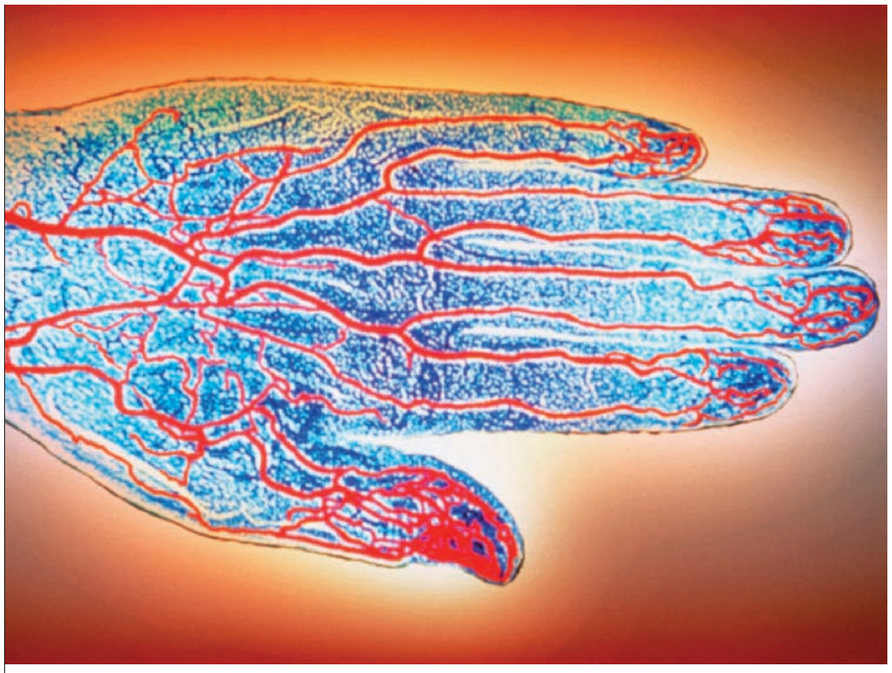


GJLP/CNRI/SPL/Photo Researchers, Inc.

Arteries of the human hand (colorized X-ray). Arteries are vessels of the circulatory system that transport molecules, such as oxygen, nutrients, hormones, and wastes, as well as certain cells, from one tissue to another.

## Study Plan



# 42 The Circulatory System

## Why It Matters

Jimmie the bulldog stood on the stage of a demonstration laboratory at a meeting of the Royal Society in London in 1909, with one front paw and one rear paw in laboratory jars containing salt water **(Figure 42.1).** Wires leading from the jars were connected to a galvanometer, a device that can detect electrical currents. Jimmie's master, Dr. Augustus Waller, a physician at St. Mary's Hospital, was relating his experiments in the emerging field of *electrophysiology*. Among other discoveries, Waller had found that his apparatus detected the electrical currents produced each time the dog's heart beat.

Waller originally made his finding by experimenting on himself. He already knew that the heart creates an electrical current as it beats; other scientists had found this out by attaching electrodes directly to the heart of experimental animals. Looking for a painless alternative to that procedure, Waller reasoned that because the human body can conduct electricity, his arms and legs might conduct the currents generated by the heart if they were connected to a galvanometer. Accordingly, Waller set up two metal pans containing salt water and connected wires from the pans to a galvanometer. He put his bare left foot in one of the pans, and his right hand in the other one. The tech-

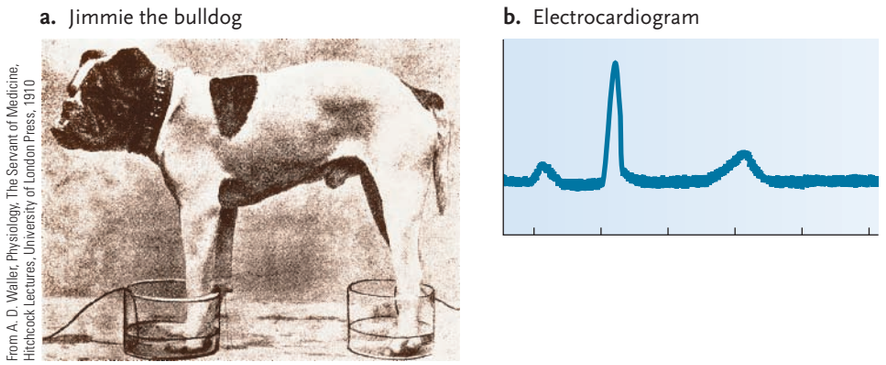



**Figure 42.1**
The first electrocardiograms. **(a)** Jimmie the bulldog standing in laboratory jars containing salt water, with wires leading to a galvanometer that recorded the electrical currents produced by his heartbeat. **(b)** One of Waller's early electrocardiograms.

nique worked; the indicator of the galvanometer jumped each time his heart beat. And, it worked with Jimmie.

