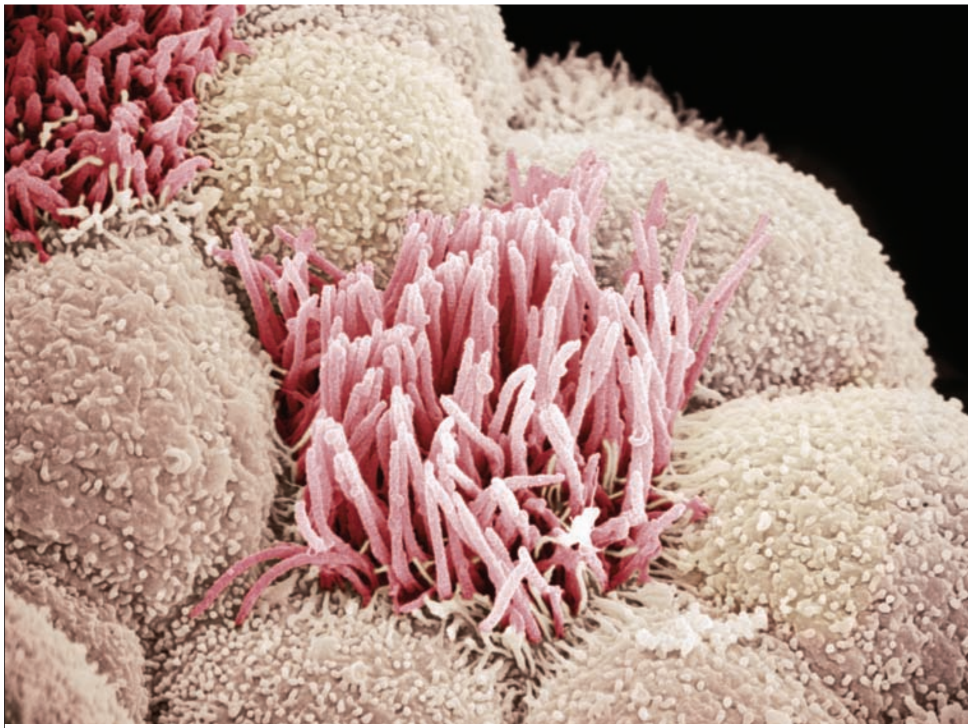
Lining of the trachea (windpipe) shown in a colorized SEM, with mucus-secreting cells (white) and epithelial cells with cilia (pink). The trachea is positioned between the larynx and the lungs, providing a conduit for air entering and leaving the body.



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STUDY PLAN

44 Gas Exchange: The Respiratory System

WHY IT MATTERS

On October 25, 1999, at 9:19 A.M., the captain lined up Learjet N47BA on the runway at Orlando International Airport and opened the throttles. Within seconds, the sleek corporate jet was airborne and climbing; 2 minutes later, at 9:21 EDT, the pilots reported passing through 9500 feet.

As the jet continued its climb, the pressure of the outside air dropped steadily and with it the availability of the oxygen (O_2) that all animal life requires, including the two pilots and three passengers on the jet. Normally, in aircraft, the cabin pressure is maintained at a level equivalent to an altitude of 8000 feet, more than sufficient to keep O_2 available to all on board. But, unknown to the pilots, the pressurization system was not functioning normally.

At 9:27 EDT, the controller at the Jacksonville Control Center instructed the jet to climb to 39,000 feet. The first officer acknowledged the instruction, her voice strong and clear. Her acknowledgment was the last radio transmission anyone was to hear from N47BA.

When humans experience increasingly higher altitudes, each breath brings less O_2 into the body. Of all the cells affected by reduced O_2, the ones most sensitive are those of the eyes and brain. Without an O_2 supply at 25,000 feet, most people progress from fully alert to unconscious in about 3 minutes; at 40,000 feet, the progression takes only 15 seconds.

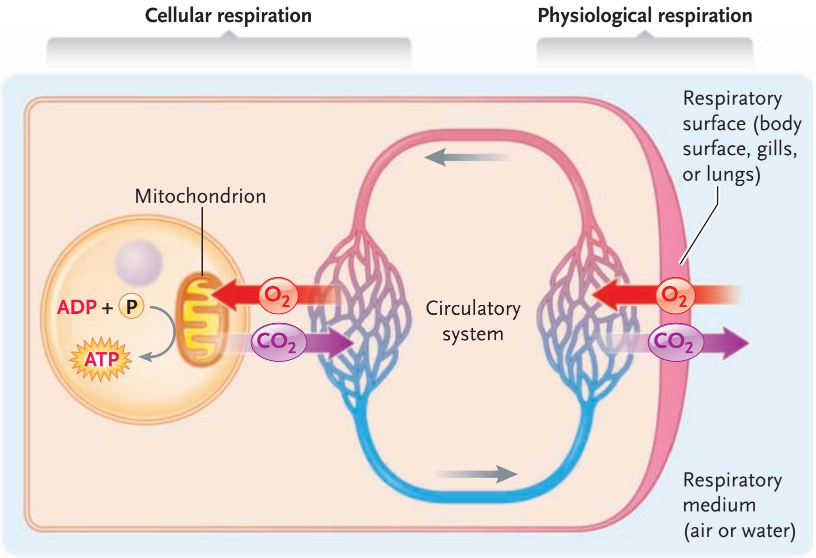
The jet continued its climb, eventually reaching an altitude of 46,000 feet. When the pilots stopped responding to communications, military jets were sent to investigate. The military pilots could see no movement in the Learjet cabin and there was no response to their transmissions. The forward windshields of the Learjet were frosted over, indicating that warm air from the engines was not ventilating the cabin correctly. Evidently, the aircraft was maintaining its course through the autopilot, without conscious human direction.

Many hours later, at 12:11 P.M. CDT, one of the two engines failed: the aircraft, now unbalanced, rolled over and entered a steep, spiraling descent that ended in a shattering impact in a field near Aberdeen, South Dakota. The subsequent investigation pointed to faulty operation of a single valve controlling cabin pressurization as a likely cause of the accident. This tragic loss of life emphasizes the vital importance of O_2 to the survival of humans and other animals. In this chapter we discuss the respiratory system, the system that allows an animal to exchange CO_2 produced in the body for O_2 from the surroundings. The respiratory systems of animals reflect the environmental conditions under which they live, and this general principle has resulted in a truly remarkable array of adaptations.

44.1 The Function of Gas Exchange

Physiological respiration is the process by which animals exchange gases with their surroundings—how they take in O_2 from the outside environment and deliver it to body cells, and remove CO_2 from body cells and deliver it to the environment **(Figure 44.1).** The absorbed O_2 is used as the final electron acceptor for the oxidative reactions that produce ATP in mitochondria (see Section 8.4). The CO_2 released to the environment is a product of those oxidative reactions. Because they use O_2 and release CO_2, these ATP-producing reactions are called *cellular respiration.*

Figure 44.1
The relationship between cellular respiration and physiological respiration.



How gas exchange occurs in an animal depends on its respiratory medium—air or water—and the nature of its respiratory surface. The **respiratory medium** is the environmental source of O_2 and the "sink" for released CO_2. For aquatic animals, of course, the respiratory medium is water; for terrestrial animals, it is air. Amphibians and some fishes use both water and air as respiratory media. The exchange of gases with the respiratory medium by animals is called **breathing**, whether the medium is air or water.

The **respiratory surface**, formed by a layer of epithelial cells, provides the interface between the body and the respiratory medium. Oxygen is absorbed across the respiratory surface, and CO_2 is released. In all animals, the exchange of gases across the respiratory surface occurs by simple diffusion, movement of molecules from a region of higher concentration to a region of lower concentration (see Section 6.2).

Generally, the concentration of O_2 is higher in the respiratory medium than on the internal side of the respiratory surface, and thus the net diffusion of O_2 is inward. Carbon dioxide moves in the opposite direction because the CO_2 concentration is higher on the internal side of the respiratory surface than in the respiratory medium.

Respiratory surfaces typically have two structural properties that favor a high rate of diffusion: they are thin, and they have large surface areas. The rate of diffusion is inversely proportional to the square of the distance over which the diffusion occurs; diffusion rates are therefore higher through thin surfaces such as the single layer of epithelial cells forming many respiratory surfaces. And, the rate of diffusion is directly proportional to the surface area across which diffusion occurs, meaning that large surface areas allow for higher rates of gas exchange than small surface areas. In addition, the rate of diffusion becomes higher with larger concentration gradients and with increasing temperature.

In some relatively small animals, such as sponges, ctenophores, roundworms, flatworms, and some annelids, the entire body surface serves as the respiratory surface. All these animals are invertebrates that live in aquatic or moist environments.

In larger animals, specialized structures, *gills* and *lungs,* form the primary respiratory surface for exchanging gases with water and air, respectively. In insects, a **tracheal system,** an extensive system of branching tubes, channels air from the outside to the internal organs and most individual cells of the animal.

Because gases must dissolve in water to enter and leave epithelial cells, the respiratory surface must be wetted to function in gas exchange, either directly by the respiratory medium or by a thin film of water. For this reason, in water-breathing animals, **gills** are *evaginations* of the body: they extend outward into the respiratory medium. In terrestrial animals, **lungs** are typically pockets or *invaginations* of the body surface, buried deeply in the body interior where they are less susceptible to drying out. Also, terrestrial animals have adaptations that moisten dry air before it reaches the respiratory surface. For example, in humans and other mammals, moisture is added to air as it passes through the mouth, nasal passages, throat, and air passages leading to the lungs.

The organ system responsible for gas exchange is termed the **respiratory system.** The respiratory system consists of all the parts of the body involved in exchanging air between the external environment and the blood. In mammals, this includes the airways leading to and into the lungs, the lungs themselves, and the structures of the chest used to move air through the airways into and out of the lungs.

Adaptations That Increase Ventilation and Perfusion of the Respiratory Surface Maximize the Rate of Gas Exchange

Two primary adaptations help animals maintain the difference in concentration between gases outside and inside the respiratory surface, thereby keeping the rate of gas exchange at maximal levels. One is **ventilation,** the flow of the respiratory medium (air or water, depending on the animal) over the external side of the respiratory surface. The second is **perfusion,** the flow of blood or other body fluids on the internal side of the respiratory surface.

Ventilation. As they respire, animals remove O_2 from the respiratory medium and replace it with CO_2. Without ventilation, the concentration of O_2 would fall in the respiratory medium close to the respiratory surface, and the concentration of CO_2 would rise, gradually reducing the concentration gradients and dropping the rate of gas exchange below the minimum level required to sustain life. Examples of ventilation include the one-way flow of water over the gills in fish and many other aquatic animals and the in-and-out flow of air in the lungs of most vertebrates and in the tracheal system of insects.

Perfusion. The constant replacement of blood or another fluid on the internal side of the respiratory surface helps to keep the inside/outside concentration differences of O_2 and CO_2 at a maximum. In animals without a circulatory system, such as roundworms and flatworms, body movements help circulate body fluids beneath the skin. Most animals without a circulatory system are small or have thin, greatly flattened bodies, because all body cells must be located close to the respiratory surface to exchange O_2 and CO_2 adequately. In animals with a circulatory system, the circulatory system brings blood to the internal side of the respiratory surface, transporting CO_2 from all cells of the body—no matter how far they are from the respiratory surface—to exchange for O_2, which is then taken to all cells of the body.

