic depolarization and contraction without nervous system input. Normally, however, cells in one part of the heart act as a pacemaker to initiate contraction. Signals from the pacemaker spread throughout the heart because specialized regions called *intercalated disks* electrically couple each cardiac muscle cell to the adjacent cells. It is this coupling that enables action potentials generated in one part of the heart to trigger contraction throughout the organ. Although these action potentials last up to 20 times longer than those of skeletal muscle fibers, a long refractory period prevents summation and tetanus.

Smooth muscle in vertebrates is found in the walls of hollow organs, such as vessels and tracts of the circulatory, digestive, and reproductive systems. In these locations it controls blood flow in the arteries, moves food through the digestive system, carries out uterine contractions during labor, and assists in regulating the temperature of the testicles. Smooth muscle is also found in the eye, where its action controls focusing and pupil diameter.

Smooth muscle cells lack striations because their actin and myosin filaments are not regularly arrayed along the length of the cell. 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. There is less myosin than in striated muscle fibers, and the myosin is not associated with specific actin strands. 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, 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; in fact, arthropod skeletal muscles are nearly identical to those of vertebrates. However, because the flight muscles of insects contract in response to stretching, the wings of some insects can actually beat up and down 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. Modification of certain proteins in these muscles allows them to remain contracted for as long as a month with only a low rate of energy consumption.

CONCEPT CHECK 50.5

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 8.18b.)

For suggested answers, see Appendix A.

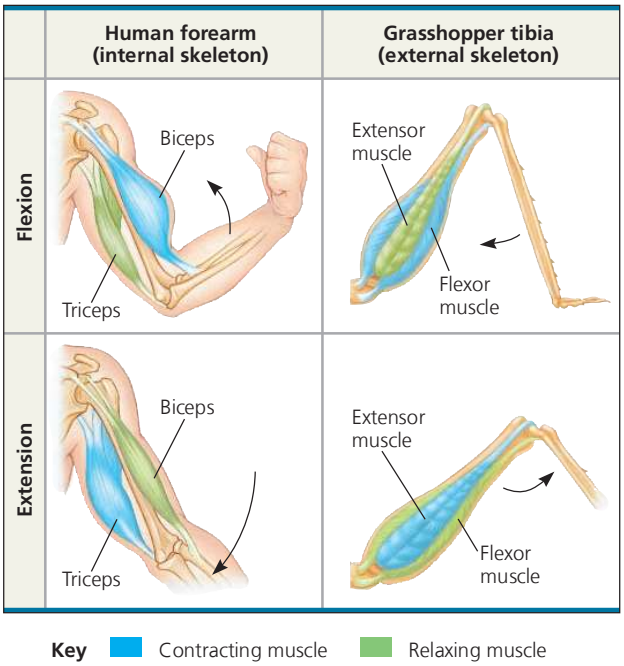
CONCEPT 50.6

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 connecting two parts of its skeleton. Often muscles are anchored to bone indirectly via connective tissue formed into a tendon.

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 in the upper portion of a human arm or grasshopper leg **(Figure 50.35)**. Although we call such 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.

▼ Figure 50.35 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.



Vital for movement, animal skeletons also function in support and protection. Most land animals would collapse if they had no skeleton to support their mass. Furthermore, an animal living in water 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, and annelids (see Figure 33.2). These animals control their form and movement by using muscles to change the shape of fluid-filled compartments. Among the cnidarians, for example, a hydra elongates by closing its mouth and constricting its central gastrovascular cavity using contractile cells in its body wall. Because water maintains its volume under pressure, the cavity must elongate when its diameter is decreased.

Worms carry out locomotion in a variety of ways. In planarians and other flatworms, body movement results mainly from muscles in the body wall exerting localized forces against the interstitial fluid. In nematodes (roundworms), 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 50.36)**.

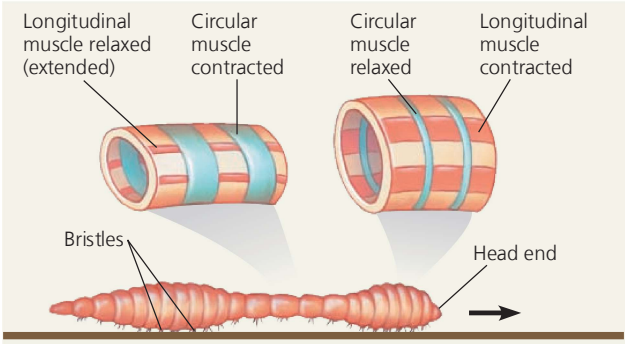
Hydrostatic skeletons are well suited for life in aquatic environments. On land, they provide support for crawling and burrowing and may cushion internal organs from shocks. However, a hydrostatic skeleton cannot support walking or running, in which an animal's body is held off the ground.

Exoskeletons

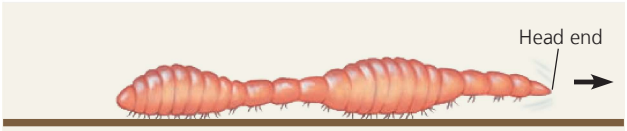
The clam shell you find on a beach once served as an **exoskeleton**, a hard covering deposited on an animal's surface. The shells of clams and most other molluscs are made of calcium carbonate secreted by the mantle, a sheet-like extension of the body wall (see Figure 33.15). Clams and other bivalves 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 exoskeleton called a *cuticle*, a coat secreted by the epidermis. About 30–50% of the arthropod cuticle consists of **chitin**, a polysaccharide similar to cellulose (see Figure 5.8). Fibrils of chitin are embedded in a protein matrix, forming a composite material that combines strength and flexibility. The cuticle may be hardened with organic compounds and, in some cases, calcium salts. In body parts that must be flexible, such as leg joints, the cuticle remains unhardened. Muscles are attached 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.

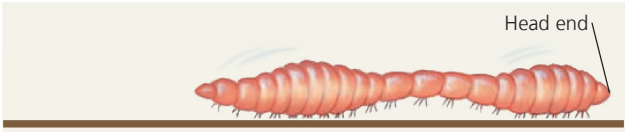
▼ Figure 50.36 Crawling by peristalsis. Contraction of the longitudinal muscles thickens and shortens the earthworm; contraction of the circular muscles constricts and elongates it.



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.

Mastering Biology Video: Earthworm Locomotion

Endoskeletons

Animals ranging from sponges to mammals have a hardened internal skeleton, or **endoskeleton**, buried within their soft tissues. In sponges, the endoskeleton consists of hard needle-like structures of inorganic material or fibers made of protein. Echinoderms' bodies are reinforced by ossicles, hard plates composed of magnesium carbonate and calcium carbonate crystals. Whereas the ossicles of sea urchins are tightly bound, the ossicles of sea stars are more loosely linked, allowing a sea star to change the shape of its arms.

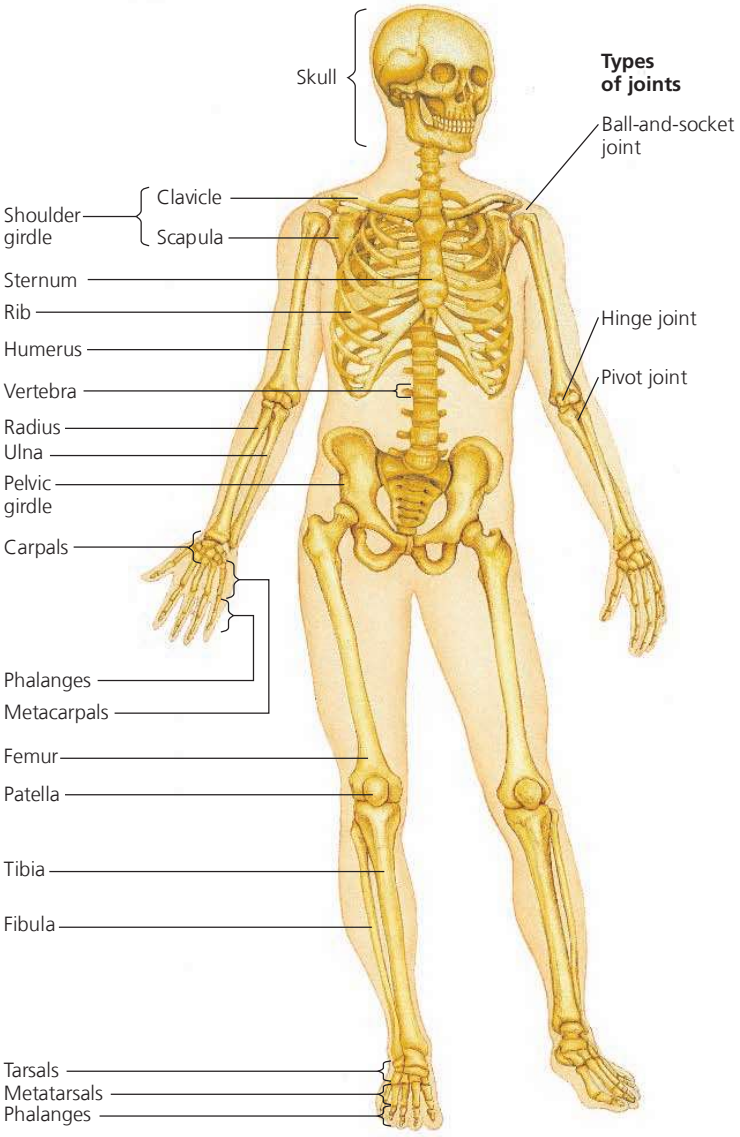
Vertebrates have an endoskeleton consisting of cartilage, bone, or some combination of these materials

(see Figure 40.5). The mammalian skeleton contains more than 200 bones, some fused together and others connected at joints by ligaments that allow freedom of movement **(Figure 50.37** and **Figure 50.38)**. Cells called *osteoblasts* secrete bone matrix and thereby build and repair bone (see Figure 40.5). *Osteoclasts* have an opposite function, resorbing bone components in remodeling of the skeleton.

How thick does an endoskeleton need to be? We can begin to answer this question by applying ideas from civil engineering. The weight of a building increases with the cube of its dimensions. However, the strength of a support depends on its cross-sectional area, which only increases with the square of its diameter. We can thus 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, the body proportions of large animals are very different from those of small ones.

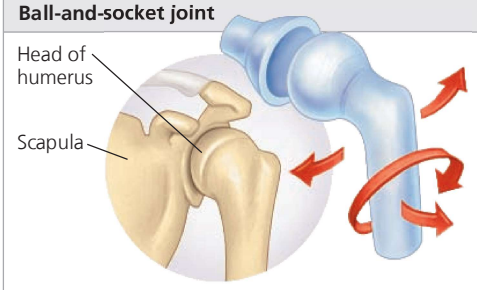
In applying the building analogy, we might also predict that the size of leg bones should be directly proportional to the strain imposed by body weight. Animal bodies, however, are complex and nonrigid. In supporting body weight, it turns out that body posture—the position of the legs relative to the main body—is more important than leg size, at least in mammals and birds. In addition, muscles and tendons, which hold the legs of large mammals relatively straight and positioned under the body, actually bear most of the load.

▼ Figure 50.37 Bones and joints of the human skeleton.



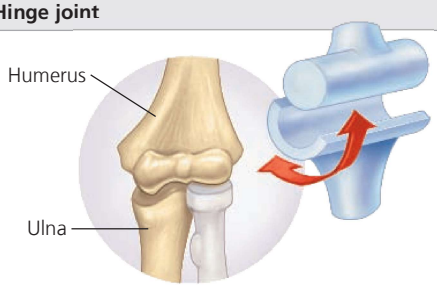
▼ Figure 50.38 Types of joints.

Ball-and-socket joint



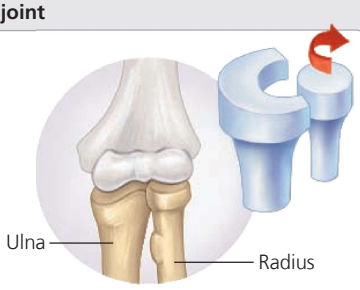
Ball-and-socket joints are found where the humerus contacts the shoulder girdle and where the femur contacts the pelvic girdle. These joints enable the arms and legs to rotate and move in several planes.

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.

Types of Locomotion

Movement is a hallmark of animals. Even animals fixed to a surface move their body parts: Sponges use beating flagella to generate water currents that draw and trap small food particles, and sessile cnidarians wave tentacles that capture prey. Most animals, however, are mobile and spend a considerable portion of their time and energy actively searching for food, escaping from danger, and seeking mates. These activities involve **locomotion**—active travel from place to place.

