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 O₂ and CO₂ 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 O₂ 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 O₂, this water nevertheless has a higher P₀₂ than the incoming blood, and O₂ transfer takes place. As the blood continues its passage, its P₀₂ 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 O₂ 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 O₂ 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,
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 have evolved in a few aquatic vertebrates as adaptations to living in oxygen-poor water or to spending part of their time exposed to air (for instance, when the water 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 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 m², 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 cigarette smoke that enter alveoli can cause a permanent reduction in lung capacity. For coal miners, inhalation of large amounts of coal dust can lead to silicosis, a disabling, irreversible, and sometimes fatal lung disease.

The film of liquid that lines alveoli is subject to surface tension, an attractive force that has the effect of minimizing a liquid’s surface area (see 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 surface-active agent, which coats the alveoli and reduces surface tension.
In the 1950s, Mary Ellen Avery did the first experiment linking a lack of surfactant to **respiratory distress syndrome (RDS)**, a disease common in infants born 6 weeks or more before their due dates (Figure 42.25). (The average full-term human pregnancy is 38 weeks.) Later studies revealed that surfactant typically appears in the lungs after 33 weeks of development. In the 1950s, RDS killed 10,000 infants annually in the United States, but artificial surfactants are now used successfully to treat early preterm infants. 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 O₂ and low CO₂ 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.
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 is called tidal volume. It averages about 500 mL in resting humans. The tidal volume during maximal inhalation and exhalation is the vital capacity, which is about 3.4 L and 4.8 L for college-age women and men, respectively. The air that remains after a forced exhalation is called the residual volume. 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.

**Visual Skills**

Suppose a person began breathing very rapidly while resting. Tracing a path along this negative-feedback control circuit, describe the effect on blood CO\(_2\) levels and the steps by which homeostasis would be restored.

**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. When you breathe deeply, a negative-feedback mechanism prevents the lungs from overexpanding. During inhalation, sensors that detect stretching of the lung tissue send nerve impulses to the control circuits in the medulla, inhibiting further inhalation.

In regulating breathing, the medulla uses the pH of the 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\(_2\)CO\(_3\)). The H\(_2\)CO\(_3\) 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.

**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.*
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 O₂ and CO₂. Here we’ll examine how blood molecules called respiratory pigments facilitate this exchange through their interaction with O₂ and CO₂. We’ll also investigate physiological adaptations that enable animals to be active under conditions of high metabolic load or very limiting P<sub>O₂</sub>. 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 O₂ and CO₂ 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<sub>O₂</sub> than the blood flowing through the alveolar capillaries. Consequently, there is a net diffusion of O₂ down its partial pressure gradient from the air in the alveoli to the blood. Meanwhile, the presence of a P<sub>CO₂</sub> in the alveoli that is higher in the capillaries than in the air drives the net diffusion of CO₂ from blood to air. 3 By the time the blood leaves the lungs in the pulmonary veins, its P<sub>O₂</sub> and P<sub>CO₂</sub> 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 O₂ out of the blood and CO₂ into the blood. These gradients exist because cellular respiration in the mitochondria of cells near each capillary removes O₂ from and adds CO₂ to the surrounding interstitial fluid. 5 Having unloaded O₂ and loaded CO₂, 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 CO₂ and partially depleted of O₂.

Respiratory Pigments

The low solubility of O₂ in water (and thus in blood) poses a problem for animals that rely on the circulatory system to deliver O₂. For example, a person requires almost 2 L of O₂ 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 O₂ can dissolve into a liter of blood in the lungs. Even if 80% of the dissolved O₂ 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 O₂ 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 O₂ that can be carried in the circulatory fluid (from 4.5 to about 200 mL of O₂ per liter in mammalian blood). In our example of an exercising human with an O₂ delivery rate of 80%, the presence of a respiratory pigment reduces the cardiac output necessary for O₂ 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 invertebrates and almost all vertebrates is hemoglobin. 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 O₂, so a hemoglobin molecule can carry four O₂ molecules. Like all respiratory pigments, hemoglobin binds O₂ reversibly, loading O₂ 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 O₂ binds to one subunit, the others change shape slightly, increasing affinity for O₂. When four O₂ molecules are bound and one subunit unloads its O₂, the other three subunits more readily unload O₂, as an associated change in shape lowers their affinity for O₂.

Cooperativity in O₂ binding and release is evident in the dissociation curve for hemoglobin (Figure 42.31a). Over the range of PₐO₂ where the dissociation curve has a steep slope, even a slight change in PₐO₂ causes hemoglobin to load or unload a substantial amount of O₂. The steep part of the curve corresponds to the range of PₐO₂ found in body tissues. When cells in a particular location begin working harder—during exercise, for instance—PₐO₂ dips in their vicinity as the O₂ is consumed in cellular respiration. Because of subunit cooperativity, a slight drop in PₐO₂ causes a relatively large increase in the amount of O₂ the blood unloads.

Hemoglobin is especially efficient at delivering O₂ to tissues actively consuming O₂. However, this increased efficiency results not from O₂ consumption, but rather from CO₂ production. As tissues consume O₂ in cell respiration, they also produce CO₂. As we have seen, CO₂ reacts with water, forming carbonic acid, which lowers the pH of its surroundings. Low pH decreases the affinity of hemoglobin for O₂, an effect called the Bohr shift (Figure 42.31b). Thus, where CO₂ production is greater, hemoglobin releases more O₂, 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 CO₂ transport, the topic we’ll explore next.