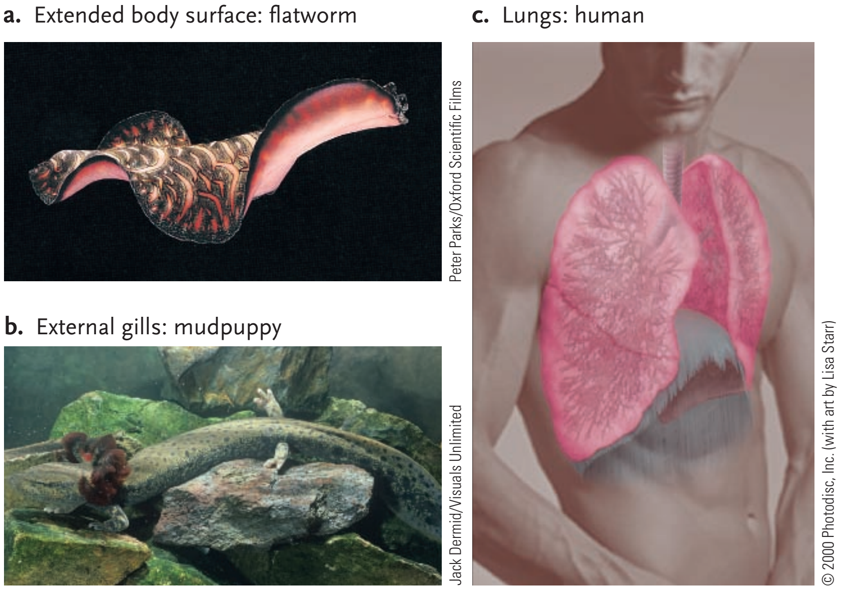
Adaptations That Increase the Area of the Respiratory Surface Maximize the Quantity of Gases Exchanged

Most animals have adaptations that increase the quantity of gases exchanged by increasing the area of the respiratory surface. In animals whose skin serves as the respiratory surface, an elongated or flattened body form increases the area of the respiratory surface **(Figure 44.2a).**

In animals with gills, the respiratory surface is increased by highly branched structures that include many fingerlike or platelike projections **(Figure 44.2b).** Similarly, in animals with lungs or tracheae, the respiratory surface is increased by a multitude of branched tubes, folds, or pockets **(Figure 44.2c).**

Water and Air Have Advantages and Disadvantages as Respiratory Media

Because their respiratory surfaces are exposed directly to the environment, water breathers have no problem keeping the respiratory surface wetted. However, aquatic animals face two main challenges in obtaining O_2 from water compared with terrestrial animals. First, water contains approximately one-thirtieth as much O_2 as air


a. Extended body surface: flatworm

b. External gills: mudpuppy

c. Lungs: human

Peter Parks/Oxford Scientific Films

Jack Dermid/Visuals Unlimited

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Figure 44.2

Adaptations increasing the area of the respiratory surface. (a) The flattened and elongated body surface of a flatworm. **(b)** The highly branched, feathery structure of the external gills in an amphibian, the mudpuppy *(Necturus)*. **(c)** The many branches and pockets expanding the respiratory surface in the human lung.

does (at 15°C). Therefore, to obtain the same amount of O_2, an aquatic animal must process 30 times as much of its respiratory medium as a terrestrial animal does. Second, water is about 1000 times as dense as air and about 50 times as viscous. Therefore, it takes significantly more energy to move water than air over a respiratory surface. For this reason, ventilation in most aquatic animals takes place in a one-way direction. In bony fishes, for instance, water enters the mouth, flows over the gills, and exits through the gill covers, all in one direction.

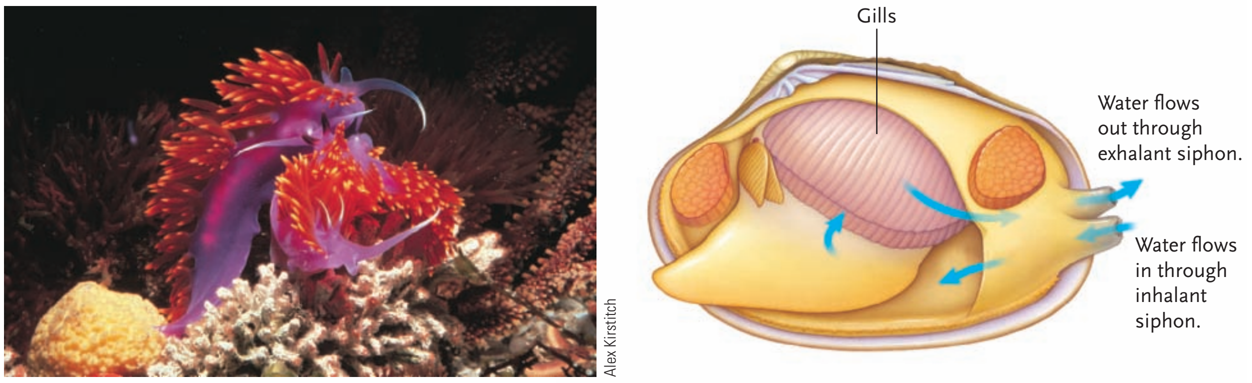
In addition, temperature and solutes affect the O_2 content of water. That is, as either the temperature or the amount of solutes increases, the amount of gas that can dissolve in water decreases. Therefore, with respect to obtaining O_2, aquatic animals that live in warm water are at a disadvantage compared with those that live in cold water. And, because levels of solutes (such as sodium chloride) are higher in seawater than in freshwater, aquatic animals living in seawater are at a disadvantage.

The relatively high O_2 content, low density, and low viscosity of air greatly reduce the energy required to ventilate the respiratory surface. These advantages allow animals with lungs to breathe in and out, reversing the direction of flow of the respiratory medium, without a large energy penalty. As you will see later, reversing the direction of flow decreases the efficiency of gas exchange.

Another advantage of breathing air is that gas molecules diffuse nearly 10,000 times faster through air than through water. This increases the rate at which molecules of the gases at the respiratory surface exchange with those located farther away in the air, and reduces the requirement for ventilation as compared with water.

A major disadvantage of air is that it constantly evaporates water from the respiratory surface unless the air is saturated with water vapor. Therefore, except in an environment with 100% humidity, animals lose water by evaporation during breathing and must replace the water to keep the respiratory surface from drying and causing the death of the surface cells.

We next turn to the adaptations that allow water-breathing and air-breathing animals to obtain O_2 and release CO_2 in aquatic and terrestrial environments. These adaptations allow animals to exploit the advantages and circumvent the disadvantages of water and air as respiratory media.



a. External gills: nudibranch

b. Internal gills: clam

Alex Kirstitch

c. Internal gills: cuttle fish

d. Internal gills: fish

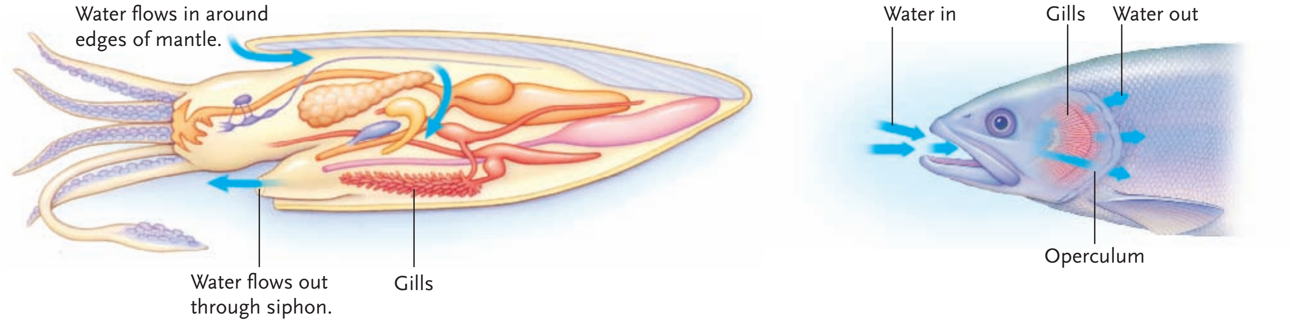


Figure 44.3
External and internal gills. (a) The external gills of a nudibranch *(Flabellina iodinea)*. **(b)** The internal gills in a clam. **(c)** The internal gills in a cuttlefish. **(d)** Internal gills of a bony fish. Water enters through the mouth and passes over the filaments of the gills before exiting through an opening at the edges of the flaplike protective covering, the operculum.

STUDY BREAK

1. Distinguish between the roles of the respiratory medium and the respiratory surface in respiratory systems.
2. What is an advantage of water over air as a respiratory medium? What are two key advantages of air over water as a respiratory medium?

44.2 Adaptations for Respiration

Although most animals that live in water exchange gases through the skin or gills, some, such as whales, seals, and dolphins, exchange gases through lungs (which originally evolved in aquatic creatures). And although most animals that live on land exchange gases through lungs, some, such as sow bugs and land crabs, exchange gases through gills, and others, such as insects, exchange gases using a tracheal system.

Aquatic Gill Breathers Exchange Gases More Efficiently Than Skin Breathers

Gills provide water-breathing animals, and a few air-breathers, with more efficient gas exchange than skin breathers have. In combination with the organized circulatory system common to these animals, gills also allow animals to live in more diverse habitats, and to achieve greater body mass, than animals that breathe primarily or exclusively through the skin.

External and Internal Gills. Gills are respiratory surfaces that are branched and folded evaginations of the body surface. **External gills** are gills that do not have protective coverings; they extend out from the body and are in direct contact with the water. **Internal gills,** by contrast, are located within chambers of the body that have a cover providing physical protection for the gills. Water must be brought to internal gills.

Because external gills have no protective coverings, they are exposed to mechanical damage and must be immersed in water to keep them from collapsing or drying. For these reasons, animals with external gills, including some annelids and mollusks **(Figure 44.3a),** aquatic insects, the larval forms of some bony fishes, and some amphibians, are limited to relatively protected aquatic environments.

The coverings of internal gills protect them from mechanical damage and drying. Covered internal gills allow animals to live in highly diverse habitats, ranging from small streams and ponds to rivers, lakes, and the open seas, and even in moist terrestrial habitats. Most crustaceans, mollusks, sharks, and bony fishes have internal gills. Some invertebrates, such as clams and oysters, use beating cilia to circulate water over their internal gills **(Figure 44.3b).** Others, such as the cuttlefish, use contractions of the muscular mantle to pump water over their gills **(Figure 44.3c).** In adult bony fishes, the gills extend into a chamber covered by gill flaps or *opercula* (singular, *operculum* = little lid) on either side of the head. The operculum also serves as part of a one-way pumping system that ventilates the gills **(Figure 44.3d).**

Many Animals with Internal Gills Use Countercurrent Flow to Maximize Gas Exchange

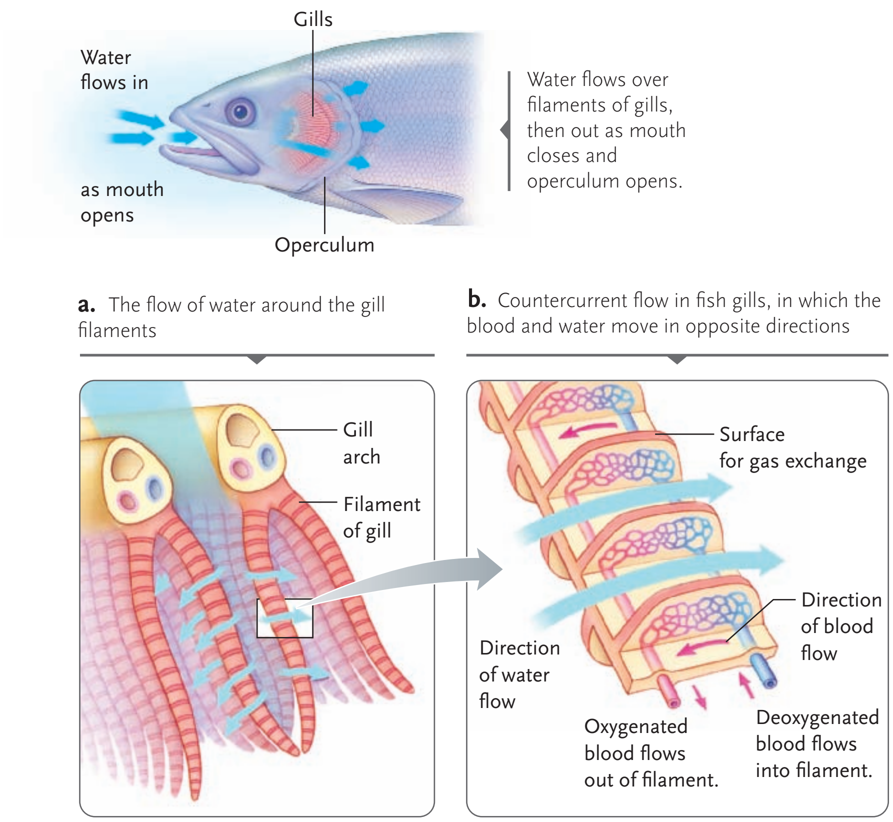
Sharks, fishes, and some crabs take advantage of one-way flow of water over the gills to maximize the amounts of O_2 and CO_2 exchanged with water. In this mechanism, called **countercurrent exchange,** the water flowing over the gills moves in a direction opposite to the flow of blood under the respiratory surface.