Friction and gravity tend to keep an animal stationary and therefore oppose locomotion. To move, an animal must expend energy to overcome these two forces. As we 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.

Locomotion on Land

On land, a walking, running, hopping, or crawling animal must be able to support itself and move against gravity, but air poses relatively little resistance, at least at moderate speeds. When a land 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 animal's leg muscles must overcome inertia by accelerating a leg from a standing start. For moving on land, powerful muscles and strong skeletal support are therefore 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 locomotion by hopping **(Figure 50.39)**. As a kangaroo lands after each leap, tendons in its hind legs momentarily store energy. Much like the energy in a compressed spring, the energy stored in the tendons from one jump is released in the next jump, reducing the energy the animal must expend to travel. The legs of an insect, dog, or human also retain some energy during walking or running, although a considerably smaller share than those of a kangaroo.

Maintaining balance is another prerequisite for walking, running, or hopping. A cat, dog, or horse maintains balance by keeping three feet on the ground when walking. Illustrating the same principle, 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. A kangaroo's large tail forms a stable tripod with its hind legs when the animal sits or moves slowly and helps balance its body during leaps. Recent studies reveal that the tail also generates significant force during hopping, helping to propel the kangaroo's forward movement.

Crawling poses a very different challenge. Having much of its body in contact with the ground, a crawling animal must exert considerable effort to overcome friction. As you have read, earthworms crawl by peristalsis. In contrast, many snakes crawl by undulating their entire body from side to side. Waves of bending propagate from head to tail, with each portion of the body eventually following the same undulating path as the head and neck. Some other snakes, such as boa constrictors and pythons, creep in a straight line, driven by muscles that lift belly scales off the ground, tilt the scales forward, and then push them backward against the ground.

▲ **Figure 50.39 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 provides extra force for leaping and helps to balance the kangaroo when it leaps as well as when it sits.

Mastering Biology
Interview with Terry Dawson: Kangaroos are "rule" breakers!

Swimming

Because most animals are reasonably buoyant in water, overcoming gravity is less of a problem for swimming animals than for species that move on land or through the air. On the other hand, water is a much denser and more viscous medium than air, and thus drag (friction) is a major problem for aquatic animals. A sleek, fusiform (torpedo-like) shape is a common adaptation of fast swimmers (see Figure 40.2).

Swimming occurs in diverse ways. Many insects and four-legged vertebrates use their legs as oars to push against the water. 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. Squids, scallops, and some cnidarians are jet-propelled, taking in water and squirting it out in bursts. In contrast, jellies appear to generate a region of low pressure in the water ahead of them such that they are pulled forward rather than pushed.

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.

Mastering Biology **Video: Soaring Hawk**

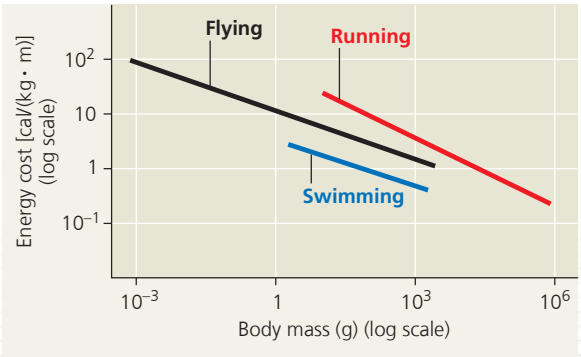
Scientific Skills Exercise

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, swam in water flumes, or flew in wind tunnels. For example, a tube connected to a plastic face mask collected gases exhaled by a parakeet during flight (see photo). 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 [calories/(kilogram · 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 here, the individual data points are not shown.)



Data from K. Schmidt-Nielsen, Locomotion: Energy cost of swimming, flying, and running, *Science* 177:222–228 (1972). Reprinted with permission from AAAS.

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 D.)
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 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 to that of flying or swimming?
5. Schmidt-Nielson calculated the swimming cost in a mallard duck and found that it was nearly 20 times as high as the swimming cost in a salmon of the same body mass. What could explain the greater swimming efficiency of salmon?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

To fly, an animal's wings must develop enough lift to overcome gravity's downward force. The key to meeting this challenge is wing shape. All wings act as 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 fusiform shape helps reduce drag in air as it does in water.

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. The low body mass of many flying animals is due to specialized structural adaptations. Birds, for example, have no urinary bladder or teeth and have relatively large bones with air-filled regions that help lessen the bird's weight (see Figure 34.30).

Flying, running, and swimming each impose different energetic demands on animals. In the **Scientific Skills Exercise**, you can interpret a graph that compares the relative energy costs of these three forms of locomotion.

CONCEPT CHECK 50.6

1. Contrast swimming and flying in terms of the main problems they pose and the adaptations that allow animals to overcome those problems.
2. **MAKE CONNECTIONS.** Peristalsis contributes to the locomotion of many annelids and to the movement of food in the digestive tract (see Concept 41.3). Using the muscles of your hand and a toothpaste tube as a model of peristalsis, how would your demonstration differ for the two processes?
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.

50 Chapter Review

Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 50.1

Sensory receptors transduce stimulus energy and transmit signals to the central nervous system *(pp. 1108–1112)*

- 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 **perceptions**. The frequency of action potentials in an axon and the number of axons activated reflect 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. **Chemoreceptors** detect either total solute concentrations or specific molecules. **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.

? *To simplify sensory receptor classification, why might it make sense to eliminate nociceptors as a distinct class?*

CONCEPT 50.2

In hearing and equilibrium, mechanoreceptors detect moving fluid or settling particles *(pp. 1112–1116)*

- 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 and for detection of water movement in fishes and aquatic amphibians. 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.

? *How are music volume and pitch encoded in signals to the brain?*

CONCEPT 50.3

The diverse visual receptors of animals depend on light-absorbing pigments *(pp. 1117–1123)*

- 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**, chemically 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 processing of sensory information sent to the vertebrate brain in vision differ from that in hearing or olfaction?*

CONCEPT 50.4

The senses of taste and smell rely on similar sets of sensory receptors *(pp. 1123–1125)*

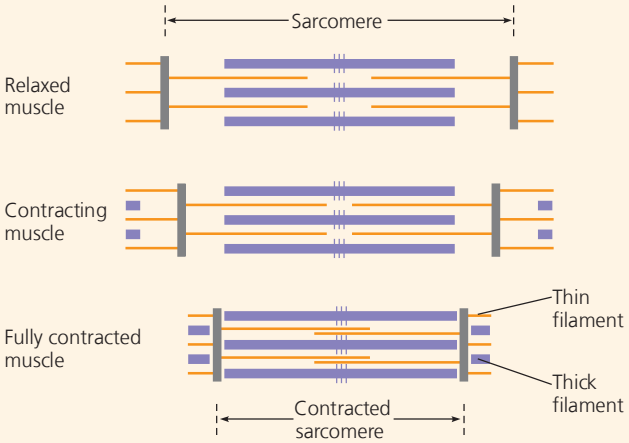
- Taste (**gustation**) and smell (**olfaction**) depend on stimulation of chemoreceptors by small dissolved molecules. In humans, sensory cells in **taste buds** express a receptor type specific for one of the five taste perceptions: sweet, sour, salty, bitter, and umami (elicited by glutamate). Olfactory receptor cells line the upper part of the nasal cavity. Hundreds of different genes code for membrane proteins that bind to specific classes of **odorants**, and each receptor cell appears to express only one of those genes.

? *Why is the flavor of food less intense when you have a head cold?*

CONCEPT 50.5

The physical interaction of protein filaments is required for muscle function *(pp. 1125–1132)*

- 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, form cross-bridges, and then release upon binding ATP anew. As this cycle repeats, the thick and thin filaments slide past each other, shortening the sarcomere and contracting the muscle fiber.



- Motor neurons release acetylcholine, triggering action potentials in muscle fibers that stimulate the release of Ca^{2+} 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 one action potential. Skeletal muscle fibers are **slow-twitch** or **fast-twitch** and oxidative or glycolytic.
- **Cardiac muscle**, found in the heart, consists of striated cells electrically connected by intercalated disks. Nervous system input controls the rate at which the heart contracts, but is not strictly required for cardiac muscle contraction. In **smooth muscles**, contractions are initiated by the muscles or by stimulation from neurons in the autonomic nervous system.

? *What are two major functions of ATP hydrolysis in skeletal muscle activity?*

CONCEPT 50.6

Skeletal systems transform muscle contraction into locomotion *(pp. 1132–1136)*

- 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 in the form of **endoskeletons**, as in vertebrates.
- Each form of **locomotion**—swimming, movement on land, or flying—presents a particular challenge. For example, swimmers need to overcome substantial 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.*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

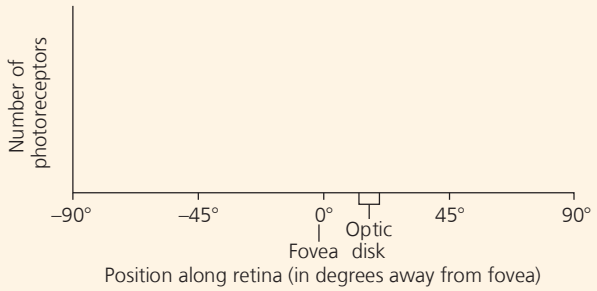
1. Which sensory receptor—category pair is correct?
   (A) hair cell—nociceptor
   (B) snake pit organ—mechanoreceptor
   (C) taste receptor—chemoreceptor
   (D) olfactory receptor—electromagnetic receptor
2. The middle ear converts
   (A) air pressure waves to fluid pressure waves.
   (B) air pressure waves to nerve impulses.
   (C) fluid pressure waves to nerve impulses.
   (D) pressure waves to hair cell movements.
3. During vertebrate skeletal muscle contraction, calcium ions
   (A) break cross-bridges as a cofactor in hydrolysis of ATP.
   (B) bind to troponin, exposing myosin-binding sites.
   (C) transmit action potentials to the muscle fiber.
   (D) spread action potentials through the T tubules.

Levels 3-4: Applying/Analyzing

4. The human brain differentiates tastes from smells because action potentials for the two sensations differ in
   (A) magnitude and shape.
   (B) threshold potential.
   (C) where they are received in the brain.
   (D) how long they take to reach the brain.
5. The transduction of sound waves into action potentials occurs
   (A) in the tectorial membrane as it is stimulated by hair cells.
   (B) when hair cells are bent against the tectorial membrane, causing them to depolarize and release neurotransmitter that stimulates afferent neurons.
   (C) as the basilar membrane vibrates at different frequencies in response to the varying volume of sounds.
   (D) within the middle ear as the vibrations are amplified by the malleus, incus, and stapes.

Levels 5-6: Evaluating/Creating

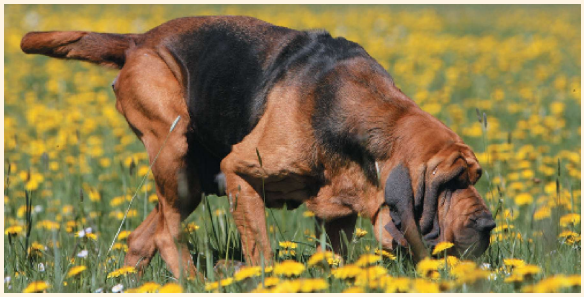
6. Metal objects cause sharks to misdirect their bites. Sharks also can find batteries buried under sand. These facts suggest that sharks track their prey just before they bite in the same way that
   (A) a rattlesnake finds a mouse in its burrow.
   (B) an insect avoids being stepped on.
   (C) a star-nosed mole locates its prey in tunnels.
   (D) a platypus locates its prey in a muddy river.
7. **DRAW IT** Based on the information in the text, fill in the following graph. Use one line for rods and another line for cones.



8. **EVOLUTION CONNECTION** In general, locomotion on land will require more energy than locomotion in water. By integrating what you learned about animal form and function in Unit 7, discuss some of the evolutionary adaptations of mammals that support the high energy requirements for moving on land.
9. **SCIENTIFIC INQUIRY • INTERPRET THE DATA** To demonstrate how energy is stored in tendons during hopping, an instructor asked student volunteers to hop at a frequency that felt "natural" and then, after resting, to hop at exactly half that frequency. Hopping was done at a standard height and volunteers' mass, O_2 consumption, and CO_2 production were measured. Here is a representative set of results calculated for one student.