**Carbon Dioxide Transport**

Only about 7% of the CO₂ 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 H₂CO₃. The H₂CO₃ readily dissociates into H⁺ and HCO₃⁻. Most H⁺ binds to hemoglobin and other proteins, minimizing change in blood pH. Most HCO₃⁻ diffuses out of the erythrocytes and is transported to the lungs in the plasma. The remaining HCO₃⁻, representing about 5% of the CO₂, binds to hemoglobin and is transported in erythrocytes.

When blood flows through the lungs, the relative partial pressures of CO₂ favor the net diffusion of CO₂ out of the blood. As CO₂ diffuses into alveoli, the amount of CO₂ in the blood decreases. This decrease shifts the chemical equilibrium in favor of the conversion of HCO₃⁻ to CO₂, enabling further
net diffusion of CO₂ into alveoli. Overall, the P<sub>CO₂</sub> gradient is sufficient to drive about a 15% reduction in P<sub>CO₂</sub> during passage of blood through the lungs.

Animation: Transport of Respiratory Gases

Respiratory Adaptations of Diving Mammals

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, even expert divers, cannot hold their breath longer than 2–3 minutes or swim deeper than 20 m, 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. 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?

One evolutionary adaptation of diving mammals to prolonged stays underwater is a capacity to store large amounts of O₂ in their bodies. The Weddell seal has about twice the volume of blood per kilogram of body mass as 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 O₂ per kilogram of body mass as a human.

Diving mammals not only have a relatively large O₂ stockpile but also have adaptations that conserve O₂. They swim with little muscular effort and glide passively for prolonged periods. During a dive, their heart rate and O₂ consumption rate decreases, 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 O₂ stored in myoglobin and then derive their ATP from fermentation instead of respiration (see Concept 9.5).

How did these adaptations arise 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 O₂ and CO₂ undergo net diffusion into or out of capillaries? Explain.
2. How does the Bohr shift help deliver O₂ to very active tissues?
3. What if? A doctor might give bicarbonate (HCO₃⁻) 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.

Chapter Review

Summary of Key Concepts

Concept 42.1

Circulatory systems link exchange surfaces with cells throughout the body (pp. 920–924)

- 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. 924–927)**

- The right ventricle pumps blood to the lungs, where it loads O₂ and unloads CO₂. Oxygen-rich blood from the lungs enters the heart at the left atrium and is pumped to the body tissues by the left ventricle. Blood returns to the heart through the right atrium.

![Diagram of heart and blood flow]

- 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. 927–931)**

- Blood vessels have structures well adapted to function. Capillaries have narrow diameters and thin walls that facilitate exchange. The velocity of blood flow is lowest in the capillary beds as a result of their large total cross-sectional area. Arteries contain thick elastic walls that maintain blood pressure. Veins contain one-way valves that contribute to the return of blood to the heart. Blood pressure is altered by changes in cardiac output and by variable constriction of arterioles.

- Fluid leaks out of capillaries and is returned to blood by the *lymphatic system*, which also defends against infection.

If 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. 932–937)**

- 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 O₂. 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. 937–942)**

- 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 O₂ 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 O₂ directly to cells. Spiders, land snails, and 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 O₂ 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 CO₂ through gas exchange?

CONCEPT 42.6

**Breathing ventilates the lungs (pp. 942–944)**

- 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 CO₂ 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 \( \text{O}_2 \) as well as \( \text{CO}_2 \) (via blood pH).

\[ \text{How does air in the lungs differ from the fresh air that enters the body during inspiration?} \]

**CONCEPT 42.7**

Adaptations for gas exchange include pigments that bind and transport gases (pp. 945–947)

- In the lungs, gradients of partial pressure favor the net diffusion of \( \text{O}_2 \) into the blood and \( \text{CO}_2 \) out of the blood. The opposite situation exists in the rest of the body. **Respiratory pigments** such as hemocyanin and hemoglobin bind \( \text{O}_2 \), greatly increasing the amount of \( \text{O}_2 \) transported by the circulatory system.
- Evolutionary adaptations enable some animals to satisfy extraordinary \( \text{O}_2 \) demands. Deep-diving mammals stockpile \( \text{O}_2 \) in blood and other tissues and deplete it slowly.

\[ \text{How are the roles of a respiratory pigment and an enzyme similar?} \]

**TEST YOUR UNDERSTANDING**

**Level 1: Knowledge/Comprehension**

1. Which of the following respiratory systems is not closely associated with a blood supply?
   (A) the lungs of a vertebrate  
   (B) the gills of a fish  
   (C) the tracheal system of an insect  
   (D) the skin of an earthworm

2. Blood returning to the mammalian heart in a pulmonary vein drains first into the
   (A) left atrium  
   (B) right atrium  
   (C) left ventricle  
   (D) right ventricle

3. Pulse is a direct measure of
   (A) blood pressure  
   (B) stroke volume  
   (C) cardiac output  
   (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 \( \text{O}_2 \)  
   (B) falling \( \text{O}_2 \)  
   (C) rising \( \text{CO}_2 \)  
   (D) falling \( \text{CO}_2 \)

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

**Level 2: Application/Analysis**

6. If a molecule of \( \text{CO}_2 \) released into the blood in your left toe is exhaled from your nose, it must pass through all of the following except
   (A) the pulmonary vein  
   (B) the trachea  
   (C) the right atrium  
   (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 \( P_{\text{O}_2} \)  
   (B) higher \( P_{\text{CO}_2} \)  
   (C) greater bicarbonate concentration  
   (D) lower pH

**Level 3: Synthesis/Evaluation**

8. **DRAW IT** Plot blood pressure against time for one cardiac cycle in humans, drawing separate lines for the pressure in the aorta, the left ventricle, and the right ventricle. Below the time axis, add a vertical arrow pointing to the time when you expect a peak in atrial blood pressure.