Figure 44.4 illustrates countercurrent exchange in the uptake of O_2. At the point where fully oxygenated water first passes over a gill filament in countercurrent flow, the blood flowing beneath it in the opposite direction is also almost fully oxygenated. However, O_2 concentration is still higher in the water than in the blood, and the gas diffuses from the water into the blood, raising the concentration of O_2 in the blood almost to the level of the fully oxygenated water. At the opposite end of the filament, much of the O_2 has been removed from the water, but the blood flowing under the filament, which has just arrived from body tissues and is fully deoxygenated, contains even less O_2. As a result, O_2 also diffuses from the water to the blood at this end of the filament. All along the gill filament, the same relationship exists, so that at any point, the water is more highly oxygenated than the blood, and O_2 diffuses from the water into the blood across the respiratory surface.

The overall effect of countercurrent exchange is the removal of 80% to 90% of the O_2 content of water as it flows over the gills. In comparison, by breathing in and out and constantly reversing the direction of air flow, mammals manage to remove only about 25% of the O_2 content of air. Efficient removal of O_2 from water is important because of the much lower O_2 content of water compared with air.

Insects Use a Tracheal System for Gas Exchange

Insects breathe air by a respiratory system consisting of air-conducting tubes called **tracheae** (singular *trachea,* or "windpipe"). The tracheae are invaginations of the outer epidermis of the animal, reinforced by rings of chitin, the material of the insect exoskeleton. They lead from the body surface and branch so extensively inside the animal that almost every cell is served



a. The flow of water around the gill filaments

b. Countercurrent flow in fish gills, in which the blood and water move in opposite directions

c. In countercurrent exchange, blood leaving the capillaries has the same O_2 content as fully oxygenated water entering the gills

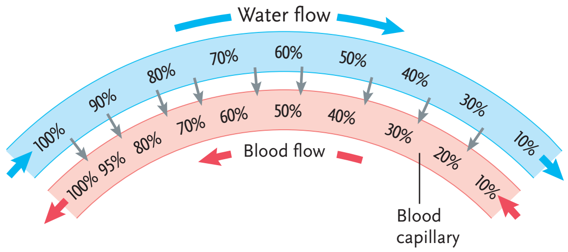


Figure 44.4
Ventilation and countercurrent exchange in bony fishes. **(a)** Water flows around the gill filaments. **(b)** Water and blood flow in opposite directions through the gill filaments. **(c)** Countercurrent exchange: oxygen from the water diffuses into the blood, raising its oxygen content. The percentages indicate the degree of oxygenation of water (blue) and blood (red).

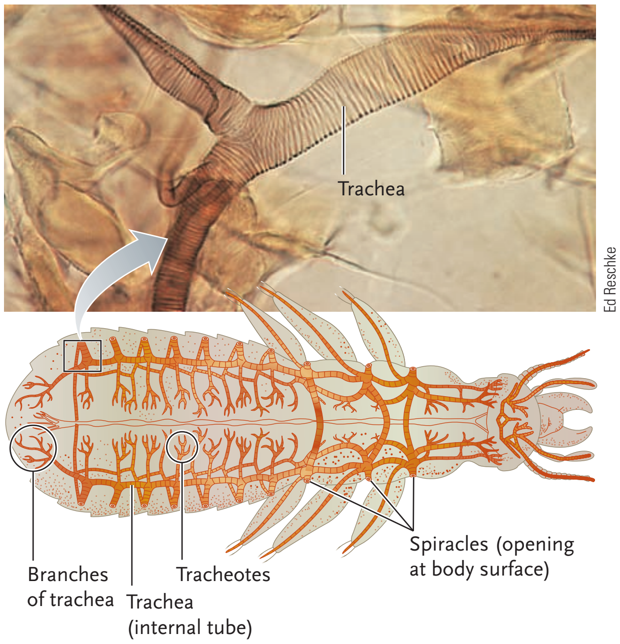


Figure 44.5
The tracheal system of insects. Chitin rings, visible in the photomicrograph, reinforce many of the tracheae.

by a microscopic branch **(Figure 44.5).** Some of the branches even penetrate inside larger cells, such as those of insect flight muscles. The finest branches of the tracheae, called *tracheoles,* form the respiratory surface of the insect system. Tracheoles are dead-end tubes with very small fluid-filled tips that are in contact with cells of the body. Air is transported by the tracheal system to those tips, and gas exchange occurs directly across the plasma membranes of the body cells in contact with the tips. At places within the body, the tracheae expand into internal air sacs that act as reservoirs to increase the volume of air in the system.

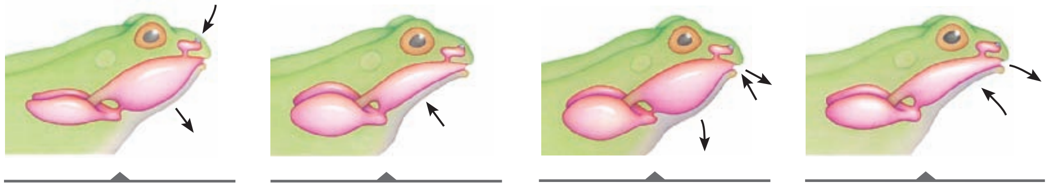
Air enters and leaves the tracheal system at openings in the insect's chitinous exoskeleton called **spiracles** (*spiraculum* = airhole). In adult insects, the spiracles are located in a row on either side of the thorax and abdomen. The spiracles open and close in coordination with body movements to compress and expand the air sacs and pump air in and out of the tracheae. During insect flight, alternating compression and expansion of the thorax by the flight muscles also pump air through the tracheal system.

Lungs Allow Animals to Live in Completely Terrestrial Environments

Lungs are one of the primary adaptations that allowed animals to fully invade terrestrial environments. Some fishes and amphibians have lungs, as do all reptiles, birds, and mammals. All lungs are invaginated structures located internally in the body.

In some fishes, such as lungfishes, lungs and air breathing evolved as adaptations to survive in oxygen-poor water or temporarily in air when the water level dropped and exposed them. The lungs of these fishes consist of thin-walled sacs, which branch off from the mouth, pharynx, or parts of the digestive system; air is obtained by **positive pressure breathing,** a gulping or swallowing motion that forces air into the lungs.

The lungs of mature amphibians such as frogs and salamanders are also thin-walled sacs with relatively



1 The frog lowers the floor of its mouth and inhales through its nostrils.

2 It closes its nostrils, opens the glottis, and elevates the floor of the mouth, forcing air into the lungs.

3 Rhythmic ventilation assists in gas exchange.

4 Air is forced out when muscles in the body wall above the lungs contract and the lungs recoil elastically.

Figure 44.6
Positive pressure breathing in an amphibian (a frog).

little folding or pocketing. Amphibians also fill their lungs by positive pressure breathing, in this case using a rhythmic motion of the floor of the mouth as the pump, in coordination with opening and closing of the nostrils **(Figure 44.6).**

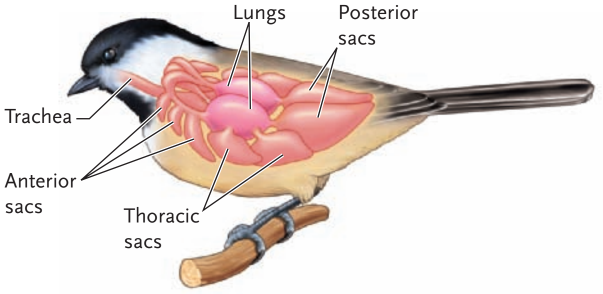
The lungs of reptiles, birds, and mammals have many pockets and folds that increase the area of the respiratory surface, which contains dense, highly branched capillary networks. Mammalian lungs consist of millions of tiny air pockets, the **alveoli,** each surrounded by dense capillary networks. Reptiles and mammals fill their lungs by **negative pressure breathing**—by muscular contractions that expand the lungs, lowering the pressure of the air in the lungs and causing air to be pulled inward. (Mammalian negative pressure breathing is described in more detail in the next section.)

In birds, a countercurrent exchange system provides the most complex and efficient vertebrate lungs **(Figure 44.7).** In addition to paired lungs, birds have nine pairs of air sacs that branch off the respiratory tract. The air sacs, which collectively contain several times as much air as the lungs, set up a pathway that allows air to flow in one direction through the lungs, rather than in and out as in other vertebrates. Within the lungs, air flows through an array of fine, parallel tubes that are surrounded by a capillary network. The blood flows in the direction opposite to the air flow, setting up a countercurrent exchange. The countercurrent exchange allows bird lungs to extract about one-third of the O_2 from the air as compared with about one-fourth in the lungs of mammals.

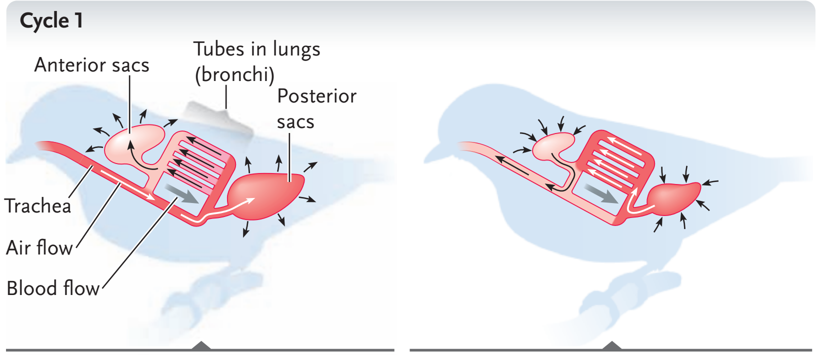
STUDY BREAK

1. What advantages do gills confer upon a water-breathing animal over skin breathing?
2. What is countercurrent exchange, and how is it beneficial for gas exchange?
3. How does the tracheal system of insects facilitate gas exchange with the cells of the body?
4. Distinguish between positive pressure breathing and negative pressure breathing in animals with lungs.

a. Lungs and air sacs of a bird

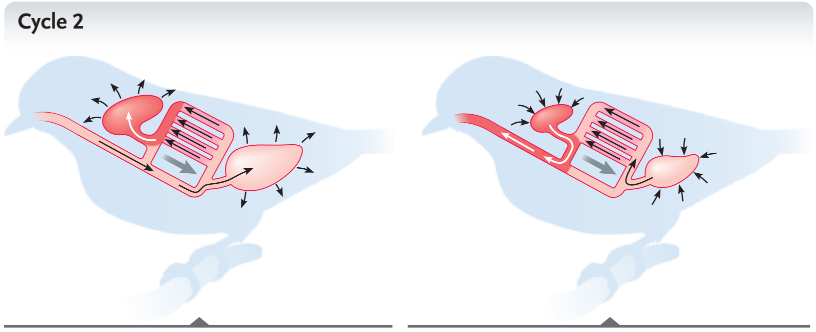


b. Countercurrent exchange



1 During the first inhalation, most of the oxygen flows directly to the posterior air sacs. The anterior air sacs also expand but do not receive any of the newly inhaled oxygen.