Frequency (hops/sec)	Energy used (joules/sec)
1.85	735
0.92	716

   The student consumed 159 joules/sec when standing. For each hop frequency, subtract this standing value from the energy used during hopping. Then divide by the hop frequency to calculate the energy cost per hop. How does the energy cost per hop differ at the two frequencies, and how might this be related to energy storage in tendons?
10. **WRITE ABOUT A THEME: ORGANIZATION** In a short essay (100–150 words), describe three ways in which the structure of the lens of the human eye is well adapted to its function in vision.
11. **SYNTHESIZE YOUR KNOWLEDGE**



   Bloodhounds, which are adept at following a scent trail even days old, have no more olfactory receptor genes than other dogs. Predict how the sensory and nervous systems of bloodhounds differ from those of other dogs in ways that contribute to their tracking ability.

For selected answers, see Appendix A.

51 Animal Behavior

KEY CONCEPTS

Study Tip

Identifying components of experimental design: Animal behavior is studied in both the wild and the laboratory and involves approaches ranging from passive observation to active intervention. As you study this chapter, note how scientific methods are applied to answer questions in diverse contexts, such as foraging in honeybees (Figure 51.5; see example started here) and fruit flies (Figure 51.13).

1) **Make observations**—returning bees do a number of different but set dances
↓
2) **Form a hypothesis**—the dances convey information about food location
↓
3) **Generate predictions**
↓
4) **Gather and analyze data**
↓
5) **Draw conclusions**

Go to Mastering Biology

For Students (in eText and Study Area)
- Get Ready for Chapter 51
- HHMI Videos: Studying Elephant Communication; How Lizards Find Their Way Home

For Instructors to Assign (in Item Library)
- Interpret the Data: Evolution of Foraging Behavior
- Tutorial: Animal Behavior and Learning
- Scientific Skills Exercise: Crow Foraging Behavior

Figure 51.1 A male magnificent frigatebird (*Fregata magnificens*) lives mostly at sea. He often feeds by piracy, harassing diving birds into coughing up their catch for his consumption. Periodically, however, he alights on an island, points his bill to the sky, and inflates an enormous red throat pouch. Clacking his beak, he produces a drumming sound that resonates in the pouch. If a curious female takes notice and lands nearby, a mating ritual ensues.

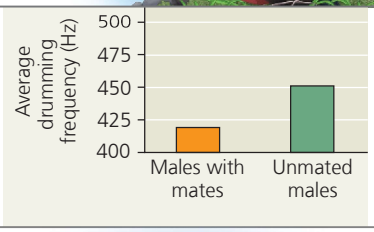
What questions do biologists seek to answer in studying animal behavior?

1. What event or signal triggers the behavior?

Males inflate their pouch only if females are nearby. The intensity of the display increases when a female circles overhead.

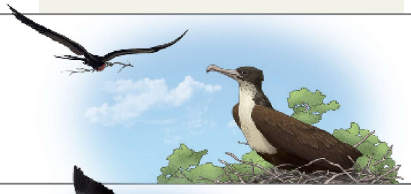
2. How does experience during growth and development influence the behavior?

Older males have larger pouches that produce lower drumming frequencies, which attract more females.



3. How does the behavior aid survival and reproduction?

After mating, males and females cooperate in nest building and feeding the chicks.



4. How has the behavior been shaped by natural selection?

The throat pouch can be inflated prominently for mating, and deflated to maximize flight efficiency.

Answering these questions can provide fundamental insights into **how** behaviors occur and **why** they arise.

CONCEPT 51.1

Discrete sensory inputs can stimulate both simple and complex behaviors

A **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 or releasing a scent to mark its territory. 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 (see Concept 40.3). In short, all of animal 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 throat pouch of a male frigatebird (see Figure 51.1) is essential for courtship. Inflating the pouch exposes its vibrantly colored surface and provides a resonating chamber that amplifies the male's drumming. As this example illustrates, the process of natural selection that shapes behaviors also influences the evolution of animal anatomy.

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 were highlighted in Figure 51.1:

1. What stimulus triggers the behavior and how do the various body systems bring it about?
2. How does the animal's experience during growth and development influence the response to the stimulus?
3. How does the behavior aid survival and reproduction?
4. What is the behavior's evolutionary history?

The 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.

Experiments on proximate causation by Tinbergen earned him a share of a Nobel Prize awarded in 1973. Such studies defined the field of *ethology*, the study of animal behavior observed in a natural environment. We'll consider those and related experiments in the early part of the chapter. The concept of ultimate causation is central to **behavioral ecology**, the study of the ecological and evolutionary basis for animal behavior. We'll explore this vibrant area of modern biological research in the rest of the chapter.

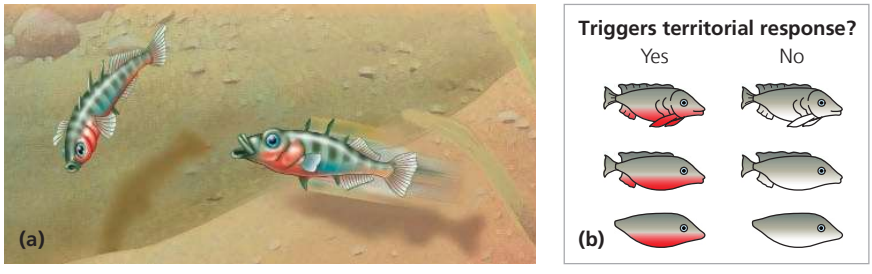
Fixed Action Patterns

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 one of Tinbergen's own experiments.

As part of his research, Tinbergen kept fish tanks containing three-spined sticklebacks (*Gasterosteus aculeatus*), a species in which males, but not females, have red bellies. Male sticklebacks attack other males that invade their nesting territories **(Figure 51.2)**. 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 the proximate cause of the attack behavior. A male stickleback will not attack a fish lacking red coloration, but will attack even unrealistic models if they contain areas of red color. 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. The fixed action pattern of certain moths takes the form of evasive flight maneuvers—loops and spirals—performed instantaneously upon hearing the sounds of an echolocating bat or an ultrasonic whistle in the same frequency range. Fixed action patterns are essentially unchangeable and, once initiated, are usually carried to completion. The trigger for the behavior is an external cue called a **sign stimulus**, such as a red object that prompts a male stickleback's aggressive behavior.

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



▶ Figure 51.2 Sign stimuli in a classic fixed action pattern. (a) A male stickleback fish attacks other male sticklebacks that invade its nesting territory. **(b)** Models, whether realistic or not, can trigger the aggressive behavior, but only if the underside is red. Researchers concluded that the red belly of the intruding male is a sign stimulus that releases the aggressive behavior.

? *Suggest an explanation for why this behavior might have evolved (its ultimate causation).*

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 has a 24-hour periodicity (see Concept 49.2). For example, experiments have shown that migrating birds orient differently relative to the sun at distinct times of the day. Nocturnal animals can instead use the North Star, which has a constant position in the night sky.

Although the sun and stars can provide useful clues for navigation, clouds can obscure these landmarks. How do migrating animals overcome this problem? A simple experiment with homing pigeons provided one answer. On an overcast day, placing a small magnet on the head of a homing pigeon prevented 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. As discussed in Concepts 40.2 and 49.2, the clock is responsible for a circadian rhythm, a daily cycle of rest and activity. 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, fiddler crab courtship behavior, which is linked to the lunar cycle. Possessed with front claws of very different size, the male fiddler crab (genus *Uca*) waves the larger claw in front of him to attract potential mates **(Figure 51.3)**. Timing this claw-waving courtship behavior to the new or full moon helps the development of offspring. How? Fiddler crabs begin their lives as larvae settling in the mudflats. The tides disperse larvae to deeper waters, where they complete early development

▼ Figure 51.3 Courtship display of male fiddler crab.

in relative safety before returning to the tidal flats. By courting at the time of the new or full moon, crabs link their reproduction to the times of greatest tidal movement.

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 organism to another is called a **signal**. The transmission and reception of signals between animals constitute **communication**, which often has a role in the proximate causation of behavior.

Mastering Biology Video: Albatross Courtship Ritual • Video: Giraffe Courtship Ritual
HHMI Video: Studying Elephant Communication

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 a *stimulus-response chain*, in which the response to each stimulus is itself a stimulus for the next behavior. In the first step, a male detects a female in his field of vision and orients his body toward hers. To confirm she belongs to his species, he uses his olfactory system to detect chemicals she releases into the air. The male then approaches and touches the female with a foreleg **(Figure 51.4)**. This touching, or tactile communication, alerts the female to the male's presence. In the third stage, the male extends and vibrates one wing, producing a courtship song. This auditory

▼ Figure 51.4 Male fruit fly tapping female with foreleg.

communication informs the female whether he is of the same species. Only if all of these forms of communication are successful will the female allow the male to attempt copulation.

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 detect and appreciate the songs and bright colors used by birds to communicate but miss many chemical cues on which other mammals base their behavior.

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 a source of nectar.

When a successful forager returns to the hive, its movements, as well as sounds and odors, quickly become the center of attention for other bees, called followers. Moving along the vertical wall of the honeycomb, the forager performs a "waggle dance" that communicates to the follower bees both the direction and distance of the food source in relation to the hive **(Figure 51.5)**. In performing the dance, the bee follows a half-circle swing in one direction, a straight run during which it waggles its abdomen, and a half-circle swing in the other direction. What von Frisch and colleagues deduced was that the angle of the straight run relative to the hive's vertical surface indicates the horizontal angle of the food in relation to the sun. Thus, if the returning bee runs at a 30° angle to the right of vertical, the follower bees leaving the hive fly 30° to the right of the horizontal direction of the sun.

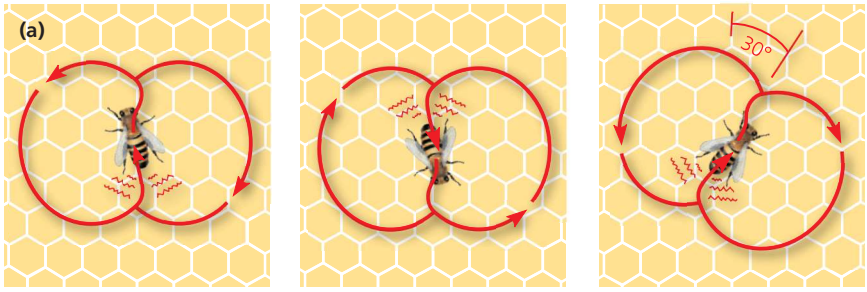
How does the waggle dance communicate distance to the nectar source? It turns out that a dance with a longer straight run, and therefore more abdominal waggles per run, indicates a greater distance to the food found by the forager. As follower bees exit the hive, they fly almost directly to the area indicated by the waggle dance. By using flower odor and other clues, they locate the source of nectar within this area.

If the food source is close to the hive (less than 50 m away), the waggle dance takes a slightly different form that primarily advertises the availability of nectar nearby. In this form of the waggle dance, which von Frisch called "round," the returning bee moves in tight circles while moving its abdomen from side to side. In response, the follower bees leave the hive and search in all directions for nearby flowers rich in nectar.

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

▼ Figure 51.5 Honeybee dance language. Honeybees returning to the hive communicate the location of food sources through the symbolic language of a dance.

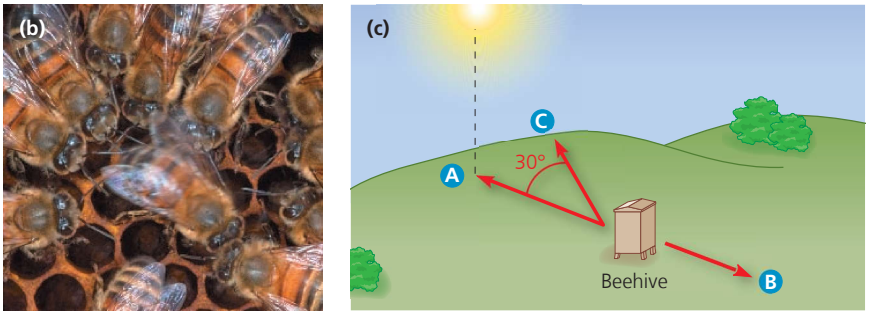


Location A: Food source is in same direction as sun.

Location B: Food source is in direction opposite sun.

Location C: Food source is 30° to right of sun.

The waggle dance, performed when food is distant, resembles a figure eight. Distance is indicated by the number of abdominal waggles performed in the straight-run part of the dance. Direction is indicated by the angle of the straight run relative to the vertical surface of the hive. The dance communicates this information to workers clustered around the dancing bee, directing them to food at a particular location.