Waller also invented a method for recording the changes in current, which became the first electrocardiogram (ECG). He constructed a galvanometer by placing a column of mercury in a fine glass tube, with a conducting salt solution layered above the mercury. Changes in the current passing through the tube caused corresponding changes in the surface tension of the mercury, which produced movements that could be detected by reflecting a beam of light from the mercury surface. By placing a moving photographic plate behind the mercury tube, Waller could record the movements of the reflected light on the plate (Figure 42.1b shows one of his records).

The beating of Jimmie's heart, recorded as an electrical trace by Augustus Waller, is part of the actions of the **circulatory system**, an organ system consisting of a fluid, a heart, and vessels for moving important molecules, and often cells, from one tissue to another. Examples of transported molecules are oxygen ($O_2$), nutrients, hormones, and wastes.

We study these systems in this chapter, with emphasis on the circulatory system of humans and other mammals. We also discuss the **lymphatic system**, an accessory system of vessels and organs that helps balance the fluid content of the blood and surrounding tissues and participates in the body's defenses against invading disease organisms.

## 42.1 Animal Circulatory Systems: An Introduction

The least complex animals, including sponges, cnidarians, and flatworms, function with no circulatory system. All of these animals are aquatic or, like parasitic flatworms, live surrounded by the body fluids of a host animal. Their bodies are structured as thin sheets of cells that lie close to the fluids of the surrounding environment. Substances diffuse between the cells and the environment through the animal's external surface, or through the surfaces of internal channels and cavities that are open to the environment.

In sponges and cnidarians, flagella or cilia help to circulate the external fluid through the internal spaces. As the water passes over the cells, they pick up $O_2$ and nutrients, and release wastes and $CO_2$.

In the sponges, water carrying nutrients and $O_2$ enters through pores in body walls surrounding a central cavity, passes through the cavity, and leaves through a large exit pore **(Figure 42.2a).** Hydras, jellyfish, sea anemones, and other cnidarians have a central *gastrovascular cavity* with a mouth that opens to the outside and extensions that radiate into the tentacles and all other body regions **(Figure 42.2b).** Water enters and leaves through the mouth, serving both digestion and circulation.

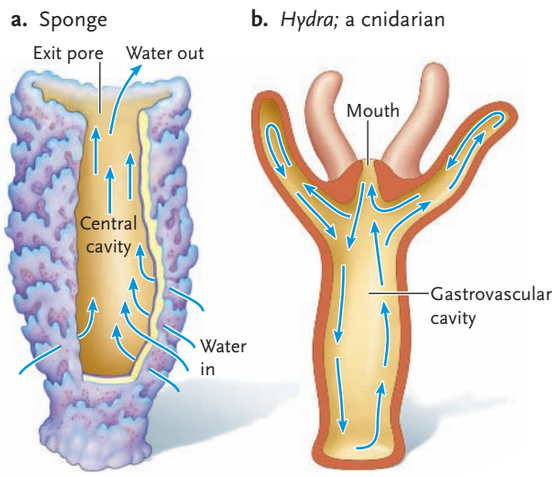



**Figure 42.2**
Invertebrates with no circulatory system.

## Animal Circulatory Systems Share Basic Elements

In larger and more complex animals, most cells lie in cell layers too deep within the body to exchange substances directly with the environment via diffusion. Instead, the animals have a set of tissues and organs—a circulatory system—that conducts $O_2$, $CO_2$, nutrients, and wastes between body cells and specialized regions of the animal where substances are exchanged with the external environment. In terrestrial vertebrates, for example, oxygen from the environment is absorbed in the lungs and is carried by the blood to all parts of the body; $CO_2$ released from body cells is carried by the blood to the lungs, where it is released to the environment. Wastes are conducted from body cells to the kidneys, which remove wastes from the circulation and excrete them into the environment.

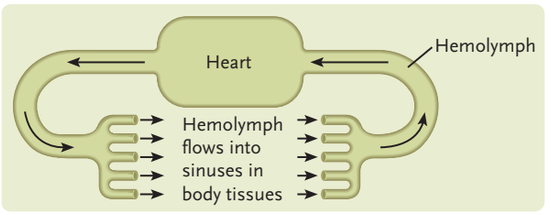
The animal circulatory systems carrying out these roles share certain basic features:

1. A specialized fluid medium, such as the blood of mammals and other vertebrates, that carries $O_2$, $CO_2$, nutrients, and wastes, and plays a major role in homeostasis (see Section 36.4).
2. A muscular heart that pumps the fluid through the circulatory system.
3. Tubular vessels that distribute the fluid pumped by the heart.

Words associated with the heart often include *cardi(o),* from *kardia,* the Greek word for heart.