2 During the following exhalation, both anterior and posterior air sacs contract. Oxygen from the posterior sacs flows into the gas-exchanging tubes (bronchi) of the lungs.



1 During the next inhalation, air from the lung (now deoxygenated) moves into the anterior air sacs.

2 In the second exhalation, air from anterior sacs is expelled to the outside through the trachea.

Figure 44.7
Countercurrent exchange in bird lungs. **(a)** Unlike mammalian lungs, bird lungs do not expand and contract. Changes in pressure in the expandable air sacs move air in and out. **(b)** Air flows in one direction through the tubes of the lungs; blood flows in the opposite direction in the surrounding capillary network. Two cycles of inhalation and exhalation are needed to move a specific volume of air through the bird respiratory system.

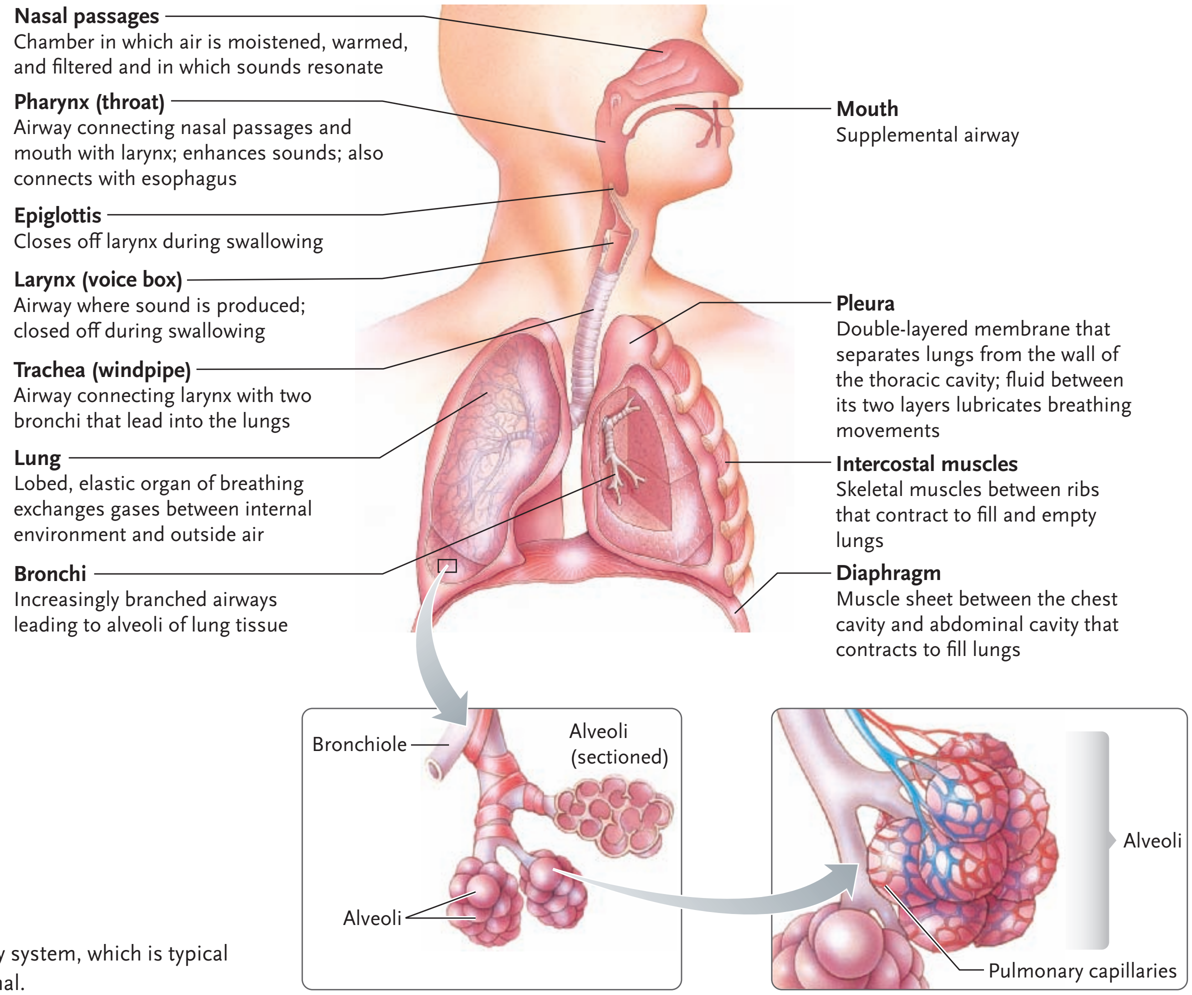


Figure 44.8
The human respiratory system, which is typical for a terrestrial mammal.

44.3 The Mammalian Respiratory System

All mammals have a pair of lungs and a diaphragm in the chest cavity that plays an important role in negative pressure breathing. Rapid ventilation of the respiratory surface and perfusion by blood flow through dense capillary networks maximizes gas exchange.

The Airways Leading from the Exterior to the Lungs Filter, Moisten, and Warm the Entering Air

The human respiratory system is typical for a terrestrial mammal **(Figure 44.8).** Air enters and leaves the respiratory system through the nostrils and mouth. Hairs in the nostrils and mucus covering the surface of the airways filter out and trap dust and other large particles. Inhaled air is moistened and warmed as it moves through the mouth and nasal passages.

Next, air moves into the throat, or **pharynx**, which forms a common pathway for air entering the **larynx** (or "voice box") and food entering the esophagus, which leads to the stomach. The airway through the larynx is open except during swallowing.

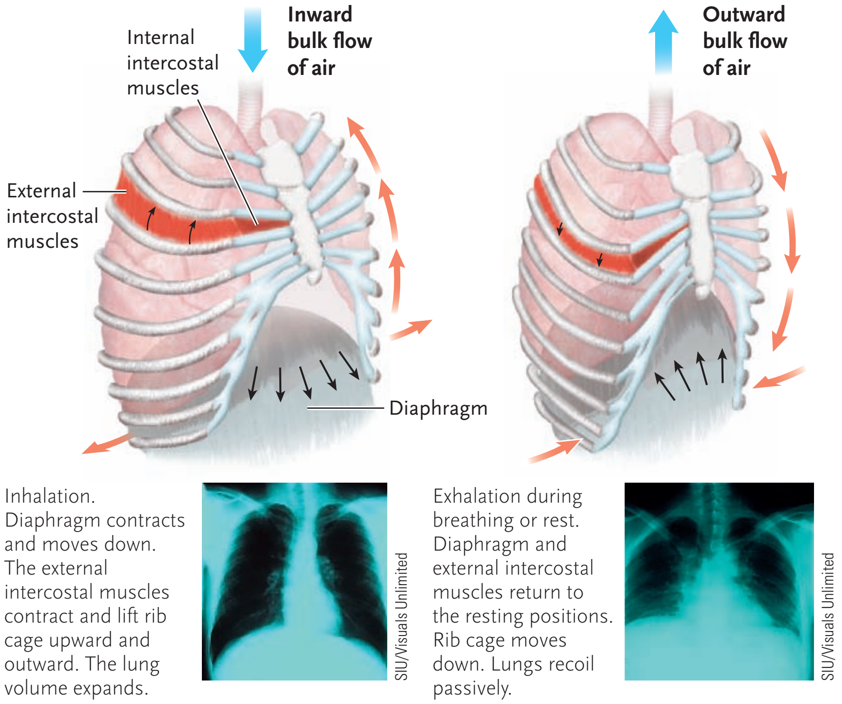
From the larynx, air moves into the trachea (or "windpipe"), which branches into two airways, the **bronchi** (singular, *bronchus*). The bronchi lead to the two elastic, cone-shaped lungs, one on each side of the chest cavity. Inside the lungs, the bronchi narrow and branch repeatedly, becoming progressively narrower and more numerous. The terminal airways, the **bronchioles,** lead into cup-shaped pockets, the alveoli (singular, *alveolus;* shown in Figure 44.8 insets).

Each of the 150 million alveoli in each lung is surrounded by a dense network of capillaries. By the time inhaled air reaches the alveoli, it has been moistened to the saturation point and brought to body temperature. The many alveoli provide an enormous area for gas exchange. If the alveoli of an adult human were flattened out in a single layer, they would cover an area approaching 100 square meters, about the size of a tennis court!

The larynx, trachea, and larger bronchi are nonmuscular tubes encircled by rings of cartilage that prevent the tubes from compressing. The largest of the rings, which reinforces the larynx, stands out at the front of the throat as the Adam's apple; smaller supporting rings can be felt at the front of the throat just below the larynx. The walls of the smaller bronchi and the bronchioles contain smooth muscle cells that contract or relax to control the diameter of these passages, and with it, the amount of air flowing to and from the alveoli.

The epithelium lining each bronchus contains cilia and mucus-secreting cells. Bacteria and airborne particles such as dust and pollen are trapped in the mucus and then moved upward and into the throat by the beating of the cilia lining the airways. Infection-fighting macrophages also patrol the respiratory epithelium.

Tobacco smoke, by paralyzing the cilia lining the respiratory tract, interferes with the processes that clear bacteria and airborne particles from the lungs. The bacteria and foreign matter persisting in the lungs can cause infections and smoker's cough.



Inhalation. Diaphragm contracts and moves down. The external intercostal muscles contract and lift rib cage upward and outward. The lung volume expands.

SIU/Visuals Unlimited

Exhalation during breathing or rest. Diaphragm and external intercostal muscles return to the resting positions. Rib cage moves down. Lungs recoil passively.

SIU/Visuals Unlimited

Figure 44.9

The respiratory movements of humans during breathing at rest. The movements of the rib cage and diaphragm fill and empty the lungs. Inhalation is powered by contractions of the external intercostal muscles and diaphragm, and exhalation is passive. During exercise or other activities characterized by deeper and more rapid breathing, contractions of the internal intercostal muscles and the abdominal muscles add force to exhalation. The X-ray images show how the volume of the lungs increases and decreases during inhalation and exhalation.

Contractions of the Diaphragm and Muscles between the Ribs Ventilate the Lungs

The lungs are located in the rib cage above the *diaphragm,* a dome-shaped sheet of skeletal muscle separating the chest cavity from the abdominal cavity. The lungs are covered by a double layer of epithelial tissue called the **pleura.** The inner pleural layer is attached to the surface of the lungs, and the outer layer is attached to the surface of the chest cavity. A narrow space between the inner and outer layers is filled with slippery fluid, which allows the lungs to move within the chest cavity without rubbing or abrasion as they expand and contract.

Contraction of muscles between the ribs and the diaphragm brings air into the lungs by a negative pressure mechanism. As an inhalation begins, the diaphragm contracts and flattens, and one set of muscles between the ribs, the *external intercostal* muscles, contracts, pulling the ribs upward and outward **(Figure 44.9).** These movements expand the chest cavity and lungs, lowering the air pressure in the lungs below that of the atmosphere. As a result, air is drawn into the lungs, expanding and filling them.