9. **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 \( P_{\text{O}_2} \) is kept low. When climbing high peaks, some mountaineers breathe from bottles of pure \( \text{O}_2 \). In a short essay (100–150 words), relate these behaviors to the mechanism of \( \text{O}_2 \) 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.*

For additional practice questions, check out the Dynamic Study Modules in MasteringBiology. You can use them to study on your smartphone, tablet, or computer anytime, anywhere!
In innate immunity, recognition and response rely on traits common to groups of pathogens.

In adaptive immunity, receptors provide pathogen-specific recognition.

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

Disruptions in immune system function can elicit or exacerbate disease.

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

Dedicated immune cells in the body fluids and tissues of most animals specifically interact with and destroy pathogens. In Figure 43.1, for example, an immune cell called a macrophage (brown) is engulfing rod-shaped bacteria (green). Some immune cells are types of white blood cells called lymphocytes (such as the one shown below with bacteria). Most lymphocytes recognize and respond to specific types of pathogens. Together, the body’s defenses make up the immune system, which enables an animal to avoid or limit many infections. A foreign molecule or cell doesn’t have to be pathogenic to elicit an immune response, but we’ll focus in this chapter 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 a skin or shell, blocks entry by many pathogens. Sealing off the entire body surface is impossible, however, because gas exchange, nutrition, and reproduction require openings.

When you see this blue icon, log in to MasteringBiology and go to the Study Area for digital resources.
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 molecular recognition provide the basis for the two types of immune defense found among animals: innate immunity, which is common to all animals, and adaptive immunity, which is found only in vertebrates. **Figure 43.2** summarizes these two types of immunity, highlighting fundamental similarities and differences.

In **innate immunity**, which includes barrier defenses, molecular recognition relies on a small set of receptor proteins that bind to molecules or structures that are absent from animal bodies but common to a group of viruses, bacteria, or other pathogens. Binding of an innate immune receptor to a foreign molecule activates internal defenses, enabling responses to a very broad range of pathogens.

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

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

In this chapter, we’ll examine how each type of immunity protects animals from disease. We’ll also investigate how pathogens can avoid or overwhelm the immune system and how defects in the immune system can imperil health.

**CONCEPT 43.1**

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

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

**Innate Immunity of Invertebrates**

The great success of insects in terrestrial and freshwater habitats teeming with diverse pathogens highlights the effectiveness of invertebrate innate immunity. In any environment, insects rely on their exoskeleton as a physical barrier against infection. Composed largely of the polysaccharide chitin, the exoskeleton provides an effective barrier defense against most pathogens. Chitin also lines the insect intestine, where it blocks infection by many pathogens ingested with food. Lysozyme, an enzyme that breaks down bacterial cell walls, further protects the insect digestive system.

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.
The major immune cells of insects are called hemocytes. Like amoebas, some hemocytes ingest and break down microorganisms, a process known as phagocytosis (Figure 43.3). One class of hemocytes produces a defense molecule that helps entrap large 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 fungi and bacteria 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, 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 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 43.4.

**Figure 43.4 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 >>** Based on this figure and the accompanying text, define 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.
Innate Immunity of Vertebrates

In jawed vertebrates, innate immune defenses coexist with the more recently evolved system of adaptive immunity. Because most 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 first the innate defenses that are similar to those found among invertebrates: barrier defenses, phagocytosis, and antimicrobial peptides. We’ll then examine some unique aspects of vertebrate innate immunity, such as natural killer cells, interferons, and the inflammatory response.

Barrier Defenses

The barrier defenses of mammals, which block the entry of many pathogens, include the mucous membranes and 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 innate immune cells dedicated to detecting, devouring, and destroying invading pathogens. In doing so, these cells often rely on a Toll-like receptor (TLR), a mammalian recognition protein similar to the Toll protein of insects. Upon recognizing pathogens, TLR proteins produce signals that initiate responses tuned to the invading microorganism.

Each TLR protein binds to fragments of molecules characteristic of a set of pathogens (Figure 43.5). 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.

Two other types of cells—dendritic cells and eosinophils—also have roles in innate defense. Dendritic cells mainly populate tissues, such as skin, that contact the environment. They stimulate adaptive immunity against pathogens that they encounter and engulf, as we’ll explore shortly. Eosinophils, often found in tissues underlying an epithelium, are important in defending against multicellular invaders, such as parasitic worms. Upon encountering such parasites, eosinophils discharge destructive enzymes.
Cellular innate defenses in vertebrates also involve **natural killer cells**. These cells circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells. Natural killer cells do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.

Many cellular innate defenses in vertebrates involve the lymphatic system, a network that distributes the fluid called lymph throughout the body (Figure 43.6). Some macrophages reside in lymph nodes, where they engulf pathogens that have entered the lymph from the interstitial fluid. Dendritic cells reside outside the lymphatic system but migrate to the lymph nodes after interacting with pathogens. Within the lymph nodes, dendritic cells interact with other immune cells, stimulating adaptive immunity.