Animal circulatory systems take one of two forms, either *open* or *closed* **(Figure 42.3).** In an **open circulatory system,** vessels leaving the heart release bloodlike fluid termed **hemolymph** directly into body spaces, called **sinuses,** that surround organs. Thus there is no distinction between hemolymph and *interstitial fluid,* the fluid immediately surrounding body cells. After flowing through the sinuses, the hemolymph reenters the heart through valves in the heart wall. In a **closed circulatory system,** the fluid—blood—is confined to blood vessels and is distinct from the interstitial fluid. Substances are exchanged between the blood and the interstitial fluid and then between the interstitial fluid and cells.

**a.** Open circulatory system: no distinction between hemolymph and interstitial fluid




**b.** Closed circulatory system: blood separated from interstitial fluid

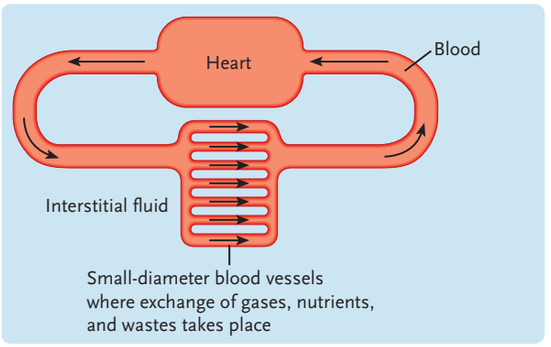



**Figure 42.3**
Open and closed circulatory systems.

## Most Invertebrates Have Open Circulatory Systems

Arthropods and most mollusks have open circulatory systems with one or more muscular hearts **(Figure 42.4).** In an open system, most of the fluid pressure generated by the heart dissipates when the hemolymph is released into the sinuses. As a result, hemolymph flows relatively slowly. Open systems operate efficiently in these animals because they lead relatively sedentary lives and, as a consequence, their tissues do not require $O_2$ and nutrients at the rate and quantities required by more active species. Among highly mobile and active species with open systems, such as insects and crustaceans, other adaptations compensate for the relatively slow distribution of hemolymph. In insects, for example, $O_2$ and $CO_2$ are exchanged efficiently with the environment by specialized air passages that branch throughout the body rather than by the hemolymph (these air passages, called *tracheae,* are discussed in Section 44.2).

## Some Invertebrates and All Vertebrates Have Closed Circulatory Systems

Annelids, cephalopod mollusks such as squids and octopuses, and all vertebrates have closed circulatory systems. In these systems, vessels called **arteries** conduct blood away from the heart at relatively high pressure. From the arteries, the blood enters highly branched networks of microscopic, thin-walled vessels called **capillaries** that are well adapted for diffusion of substances. Nutrients and wastes are exchanged between the blood and body tissues as the blood moves through the capillaries. The blood then flows at relatively low