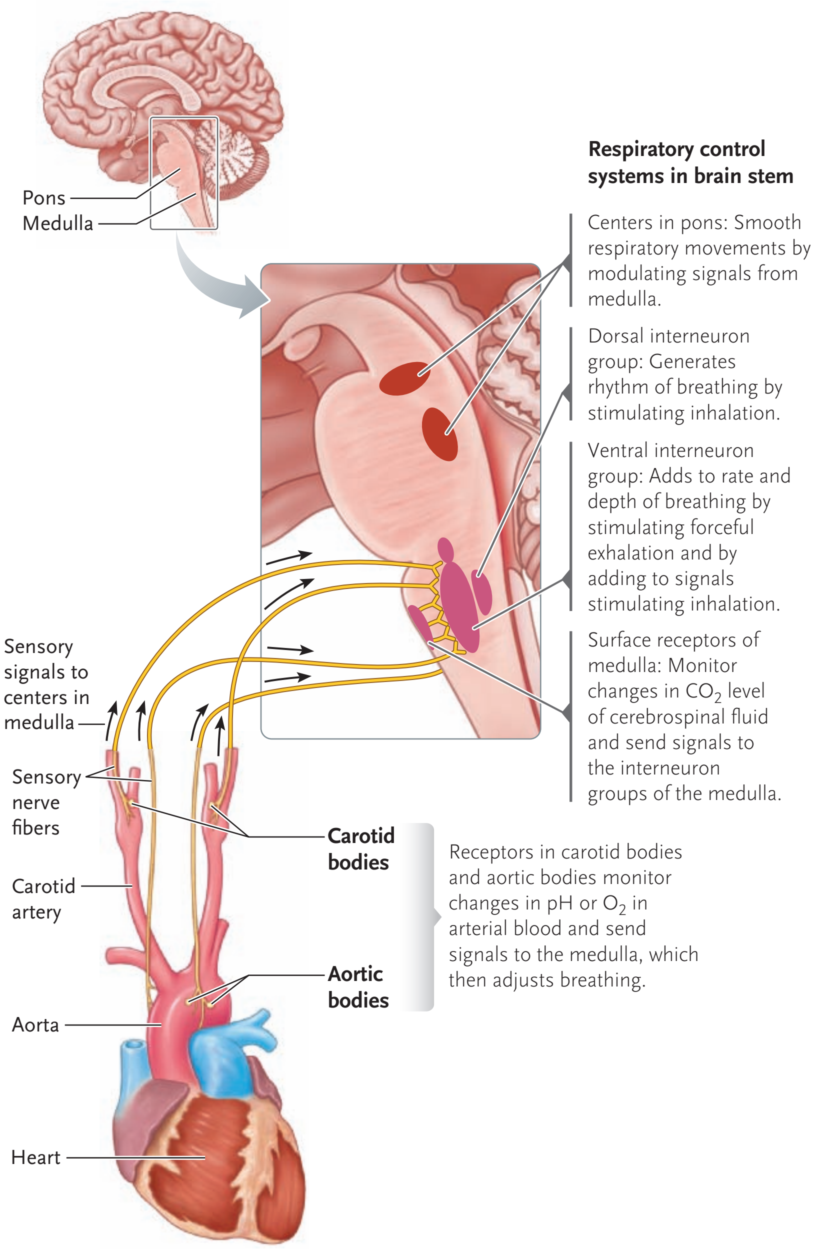
The expansion of the lungs is much like filling two rubber balloons. Like balloons, the lungs are elastic, and resist stretching as they are filled. Also like balloons, the stretching stores energy, which can be released to expel air from the lungs. When a person at rest exhales, the diaphragm and muscles between the ribs relax, and the elastic recoil of the lungs expels the air.

When physical activity increases the body's demand for O_2, other muscles help expel the air by forcefully reducing the volume of the chest cavity. Contractions of abdominal wall muscles increase abdominal pressure, exerting an upward-directed force on the diaphragm and thus pushing it upward. Contractions of *internal intercostal* muscles pull the chest wall inward and downward, causing it to flatten. As a result, the dimensions of the chest cavity decrease.

The Volume of Inhaled and Exhaled Air Varies over Wide Limits

The volume of air entering and leaving the lungs during inhalation and exhalation is called the **tidal volume.** In a person at rest, the tidal volume amounts to about 500 mL. As physical activity increases, the tidal volume increases to match the body's needs for O_2; at maximal levels, the tidal volume reaches about 3400 mL in females and 4800 mL in males. The maximum tidal volume is called the **vital capacity** of an individual.

Even after the most forceful exhalation, about 1200 mL of air remains in the lungs in males, and about 1000 mL in females; this is the **residual volume** of the lungs. In fact, the lungs cannot be deflated completely because small airways collapse during forced exhalation, blocking further outflow of air. Because air cannot be removed from the lungs completely, some gas exchange can always occur between blood flowing through the lungs and the air in the alveoli.



Respiratory control systems in brain stem

Centers in pons: Smooth respiratory movements by modulating signals from medulla.

Dorsal interneuron group: Generates rhythm of breathing by stimulating inhalation.

Ventral interneuron group: Adds to rate and depth of breathing by stimulating forceful exhalation and by adding to signals stimulating inhalation.

Surface receptors of medulla: Monitor changes in CO_2 level of cerebrospinal fluid and send signals to the interneuron groups of the medulla.

Receptors in carotid bodies and aortic bodies monitor changes in pH or O_2 in arterial blood and send signals to the medulla, which then adjusts breathing.

Figure 44.10

Control of breathing. Centers in the pons and medulla control the rhythm, rate, and depth of breathing. Receptors in the carotid arteries and aorta detect changes in the levels of O_2 and CO_2 in blood and body fluids. Signals from these receptors are integrated in the respiratory centers of the medulla and pons.

The Centers That Control Breathing Are Located in the Brain Stem

Breathing is controlled by centers in the medulla and pons, which form part of the brain stem **(Figure 44.10).** Groups of interneurons in the centers regulate the rate and depth of breathing, ranging from shallow, slow breathing when the body is at rest to the deep and rapid breathing of intense physical exercise, excitement, or fear. Over these extremes, the air entering and leaving lungs of a human male varies from as little as 5 to 6 L per minute to (for a brief time only) as much as 150 L per minute.

Interneurons That Regulate Breathing. Signals from interneurons in the medulla carried by efferent (motor) neurons of the autonomic system produce the breathing movements. A set of signals from a dorsal group of interneurons acts as the primary stimulator of inhalation by causing the diaphragm and the external intercostal muscles to contract, which expands the chest cavity and produces an inhalation. In a person at rest, the signal is switched off as the lungs become moderately full: the rib muscles and the diaphragm relax, and a passive exhalation occurs. These signals act as the primary generator of breathing rhythm.

A ventral group of interneurons in the medulla can send signals for both inhalation and exhalation. These neurons become active only during physical exercise, fear, or other situations that require more oxygen when active rather than passive exhalation is needed. In that case, some of the ventral neurons send signals that stimulate the abdominal and internal intercostal muscles to contract, thereby causing active exhalation. Other neurons in the ventral group become stimulated by signals from the dorsal group, and then help increase inhalation activity when faster and deeper breathing is required.

Two interneuron groups in the pons modulate the signals originating from the medulla, fine-tuning and smoothing the muscle contractions so that inhalations and exhalations are gradual and controlled rather than sudden and abrupt. Signals sent from higher brain centers in the cerebrum can override the control of respiratory rate and depth by the brain stem. For example, as we speak or sing, or hold our breath, we can consciously alter or stop breathing to match the demands of these activities. Breathing rate and depth are also modified by emotional states, controlled by centers in the limbic system of the brain (see Section 38.3). Thus breathing is altered as we laugh, gasp, groan, cry, and sigh.

Receptors That Send Information to the Brain Centers. The brain centers controlling the rate and depth of breathing integrate sensory information sent by receptors that monitor O_2 and CO_2 levels in the blood and body fluids. The integration of sensory information serves to match breathing rate to the metabolic demands of the body. These *chemoreceptors* are located centrally on the surface of the medulla, and peripherally in **carotid bodies** in the carotid arteries leading to the brain and in **aortic bodies** in the large arteries leaving the heart (see Figure 44.10).

The receptors of the medulla detect changes in pH in the cerebrospinal fluid; the pH is determined mostly by the CO_2 concentration in the blood. (Remember that pH decreases as CO_2 levels increase.) The receptors in the carotid and aortic bodies detect changes in CO_2 and O_2 concentrations in the blood.

The CO_2 receptors in the medulla have the greatest effects on breathing. If increased body activities cause the CO_2 concentration to rise in the blood, the medulla receptors trigger interneuron groups in the medulla that increase the rate and depth of breathing. If CO_2 concentration falls, the receptors send signals to the medulla that lead to a slowing of the rate and depth of breathing.

The peripheral receptors in the carotid and aortic bodies detect changes in pH or O_2 concentration in arterial blood. When these receptors detect a rise in blood pH they send signals to the medulla that cause the medulla to increase the rate and depth of breathing. Although the receptors in the carotid and aortic bodies also detect the O_2 level in arterial blood, the receptors do not respond until blood O_2 level falls below 60% of normal. This reaction makes the O_2 receptors act as a backup system that comes into play only when blood O_2 concentration falls to critically low levels.

Thus, the level of CO_2 in the blood and body fluids is much more closely monitored, and has a much greater effect on breathing, than the O_2 level. This reflects the fact that small fluctuations in blood pH have much greater effects on the ability of hemoglobin to carry oxygen, and on enzyme activity in the blood and interstitial fluid, than fluctuations in the O_2 level.

Local Controls. Other, automated controls within the lungs match the rates of ventilation and perfusion by responding to O_2 concentrations in the blood. If air flow lags behind capillary blood flow, so that the O_2 level falls in the blood, the reduced O_2 concentration causes smooth muscles in the walls of arterioles in the lungs to contract. This reduces the flow of blood, thereby giving it more time to pick up O_2. Conversely, if blood flow lags behind, the rising blood O_2 concentration causes the smooth muscle cells in arteriole walls to relax, dilating the arterioles and increasing the rate of blood flow through lung capillaries. These local controls, in combination with the neural controls that regulate rate and depth of breathing, ensure that the respiratory system meets the body's varying need to obtain O_2 and release CO_2.

STUDY BREAK

1. Explain how inhalation and exhalation occur in a mammal at rest.
2. You can consciously initiate and sustain an exhalation. What is going on muscularly in this case?
3. What is the most important feedback stimulus for breathing?
4. What is the role of the chemoreceptors in the medulla?

44.4 Mechanisms of Gas Exchange and Transport

In both the lungs and body tissues, gas exchange occurs when the gas diffuses from an area of higher concentration to an area of lower concentration. In this section, we consider the mechanics of gas exchange between air and the blood in mammals, and the means by which gases are transported between the lungs and other body tissues. A major part of this story involves hemoglobin, the vertebrate respiratory pigment.

The Proportion of a Gas in a Mixture Determines Its Partial Pressure

For gases, it is often more accurate and convenient to consider concentration differences as differences in pressure. When gases are present in a mixture, the pressure of each individual gas, called its *partial pressure,* is determined by its proportion in the mixture. Air, water, and blood all contain mixtures of gases, including oxygen, carbon dioxide, nitrogen, and other gases, so each gas exerts only a part of the total gas pressure. For example, the proportion of O_2 in dry air is about 21%, or 21/100. In dry air at sea level, the total atmospheric pressure under standard conditions is 760 mm Hg. The partial pressure of O_2, written as P_{O_2}, is equivalent to $760 \times 21/100$, or about 160 mm Hg. The proportion of CO_2 in dry air is about 0.04%, so its partial pressure, P_{CO_2}, is equivalent to $760 \times 0.04/100$, or about 0.3 mm Hg. For O_2 to diffuse inward across a respiratory surface, its partial pressure outside the surface must be greater than inside; for CO_2 to diffuse outward, its partial pressure inside must be greater inside than outside.

In the lungs, even though the P_{O_2} is reduced by mixing with the air in the residual volume, it is still much higher than the P_{O_2} in deoxygenated blood entering the network of capillaries in the lungs **(Figure 44.11).** As a result, O_2 readily diffuses from the alveolar air into the plasma solution in the capillaries.

Hemoglobin Greatly Increases the O_2-Carrying Capacity of the Blood

After entering the plasma, O_2 diffuses into erythrocytes, where it combines with hemoglobin. The combination with hemoglobin removes O_2 from the plasma, lowering the P_{O_2} of the plasma and allowing additional O_2 molecules to diffuse from alveolar air to the blood.