**Antimicrobial Peptides and Proteins**

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

**Interferons** are proteins that provide innate defense by interfering with viral infections. Virus-infected body cells secrete 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, our next topic, as well as in the adaptive defenses discussed later in the chapter.


**Inflammatory Response**

When a splinter lodges under your skin, the surrounding area becomes swollen and warm to the touch. Both changes reflect a local inflammatory response, a set of events triggered by signaling molecules released upon injury or infection (Figure 43.7). Activated macrophages discharge cytokines, signaling molecules that recruit neutrophils to the site of injury or infection. In addition, mast cells, immune cells found in connective tissue, 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).

During inflammation, cycles of signaling and response transform the site of injury and infection. Activated complement proteins promote further release of histamine, attracting more phagocytic cells (see Figure 43.7) that carry out additional phagocytosis. At the same time, enhanced blood flow to the site helps deliver antimicrobial peptides. The result is an accumulation of pus, a fluid rich in white blood cells, dead pathogens, and debris from damaged tissue.

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 several-fold 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). There is good evidence that fever can be beneficial in fighting certain infections, although the underlying mechanism is 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 known as 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 roughly one-third of cases and contributes to the death of more than 200,000 people each year in the United States alone.

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

**Figure 43.7 Major events in a local inflammatory response.**

1. At the injury site, mast cells release histamines, which cause nearby capillaries to dilate. Macrophages release other signaling molecules that attract neutrophils.
2. Capillaries widen and become more permeable, allowing neutrophils and fluid containing antimicrobial peptides to enter the tissue.
3. Neutrophils digest pathogens and cell debris at the site of injury, and the tissue heals.

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

Animation: Overview of the Inflammatory Response
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. Why can 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 both adaptive and innate immunity. The adaptive response 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.)

Any substance that elicits a B or T cell response is called an antigen. In adaptive immunity, recognition occurs when a B cell or T cell binds to an antigen, such as a bacterial or viral protein, via a protein called an antigen receptor. 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 large foreign 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.

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. Disulfide bridges link the chains together (Figure 43.9).
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 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 any 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.

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 \( \alpha \) chain and a \( \beta \) 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 \( \alpha \) and \( \beta \) chains together form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

Whereas the antigen receptors of B cells bind to epitopes of intact antigens 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 and recognition of protein antigens begin when a pathogen infects a cell of the animal host or parts of a pathogen are taken in by an immune cell (Figure 43.12a). Inside the animal cell, enzymes cleave each antigen into antigen fragments, which are smaller peptides. Each antigen fragment binds to an MHC molecule, which transports the bound peptide to the cell surface. The result is antigen presentation, the display of the antigen fragment in an exposed groove of the MHC protein. Figure 43.12b shows a close-up view of antigen presentation, a process advertising 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. Proliferation of cells and the formation of immunological memory occur later, after a mature lymphocyte encounters and binds to a specific antigen. We’ll consider these four characteristics in the order in which they develop.

Generation of B Cell and T Cell Diversity

Each person makes more than 1 million different B cell antigen receptors and 10 million different T cell antigen receptors. Yet there are only about 20,000 protein-coding genes in the human genome. How, then, do we generate so many different antigen receptors? The answer lies in combinations. Think of selecting a cell phone 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
The Immune System

Gene in a series (Figure 43.13). Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 different ways ($40V \times 5J \times 1C$). The number of different heavy-chain combinations is even greater, resulting in even more diversity.

Assembling a functional Ig gene requires rearranging the DNA. Early in B cell development, an enzyme complex called recombinase links one light-chain $V$ gene segment to one $J$ gene segment. This recombination event eliminates the long stretch of DNA between the segments, forming a single exon that is part $V$ and part $J$.

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 43.13). 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 $3.5 \times 10^6$. Furthermore, mutations introduced during $VJ$ recombination add additional 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 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, 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.

The proliferation of a B cell or T cell into a clone of cells occurs in response to a specific antigen and to immune cell signals. 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. Cells that have antigen receptors specific for other antigens do not respond.

**Figure 43.14** summarizes the process of clonal selection, using the example of B cells, which generate memory cells and plasma cells. When T cells undergo clonal selection, they generate memory T cells and effector T cells (cytotoxic T cells and helper T cells).

**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 43.15).

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 decades. (Most effector cells have much shorter life spans.) If an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of clones of thousands of effector cells also specific for that antigen, thus generating a greatly enhanced immune defense.

Although the processes for antigen recognition, clonal selection, and immunological memory are similar for B cells and T cells, these two classes of lymphocytes fight infection in different ways and in different settings, as we’ll explore 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. Label the antigen-binding sites, disulfide bridges, and transmembrane region. Where are these features located relative to the V and C regions?
2. Explain two advantages of having memory cells when a pathogen is encountered for a second time.
3. **WHAT IF?** If both copies of a light-chain gene and a heavy-chain gene recombined in each (diploid) B cell, how would this affect B cell development and function?