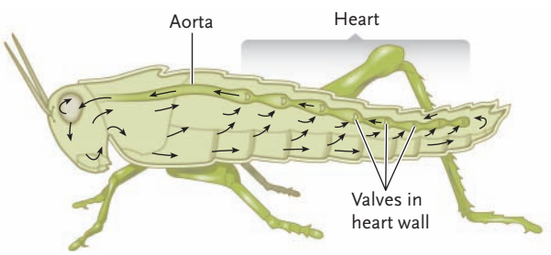



**Figure 42.4**
Open circulatory system of a grasshopper.

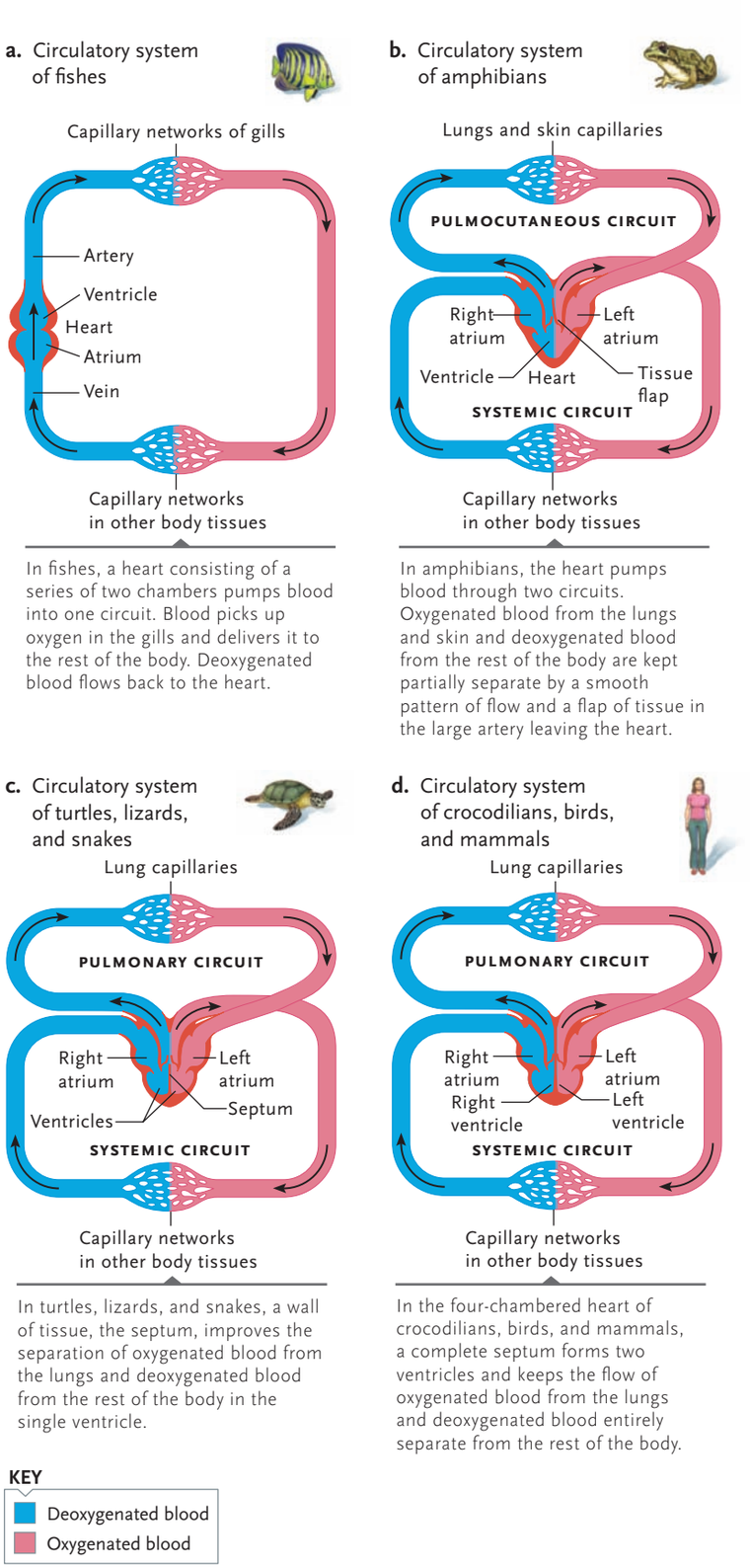



**Figure 42.5**
Evolutionary developments in the heart and circulatory system of major vertebrate groups.

pressure from the capillaries to larger vessels, the **veins**, which carry the blood back to the heart.

Typically, the blood is maintained at higher pressure and moves more rapidly through the body in closed systems than in open systems. Closed systems are highly efficient in the distribution of $O_2$ and nutrients and in the clearance of $CO_2$ and wastes.

In many animals, but particularly the vertebrates, closed systems allow precise control of the distribution and rate of blood flow to different body regions by means of muscles that contract or relax to adjust the diameter of the blood vessels.

## Vertebrate Circulatory Systems Have Evolved from Single to Double Blood Circuits

A comparison of the different vertebrate groups reveals several evolutionary trends that accompanied the invasion of terrestrial habitats. Among the most striking is a trend from an effectively single circuit of blood pumped by the heart in sharks and bony fishes to the two completely separate circuits of birds and mammals. As part of this development, the heart evolved from one series of chambers to a double pump acting in two parallel series. In other words, depending on the vertebrate, the heart may consist of one or two **atria** (singular, *atrium*), the chambers that receive blood returning to the heart, and one or two **ventricles**, the chambers that pump blood from the heart.

**The Single Blood Circuit of Fishes.** In fishes, the heart consists of two chambers arranged in a single line **(Figure 42.5a).** The ventricle of the heart pumps blood into arteries leading to capillary networks in the gills, where the blood releases $CO_2$ and picks up $O_2$. The oxygenated blood—now moving more slowly and at lower pressure after passing through the gill capillaries—flows through another series of arteries and is delivered to capillary networks in other body tissues where it delivers $O_2$ and picks up $CO_2$. The comparatively slow movement of the blood through this segment of the circulatory system is accelerated by the contractions of skeletal muscles as the animal swims. In some fishes, a vein in the tail is expanded and surrounded by a mass of skeletal muscle that contracts rhythmically, forming an accessory *caudal heart,* which pumps venous blood toward the anterior end of the body. Eventually, the deoxygenated blood enters veins that carry it back to the atrium of the heart, and the single circuit is repeated.

The circulatory system of fishes is highly suited to the environments in which these animals live. Their bodies, supported by water and adapted for swimming, do not use as much energy in locomotion as do animals of an equivalent size moving on the land or in the air. Hence, fishes require less $O_2$ for

their activities than terrestrial vertebrates do, and their relatively simple circulatory systems fully meet their $O_2$ requirements.

**Double Blood Circuits.** Vertebrate hearts changed significantly when the first air-breathing fishes such as the lungfish evolved. In these fishes, the lung evolved as a respiratory organ in addition to gills. The lung necessitated a separate circuit because it is an additional organ for oxygenating the blood and, unlike other organs, does not need to receive oxygenated blood from the gills.