Recall from Section 42.2 that a mammalian hemoglobin molecule has four heme groups, each containing an iron atom that can combine reversibly with an O_2 molecule. A hemoglobin molecule can therefore bind a total of four molecules of O_2. The combination of O_2 with hemoglobin allows blood to carry about

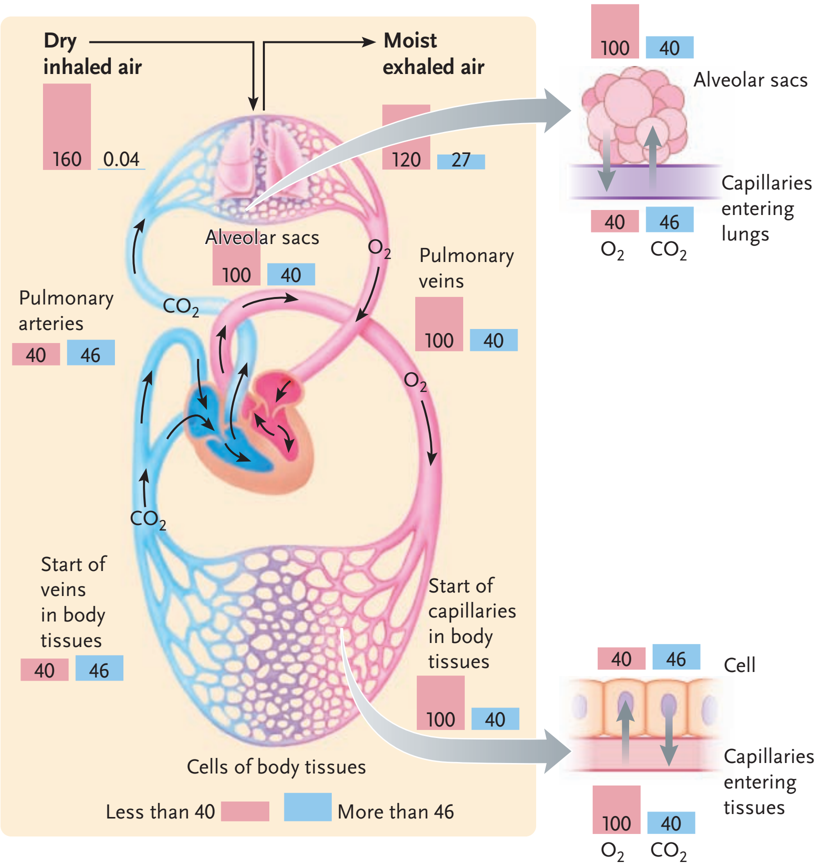


Figure 44.11
The partial pressures of O_2 (pink) and CO_2 (blue) in various locations in the body.

60 times more O_2 (about 200 mL per liter) than it could if the O_2 simply dissolved in the plasma (about 3 mL per liter). About 98.5% of the O_2 in blood is carried by hemoglobin and about 1.5% is carried in solution in the blood plasma.

The reversible combination of hemoglobin with O_2 is related to the partial pressure of O_2 in a pattern shown by the *hemoglobin-O_2* dissociation curve in **Figure 44.12.** (The curve is generated by measuring the amount of hemoglobin saturated at a given P_{O_2}.) The curve is S-shaped with a plateau region, rather than linear. The top, plateau part of the curve above 60 mm Hg is in the blood P_{O_2} range found in the pulmonary capillaries where O_2 is binding to hemoglobin. For this part of the curve, the blood remains highly saturated with O_2 over a relatively large range of P_{O_2}. Even at P_{O_2} levels much higher than shown on the graph (P_{O_2} theoretically can go up to 760 mm Hg), only a small extra amount of O_2 will bind to hemoglobin. The steep part of the curve between 0 and 60 mm Hg is in the blood P_{O_2} range found in the capillaries in the rest of the body. For this part of the curve, small changes in P_{O_2} result in a large change in the amount of O_2 bound to hemoglobin.

Because the partial pressure of O_2 in alveolar air is about 100 mg Hg, most of the hemoglobin molecules are fully saturated in the blood leaving the alveolar networks, meaning that most of the hemoglobin molecules are bound to four O_2 molecules (see Figure 44.12a). The P_{O_2} of the O_2 in solution in the blood plasma has risen to approximately the same level as in the alveolar air, about 100 mm Hg. The blood has also changed color, reflecting the bright red color of oxygenated hemoglobin as compared with the darker red color of deoxygenated hemoglobin.

The oxygenated blood exiting from the alveoli collects in venules, which merge into the pulmonary veins leaving the lungs. These veins carry the blood to the heart, which pumps the blood through the systemic circulation to all parts of the body.

As the oxygenated blood enters the capillary networks of body tissues, it encounters regions in which the P_{O_2} in the interstitial fluid and body cells is lower than that in the blood, ranging from about 40 mm Hg downward to 20 mm Hg or less (see Figure 44.12b). As a result, O_2 diffuses from the blood plasma into the interstitial fluid, and from the fluid into body cells. As O_2 diffuses from the blood plasma into body tissues, it is replaced by O_2 released from hemoglobin.

Several factors contribute to the release of O_2 from hemoglobin, including increased acidity (lower pH) in active tissues. The acidity increases because oxidative reactions release CO_2, which combines with water to form carbonic acid (H_2CO_3). The lowered pH alters hemoglobin's conformation, reducing its affinity for O_2, which is released and used in cellular respiration.

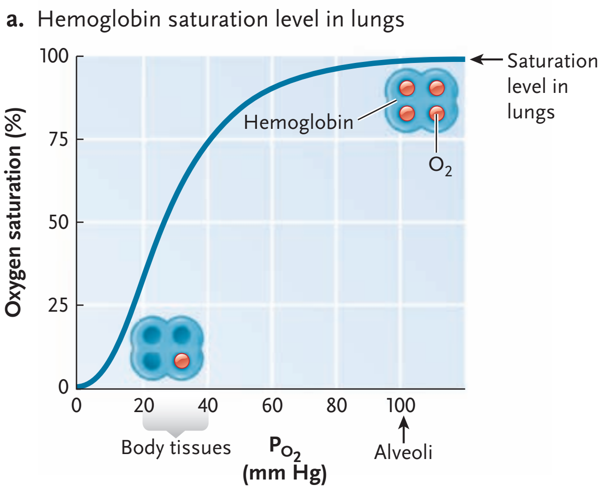
The net diffusion of O_2 from blood to body cells continues until, by the time the blood leaves the capillary networks in the body tissues, much of the O_2 has been removed from hemoglobin. The blood, now with a P_{O_2} of 40 mm Hg or less, returns in veins to the heart, which pumps it through the pulmonary arteries to the lungs for another cycle of oxygenation.

Carbon Dioxide Diffuses down Concentration Gradients from Body Tissues into the Blood and Alveolar Air

The CO_2 produced by cellular oxidations diffuses from active cells into the interstitial fluid, where it reaches a partial pressure of about 46 mm Hg. Because this P_{CO_2} is higher than the 40 mm Hg P_{CO_2} in the blood entering the capillary networks of body tissues (see Figure 44.10), CO_2 diffuses from the interstitial fluid into the blood plasma **(Figure 44.13a).**

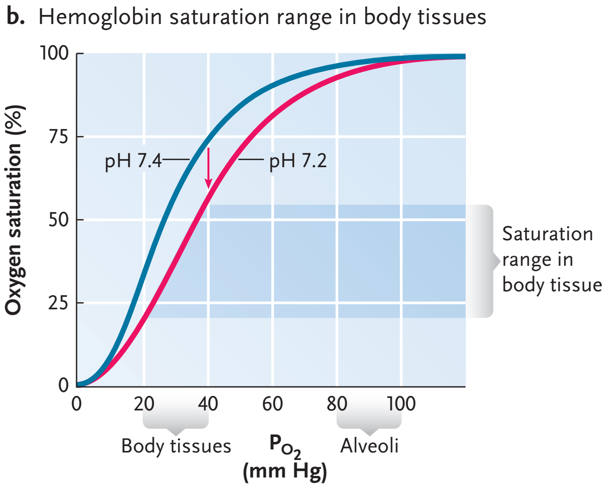
Some of the CO_2 remains in solution as a gas in the plasma. However, most of the CO_2, about 70%, combines with water to produce carbonic acid (H_2CO_3), which dissociates into bicarbonate (HCO_3^-) and H^+ ions. The reaction takes place both in the blood plasma and inside erythrocytes, where an enzyme, *carbonic anhydrase,* greatly speeds the reaction.

Most of the H^+ ions produced by the dissociation of carbonic acid combine with hemoglobin or with proteins in the plasma. The combination, by removing excess H^+ from the blood solution, *buffers* the



a. Hemoglobin saturation level in lungs

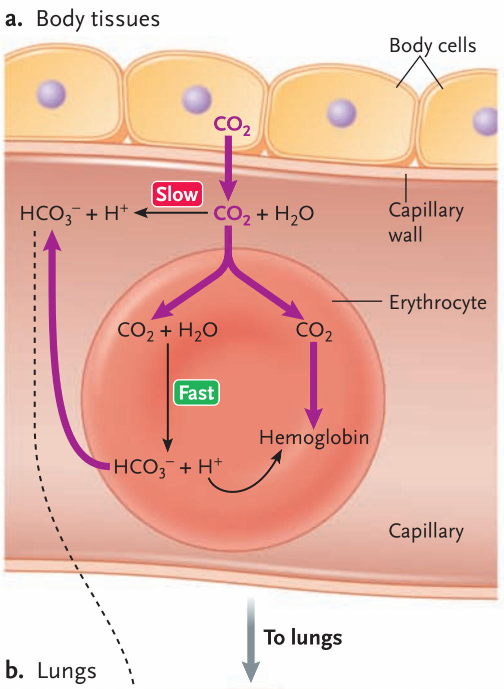
In the alveoli, in which the P_{O_2} is about 100 mm Hg and the pH is 7.4, most hemoglobin molecules are 100% saturated, meaning that almost all have bound four O_2 molecules.



b. Hemoglobin saturation range in body tissues

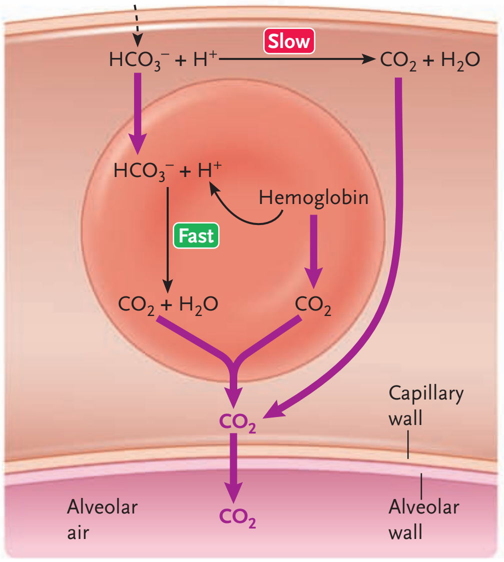
In the capillaries of body tissues, where the P_{O_2} varies between about 20 and 40 mm Hg depending on the level of metabolic activity and the pH is about 7.2, hemoglobin can hold less O_2. As a result, most hemoglobin molecules release two or three of their O_2 molecules to become between 25% and 50% saturated. Note that the drop in pH to 7.2 (red line) in active body tissues reduces the amount of O_2 hemoglobin can hold as a compared with pH 7.4. The reduction in binding affinity at lower pH increases the amount of O_2 released in active tissues.