*For suggested answers, see Appendix A.*

**CONCEPT 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 occurs in 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 immune response 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 antigens on their surface. What then distinguishes an antigen-presenting cell? The answer lies in the existence of two classes of MHC molecules. Most body cells have only the class I MHC molecules, but antigen-presenting cells have class I and class II MHC molecules. Class II molecules provide a molecular signature by which an antigen-presenting cell is recognized.
A helper T cell and the antigen-presenting cell displaying its specific epitope have a complex interaction (Figure 43.16). The antigen receptors on the surface of the helper T cell bind to the antigen fragment and to the class II MHC molecule displaying that fragment on the antigen-presenting cell. At the same time, an accessory protein called CD4 on the helper T cell surface binds to the class II MHC molecule, helping keep the cells joined. As the two cells interact, signals in the form of cytokines are exchanged. 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.

Antigen-presenting cells interact with helper T cells in several contexts. Antigen presentation by a dendritic cell or macrophage activates a helper T cell, which 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 themselves. Activated helper T cells also help stimulate cytotoxic T cells, as you’ll see shortly.

B Cells and Antibodies: A Response to Extracellular Pathogens

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

**Activation of B Cells**

As illustrated in Figure 43.17, 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 43.17).

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 43.17). 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.
Antibodies do not directly kill pathogens, but by binding to antigens, they interfere with pathogen activity or mark 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 43.18). The bound antibodies prevent infection of a host cell, thus neutralizing the virus. Similarly, antibodies sometimes bind to toxins released in body fluids, preventing the toxins from entering body cells.

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 43.19). 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.
Antibodies sometimes work together with the proteins of the complement system (Figure 43.20). (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 the generation of a *membrane attack complex* that forms pores in the cell’s membrane, allowing water and ions to rush in. The cell swells and lyses. Whether activated as part of innate or adaptive defenses, this cascade of complement protein activity results in the lysis of foreign cells and produces factors that promote inflammation or stimulate phagocytosis.

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 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 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 (Figure 43.21). 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. 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 cytotoxic T cells. As with helper T cells, cytotoxic T cells have an accessory protein that binds to the MHC molecule. This accessory protein, called CD8, helps keep the two cells in contact while the cytotoxic T cell is activated.

The targeted destruction of an infected host cell by a cytotoxic T cell involves the secretion of proteins that disrupt membrane integrity and trigger cell death (apoptosis; see Figure 43.21). 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 and 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 43.22** summarizes adaptive immunity, reviews the events that initiate humoral and cell-mediated immune responses, highlights the difference in response to pathogens in body fluids versus in body cells, and emphasizes the central role of the helper T cell.

![Figure 43.22 An overview of the adaptive immune response.](image_url)

**VISUAL SKILLS** Identify each arrow as representing part of the primary response or secondary response.
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. Today, immunizations are carried out with vaccines—preparations of antigen—obtained from many sources, including inactivated bacterial toxins, killed or weakened pathogens, and 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 43.15).

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 43.23). 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. Side effects of immunization are remarkably rare, with fewer than one in a million children suffering a significant allergic reaction to the measles vaccine. The disease remains quite dangerous to this day, however, killing more than 200,000 people worldwide each year. Declines in vaccination rates in parts of the United Kingdom, Russia, and the United States have resulted in a number of recent measles outbreaks and many preventable deaths. In 2014–2015, a measles outbreak triggered by a visitor to a Disney theme park in Southern California spread to multiple states and affected people ranging in age from 6 weeks to 70 years.

Active and Passive Immunity

The 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 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. Because passive immunity does not involve the recipient’s B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months).

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 43.23 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 injected as a therapy for a number of human diseases, including certain cancers.

One of the most recently developed antibody tools uses a single drop of blood to identify every virus that a person has encountered through infection or vaccination. To detect the antibodies formed against these viruses, researchers generate 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 43.24** provides an overview of how this technique works.

**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 graft or transplant, 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).

**Figure 43.24 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 an 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?
**Blood Groups**

In the case of blood transfusions, the recipient’s immune system can recognize carbohydrates 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 offers significant protection against a wide range of 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 43.25). 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. Cross-linking of adjacent IgE molecules triggers release of histamine and other chemicals, leading to allergy symptoms.

![Figure 43.25 Mast cells, IgE, and the allergic response](image-url)

In this example, pollen grains act as the allergen.
The 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. Studies of marathon runners support the conclusion that exercise intensity is the critical variable. On average, such runners get sick less often than their more sedentary peers during training, a time of moderate exertion, but markedly more often in the period immediately following the grueling race itself. Similarly, psychological stress has been shown to disrupt immune system regulation by altering the interplay of the hormonal, nervous, and immune systems (see Figure 45.20). Research also confirms 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. 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).

Hereditry, 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 afflict females more often than males. Women are nine times as likely to suffer from lupus and two to three times as likely to develop rheumatoid arthritis, a damaging and painful inflammation of the cartilage and bone in joints (Figure 43.26). 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.