In amphibians, the separation into two circuits was accomplished by division of the atrium into two parallel chambers, the left and right atria, to produce a three-chambered heart, and by adaptations that keep oxygenated and deoxygenated blood partially separate as they are pumped by the single ventricle **(Figure 42.5b).** Amphibians obtain $O_2$ from gas exchange across their moist skin as well as in their gills or lungs. Oxygenated blood from these organs enters veins that lead to the left atrium, while $O_2$-depleted blood from the rest of the body enters the right atrium. The atria contract simultaneously, pumping the oxygenated and deoxygenated blood into the single ventricle. The two types of blood remain mostly separated because they differ in density, although some mixing occurs. As the blood is pumped from the ventricle, most of the oxygenated blood enters the branch that leads to the **systemic circuit** of the body, which provides the blood supply for most of the tissues and cells of the body. The deoxygenated blood is directed into the other branch, which leads to the skin and lungs or gills, called the **pulmocutaneous circuit.** Because the blood flows through separate systemic and pulmocutaneous circuits in the amphibians, the blood leaving the heart flows through only one capillary network in each circuit before returning to the heart. This separation greatly increases the blood pressure and flow in the systemic circuit as compared with that of fishes.

Reptiles also have two atria and a single ventricle. The ventricle is divided into right and left halves by a flap of connective tissue called the *septum,* which keeps the flow of oxygenated and deoxygenated blood almost completely separate in a systemic circuit and a **pulmonary circuit,** a branch leading to the lungs **(Figure 42.5c).** The septum is incomplete in turtles, lizards, and snakes, allowing some mixing of oxygenated and deoxygenated blood. In crocodilians (crocodiles and alligators), the septum is complete **(Figure 42.5d).**

Birds (which share ancestry with crocodilians) and mammals have a double heart consisting of two atria and two ventricles (as in Figure 42.5d). In effect, each half of the heart operates as a separate pump, restricting the blood circulation to completely separate pulmonary and systemic circuits. Blood is pumped by a ventricle in each circuit, so that both operate at relatively high pressure.

### Study Break

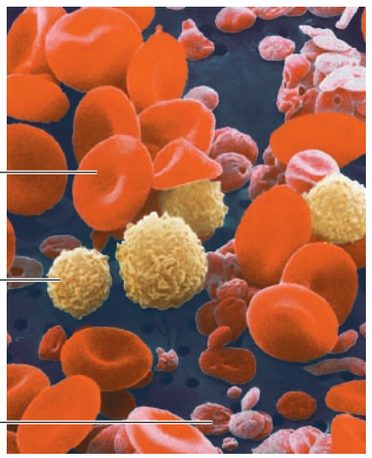
1. What are the three basic features of animal circulatory systems?
2. Distinguish between an open circulatory system and a closed circulatory system. Why do you think humans could not function with an open circulatory system?
3. Distinguish among atria, ventricles, arteries, and veins.
4. Distinguish among the systemic, pulmocutaneous, and pulmonary circuits.

## 42.2 Blood and Its Components

In vertebrates, blood is a complex connective tissue containing blood cells suspended in a liquid matrix called the *plasma.* In addition to transporting molecules, blood helps stabilize the internal pH and salt composition of body fluids, and serves as a highway for cells of the immune system and the antibodies produced by some of these cells. It also helps regulate body temperature by transferring heat between warmer and cooler body regions, and between the body and the external environment (the role of the blood in temperature regulation is discussed in Chapter 46).

For an average-sized adult human, the total blood volume is about 4 to 5 liters—more than a gallon—and makes up about 8% of body weight. The *plasma,* a clear, straw-colored fluid, makes up about 55% of the volume of blood in human males and 58% in human females on average. Suspended in the plasma are three main types of blood cells—*erythrocytes, leukocytes,* and *platelets*—which make up the remainder of the blood volume; on average about 45% and 42% for human males and females, respectively. The typical components of human blood are shown in **Figure 42.6.**

In humans, blood cells develop in red bone marrow primarily in the vertebrae, sternum (breastbone), ribs, and pelvis. Blood cells originate in a single type of cells called *pluripotent* (*plura* = multiple; *potens* = power) *stem cells,* which retain the embryonic capacity to divide **(Figure 42.7).** Pluripotent stem cells differentiate into two other types of stem cells, myeloid stem cells and lymphoid stem cells. The myeloid stem cells give rise to erythrocytes, platelets, and several types of leukocytes, namely neutrophils, basophils, eosinophils, and monocyte/macrophages. The lymphoid stem cells give rise to other types of leukocytes, namely the natural killer cells, T lymphocytes, and B lymphocytes.