VISUAL SKILLS *What information, if any, might be conveyed by the portions of the waggle dance between the straight runs? Explain.*

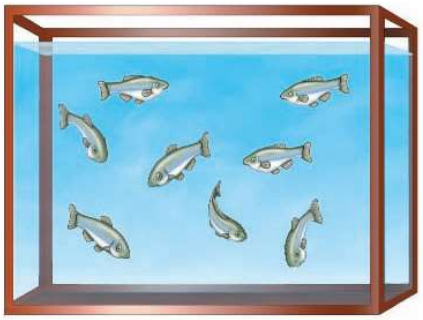
courtship (see Figure 51.4). Pheromones are not limited to short-distance signaling, however. Male silkworm moths have receptors that can detect the pheromone from a female moth from several kilometers away (see Figure 50.6).

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.

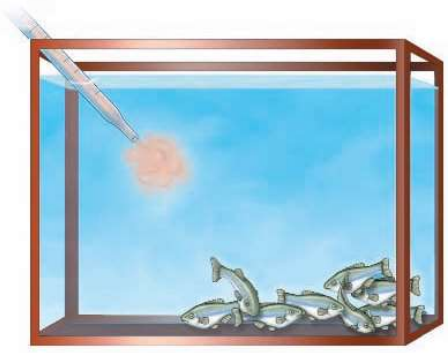
Pheromones can also serve as alarm signals. For example, when a minnow is injured, a substance released from the fish's skin disperses in the water, inducing a fright response in other minnows in the area. These nearby fish become more vigilant and often form tightly packed schools near the river or lake bottom, where they are safer from attack **(Figure 51.6)**. Pheromones can be very effective at remarkably low concentrations. For instance, just 1 cm^2 of skin from a fathead minnow contains sufficient alarm substance to induce a reaction in 58,000 L of water.

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—involves the nervous, muscular, and skeletal systems explored elsewhere in this unit: Stimuli activate sensory systems, 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.

▼ Figure 51.6 Fathead minnows (*Pimephales promelas*) responding to the presence of an alarm substance.



1 Minnows are widely dispersed in an aquarium before an alarm substance is introduced.



2 Within seconds of the alarm substance being introduced, minnows aggregate near the bottom of the aquarium and reduce their movement.

CONCEPT CHECK 51.1

1. If an egg rolls out of a greylag goose's nest, the mother 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. **WHAT IF?** Suppose you exposed various fish species from the minnows' environment to the alarm substance from minnows. Thinking about natural selection, suggest why some species might respond like minnows, some might increase their activity, and some might show no change.
3. **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 39.3.)

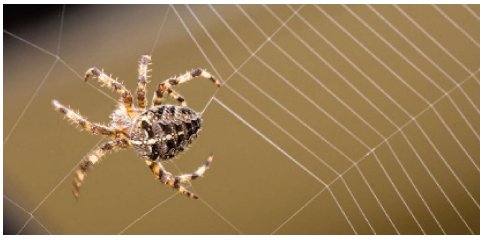
For suggested answers, see Appendix A.

CONCEPT 51.2

Learning establishes specific links between experience and behavior

Some behaviors—such as a fixed action pattern, a courtship stimulus-response chain, or pheromone signaling—are performed by all individuals the same way each time. Behavior that is developmentally fixed in this way is known as **innate behavior**. Consider, for example, the construction of a spider's web. Although a spider's web is quite complex, web building is innate, not learned. Many other behaviors, however, vary considerably with experience.

▶ A spider in family Theridiidae spinning a web



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 in the same or a similar environment. 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. Male California mice (*Peromyscus californicus*)

Table 51.1 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.

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. Cross-fostering—placing pups in the nests of the other species—altered some behaviors of both species **(Table 51.1)**. 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.

For humans, the influence of genetics and environment on 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 disorders that alter human behavior, such as anxiety disorders, schizophrenia, and alcoholism.

▼ Identical twins who were raised separately

Learning

One powerful way that an animal's environment can influence its behavior is through **learning**, the modification of behavior as a result of specific experiences. The capacity for learning 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 49.4). Therefore, the essential challenge for research into learning is not to decide between nature and nurture, but rather to explore the contributions of *both* nature (genes) and nurture (environment) in shaping learning and, more generally, behavior.

Imprinting

In some species, the ability of offspring to recognize and be 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 or object. Imprinting can take place only during a specific time period 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, experiments 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 a person rather than with a goose, they imprinted on the human and steadfastly followed that person from then on **(Figure 51.7)**. 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.

Until recently, scientists made further use of imprinting to teach cranes born in captivity to migrate along safe routes. Young whooping cranes were imprinted on humans in "crane suits" and then allowed to follow these "parents" as they flew ultralight aircraft along selected migration routes. Beginning in 2016, efforts shifted to a focus on minimizing human intervention as part of an overall strategy aimed at fostering self-sustaining crane populations.

Spatial Learning and Cognitive Maps

Every natural environment has spatial variation, as in locations of nest sites, hazards, food, and prospective mates.

▼ **Figure 51.7 Imprinting.** Young graylag geese imprinted on a man.

WHAT IF? *Suppose the geese were bred to each other. How might their imprinting on a human affect their offspring? Explain.*

Mastering Biology **Video: Ducklings**

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.

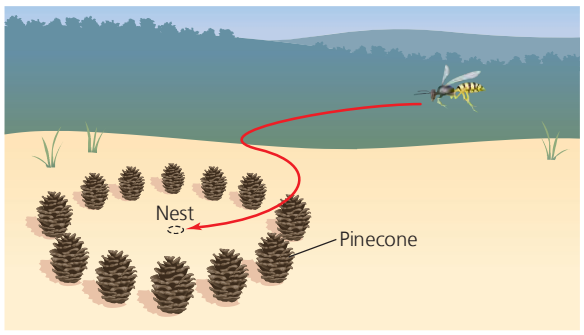
The idea of spatial learning intrigued Tinbergen while he was a graduate student in the Netherlands. At that time, he was studying females of a digger wasp species (*Philanthus triangulum*) that nests in small burrows dug into sand dunes. When a wasp leaves her nest to go hunting, she hides the entrance 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 51.8)**. By manipulating objects around nest entrances, he demonstrated that digger wasps engage in spatial learning. This experiment was so simple and informative that it could be summarized very concisely. In fact, at 32 pages, Tinbergen's Ph.D. thesis from 1932 is still the shortest ever approved at Leiden University.

In some animals, spatial learning involves formulating a **cognitive map**, a representation in an animal's nervous

▼ **Figure 51.8 Inquiry**

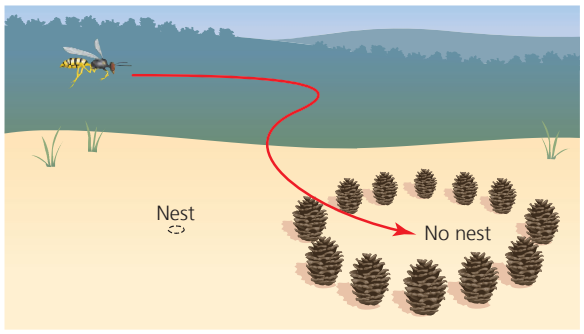
Does a digger wasp use landmarks to find her nest?

Experiment A female digger wasp covers the entrance to her nest while foraging for food, but finds the correct wasp nest reliably upon her return 30 minutes or more later. Niko Tinbergen wanted to test the hypothesis that a wasp learns visual landmarks that mark her nest before she leaves on hunting trips. First, he marked one nest with a ring of pinecones while the wasp was in the burrow. 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.

Data from 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?

Mastering Biology **Animation: Digger Wasps and Landmarks**

system of the spatial relationships between objects in its 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 the birds kept track of the halfway point between landmarks, rather than a fixed distance, to find their hidden food stores.

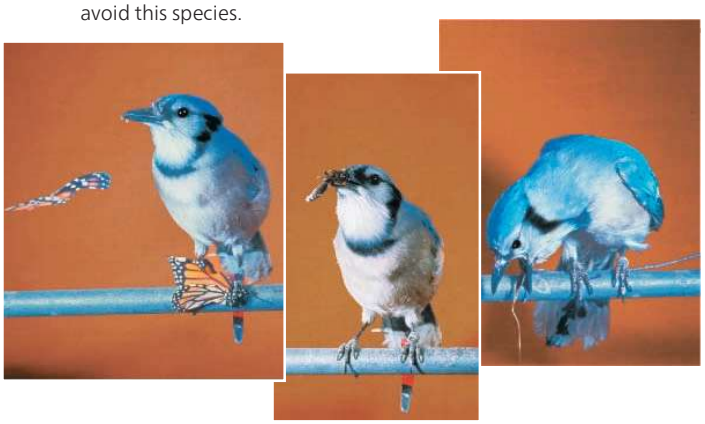
Mastering Biology **HHMI Video: How Lizards Find Their Way Home**

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 51.9)**. 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**.

Associative learning is well suited to study in the laboratory. In the 1890s, Russian physiologist Ivan Pavlov demonstrated that if he always rang a bell just before feeding a dog, the dog would eventually salivate when the bell sounded, anticipating food. This form of learning, in which an arbitrary stimulus becomes associated with a particular outcome, is known as *classical conditioning*. Four decades later, the American researcher B. F. Skinner explored how a rat learns through trial and error to obtain food by pressing a lever. Such learning, in which a behavior becomes associated with a reward or punishment, is known as trial-and-error learning or operant conditioning (see Figure 51.9).

▼ Figure 51.9 Associative learning. Having ingested and vomited a monarch butterfly, a blue jay has probably learned to avoid this species.



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.

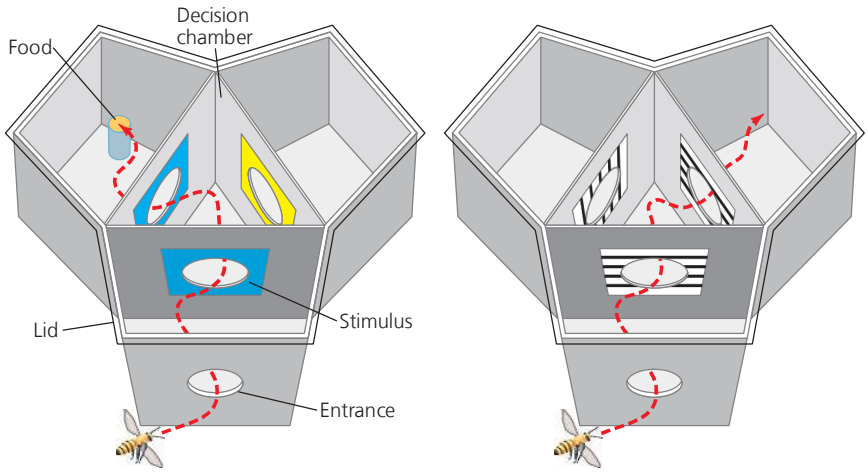
Cognition and Problem Solving

The most complex forms of learning involve **cognition**—the process of knowing that involves awareness, reasoning, recollection, and judgment. Although it was once argued that only primates and certain marine mammals have high-level thought processes, many other groups of animals, including insects, appear to exhibit cognition in controlled laboratory studies. For example, an experiment using Y-shaped mazes provided evidence for abstract thinking in honeybees. One maze had different colors, and one had different black-and-white striped patterns, either vertical or horizontal bars. Two groups of honeybees were trained in the color maze. Upon entering, a bee would see a sample color and could then choose between an arm of the maze with the same color or an arm with a different color. Only one arm contained a food reward. The first group of bees were rewarded for flying into the arm with the *same* color as the sample **(Figure 51.10, 1)**; the second group were rewarded for choosing the arm with the *different* color. Next, bees from each group were tested in the bar maze, which had no food reward. After encountering a sample black-and-white pattern of bars, a bee could choose an arm with the same pattern or an arm with a different pattern. The bees in the first group most often chose the arm with the same pattern **(Figure 51.10, 2)**, whereas those in the second group typically chose the arm with the different pattern.

The maze experiments provide strong experimental support for the hypothesis that honeybees can distinguish on the basis of "same" and "different." Remarkably, research published in 2010 indicates that honeybees can also learn to distinguish human faces.

The information-processing ability of a nervous system can also be revealed in **problem solving**, the cognitive

▼ Figure 51.10 A maze test of abstract thinking by honeybees. These mazes are designed to test whether honeybees can distinguish "same" from "different."