Figure 44.12
Hemoglobin–O_2 dissociation curves, which show the degree to which hemoglobin is saturated with O_2 at increasing P_{O_2}.



a. Body tissues

In body tissues, some of the CO_2 released into the blood combines with water in the blood plasma to form HCO_3^- and H^+. However, most of the CO_2 diffuses into erythrocytes, where some combines directly with hemoglobin and some combines with water to form HCO_3^- and H^+. The H^+ formed by this reaction combines with hemoglobin; the HCO_3^- is transported out of erythrocytes to add to the HCO_3^- in the blood plasma.



b. Lungs

In the lungs, the reactions are reversed. Some of the HCO_3^- in the blood plasma combines with H^+ to form CO_2 and water. However, most of the HCO_3^- is transported into erythrocytes, where it combines with H^+ released from hemoglobin to form CO_2 and water. CO_2 is released from hemoglobin. The CO_2 diffuses from the erythrocytes and, with the CO_2 in the blood plasma, diffuses from the blood into the alveolar air.

Figure 44.13
The reactions occurring during the transfer of CO_2 from body tissues to alveolar air.

blood pH, helping to maintain it at its near-neutral set point of 7.4. (Buffers are discussed in Section 2.5.) The combined pathways absorbing CO_2 in the blood—solution in the plasma, conversion to bicarbonate, and combination with hemoglobin—help maintain the concentration gradient for gaseous CO_2 and keep its diffusion from the interstitial fluid into the blood at optimal levels.

The blood leaving the capillary networks of body tissues is collected in venules and veins and returned to the heart, which pumps it through the pulmonary arteries into the lungs. As the blood enters the capillary networks surrounding the alveoli, the entire process of CO_2 uptake is reversed **(Figure 44.13b).** The P_{CO_2} in the blood, now about 46 mm Hg, is higher than the P_{CO_2} in the alveolar air, about 40 mm Hg (see Figure 44.10). As a result, CO_2 diffuses from the blood into the air. The diminishing CO_2 concentrations in the plasma, along with the lower pH encountered in the lungs, promote the release of CO_2 from hemoglobin. As CO_2 diffuses away, bicarbonate ions in the blood combine with H^+ ions, forming carbonic acid molecules that break down into water and additional CO_2. This CO_2 adds to the quantities diffusing from the blood into the alveolar air. By the time the blood leaves the capillary networks in the lungs, its P_{CO_2} has been reduced to the same level as that of the alveolar air, about 40 mm Hg (see Figure 44.10).

INSIGHTS FROM THE MOLECULAR REVOLUTION

Giving Hemoglobin and Myoglobin Air

Carbon monoxide, like O_2, combines directly with the heme group in the proteins myoglobin and hemoglobin. The heme group by itself, unassociated with the polypeptide chain of hemoglobin or myoglobin, has an affinity for CO some 10,000 times greater than for O_2. Combination of the heme group with the proteins reduces its affinity for CO to only 250 times greater than O_2 for hemoglobin and 30 times greater for myoglobin.

How does combination with the proteins reduce the affinity of the heme group for CO so effectively? One hypothesis is that the reduction depends on a stabilizing hydrogen bond between O_2 and an amino acid, histidine, located in a protein pocket formed by a fold in the amino acid chain near the iron atom of the heme group. According to this proposal, the hydrogen bond allows O_2 to displace a water molecule that occupies the pocket when neither O_2 nor CO is bound. Because carbon monoxide cannot form this hydrogen bond, it displaces the water molecule less readily than O_2 does.

Research with myoglobin, conducted by John S. Olson and George Phillips and their colleagues at Rice University, supports the hydrogen-bond hypothesis. For their study, the team used a myoglobin gene isolated from a sperm whale. They chemically altered the DNA of the myoglobin gene so that one of seven other amino acids was substituted for the histidine in the pocket. A highly active bacterial promoter was added to the altered genes, which were then introduced one at a time into *Escherichia coli* bacteria. The bacteria expressed the genes, producing the altered myoglobin molecules in quantity, thereby providing the researchers with seven different forms of myoglobin to test for binding affinity for O_2.

The seven amino acids substituted for the histidine—glycine, alanine, leucine, phenylalanine, threonine, valine, and glutamine—are all nonpolar, or uncharged (histidine is positively charged), and thus unlikely to form a hydrogen bond with O_2. Further, none of these amino acids except glycine and glutamine should be able to hold a water molecule stably in the binding pocket. If the hydrogen-bond hypothesis is correct, the affinity of O_2 for the altered myoglobin should be greatly reduced in the mutant forms of the molecule.

Binding tests showed that the substitutions indeed reduced the affinity for O_2 by a factor that varied between 10 and 100 times. The greatest reduction was produced by the most nonpolar of the amino acids, leucine and phenylalanine. The smallest reduction was observed for glycine and glutamine. Thus the results strongly support the hydrogen-bond hypothesis.

Carbon monoxide (CO), a colorless, odorless gas produced when fuels are incompletely burned, as in automobile exhaust and in faulty furnaces, gas appliances, or space heaters, also binds to hemoglobin if it is inhaled into the lungs. It binds so strongly that it displaces O_2 from hemoglobin and drastically reduces the amount of O_2 carried to body tissues. If CO is inhaled in high quantity for even a few minutes, the reduction in oxygen delivered to the brain can lead to unconsciousness and brain damage. Sustained exposure leads to death by hypoxia (lack of oxygen). Because the brain regulates breathing based on CO_2 levels in blood rather than on O_2 levels, victims breathing CO can die from hypoxia without noticing anything amiss up to the point of unconsciousness. Interestingly, the combination of CO with hemoglobin, carboxyhemoglobin, is bright red. This has led to a myth often seen in textbooks that victims of CO poisoning turn a “classic cherry red” in color. However, this actually occurs in less than 2% of cases. *Insights from the Molecular Revolution* describes recent research testing the molecular basis for the binding of CO to hemoglobin and to *myoglobin,* a muscle protein with structure and properties similar to hemoglobin (myoglobin is discussed in Section 41.1).

STUDY BREAK

1. Explain the role of hemoglobin in gas exchange.
2. Why is carbon monoxide potentially lethal?

44.5 Respiration at High Altitudes and in Ocean Depths

This chapter’s introduction described some challenges to respiration that arise when humans travel to high altitude. In this concluding section we look more closely at the effects of high altitude on respiration, along with the effects of increased pressures when humans and other mammals dive under water.

High Altitudes Reduce the P_{O_2} of Air Entering the Lungs

As altitude increases, atmospheric pressure decreases, and with it, the P_{O_2} of alveolar air and the concentration gradient of O_2 across the respiratory surface. At 20,000 feet, where most people become unconscious unless they have supplemental O_2, the dry air pressure is about 380 mm Hg and the P_{O_2} is only $380 \times 21/100 =$ about 80 mm Hg, half that at sea level.

Humans who travel from sea level to elevations of 6000 feet or more often experience one or more unpleasant symptoms, including headache, blurred vision, dizziness, nausea, and fatigue. However, after a few weeks at higher elevation, the body adjusts by increasing the number of erythrocytes in the blood. The increase in erythrocyte production is stimulated primarily by a hormone, *erythropoietin* (EPO), which the kidneys secrete in greater quantities in response to a drop in blood O_2. Erythrocyte production slows when people return to lower altitudes. However, the erythrocyte count remains high for several weeks after high-altitude exposure. Athletes often train at high altitudes to increase their erythrocyte count, with the idea that it will improve their stamina and endurance at lower altitudes.

People who live at high altitudes from childhood develop more permanent changes, including an increase in the number of alveoli and more extensive capillary networks in the lungs. These developments are retained if they move to lower altitudes.

Some mammals evolutionarily adapted to high altitudes show genetically determined changes that are present throughout life. For example, llamas, which customarily live at altitudes as high as 4500 m (14,000 feet), have hemoglobin molecules with greater affinity for O_2 than does the hemoglobin of sea level-dwelling mammals. As a result, hemoglobin becomes saturated with O_2 at the lower partial pressures typical of high altitudes. The same adaptation occurs in birds adapted to life at high altitudes, such as the bar-headed goose (*Anser indicus*). These birds have been observed flying over the peaks of the Great Himalayas, which have altitudes greater than 6000 m.

Diving Mammals Are Adapted to Survive the High Partial Pressures of Gases at Extreme Depths

As a mammal such as a seal or whale dives from the surface, each additional 10 m of depth increases the partial pressure of dissolved gases by about 1 atmo-

UNANSWERED QUESTIONS

Does prenatal nicotine exposure alter development of respiratory neurons in the brainstem?

In this chapter you learned that the muscles of breathing are controlled in the brainstem, by groups of interneurons in the medulla oblongata and pons. The control of respiratory muscles (and thus breathing) by these neurons is called "central ventilatory control." Neonatal mammals that were exposed to nicotine in utero show various breathing abnormalities, such as reduced ventilatory output, increased frequency and duration of apneas (suspension of breathing), and delayed arousal in response to hypoxia (reduced blood oxygen levels) during sleep. One or several of these abnormalities may underlie sudden infant death syndrome (SIDS), also called "crib death" because victims are typically found dead in their crib. Clinical studies have shown that exposure to tobacco smoke is the number one risk factor for SIDS. Accordingly, laboratories, such as our own, are using animal models to examine how nicotine exposure alters development of central ventilatory control.

Several research methods can be used, depending on the particular question being addressed. In all of our experiments, neonatal rodents are exposed to nicotine in utero by implanting a small osmotic pump under the skin of a female rat that is 4 days pregnant. The pump releases nicotine at a prescribed rate, and the developing neonates are exposed as the nicotine passes from mother to neonate via the placenta. When the neonates are born (on the 21st day of pregnancy), we study their breathing responses while they are awake or asleep using a device called a plethysmograph. This device senses the tiny pressure changes that accompany breathing in these small animals, and by adjusting chamber size, animals can be studied from birth to adulthood.

We can also dissect the brainstem, spinal cord, and rib cage from a neonatal animal, and place the preparation in a chamber for in vitro studies. Remarkably, this preparation is able to maintain rhythmic firing of respiratory neurons for up to 6 hours, allowing us to apply drugs and neurotransmitters to brainstem respiratory neurons while recording the electrical activity of neurons and respiratory muscle nerves.

Finally, we can prepare a brainstem slice, containing the most important central respiratory neurons and the hypoglossal nerve (this nerve innervates the tongue muscles, and it contains axons with rhythmic, respiratory-related activity), for detailed electrophysiological studies using the patch clamp technique (see Section 37.2). This preparation allows us to examine how prenatal nicotine exposure influences the membrane potential and firing properties of respiratory neurons.

To date, our studies have demonstrated abnormal breathing in awake neonates, as well as an increase in inhibitory neurotransmission in respiratory neurons. Current and future studies are directed at understanding the detailed cellular mechanisms that lead to the increase in inhibitory neurotransmission caused by prenatal nicotine exposure. Understanding how this occurs will hopefully lead to the development of drugs that can counteract nicotine's impact on the brain, as well as to an increased awareness and acceptance of the link between prenatal nicotine exposure and breathing abnormalities, resulting in more aggressive prevention strategies.

Ralph Fregosi is professor of physiology and neurobiology at the University of Arizona at Tucson. He does research on the neural control of breathing and teaches physiology to undergraduate and graduate students. Learn more about his research at http://www.physiology.arizona.edu/labs/rnlab/.

sphere. Below about 25 m or so, the pressure becomes so great that the lungs collapse and cease to function. Adaptations of diving mammals such as seals and whales allow these animals to survive the extreme pressure and lack of lung function, in some species for over an hour at ocean depths of more than a mile.

Among these adaptations are more blood per unit of body weight and more red blood cells, which are stored in the spleen and released during a dive. In addition, the muscles of these animals contain much greater quantities of the O_2-binding protein myoglobin than the muscles of land-dwelling mammals do. In all, the adaptations pack about twice as much O_2 per kilogram of body weight into a seal, for example, than into a human.