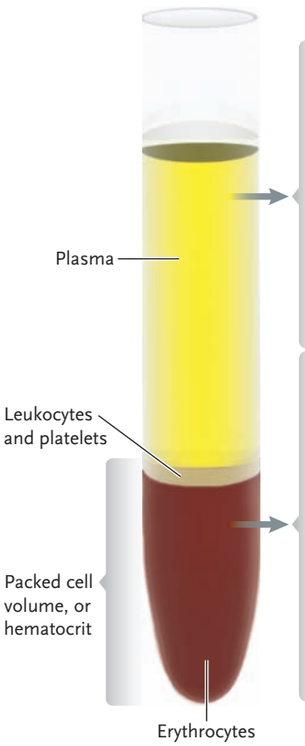




**Figure 42.6**
**Typical components of human blood.** The colorized scanning electron micrograph shows the three major cellular components. The sketch of the test tube shows what happens when you centrifuge a blood sample. The blood separates into three layers: a thick layer of straw-colored plasma on top, a thin layer containing leukocytes and platelets, and a thick layer of erythrocytes. The table shows the relative amounts and functions of the various components of blood.

| Components | Relative Amounts | Functions |
|---|---|---|
| **Plasma Portion (55%–58% of total volume):** | | |
| 1. Water | 91%–92% of plasma volume | Solvent |
| 2. Plasma proteins (albumin, globulins, fibrinogen, etc.) | 7%–8% | Defense, clotting, lipid transport, roles in extracellular fluid volume, etc. |
| 3. Ions, sugars, lipids, amino acids, hormones, vitamins, dissolved gases | 1%–2% | Roles in extracellular fluid volume, pH, etc. |
| **Cellular Portion (45%–42% of total volume):** | | |
| 1. Erythrocytes (red blood cells) | 4,800,000–5,400,000 per microliter | Oxygen, carbon dioxide transport |
| 2. Leukocytes (white blood cells) | | |
| Neutrophils | 3,000–6,750 | Phagocytosis during inflammation |
| Lymphocytes | 1,000–2,700 | Immune response |
| Monocytes/macrophages | 150–720 | Phagocytosis in all defense responses |
| Eosinophils | 100–360 | Defense against parasitic worms |
| Basophils | 25–90 | Secrete substances for inflammatory response and for fat removal from blood |
| 3. Platelets | 250,000–300,000 | Roles in clotting |

## Plasma Is an Aqueous Solution of Proteins, Ions, Nutrient Molecules, and Gases

**Plasma** is so complex that its complete composition is unknown. Among its known components are water (91%–92% of its volume), glucose and other sugars, amino acids, plasma proteins, dissolved gases (mostly $O_2$, $CO_2$, and nitrogen), ions, lipids, vitamins, hormones and other signal molecules, and metabolic wastes, including urea and uric acid.

The plasma proteins fall into three classes, the *albumins,* the *globulins,* and *fibrinogen*. The **albumins,** the most abundant proteins of the plasma, are important for osmotic balance and pH buffering. They also transport a wide variety of substances through the circulatory system, including hormones, therapeutic drugs, and metabolic wastes. The **globulins** transport lipids (including cholesterol) and fat-soluble vitamins; a specialized subgroup of globulins, the *immunoglobulins,* constitute antibodies and other molecules contributing to the immune response. Some globulins are also enzymes. **Fibrinogen** plays a central role in the mechanism clotting the blood.

The ions of the plasma include $Na^+$, $K^+$, $Ca^{2+}$, $Cl^-$, and $HCO_3^-$ (bicarbonate) ions. The $Na^+$ and $Cl^-$ ions—the components of common table salt—are the most abundant ions. Some of the ions, particularly the bicarbonate ion, help maintain arterial blood at its characteristic pH, which in humans is slightly on the basic side at pH 7.4 (the bicarbonate ion and its role in pH balance are discussed further in Chapter 44).