1 Bees were trained in a color maze. As shown here, one group was rewarded for choosing the same color as the stimulus.

2 Bees were tested in a pattern maze. If previously rewarded for choosing the same color, bees most often chose lines oriented the same way as the stimulus.

VISUAL SKILLS *Describe how you would set up the pattern maze to control for an inherent preference for or against a particular orientation of the black bars.*

activity of devising a method to proceed from one condition to another in the face of real or apparent 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 chimpanzee can assess the situation and stack the boxes, enabling it to reach the food. 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.

Development of Learned Behaviors

Most of the learned behaviors we have discussed develop over a relatively short time. Some behaviors develop more gradually. For example, some bird species learn songs in stages. In the case of the white-crowned sparrow (*Zonotrichia leucophrys*), the first stage of song learning takes place early in life, when the fledgling sparrow first hears the song. If a fledgling is prevented from hearing real sparrows or recordings of sparrow songs during the first 50 days of its life, it fails to develop the adult song of its species.

Although a young sparrow does not sing during the sensitive period, it memorizes the song of its species by listening to other white-crowned sparrows sing. During the sensitive period, fledglings chirp more in response to songs of their own species than to songs of other species. Thus, when young white-crowned sparrows learn the songs they will sing later on, that learning appears to be bounded by genetically controlled preferences.

The sensitive period when a white-crowned sparrow memorizes its species' song is followed by a second learning phase when the juvenile bird sings tentative notes called a subsong. The juvenile bird hears its own singing and compares it with the song memorized during the sensitive period. Once a sparrow's own song matches the one it memorized, the song "crystallizes" as the final song, and the bird sings only this adult song for the rest of its life.

Song learning is one of many examples of how animals learn from other members of their species. In finishing our exploration of learning, we'll look at several more examples that reflect the more general phenomenon of social learning.

Social Learning

Many animals learn to solve problems by observing the behavior of other individuals. Learning through observing and interpreting behaviors and their consequences is called **social learning**. Young wild chimpanzees, for example, learn how to crack open oil palm nuts with two stones by copying experienced chimpanzees **(Figure 51.11)**.

▼ Figure 51.11 A young chimpanzee (*Pan troglodytes*) learning to crack oil palm nuts by observing an elder.

Mastering Biology Video: Chimp Cracking Nut

Another example of how social learning can modify behavior comes from studies of the vervet monkeys (*Chlorocebus pygerythrus*) in Amboseli National Park, Kenya. Vervet monkeys, which are about the size of a domestic cat, produce a complex set of alarm calls. Amboseli vervets give distinct alarm calls for leopards, eagles, and snakes. When a vervet sees a leopard, it gives a loud barking sound; when it sees an eagle, it gives a short double-syllable cough; and the snake alarm call is a "chutter." Upon hearing a particular alarm call, other vervets in the group behave in an appropriate way: They run up a tree on hearing the alarm for a leopard (vervets are nimbler than leopards in the trees); look up on hearing the alarm for an eagle; and look down on hearing the alarm for a snake **(Figure 51.12)**.

Infant vervet monkeys give alarm calls, but in a relatively undiscriminating way. For example, they give the "eagle" alarm on seeing any bird, including harmless birds such as bee-eaters. With age, the monkeys improve their accuracy. In fact, adult vervet monkeys give the eagle alarm only on seeing an eagle belonging to either of the two species that eat vervets. Infants probably learn how to give the right call by observing other members of the group and receiving social confirmation. For instance, if the infant gives the call on the right occasion—say, an eagle alarm when there is an eagle overhead—another member of the group will also give the eagle call. But if the infant gives the call when a bee-eater flies by, the adults in the group are silent. Thus, vervet monkeys have an initial, unlearned tendency to give calls upon seeing potentially threatening objects in the environment. Learning fine-tunes the call so that adult vervets give calls only in response to genuine danger and can fine-tune the alarm calls of the next generation.

▼ Figure 51.12 Vervet monkeys learning correct use of alarm calls. On seeing a python (foreground), vervet monkeys give a distinct "snake" alarm call (inset), and the members of the group stand upright and look down.

Social learning forms the roots of **culture**, 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.

Changes in behavior that result from natural selection occur on a much longer time scale than does learning. In Concept 51.3, we'll examine the relationship between particular behaviors and the processes of selection related to survival and reproduction.

CONCEPT CHECK 51.2

1. How might associative learning explain why different species of distasteful or stinging insects have similar colors?
2. **WHAT IF?** How might you position and manipulate a few objects in a lab to test whether an animal can use a cognitive map to remember the location of a food source?
3. **MAKE CONNECTIONS** How might a learned behavior contribute to speciation? (See Concept 24.1.)

For suggested answers, see Appendix A.

CONCEPT 51.3

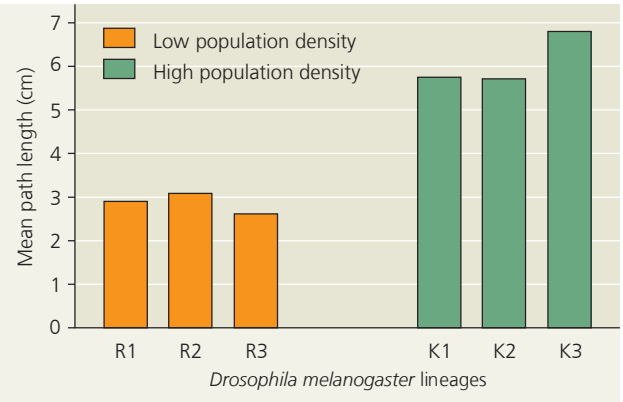
Selection for individual survival and reproductive success can explain diverse behaviors

EVOLUTION We turn now to Tinbergen's third question—how behavior enhances survival and reproduction in a population. The focus thus shifts from proximate causation—the "how" questions—to ultimate causation—the "why" questions. We'll begin by considering the activity of 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

The fruit fly allows us to examine one way that 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 do larvae with the for^S ("sitter") allele.

▼ Figure 51.13 Evolution of foraging behavior by laboratory populations of *Drosophila melanogaster*. After 74 generations of living at low population density, *Drosophila* larvae (populations R1–R3) followed foraging paths significantly shorter than those of *Drosophila* larvae that had lived at high density (populations K1–K3).



INTERPRET THE DATA *What alternative hypothesis is made far less likely by having three R and K lines, rather than one of each?*

Both the for^R and for^s alleles are present in natural populations. What circumstances might favor one or the other allele? An 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 51.13)**. 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 enable larvae to move beyond areas depleted of food. Thus, an interpretable evolutionary change in behavior occurred in the course of the experiment.

Optimal Foraging Model

To study the ultimate causation of foraging strategies, biologists sometimes apply a type of cost-benefit analysis used in economics. This idea proposes that foraging behavior is a compromise between the benefits of nutrition and the costs of obtaining food. These costs might include the energy expenditure of foraging as well as the risk of being eaten while foraging. According to this **optimal foraging model**, natural selection should favor a foraging behavior that minimizes the costs of foraging and maximizes the benefits. The **Scientific Skills Exercise** provides an example of how this model can be applied to animals in the wild.

Balancing Risk and Reward

One of the most significant potential costs to a forager is risk of predation. Maximizing energy gain and minimizing energy costs are of little benefit if the behavior makes the forager a likely meal for a predator. It seems logical, therefore, that predation risk would influence foraging behavior. Such appears to be the case for the mule deer (*Odocoileus hemionus*), which lives in the mountains of western North America. Researchers found that the food available for mule deer was fairly uniform across the potential foraging areas, although somewhat lower in open, nonforested areas. In contrast, the risk of predation differed greatly; mountain lions (*Puma concolor*), the major predator, killed large numbers of mule deer at forest edges and only a small number in open areas and forest interiors.

How does mule deer foraging behavior reflect the differences in predation risk in particular areas? Mule deer feed predominantly in open areas. Thus, it appears that mule deer foraging behavior reflects the large variation in predation risk and not the smaller variation in food availability. This result underscores the point that behavior typically reflects a compromise between competing selective pressures.

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

For humans and other animal species, there is considerable variation in patterns of sexual contact. In the context of reproduction, biologists describe differences in *mating systems*, the length and number of relationships between males and females. In some animal species, mating is *promiscuous*, with 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 many 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. 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

Scientific Skills Exercise

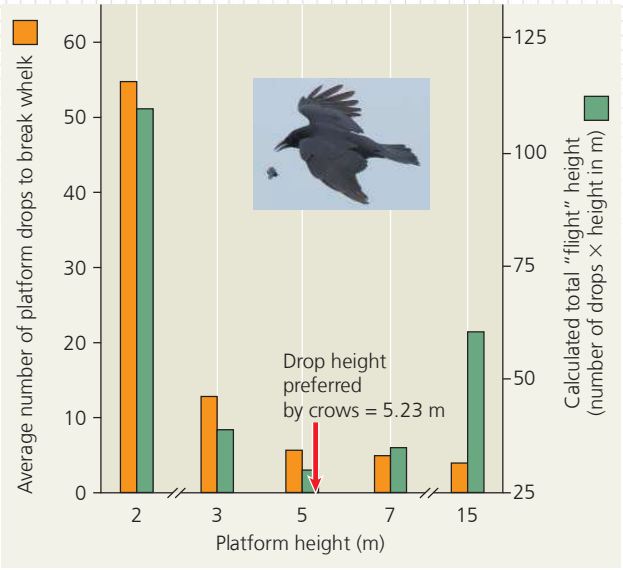
Testing a Hypothesis with a Quantitative Model

Do Crows Display Optimal Foraging Behavior? On islands off British Columbia, Canada, Northwestern crows (*Corvus caurinus*) search rocky tide pools for sea snails called whelks. After spotting a whelk, the crow picks it up in its beak, flies upward, and drops the whelk onto the rocks. If the drop is successful, the shell breaks and the crow can dine on the whelk's soft parts. If not, the crow flies up and drops the whelk again and again until the shell breaks. What determines how high the crow flies? If energetic considerations dominated selection for the crow's foraging behavior, the average drop height might reflect a trade-off between the cost of flying higher and the benefit of more frequent success. In this exercise you'll test how well this optimal foraging model predicts the average drop height observed in nature.

How the Experiments Were Done There were two parts to the experiment. First, the researcher measured the height of drops made by crows in the wild by referring to a marked pole erected nearby. Second, the researcher built a device that dropped a whelk onto the rocks from a fixed platform. For each whelk, he kept track of the number of drops carried out before the whelk broke open. Averaging over many trials with the device and combining the data for each platform height, he calculated a predicted total "flight" height: the height of the platform times the average number of drops required to break open the whelk.

Data from the Experiment The graph summarizes the results of the experiment, comparing the behavior of crows in the wild with the measurements using the whelk-dropping device.

Data from R. Zach, Shell-dropping: Decision-making and optimal foraging in northwestern crows, *Behavior* 68:106–117 (1979).



INTERPRET THE DATA

1. How does the average number of drops required to break open a whelk depend on platform height for a drop of 5 meters or less? For drops of more than 5 meters?
2. Total flight height can be considered to be a measure of the total energy required to break open a whelk. Why is this value lower for a platform set at 5 meters than for one at 2 or 15 meters?
3. Compare the drop height preferred by crows with the graph of total flight height for the platform drops. Are the data consistent with the hypothesis of optimal foraging? Explain.
4. In testing the optimal foraging model, it was assumed that changing the height of the drop only changed the total energy required. Do you think this is a realistic limitation, or might other factors than total energy be affected by height?
5. Researchers observed that the crows only gather and drop the largest whelks. What are some reasons crows might favor larger whelks?
6. It turned out that the probability of a whelk breaking was the same for a whelk dropped for the first time as for an unbroken whelk dropped several times previously. If the probability of breaking instead increased, what change might you predict in the crow's behavior?

Instructors: A version of this Scientific Skills Exercise can be assigned in **Mastering Biology**.

the opposite sex **(Figure 51.14)**. 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 it would by going off to seek additional mates. This may explain why many bird species 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, and 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 if there is a strong pair-bond, a male other than the female's

▼ Figure 51.14 Relationship between mating system and male and female forms.

(a) Monogamy (one male, one female)

In monogamous species, such as these western gulls (*Larus occidentalis*), males and females are difficult to distinguish using external characteristics only.

(b) Polygyny (one male, multiple females)

Among polygynous species, such as elk (*Cervus canadensis*), the male (right) is often highly ornamented.