Other adaptations decrease O_2 consumption during a deep and prolonged dive. The heart rate slows by about 80% to 90% and the circulation of blood to internal organs and muscles is cut by as much as 95%, leaving only the brain with its normal blood supply. Even though most of the blood supply to muscles is cut off, the muscles continue to work by shifting to anaerobic oxidation. The lactic acid produced by anaerobic respiration in the muscles is not released into the blood until the animal returns to the surface.

These combined adaptations give seals and whales an amazing ability to dive to great depths and remain under water for extended periods. Although average dives are on the order of 10 to 20 minutes, some sperm whales, tracked by sonar, have reached depths of 2250 m (more than 7000 feet) and remained under water for as long as 82 minutes.

STUDY BREAK

List the key adaptations that diving mammals use to survive at significant ocean depths.

Review

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44.1 The Function of Gas Exchange

- Physiological respiration is the process by which animals exchange O_2 and CO_2 with the environment (Figure 44.1).
- The two primary operating features of gas exchange are the respiratory medium, either air or water, and the respiratory surface, a wetted epithelium over which gas exchange takes place.
- In some invertebrates, the skin serves as the respiratory surface. In other invertebrates and all vertebrates, gills or lungs provide the primary respiratory surface (Figure 44.2).
- Simple diffusion of molecules from regions of higher concentration to regions of lower concentration drives the exchange of gases across the respiratory surface. The area of the respiratory surface determines the total quantity of gases exchanged by diffusion.
- The concentration gradients of O_2 and CO_2 across the respiratory surface are kept at optimal levels by ventilation and perfusion.

Animation: Examples of respiratory surfaces

44.2 Adaptations for Respiration

- Animals breathing water keep the respiratory surface wetted by direct exposure to the environment. The high density and viscosity of water, and its relatively low O_2 content as compared with air, requires water-breathing animals to expend significant energy to keep their respiratory surface ventilated.
- Air is high in O_2 content, allowing air-breathing animals to maintain higher metabolic levels than water breathers. The low density and viscosity of air as compared with water allows air breathers to ventilate the respiratory surface with relatively little energy. To accommodate water loss by evaporation, lungs typically are invaginations of the body surface, allowing air to become saturated with water before it reaches the respiratory surface.
- Gills are evaginations of the body surface. Water moves over the gills by the beating of cilia or is pumped over the gills by contractions of body muscles (Figures 44.2b and 44.3a–d).
- Water moves in a one-way direction over the gills of sharks, bony fishes, and some crabs, allowing these animals to use countercurrent exchange to maximize the exchange of gases over the respiratory surface (Figure 44.4).
- Insects breathe by means of tracheae, air-conducting tubes that lead from the body surface and send branches to essentially every cell in the body. Gas exchange takes place in the fluid-filled tips at the ends of the branches (Figure 44.5).
- Lungs consist of an invaginated system of branches, folds, and pockets. They may be filled by positive pressure breathing, in which air is forced into the lungs by muscle contractions, or by negative pressure breathing, in which muscle contractions expand the lungs, lowering the air pressure inside them and allowing air to be pulled into the lungs (Figures 44.6 and 44.9).

Animation: Bony fish respiration

Animation: Frog respiration

Animation: Vertebrate lungs

Animation: Bird respiration

44.3 The Mammalian Respiratory System

- Air enters the respiratory system through the nose and mouth and passes through the pharynx, larynx, and trachea. The trachea divides into two bronchi, which lead to the lungs. Within the lungs, the bronchi branch into bronchioles, which lead into the alveoli, which are surrounded by dense networks of blood capillaries (Figure 44.8).
- Mammals inhale by a negative pressure mechanism. Air is exhaled passively by relaxation of the diaphragm and the external intercostal muscles between the ribs, and elastic recoil of the lungs. During deep and rapid breathing, the expulsion of air is

forceful, driven by contraction of the internal intercostal muscles (Figure 44.9).

- The tidal volume of the lungs is the air moved in and out of the lungs during an inhalation and exhalation. The vital capacity is the total volume of air a person can inhale and exhale by breathing as deeply as possible. The air remaining in the lungs after as much air as possible is exhaled is the residual volume of the lungs.
- Breathing is controlled by a combination of local chemical controls and regulation by centers in the brain stem. These controls match the rate of air and blood flow in the lungs, and link the rate and depth of breathing to the body's requirements for O_2 uptake and CO_2 release (Figure 44.10).
- The basic rhythm of breathing is produced by interneurons in the medulla. When more rapid breathing is required, another group of interneurons in the medulla sends signals reinforcing inhalation and producing forceful exhalation. Two interneuron groups in the pons smooth and fine-tune breathing by stimulating or inhibiting the inhalation center in the medulla.
- Sensory receptors in the medulla, the carotid bodies, and the aortic bodies detect changes in the levels of O_2 and CO_2 in the blood and body fluids. The control centers in the medulla and pons adjust the rate and depth of breathing to compensate for changes in the blood gases.

Animation: Human respiratory system

Animation: Structure of an alveolus

Animation: Respiratory cycle

Animation: Changes in lung volume and pressure

Animation: Partial pressure gradients

Animation: Pressure-gradient changes during respiration

44.4 Mechanisms of Gas Exchange and Transport

- The partial pressure of O_2 is higher in the alveolar air than in the blood in the capillary networks surrounding the alveoli causing O_2 to diffuse from the alveolar air into the blood. Most of the O_2 entering the blood combines with hemoglobin inside erythrocytes (Figure 44.11).
- A hemoglobin molecule can combine with four O_2 molecules. The large quantities of O_2 that combine with hemoglobin maintain a large gradient in partial pressure between O_2 in the alveolar air and in the blood (Figure 44.12).
- In body tissues outside the lungs, the O_2 concentration in the interstitial fluid and body cells is lower than in the blood plasma. As a result, O_2 diffuses from the blood into the interstitial fluid, and from the fluid into body cells.
- The partial pressure of CO_2 is higher in the tissues than in the blood. About 10% of this CO_2 dissolves in the blood plasma; 70% is converted into H^+ and HCO_3^- (bicarbonate) ions. The remaining 20% combines with hemoglobin (Figures 44.11 and 44.13a).
- In the lungs, the partial pressure of CO_2 is higher in the blood than in the alveolar air. As a result, the reactions packing CO_2 into the blood are reversed, and the CO_2 is released from the blood into the alveolar air (Figure 44.13b).

Animation: Globin and hemoglobin structure

44.5 Respiration at High Altitudes and in Ocean Depths

- In mammals that move to high altitudes, the number of red blood cells and the amount of hemoglobin per cell increase. These changes are reversed if the animals return to lower altitudes.
- Humans living at higher altitudes from birth develop more alveoli and capillary networks in the lungs.
- Some mammals and birds adapted to high altitudes have forms of hemoglobin with greater affinity for O_2, allowing saturation at the lower P_{O_2} typical of high altitudes.
- Marine mammals adapted to deep diving have a greater blood volume per unit of body weight, and their blood contains more red blood cells, with a higher hemoglobin content, than other mammals. Their muscles also contain more myoglobin than those of land mammals, allowing more O_2 to be stored in muscle tissues. During a dive, the heartbeat slows, and circulation is reduced to all parts of the body except the brain.

Questions

Self-Test Questions

1. Which of the following describes a respiratory medium?
   a. In the liver the rate of diffusion is high.
   b. In the brain CO_2 moves from the neurons to the blood.
   c. In the big toe O_2 moves from blood to tissues.
   d. Epithelial cells form thin surfaces in the lungs.
   e. A running brook provides O_2 to fish.
2. Which of the following describes a respiratory surface?
   a. a surface consisting of multiple layers of epithelial cells
   b. the exoskeleton of an insect
   c. the nasal passages of a mammal
   d. a thin surface consisting of a single layer of epithelial cells
   e. the outer membrane of a mitochondrion.
3. At the end of a basketball game, the opposing teams line up and file past each other and shake hands. This efficient exposure of the teams to each other is analogous to:
   a. countercurrent exchange of gases in fish gills and bird lungs.
   b. diffusion of O_2 from blood to cells in shark tissues.
   c. diffusion of CO_2 from cells to blood in crabs.
   d. utilization of O_2 in cells in insects.
   e. excretion of CO_2 from mammalian cells.
4. Tracheal systems are characterized by:
   a. closed circulatory tubes that move gases.
   b. spiracles that move gases between cells and body fluids.
   c. body movements that compress and expand air sacs to pump air.
   d. positive pressure breathing, which swallows air into the body.
   e. negative pressure breathing, which lowers air pressure at the respiratory surfaces.
5. The structures at which one third of O_2 in the atmosphere moves into the blood of humans are:
   a. alveoli.
   b. bronchi.
   c. bronchioles.
   d. tracheae.
   e. pharynges.
6. A speed skater is finishing his last lap. At this time:
   a. the diaphragm and rib muscles contract when he exhales.
   b. positive pressure brings air into his lungs.
   c. his lungs undergo an elastic recoil when he inhales.

d. his tidal volume is at vital capacity.
e. his residual volume momentarily reaches zero.

7. A teenager is frightened when she is about to step onto the stage but then remembers to breathe deeply and slowly as she faces the audience. What is occurring here?
   a. Interneurons in the medulla cause the rib muscles to relax, followed later by stimulation and contraction of the intercostal muscles.
   b. Signals from the pons override the initial brain stem stimuli.
   c. The limbic system stabilized her emotional state, so there is no change in the mechanical movement of air.
   d. The brain signals the aortic bodies in the carotid arteries to adjust the breathing rate.
   e. Initial low CO_2 blood levels causing high pH are followed by increased CO_2 levels that lower pH.
8. Oxygen enters the blood in the lungs because relative to alveolar air:
   a. the CO_2 concentration in the blood is high.
   b. the CO_2 concentration in the blood is low.
   c. the O_2 concentration in the blood is high.
   d. the O_2 concentration in the blood is low.
   e. the process is independent of gas concentrations in the blood.
9. The hemoglobin O_2 dissociation curve:
   a. reflects about 50% saturation of hemoglobin in the alveoli.
   b. shifts to the left when pH rises.
   c. demonstrates that hemoglobin holds less O_2 when the pH is higher.
   d. proves lack of dependence on CO_2 levels.
   e. explains how hemoglobin can bind O_2 at high pH in the lungs and release it at lower pH in the tissues.
10. The majority of CO_2 in the blood:
   a. is in the form of carbonic acid and bicarbonate ions
   b. dissociates to add H^+ to the blood to raise its pH to 7.4.
   c. has a lower P_{CO_2} than the P_{CO_2} in the alveolar air.
   d. increases in the lung capillaries, which have a higher pH than the tissue capillaries.
   e. can be displaced on the hemoglobin molecule by CO if CO is inhaled.

Questions for Discussion

1. Smoking has traditionally been considered to reduce the ability of athletes to run without becoming exhausted. Why might this be true?
2. People are occasionally found unconscious from breathing too much CO_2 (as from a charcoal heater placed indoors) or too much CO (as from auto exhaust in a closed garage). Would it be more advantageous to give pure O_2 to a person breathing too much CO_2 than simply moving the person to fresh air? Why? Which—pure O_2 or fresh air—would be best for a person unconscious from breathing CO? Why?
3. Hyperventilation, or overbreathing, is breathing faster or deeper than necessary to meet the body's needs. Hyperventilation reduces the CO_2 content of blood, but does not significantly increase the amount of O_2 available to tissues. Why might this be so?

Experimental Analysis

Propose a hypothesis for the effect of zero gravity on respiration, and design an experiment to test the hypothesis.

Evolution Link

From what you have learned in this chapter and in Chapter 30, do you think lungs evolved once, or on several occasions? Justify your answer.

How Would You Vote?

Tobacco is a worldwide threat to health and a profitable product for American companies. As tobacco use by its citizens declines, should the United States encourage international efforts to reduce tobacco use around the globe? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.