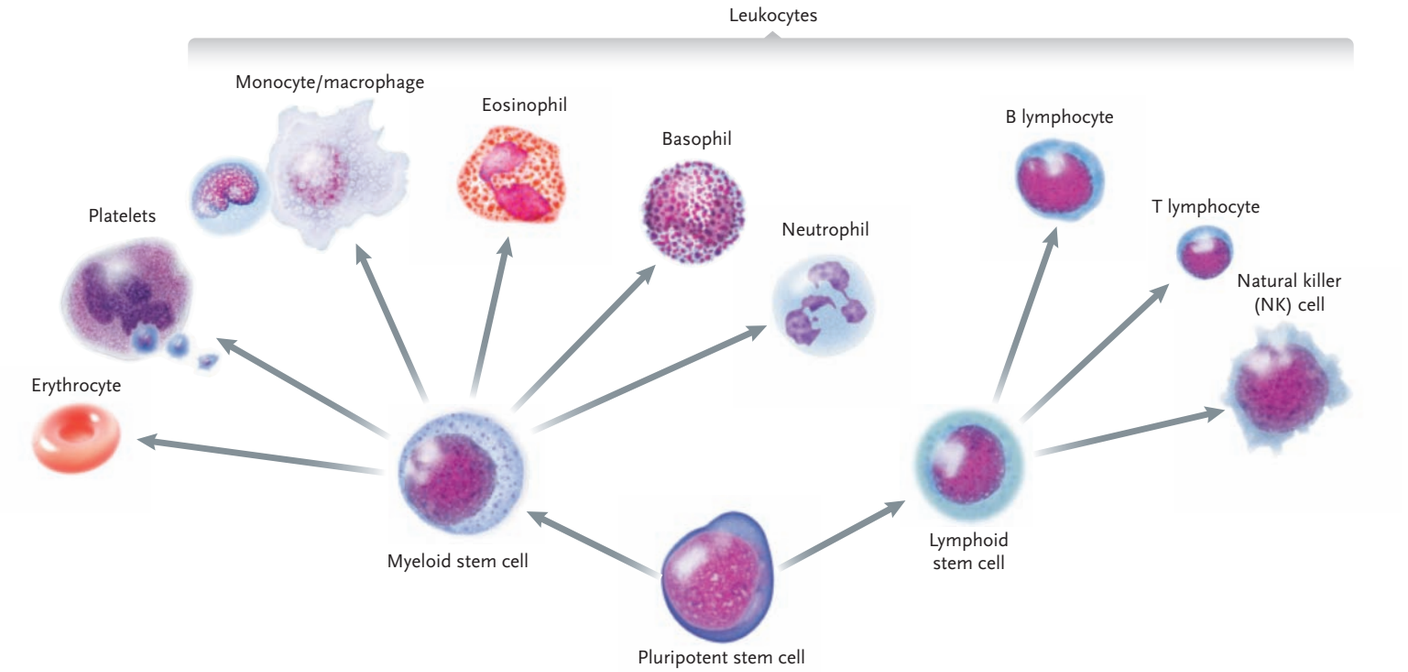



**Figure 42.7**
Major cellular components of mammalian blood and their origins from stem cells.

## Erythrocytes Are the Oxygen Carriers of the Blood

**Erythrocytes**—the red blood cells—carry $O_2$ from the lungs to body tissues. Each microliter of human blood normally contains about 5 million erythrocytes, which are small, flattened, and disclike. Indentations on each flattened surface make them *biconcave*—thinner in the middle than at the edges (see Figure 42.6). They measure about 7 μm in diameter and 2 μm in thickness. Erythrocytes are highly flexible cells, able to squeeze through narrow capillaries.

As they mature, mammalian erythrocytes lose their nucleus, cytoplasmic organelles, and ribosomes, thereby limiting their metabolic capabilities and life span. The remaining cytoplasm contains enzymes, which carry out glycolysis, and large quantities of *hemoglobin,* the $O_2$-carrying protein of the blood. Most of the ATP produced by glycolysis is used to power active transport mechanisms that move ions in and out of erythrocytes.

Hemoglobin, the molecule that gives erythrocytes and the blood its red color, consists of four polypeptides, each linked to a nonprotein *heme* group that contains an iron atom in its center (see Figure 3.18). The iron atom binds $O_2$ molecules as blood circulates through the lungs and releases the $O_2$ as blood flows through other body tissues.

Hemoglobin can also combine with carbon monoxide (CO), which is common in the exhaust gases of cars and boats, and may be produced by appliances fueled with natural gas or oil. The combination, which is essentially irreversible, blocks hemoglobin's ability to combine with $O_2$, which can quickly lead to death if exposure continues. CO is also present in cigarette smoke.

Some 2 million to 3 million erythrocytes are produced in the average human each *second*. The life span of an erythrocyte in the circulatory system is about 120 days. At the end of their useful life, erythrocytes are engulfed and destroyed by *macrophages* (*makros* = big; *phagein* = to eat), a type of large leukocyte, in the spleen, liver, and bone marrow.

A negative feedback mechanism keyed to the blood's $O_2$ content stabilizes the number of erythrocytes in blood. If the $O_2$ content drops below the normal level, the kidneys synthesize **erythropoietin** (EPO), a hormone that stimulates stem cells in bone marrow to increase erythrocyte production. Erythropoietin is also secreted after blood loss and when mammals move to higher altitudes. As new red blood cells enter the bloodstream, the $O_2$-carrying capacity of the blood rises. If the $O_2$ content of the blood rises above normal levels, erythropoietin production falls in the kidneys and red blood cell production drops. The gene encoding human erythropoietin has been cloned, allowing researchers to produce this protein in large quantities. It can then be injected into the body to stimulate erythrocyte production, for example, in patients with anemia (lower-than-normal hemoglobin levels) caused by kidney failure or chemotherapy. It can also supplement or even replace blood transfusions. Some endurance athletes such as triathletes, bicycle racers, marathon runners, and cross-country skiers have used EPO to increase their erythrocyte levels in order to enhance performance. Such blood doping is deemed illegal by

the governing organizations of most endurance sports and, as a result, many athletes have been sanctioned or banned in recent years.