(c) Polyandry (one female, multiple males)

In polyandrous species, such as these red-necked phalaropes (*Phalaropus lobatus*), females (right) are generally more ornamented than males.

usual mate may on occasion father offspring with that female. 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 be one reason that 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 51.15**; see also Figure 46.6). Among fishes and amphibians, parental care occurs in fewer than 10% of species with internal fertilization but in more than half of species with external fertilization.

It is important to point out 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. The intriguing relationship between certainty of paternity and male parental care remains an area of active research.

Sexual Selection and Mate Choice

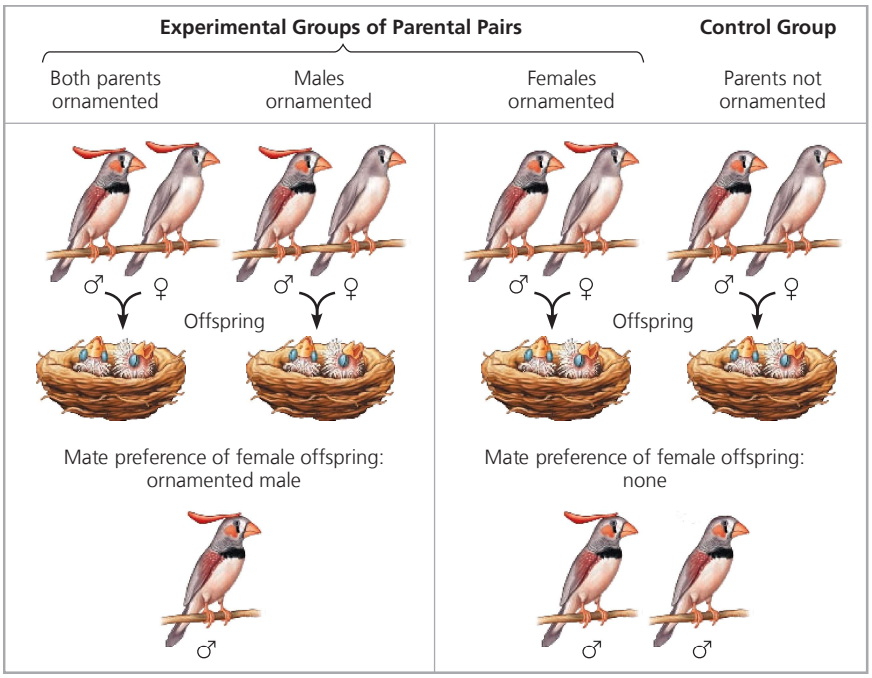
Sexual dimorphism results from sexual selection, a form of natural selection in which differences in reproductive success among individuals are a consequence of differences in mating success (see Concept 23.4). Sexual selection can

▼ Figure 51.15 Paternal care by a male yellowhead jawfish (*Opistognathus aurifrons*). 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 predators until the young fish hatch.

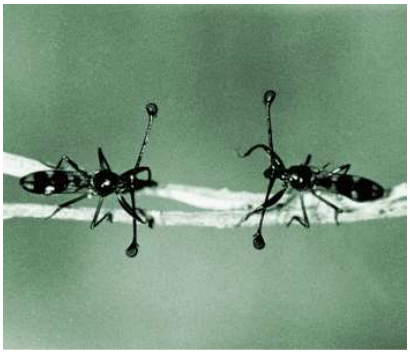
take the form of *intersexual selection*, in which members of one sex choose mates on the basis of characteristics of the other sex, such as courtship songs, or *intrasexual selection*, which involves competition between members of one sex for mates.

Mate Choice by Females 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. 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 and bright coloration in birds correlate in general with health and vitality. A female whose mate choice is a healthy male is likely to produce more offspring that survive to reproduce. As a result, males may compete with each other in ritualized contests to attract female attention **(Figure 51.16)**.

▼ Figure 51.18 Sexual selection influenced by imprinting. Experiments demonstrated that female zebra finch chicks that had imprinted on artificially ornamented fathers preferred ornamented males as adult mates. For all experimental groups, male offspring showed no preference for either ornamented or non-ornamented female mates.



▶ Figure 51.16 A face-off between male stalk-eyed flies (*Cyrtodiopsis whitei*) competing for female attention.



▶ Figure 51.17 Appearance of zebra finches in nature. The male zebra finch (right) is more highly patterned and colorful than the female zebra finch (left).

In face-offs between male stalk-eyed flies, the male whose eyestalk length is smaller usually retreats peacefully.

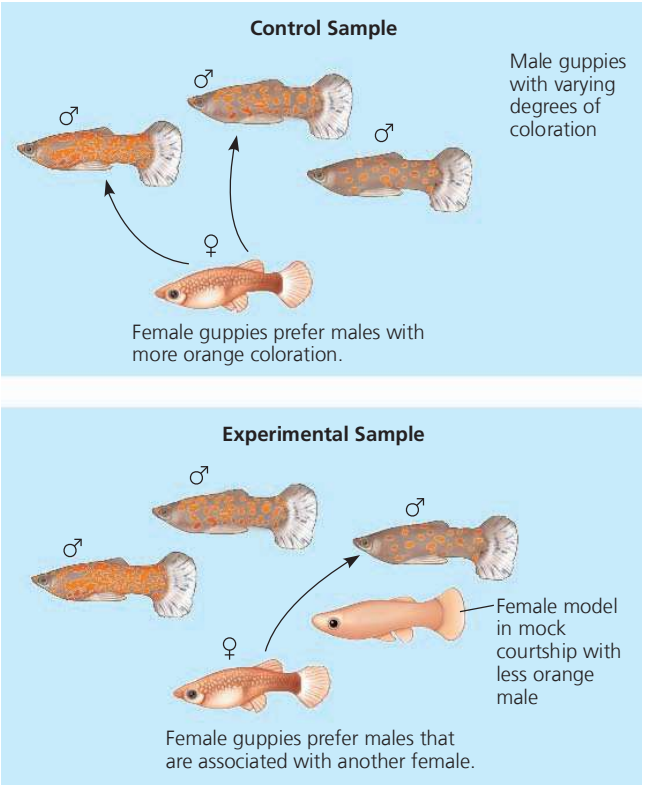
Mate choice can also be influenced by imprinting, as revealed by experiments carried out with zebra finches (*Taeniopygia guttata*). Both male and female zebra finches normally lack any feather crest on their head **(Figure 51.17)**. To explore whether parental appearance affects mate preference in offspring independent of any genetic influence, researchers provided zebra finches with artificial ornamentation. A 2.5-cm-long red feather was taped to the forehead feathers of either or both zebra finch parents when their chicks were 8 days old, approximately 2 days before they opened their eyes. A control group of zebra finches was raised by unadorned parents. When the chicks matured, they were presented with prospective mates that were either artificially ornamented with a red feather or non-ornamented **(Figure 51.18)**. Males showed no preference. Females raised by a male parent that was not ornamented also showed no preference. However, females raised by an ornamented male parent preferred ornamented males as their own mates. Thus, female finches apparently take cues from their fathers in choosing mates.

Mate-choice copying, a behavior in which individuals in a population copy the mate choice of others, has been studied in the guppy, *Poecilia reticulata*. When a female guppy chooses between males with no other females

present, the female almost always chooses the male with more orange coloration. To explore if the behavior of other females could influence this preference, an experiment was set up using both living females and artificial model females **(Figure 51.19)**. If a female guppy observed the model "courting" a male with less extensive orange markings, she often copied the preference of the model female. That is, the female chose the male that had been presented in association with a model female rather than a more orange alternative. The exceptions were also informative. Mate-choice copying typically did not change when the difference in coloration was particularly large; that is, the female guppy chose the male with the much stronger coloration even if a model female was associated with the less orange male. Mate-choice copying can thus mask genetically controlled female preference below a certain threshold of difference, in this case for male color.

Mate-choice copying, a form of social learning, has also been observed in several other fish and bird species. What is the selective pressure for such a mechanism? One possibility is that a female that mates with males that are attractive to other females increases the probability that her male offspring will also be attractive and have high reproductive success.

▼ Figure 51.19 Mate choice copying by female guppies (*Poecilia reticulata*). In the absence of other females (control group), female guppies generally choose males with more orange coloration. However, when a female model is placed near one of the males (experimental group), female guppies often copy the apparent mate choice of the model, even if the male is less colorful than others. Guppy females ignored the mate choice of the model only if an alternative male had much more orange coloration.



Male Competition for Mates The previous examples show how female choice can select for one best type of male in a given situation, resulting in low variation among males. Similarly, male competition for mates can reduce variation among males. Such competition may involve *agonistic behavior*, a contest, typically ritualized, that determines which competitor gains access to a resource, such as food or a mate **(Figure 51.20**; see also Figure 51.16).

Despite the potential for male competition to select for reduced variation, behavioral and morphological variation in males is extremely high in some vertebrate species, including species of fish and deer, as well as in a wide variety of invertebrates. In some species, sexual selection has led to the evolution of alternative male mating behavior and morphology. How do scientists analyze situations where more than one mating behavior can result in

▼ Figure 51.20 Agonistic interaction. Male eastern grey kangaroos (*Macropus giganteus*) often "box" in contests that determine which male is most likely to mate with an available female. Typically, one male snorts loudly and strikes the other with his forelimbs. If the male under attack does not retreat, the fight may escalate into grappling or the two males balancing on their tails while attempting to kick each other with the sharp toenails of their hind feet.

Mastering Biology Video: Agonistic Behavior in Wolves • Video: Snake Ritual Wrestling

successful reproduction? One approach relies on the rules that govern games.

Applying Game Theory

Often, the fitness of a particular behavioral phenotype is influenced by other behavioral phenotypes in the population. In studying such situations, behavioral ecologists use a range of tools, including game theory. Developed by American mathematician John Nash and others to model human economic behavior, **game theory** evaluates alternative strategies in situations where the outcome depends on the strategies of all the individuals involved.

As an example of applying game theory to mating behavior, let's consider the common side-blotched lizard (*Uta stansburiana*) of California. Genetic variations give rise to males with orange, blue, or yellow throats **(Figure 51.21)**. One would expect that natural selection would favor one of the three color types, yet all three persist. Why? The answer appears to lie in the fact that each throat color is associated with a different pattern of behavior: Orange-throat males are the most aggressive and defend large territories that contain many females. Blue-throat males are also territorial but defend smaller territories and fewer females. Yellow-throats are nonterritorial males that mimic females and use "sneaky" tactics to gain the chance to mate.

Evidence indicates that the mating success of each male lizard type is influenced by the relative abundance of the other types, an example of frequency-dependent selection. In one study population, the most frequent throat coloration changed over a period of several years from blue to orange to yellow and back to blue.

By comparing the competition between common side-blotched lizard males to the children's game of rock-paper-scissors, scientists devised an explanation for the cycles of variation in the lizard population. In the game, paper defeats rock, rock defeats scissors, and scissors defeats paper. Each hand symbol thus wins one matchup but loses the other. Similarly, each type of male lizard has an advantage over one of the other two types:

- When blue-throats are abundant, they can defend the few females in their territories from the advances of the sneaky yellow-throat males. However, blue-throats cannot defend their territories against the hyperaggressive orange-throats.
- Once the orange-throats become the most abundant, the larger number of females in each territory provides the opportunity for the yellow-throats to have greater mating success.
- The yellow-throats become more frequent, but then give way to the blue-throats, whose tactic of guarding small territories once again allows them the most success.

Thus, following the population over time, one sees a persistence of all three color types and a periodic shift in which type is most prevalent.

Game theory provides a way to think about complex evolutionary problems in which relative performance (reproductive success relative to other phenotypes), not absolute performance, is the key to understanding the evolution of behavior. This makes game theory an important tool because the relative performance of one phenotype compared with others is a measure of Darwinian fitness.

▼ Figure 51.21 Male polymorphism in the common side-blotched lizard (*Uta stansburiana*). An orange-throat male, left; a blue-throat male, center; a yellow-throat male, right.

CONCEPT CHECK 51.3

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 23.4). 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.
3. **WHAT IF?** Suppose an infection in a common side-blotched lizard population killed many more males than females. What would be the immediate effect on male competition for reproductive success?

For suggested answers, see Appendix A.

CONCEPT 51.4

Genetic analyses and the concept of inclusive fitness provide a basis for studying the evolution of behavior

EVOLUTION We'll now explore issues related to Tinbergen's fourth question—the evolutionary history of behaviors. We will first look at the genetic control of a behavior. Next, we will examine the genetic variation underlying the evolution of particular behaviors. Finally, we will see how expanding the definition of fitness beyond individual survival can help explain "selfless" behavior.