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. Studies of marathon runners support the conclusion that exercise intensity is the critical variable. On average, such runners get sick less often than their more sedentary peers during training, a time of moderate exertion, but markedly more often in the period immediately following the grueling race itself. Similarly, psychological stress has been shown to disrupt immune system regulation by altering the interplay of the hormonal, nervous, and immune systems (see Figure 45.20). Research also confirms 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 is for a pathogen to alter how it appears to the immune system. Immunological memory is a record of the foreign epitopes an animal has encountered. If the pathogen that expressed those epitopes no longer does so, it can reinfest or remain in a host without triggering the rapid and robust response that memory cells provide. 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’ll 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 replicates in one human host after another, the virus undergoes frequent mutations. Because any change that lessens recognition by the immune system provides a selective advantage, the virus steadily accumulates mutations that change its surface proteins, reducing the effectiveness of the host immune response. As a result, a new flu vaccine must be developed, produced, and distributed each year. In addition, the human influenza 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, which establish themselves in human sensory neurons, provide a good example of latency. The type 1 virus causes most oral herpes infections, whereas the type 2 virus is responsible for most cases of genital herpes. Because sensory neurons express relatively few MHC I molecules, the infected cells are inefficient at presenting viral antigens to circulating lymphocytes. Stimuli such as fever, emotional stress, or menstruation reactivate the virus to replicate and infect surrounding epithelial tissues. Activation of the type 1 virus can result in blisters around the mouth that are called “cold” sores. The type 2 virus can cause genital sores, but people infected with either the type 1 or type 2 virus often have no symptoms. Infections of the type 2 virus, which is sexually transmitted, pose a serious threat to the babies of infected mothers and can increase transmission of the virus that causes AIDS.

**Attack on the Immune System: HIV**

The human immunodeficiency virus (HIV), the pathogen that causes AIDS, both escapes and attacks the adaptive immune response. Once introduced into the body, HIV infects helper T cells with high efficiency by binding specifically to the CD4 accessory protein (see Figure 43.17). 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. The continued presence of HIV is also helped by latency while the viral DNA is integrated in the host cell’s genome. This latent DNA is shielded from the immune system as well as from antiviral agents currently used against HIV, which attack only actively replicating viruses.
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 of the trypanosome’s ever-shifting surface glycoproteins and the host’s immune response.

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Number of Parasites (in millions) per mL of Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>1.2</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>18</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Part A: Interpret The Data

1. Plot the data in the above table as a line graph. Which column is the independent variable, and which is the dependent variable? Put the independent variable on the x-axis. (For additional information about graphs, see the Scientific Skills Review in Appendix F.)

2. Visually displaying data in a graph can help make patterns in the data more noticeable. Describe any patterns revealed by your graph.

3. Assume that a drop in parasite abundance reflects an effective immune response by the host. Formulate a hypothesis to explain the pattern you described in question 2.

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Antibody Specific to Glycoprotein Variant A</th>
<th>Antibody Specific to Glycoprotein Variant B</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Part B: Interpret The Data

4. Note that these data were collected over the same period of infection (days 4–24) as the parasite abundance data you graphed in part A. Therefore, you can incorporate these new data into your first graph, using the same x-axis. However, since the antibody level data are measured in a different way than the parasite abundance data, add a second set of y-axis labels on the right side of your graph. Then, using different colors or sets of symbols, add the data for the two antibody types. Labeling the y-axis two different ways enables you to compare how two dependent variables change relative to a shared independent variable.

5. Describe any patterns you observe by comparing the two data sets over the same period. Do these patterns support your hypothesis from part A? Do they prove that hypothesis? Explain.

6. Scientists can now also distinguish the abundance of trypanosomes recognized specifically by antibodies type A and type B. How would incorporating such information change your graph?

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

Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it (Figure 43.27). 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 pneumonia in people with AIDS. Such opportunistic diseases, as well as nerve damage and body wasting, are the primary causes of death in AIDS patients, 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 (typically 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 produce HIV-specific antibodies that can be detected in a blood test. Currently, 10–50% of all new HIV infections appear to be caused by recently infected individuals. Although no cure has been found for HIV infection, drugs that can significantly slow HIV replication and the progression to AIDS have been developed.

Cancer and Immunity

When adaptive immunity is inactivated, the frequency of certain cancers increases dramatically. For example, the risk of developing Kaposi’s sarcoma is 20,000 times greater for untreated AIDS patients than for healthy people. This observation was at first 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. A vaccine introduced in 1986 for hepatitis B virus helps prevent liver cancer, the first cancer for which a human vaccine became available.

In the 1970s, Harald zur Hausen, working in Heidelberg, Germany, proposed that human papillomavirus (HPV) causes cervical cancer. Many scientists were skeptical that cancer could result from infection by HPV, the most common sexually transmitted pathogen. However, after more than a decade of work, zur Hausen isolated two particular types of HPV from patients with cervical cancer. He quickly made samples available to other scientists, leading in 2006 to the development of highly effective vaccines against HPV. The computer graphic image of an HPV particle in Figure 43.28 illustrates the abundant copies of the capsid protein (yellow) that is used as the antigen in vaccination.

Cervical cancer kills more than 4,000 women annually in the United States and is the fifth-most common cause of cancer deaths among women worldwide. Administering an HPV vaccine, either Gardasil or Cervarix, to young adults greatly reduces their chance of being infected with the HPV viruses that cause cervical and oral cancers, as well as genital warts. In 2008, zur Hausen shared the Nobel Prize in Physiology or Medicine for his discovery.

For suggested answers, see Appendix A.
In innate immunity, recognition and response rely on traits common to groups of pathogens (pp. 951–956)

- In both invertebrates and vertebrates, **innate immunity** is mediated by physical and chemical barriers as well as cell-based defenses. Activation of innate immune responses relies on recognition proteins specific for broad classes of pathogens. 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.

- 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?

In adaptive immunity, receptors provide pathogen-specific recognition (pp. 956–961)

- **Adaptive immunity** relies on two types of lymphocytes that arise from stem cells in the bone marrow: **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. Activated B and T cells called memory cells defend against future infections by the same pathogen.