Genetic Basis of Behavior

In exploring the genetic basis of behavior, we'll begin with the courtship behavior of the male fruit fly (see Figure 51.4). During courtship, the male fly carries out a complex series of actions in response to multiple sensory stimuli. Genetic studies have revealed that a single gene called *fru* controls this entire courtship ritual. If the *fru* gene is mutated to an inactive form, males do not court or mate with females. (The name *fru* is short for *fruitless*, reflecting the absence of offspring from the mutant males.) Normal male and female flies express distinct forms of the *fru* gene. When females are genetically manipulated to express the male form of *fru*, they court other females, performing the role normally played by the male.

How does the *fru* gene control so many different actions? Experiments carried out cooperatively in several laboratories demonstrated that *fru* is a master regulatory gene that directs the expression and activity of many genes with narrower functions. Together, genes that are controlled by the *fru* gene bring about sex-specific development of the fly nervous system. In effect, *fru* programs the fly for male courtship behavior by overseeing a male-specific wiring of the central nervous system.

In many cases, differences in behavior arise not from gene inactivation, but from variation in the activity or amount of a gene product. One striking example comes from the study of two 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 51.22)**. Male prairie voles provide care for their young pups, hovering over them, licking them, and carrying them, while acting aggressively toward intruders.

A neurotransmitter released during mating is critical for the partnering and parental behavior of male voles. Known as **antidiuretic hormone (ADH) or vasopressin** (see Concept 44.5), this peptide is released during mating and binds to a specific receptor in the central nervous system. When male prairie voles are given a drug that inhibits the receptor in the brain that detects vasopressin, the male voles fail to form pair-bonds after mating.

The vasopressin receptor gene is much more highly expressed in the brain of prairie voles than in the brain of meadow voles. Testing the hypothesis that the level of vasopressin receptor in the brain regulates postmating behavior, researchers inserted the vasopressin receptor gene from prairie voles into the genome of 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 in male voles, a change in the level of expression of the vasopressin receptor is sufficient to alter the development of these behaviors.

▼ Figure 51.22 A pair of prairie voles (*Microtus ochrogaster*) huddling. Among North American prairie voles, males 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 but are often less obvious. When behavioral variation between populations of a species correlates with variation in environmental conditions, it may reflect natural selection.

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*). 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 51.23 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 more by genetics than by environment.

When researchers offered banana slugs to snakes collected from each wild population, most coastal snakes readily ate them **(Figure 51.23)**. In contrast, inland snakes tended to refuse. To what extent does genetic variation among snake species contribute to a fondness for banana slugs? To answer this question, researchers collected pregnant snakes from the wild coastal and inland populations and then housed these females in separate cages in the laboratory. While the offspring were still very young, they were each offered a small piece of banana slug on ten successive 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. Perhaps not surprisingly, 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 two 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.

Case Study: *Variation in Migratory Patterns*

Another species suited to the study of behavioral variation is the blackcap (*Sylvia atricapilla*), a small migratory warbler. Blackcaps that breed in Germany generally migrate southwest to Spain and then south to Africa for the winter. In the 1950s, a few blackcaps began to spend their winters in Britain, and over time the population of blackcaps wintering in Britain grew to many thousands. Leg bands showed that some of these birds had migrated westward from central Germany. Was this change in the pattern of migration the outcome of natural selection? If so, the birds wintering in Britain must have a heritable difference in migratory behavior. To test this hypothesis, researchers at the Max Planck Institute for Ornithology in Radolfzell, Germany, devised a strategy to study migratory orientation in the laboratory **(Figure 51.24)**. The results demonstrated that the two patterns of migration—to the west and to the southwest—do in fact reflect genetic differences between the two populations.

The study of western European blackcaps indicated that the change in their migratory behavior occurred both recently and rapidly. Before the year 1950, there were no known westward-migrating blackcaps in Germany. By the 1990s, westward migrants made up 7–11% of the blackcap populations of Germany. Once westward migration began, it persisted and increased in frequency, perhaps due to the widespread use of winter bird feeders in Britain, as well as shorter migration distances.

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 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.

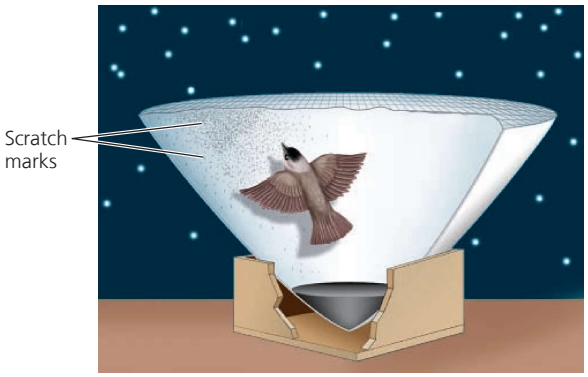
In discussing selflessness, we will use the term **altruism** to describe a behavior that reduces an animal's individual fitness but increases the fitness of other individuals in the population. Consider, for example, the Belding's ground squirrel (*Urocitellus beldingi*), which lives in the western 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. In warning others, however, this squirrel brings attention to its location and thus increases its own risk of being killed.

Another example of altruistic behavior occurs in honeybee societies, in which the workers are sterile. The workers themselves never reproduce, but they labor on behalf of a single fertile queen. Furthermore, the workers sting intruders, a behavior that helps defend the hive but results in the death of those workers.

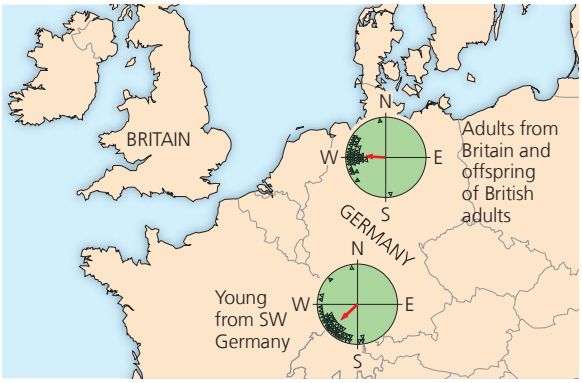
▼ Figure 51.24 Inquiry

Are differences in migratory orientation within a species genetically determined?

Experiment Birds known as blackcaps that live in Germany winter elsewhere. Most migrate to Spain and Africa, but a few fly to Britain, where they find food left out by city dwellers. German scientist Peter Berthold and colleagues wondered if this change had a genetic basis. To test this hypothesis, they captured blackcaps wintering in Britain and bred them in Germany in an outdoor cage. They also collected young blackcaps from nests in Germany and raised them in cages. In the autumn, the blackcaps captured in Britain and the birds raised in cages were placed in large, glass-covered funnel cages. When the funnels were lined with carbon-coated paper and placed outside at night, the birds moved around, making marks on the paper that indicated the direction in which they were trying to "migrate."



Results The wintering adult birds captured in Britain and their laboratory-raised offspring both attempted to migrate to the west. In contrast, the young birds collected from nests in southern Germany attempted to migrate to the southwest.



Conclusion The young of the British blackcaps and the young birds from Germany (the control group) were raised under similar conditions but showed very different migratory orientations, indicating that their migratory orientation has a genetic basis.

Data from P. Berthold et al., Rapid microevolution of migratory behavior in a wild bird species, *Nature* 360:668–690 (1992).

WHAT IF? *Suppose the birds had not shown a difference in orientation in these experiments. Could you conclude that the behavior was not genetically based? Explain.*

▼ Figure 51.25 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.

Altruism is also observed in naked mole rats (*Heterocephalus glaber*), highly social rodents that live in underground chambers and tunnels in southern and northeastern Africa. The naked mole rat, which is almost hairless and nearly blind, lives in colonies of 20 to 300 individuals **(Figure 51.25)**. 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 that invade the colony.

Inclusive Fitness

With these examples from ground squirrels, honeybees, and mole rats in mind, let's return to the question of how altruistic behavior arises during evolution. The easiest case to consider is that of parents sacrificing for their offspring. When parents sacrifice their own well-being to produce and aid offspring, this act actually increases the fitness of the parents because it maximizes their genetic representation in the population. By this logic, altruistic behavior can be maintained by evolution even though it does not enhance the survival and reproductive success of the self-sacrificing individuals.

What about circumstances when individuals help others who are not their offspring? By considering a broader group of relatives than just parents and offspring, biologist William Hamilton found an answer. He began by proposing 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 thinking led Hamilton to the 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

The power of Hamilton's hypothesis was that it provided a way to measure, or quantify, the effect of altruism on fitness. 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**.

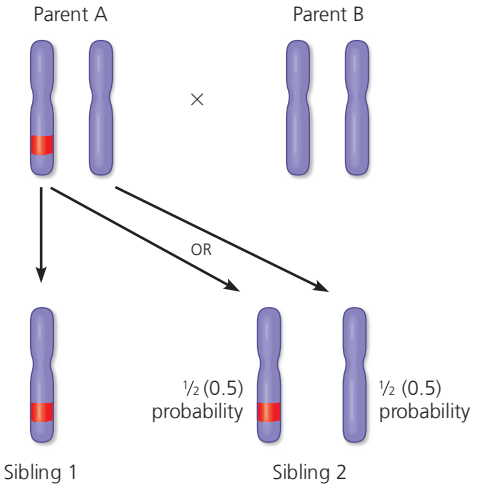
To better understand Hamilton's rule, let's apply it to a human population in which the average individual has two children. We'll imagine that a young man is close to drowning in heavy surf, and his sister risks her life to swim out and pull her sibling to safety. If the young man had drowned, his reproductive 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 does his sister incur? 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 separation of homologous chromosomes that occurs during meiosis of gametes **(Figure 51.26**; see also Figure 13.7).

We can use our values of *B, C*, and *r* to evaluate whether natural selection would favor the altruistic act in our imaginary scenario. For the surf rescue, $rB = 0.5 \times 2 = 1$, whereas $C = 0.5$. Because *rB* is greater than *C*, Hamilton's rule is satisfied; thus, natural selection would favor this altruistic act.

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. Siblings have an *r* of 0.5, but between an aunt and her niece, $r = 0.25$ (¼), and between first cousins, $r = 0.125$ (⅛). Notice that as the degree of relatedness decreases, the *rB* term in the Hamilton inequality also decreases. Would natural selection favor rescuing a cousin? Not unless the surf were less treacherous. For the original conditions, $rB = 0.125 \times 2 = 0.25$, which is only half the value of *C* (0.5). British geneticist J. B. S. Haldane appears to have anticipated these ideas when he jokingly stated that he would not lay down his life for one brother, but would do so for two brothers or eight cousins.

▼ Figure 51.26 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.



WHAT IF? *The coefficient of relatedness of an individual to a full (nontwin) sibling or to either parent is the same: 0.5. Does this value also hold true in cases of polyandry and polygyny?*

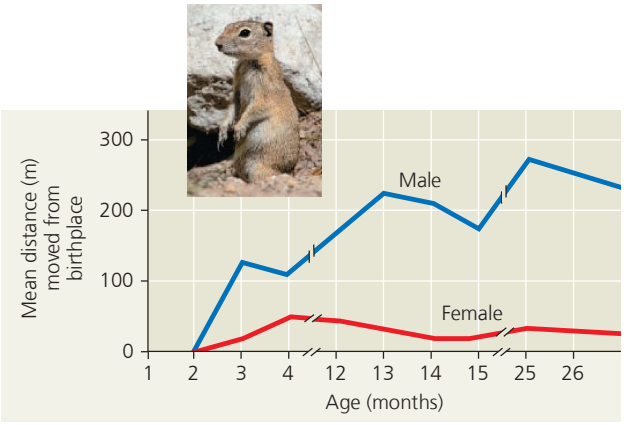
If kin selection explains altruism, then the examples of unselfish behavior we observe among diverse animal species should involve close relatives. This is apparently the case, but often in complex ways. Like most mammals, female Belding's ground squirrels settle close to their site of birth, whereas males settle at distant sites **(Figure 51.27)**. Since nearly all alarm calls are given by females, they are most likely aiding close relatives. In the case of worker bees, who are all sterile, anything they do to help the entire hive benefits the only permanent member who is reproductively active—the queen, who is their mother.