> 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. 961–968)

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

- **Active immunity** develops in response to infection or to immunization. The transfer of antibodies in passive immunity provides immediate, short-term protection.

- 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.
Disruptions in immune system function can elicit or exacerbate disease (pp. 968–972)

1. 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.

2. Antigenic variation, latency, and direct assault on the immune system allow some pathogens to thwart immune responses. HIV infection destroys helper T cells, leaving the patient prone to disease. Immune defense against cancer appears to primarily involve action against viruses that can cause cancer and cancer cells that harbor viruses.

3. **Is being infected with HIV the same as having AIDS?** Explain.

### Level 1: Knowledge/Comprehension

1. Which of these is **not** part of insect immunity?
   - (A) enzyme activation of pathogen-killing chemicals
   - (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.

### Level 2: Application/Analysis

4. Which of the following statements is **not** true?
   - (A) An antibody has more than one antigen-binding site.
   - (B) A lymphocyte has receptors for multiple different antigens.
   - (C) An antigen can have different epitopes.
   - (D) A liver or muscle cell makes one class of MHC molecule.

5. Which of the following should be the same in identical twins?
   - (A) the set of antibodies produced
   - (B) the set of MHC molecules produced
   - (C) the set of T cell antigen receptors produced
   - (D) the set of immune cells eliminated as self-reactive

### Level 3: Synthesis/Evaluation

6. Vaccination increases the number of
   - (A) different receptors that recognize a pathogen.
   - (B) lymphocytes with receptors that can bind to the pathogen.
   - (C) epitopes that the immune system can recognize.
   - (D) MHC molecules that can present an antigen.

7. Which of the following would **not** help a virus avoid triggering an adaptive immune response?
   - (A) having frequent mutations in genes for surface proteins
   - (B) infecting cells that produce very few MHC molecules
   - (C) producing proteins very similar to those of other viruses
   - (D) infecting and killing helper T cells

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 of lipopolysaccharide (LPS) from bacteria in the blood. Suppose you have available purified LPS and several strains of mice, each with a mutation that inactivates a particular TLR gene. How might you 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**

   ![](image)

   This photo shows a child receiving an oral vaccine against polio, a disease caused by a virus that infects neurons. Given that the body cannot readily replace most neurons, why is it important that a polio vaccine stimulate not only a cell-mediated response but also a humoral response?

   *For selected answers, see Appendix A.*

---

For additional practice questions, check out the Dynamic Study Modules in MasteringBiology. You can use them to study on your smartphone, tablet, or computer anytime, anywhere!
Osmoregulation and Excretion

Figure 44.1 How does an albatross drink salt water without ill effect?

**KEY CONCEPTS**

- **44.1** Osmoregulation balances the uptake and loss of water and solutes
- **44.2** An animal’s nitrogenous wastes reflect its phylogeny and habitat
- **44.3** Diverse excretory systems are variations on a tubular theme
- **44.4** The nephron is organized for stepwise processing of blood filtrate
- **44.5** Hormonal circuits link kidney function, water balance, and blood pressure

**A Balancing Act**

At 3.5 m, the wingspan of a wandering albatross (*Diomedea exulans*) is the largest of any living bird. But the albatross commands attention for more than just its size. This massive bird remains at sea day and night throughout the year, returning to land only to reproduce. A human with only seawater to drink would die of dehydration, but faced with the same conditions, the albatross thrives (Figure 44.1).

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

A number of mechanisms for water and solute control have arisen during evolution, reflecting the varied and often severe osmoregulatory challenges presented by an animal’s surroundings. Animals living in the arid conditions of a desert, for instance, can quickly lose body water. So too can albatrosses and other marine animals. Survival in these dehydrating environments depends on conserving body water and, for marine birds and fishes, eliminating excess salts. Freshwater animals face a distinct challenge: a watery environment that threatens...
to dilute their body fluids. These organisms survive by con-

In safeguarding their internal fluids, animals must deal
with ammonia, a toxic metabolite produced by the disman-

tling 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 excretion and osmoregulation 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

Just as thermoregulation depends on balancing heat loss and

gain (see Concept 40.3), regulating the chemical composition

of body fluids depends on balancing the uptake and loss of

water and solutes. If water uptake is excessive, animal cells

swell and burst; if water loss is substantial, cells shrivel and
die. Ultimately, the driving force for the movement of both

water and solutes—in animals as in all other organisms—is

a concentration gradient of one or more solutes across the

plasma 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 (Figure 44.2). 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
isosmotic. 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 solu-
tions. When two solutions differ in osmolarity, the solution
with the higher concentration of solutes is said to be hyperos-
motic, 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 differ-
ence for both solutes and free water (see Figure 44.2).

In this chapter, we use the terms isosmotic, 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 surround-
ings. 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 com-
position 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. 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 44.3).

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
allows many marine animals to maintain an internal osmolar-
ity different from that of seawater.

Figure 44.1 Osmoregulation balances the uptake and loss of water and solutes.

Figure 44.2 Solute concentration and osmosis.

Figure 44.3 Sockeye salmon (Oncorhynchus nerka), osmoregulators that migrate between rivers and the ocean.
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 eury, 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 44.3).

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 substantial challenges in water balance. Nevertheless, they actively transport specific solutes that establish levels in hemolymph (circulatory fluid) different from those in the ocean. For example, homeostatic mechanisms in the Atlantic lobster (*Homarus americanus*) maintain a magnesium ion (Mg$^{2+}$) concentration of less than 9 mM (millimolar, or $10^{-3}$ mol/L), far below the 50 mM 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 chondrichthans (cartilaginous animals; see Concept 34.3).

Cod, shown in Figure 44.4a, 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.

As noted earlier, osmoregulation is frequently coupled to elimination of nitrogenous waste products, such as urea. Eliminating urea is important because high concentrations of urea can denature (unfold) proteins and thus disrupt cellular functions. Sharks, however, have a high concentration of urea in their body. Why isn’t urea toxic for these animals? The answer lies in an organic molecule, trimethylamine oxide (TMAO), produced by shark tissues. TMAO protects proteins from the denaturing effect of urea.

TMAO has another function in sharks: osmoregulation. Like bony fishes, sharks have an internal salt concentration much lower than that of seawater. Thus, salt tends to diffuse from the water into their bodies, especially across their gills. However, the combination of TMAO with salts, urea, and other compounds results in a solute concentration in shark tissues that is actually somewhat higher than 1,000 mOsm/L. For this reason, 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. In many freshwater animals, including bony fishes such as the perch, shown in Figure 44.4b, water balance relies on excreting large amounts of very dilute urine and drinking almost no water. In addition, salts lost by diffusion and in the urine are replenished by eating and by salt uptake across their gills.

<table>
<thead>
<tr>
<th>(a) Osmoregulation in a marine fish</th>
<th>(b) Osmoregulation in a freshwater fish</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain</strong> of water and salt ions from food</td>
<td><strong>Gain</strong> of water and some ions in food</td>
</tr>
<tr>
<td><strong>Excretion</strong> of salt ions from gills</td>
<td><strong>Uptake</strong> of salt ions by gills</td>
</tr>
<tr>
<td><strong>Osmotic water loss</strong> through gills and other parts of body surface</td>
<td><strong>Osmotic water gain</strong> through gills and other parts of body surface</td>
</tr>
<tr>
<td><strong>Gain</strong> of water and salt ions from drinking seawater</td>
<td><strong>Excretion</strong> of salt ions and large amounts of water in dilute urine from kidneys</td>
</tr>
</tbody>
</table>

**Figure 44.4** Osmoregulation in marine and freshwater bony fishes: a comparison.
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. As a result of these and other physiological changes, salmon in salt water 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 1 mm long (Figure 44.5). 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 and space. Now, however, the manufacture of materials modeled after the protectants found in anhydrobiotic species has enabled such samples to be stored in compact chambers at room temperature.

**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 these and other adaptations, most terrestrial animals lose water through many routes: in urine and feces, across the skin, and from the surfaces of gas exchange organs. Land animals maintain water balance by drinking and eating moist foods and by producing water metabolically through cellular respiration.

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. Also, they can lose 25% of their body water and survive. (In contrast, a human who loses half this amount 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...
SCIENTIFIC SKILLS EXERCISE

Describing and Interpreting Quantitative Data

How Do Desert Mice Maintain Osmotic Homeostasis?  The sandy inland mouse (now known 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

<table>
<thead>
<tr>
<th>Access to Water</th>
<th>Mean Osmolarity (mOsm/L)</th>
<th>Mean Urea Concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine</td>
<td>Blood</td>
</tr>
<tr>
<td>Part A: Unlimited</td>
<td>490</td>
<td>350</td>
</tr>
<tr>
<td>Part B: None</td>
<td>4,700</td>
<td>320</td>
</tr>
</tbody>
</table>

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 would you draw from these ratios?
3. If the amount of urine produced were different in the two conditions, how would that affect your calculation? Explain.

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


Transport Epithelia in Osmoregulation

The ultimate function of osmoregulation is to control solute concentrations in cells, but most animals do this indirectly by managing the solute content of an internal 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 explore this question, researchers gave captive marine birds only seawater to drink. Although...
very little salt appeared in the birds’ urine, fluid dripping from the tip of their beaks was a concentrated solution of salt (NaCl). The source of this solution was a pair of nasal salt glands packed with transport epithelia (Figure 44.6). 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 44.6 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**

Because most metabolic wastes must be dissolved in water to be excreted from the body, the type and quantity of an animal’s waste products may have a large impact on its water balance. In this regard, some of the most significant waste products are the nitrogenous breakdown products of proteins and nucleic acids. When proteins and nucleic acids are broken apart for energy or converted to carbohydrates or fats, enzymes remove nitrogen in the form of ammonia (NH₃). Ammonia is very toxic, in part because its ion, ammonium (NH₄⁺), can interfere with oxidative phosphorylation. Although some animals excrete ammonia directly, many species expend energy to convert it to less toxic compounds prior to excretion.

**Forms of Nitrogenous Waste**

Animals excrete nitrogenous wastes as ammonia, urea, or uric acid (Figure 44.7). These different forms vary significantly in their toxicity and the energy costs of producing them.

**Ammonia**

Animals that excrete ammonia need access to lots of water because ammonia can be tolerated only at very low concentrations. Therefore, ammonia excretion is most common in aquatic species. The highly soluble ammonia molecules, which interconvert between NH₃ and NH₄⁺ forms, 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.

**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...
While 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.

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.