In the case of naked mole rats, DNA analyses have shown that all the individuals in a colony are closely related. Genetically, the queen appears to be a sibling, daughter, or mother of the kings, and the nonreproductive mole rats are the queen's direct descendants or her siblings. Therefore, when a nonreproductive individual enhances a queen's or king's chances of reproducing, the altruist increases the chance that some genes identical to its own will be passed to the next generation.

Reciprocal Altruism

Some animals occasionally behave altruistically toward others who are not relatives. A baboon may help an unrelated companion in a fight, or a wolf may offer food to another wolf

▼ Figure 51.27 Kin selection and altruism in Belding's ground squirrels. This graph helps explain the male-female difference in altruistic behavior of ground squirrels. Once weaned (pups are nursed for about one month), females are more likely than males to live near close relatives. Alarm calls that warn these relatives increase the inclusive fitness of the female altruist.



even though they share no kinship. Such behavior can be adaptive if the aided individual returns the favor in the future. This sort of exchange of aid, called **reciprocal altruism**, is commonly invoked to explain altruism that occurs between unrelated humans. Reciprocal altruism is rare in other animals; it is limited largely to species (such as chimpanzees) with social groups stable enough that individuals have many chances to exchange aid. It is generally thought to occur when individuals are likely to meet again and when there would be negative consequences associated with not returning favors to individuals who had been helpful in the past, a pattern of behavior that behavioral ecologists refer to as "cheating."

Since cheating may benefit the cheater substantially, how could reciprocal altruism evolve? Game theory provides a possible answer in the form of a behavioral strategy called *tit for tat*. In the tit-for-tat strategy, an individual treats another in the same way it was treated the last time they met. Individuals adopting this behavior are always altruistic, or cooperative, on the first encounter with another individual and will remain so as long as their altruism is reciprocated. When their cooperation is not reciprocated, however, individuals employing tit for tat will retaliate immediately but return to cooperative behavior as soon as the other individual becomes cooperative. The tit-for-tat strategy has been used to explain the few apparently reciprocal altruistic interactions observed in animals—ranging from blood sharing between nonrelated vampire bats to social grooming in primates.

Evolution and Human Culture

As animals, humans behave (and, sometimes, misbehave). Just as humans vary extensively in anatomical features, we display substantial variations in behavior. Environment intervenes in the path from genotype to phenotype for physical traits, but does so much more profoundly for behavioral traits. Furthermore, as a consequence of our marked capacity for learning, humans are probably more able than any other animal to acquire new behaviors and skills **(Figure 51.28)**.

Some human activities have a less easily defined function in survival and reproduction than do, for example, foraging or courtship. One of these activities is play, which is sometimes defined as behavior that appears purposeless. We recognize play in children and what we think is play in the young of other vertebrates. Behavioral biologists describe "object play," such as chimpanzees playing with leaves, "locomotor play," such as the acrobatics of an antelope, and "social play," such as the interactions and antics of lion cubs. These categories, however, do little to inform us about the function of play. One idea is that, rather than generating specific skills or experience, play serves as preparation for unexpected events and for circumstances that cannot be controlled.

Human behavior and culture are related to evolutionary theory in the discipline of *sociobiology*. The main premise of sociobiology is that certain behavioral characteristics exist because they are expressions of genes that have been perpetuated by natural selection. In his seminal 1975 book *Sociobiology: The New Synthesis,* E. O. Wilson speculated about the evolutionary basis of certain kinds of social behavior. By including a few examples from human culture, he sparked a debate that continues today.

Over our recent evolutionary history, we have built up structured societies with governments, laws, cultural values, and religions that define what is acceptable behavior and what is not, even when unacceptable behavior might enhance an individual's Darwinian fitness. Perhaps it is our social and cultural

▶ Figure 51.28 Learning a new behavior.

institutions that make us distinct and that provide those qualities that at times make less apparent the continuum between humans and other animals. One such quality, our considerable capacity for reciprocal altruism, will be essential as we tackle current challenges, including global climate change, in which individual and collective interests often appear to be in conflict.

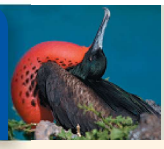
Mastering Biology
Interview with E. O. Wilson: Pioneering the field of sociobiology

CONCEPT CHECK 51.4

1. Explain why geographic variation in garter snake prey choice might indicate that the behavior evolved by natural selection.
2. Suppose an individual organism aids the survival and reproductive success of the offspring of its sibling. How might this behavior result in indirect selection for certain genes carried by that individual?
3. **WHAT IF?** Suppose you applied Hamilton's logic to a situation in which one individual is past reproductive age. Could there still be selection for an altruistic act?

For suggested answers, see Appendix A.

51 Chapter Review



Go to **Mastering Biology** for Assignments, the eText, the Study Area, and Dynamic Study Modules.

SUMMARY OF KEY CONCEPTS

To review key terms, go to the **Vocabulary Self-Quiz** in the **Mastering Biology** eText or Study Area, or go to goo.gl/zkjz9t.

CONCEPT 51.1

Discrete sensory inputs can stimulate both simple and complex behaviors *(pp. 1140–1143)*

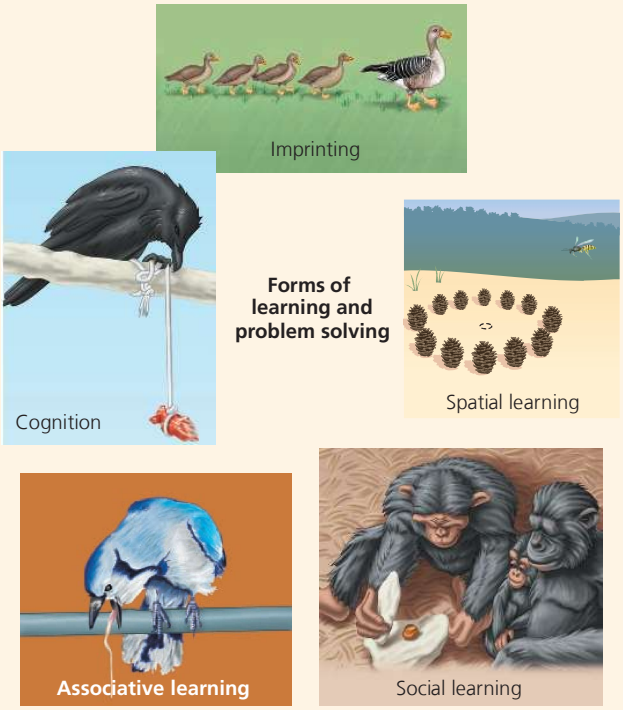
- **Behavior** is the sum of an animal's responses to external and internal stimuli. In behavior studies, proximate, or "how," questions focus on the stimuli that trigger a behavior and on genetic, physiological, and anatomical mechanisms underlying a behavioral act. Ultimate, or "why," questions address 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 the seasons.
- The transmission and reception of **signals** constitute animal **communication**. Animals use visual, auditory, chemical, and tactile signals. Chemical substances called **pheromones** transmit species-specific 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 51.2

Learning establishes specific links between experience and behavior *(pp. 1143–1148)*

- Cross-fostering studies can be used to measure the influence of social environment and experience on behavior.
- **Learning**, the modification of behavior as a result of experience, can take many forms, as summarized in the diagram that follows.



? *How do imprinting in geese and song development in sparrows differ with regard to the resulting behavior?*

CONCEPT 51.3

Selection for individual survival and reproductive success can explain diverse behaviors *(pp. 1148–1154)*

- Controlled experiments in the laboratory can give rise to interpretable evolutionary changes in behavior.
- An **optimal foraging model** is based on the idea that natural selection should favor **foraging** behavior that minimizes the costs of foraging and maximizes the benefits.
- Sexual dimorphism correlates with the types of mating relationship, which include **monogamous** and **polygamous** mating

systems. Variations in mating system and mode of fertilization affect certainty of paternity, which in turn, through evolution, influences mating behavior and parental care.
- **Game theory** provides a way of thinking about evolution in situations where the fitness of a particular behavioral phenotype is influenced by other behavioral phenotypes in the population.

? *In some spider species, the female eats the male immediately after copulation. How might you explain this behavior from an evolutionary perspective?*

CONCEPT **51.4**

Genetic analyses and the concept of inclusive fitness provide a basis for studying the evolution of behavior

(pp. 1154–1160)

- Genetic studies in insects have revealed the existence of master regulatory genes that control complex behaviors. Within the underlying hierarchy, multiple genes influence specific behaviors, such as a courtship song. Research on voles illustrates how variation in a single gene can determine differences in complex behaviors.
- Behavioral variation within a species that corresponds to environmental variation may be evidence of past evolution.
- **Altruism** can be explained by the concept of **inclusive fitness**, the effect an individual has on proliferating its genes by producing its own offspring *and* by providing aid that enables close relatives to reproduce. The **coefficient of relatedness** and **Hamilton's rule** provide a way of measuring the strength of the selective forces favoring altruism against the potential cost of the "selfless" behavior. **Kin selection** favors altruistic behavior by enhancing the reproductive success of relatives.

? *What insight about the genetic basis of behavior emerges from studying the effects of courtship mutations in fruit flies and of pair-bonding in voles?*

TEST YOUR UNDERSTANDING

For more multiple-choice questions, go to the **Practice Test** in the **Mastering Biology** eText or Study Area, or go to goo.gl/GruWRg.

Levels 1-2: Remembering/Understanding

1. 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 expressed in most individuals in a population.
   (D) They occur in invertebrates and some vertebrates but not mammals.
2. 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.
3. Female spotted sandpipers aggressively court males and, after mating, leave the clutch of young for the male to incubate. This sequence may be repeated several times with different males until no available males remain, forcing the female to incubate her last clutch. Which of the following terms best describes this behavior?
   (A) polygyny
   (B) polyandry
   (C) promiscuity
   (D) certainty of paternity

Levels 3-4: Applying/Analyzing

4. A region of the canary forebrain shrinks during the nonbreeding season and enlarges when breeding season begins. This change is probably associated with the annual
   (A) addition of new syllables to a canary's song repertoire.
   (B) crystallization of subsong into adult songs.
   (C) sensitive period in which canary parents imprint on new offspring.
   (D) elimination of the memorized template for songs sung the previous year.
5. Although many chimpanzees live in environments with 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.
6. 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.

Levels 5-6: Evaluating/Creating

7. **DRAW IT** You are considering two optimal foraging models for the behavior of a mussel-feeding shorebird, the oystercatcher. In model A, the energetic reward increases solely with mussel size. In model B, you take into consideration that larger mussels are more difficult to open. Draw a graph of reward (energy benefit on a scale of 0–10) versus mussel length (scale of 0–70 mm) for each model. Assume that mussels under 10 mm provide no benefit and are ignored by the birds. Also assume that mussels start becoming difficult to open when they reach 40 mm in length and impossible to open when 70 mm long. Considering the graphs you have drawn, indicate what observations and measurements you would want to make in this shorebird's habitat to help determine which model is more accurate.
8. **EVOLUTION CONNECTION** We often explain our behavior in terms of subjective feelings, motives, or reasons, but evolutionary explanations are based on reproductive fitness. Can both kinds of explanation be valid? For instance, is an explanation for behavior such as "falling in love" incompatible with an evolutionary explanation?

9. **SCIENTIFIC INQUIRY** Scientists studying scrub jays found that "helpers" often assist mated pairs of birds by gathering food for their offspring. (a) 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. (b) Explain how you would test your hypothesis. If it is correct, what results would you expect your tests to yield?

10. **SCIENCE, TECHNOLOGY, AND SOCIETY** Researchers are very interested in studying identical twins separated at birth and raised apart. So far, the data reveal that such twins frequently have similar personalities, mannerisms, habits, and interests. What general question do you think researchers hope to answer by studying such twins? Why do identical twins make good subjects for this research? What are the potential pitfalls of this research? What abuses might occur if the studies are not evaluated critically? Explain your thinking.

11. **WRITE ABOUT A THEME: INFORMATION** Learning is defined as a change in behavior as a result of experience. In a short essay (100–150 words), describe how heritable information contributes to the acquisition of learning, using some examples from imprinting and associative learning.

12. **SYNTHESIZE YOUR KNOWLEDGE**

Acorn woodpeckers (*Melanerpes formicivorus*) stash acorns in storage holes they drill in trees. When these woodpeckers breed, the offspring from previous years often help with parental duties. Activities of these nonbreeding helpers include incubating eggs and defending stashed acorns. Propose some questions that a behavioral biologist could ask about the proximate and ultimate causation of these behaviors.

For selected answers, see Appendix A.