Disorders of erythrocytes are responsible for a number of human disabilities and diseases. The *anemias,* which result from too few or malfunctioning erythrocytes, prevent $O_2$ from reaching body tissues in sufficient amounts. Shortness of breath, fatigue, and chills are common symptoms of anemia. Anemia can be produced, for example, by blood loss from a wound or bleeding ulcer, or by certain infections.

### Leukocytes Provide the Body's Front Line of Defense against Disease

**Leukocytes** eliminate dead and dying cells from the body, remove cellular debris, and provide the body's first line of defense against invading organisms. They are called white cells because they are colorless, in contrast to the strongly pigmented red blood cells. Also unlike red blood cells, leukocytes retain their nuclei, cytoplasmic organelles, and ribosomes as they mature, and hence are fully functional cells.

Like red blood cells, leukocytes arise from the division of stem cells in red bone marrow (see Figure 42.7). As they mature, they are released into the bloodstream, from which they enter body tissues in large number. Some types of leukocytes are capable of continued division in the blood and body tissues. The specific types of leukocytes and their functions in the immune reaction are discussed in Chapter 43.

### Platelets Induce Blood Clots That Seal Breaks in the Circulatory System

Blood **platelets** are oval or rounded cell fragments about 2 to 4 μm in diameter, each enclosed in its own plasma membrane. They are produced in red bone marrow by the division of stem cells (see Figure 42.7).

Platelets contain enzymes and other factors that take part in blood clotting. When blood vessels are damaged, collagen fibers in the extracellular matrix are exposed to the leaking blood. Platelets in the blood then stick to the collagen fibers and release signaling molecules that induce additional platelets to stick to them. The process continues, forming a plug that helps seal off the damaged site. As the plug forms, the platelets release other factors that convert the soluble plasma protein, fibrinogen, into long, insoluble threads of **fibrin.** Cross-links between the fibrin threads form a meshlike network that traps blood cells and platelets and further seals the damaged area **(Figure 42.8).** The entire mass is a blood clot.

Mutations or diseases that interfere with the enzymes and factors taking part in the clotting mechanism can have serious effects and lead to uncontrolled bleeding. In the most common form of hemophilia, for example, a mutation in a single protein (called *clotting factor VIII*) interferes with the clotting reaction. Bleeding is uncontrolled in afflicted individuals; even small cuts and bruises can cause life-threatening blood loss.

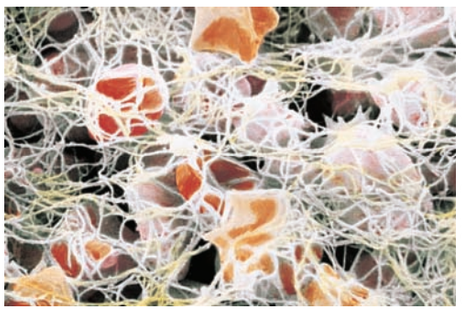




**Figure 42.8**
Red blood cells caught in a meshlike network of fibrin threads during formation of a blood clot.

## Study Break

1. Outline the life cycle of an erythrocyte.
2. How does the body compensate for a lower-than-normal level of oxygen in the blood?
3. What are the roles of leukocytes and platelets?

## 42.3 The Heart

In mammals, the heart is structured from cardiac muscle cells (see Figure 36.6) forming a four-chambered pump, with two atria at the top of the heart pumping blood into two ventricles at the bottom of the heart **(Figure 42.9).** The powerful contractions of the ventricles push the blood at relatively high pressure into arteries leaving the heart. This arterial pressure is responsible for the blood circulation. Valves between the atria and the ventricles and between the ventricles and the arteries leaving the heart keep the blood from flowing backward.

The heart of mammals pumps the blood through two completely separate circuits of blood vessels: the systemic circuit and the pulmonary circuit **(Figure 42.10).** The right atrium (toward the right side of the body) receives blood returning to the heart in vessels coming from the entire body, except for the lungs: the *superior vena cava* conveys blood from the head and forelimbs, and the *inferior vena cava* conveys blood from the abdominal organs and the hind limbs. This blood is depleted of $O_2$ and has a high $CO_2$ content. The right atrium pumps blood into the right ventricle, which contracts to push the blood into the *pulmonary arteries* leading to the lungs. In the capillaries of the lungs, the blood releases $CO_2$ and picks up $O_2$. The

oxygenated blood completes this pulmonary circuit by returning in *pulmonary veins* to the heart.

Blood returning from the pulmonary circuit enters the left atrium, which pumps the blood into the left ventricle. This ventricle, the most thick-walled and powerful of the heart's chambers, contracts to send the oxygenated blood coursing into a large artery, the **aorta,** which branches into arteries leading to all body regions except the lungs. In the capillary networks of these body regions, the blood releases $O_2$ and picks up $CO_2$. The $O_2$-depleted blood collects in veins, which complete the systemic circuit. The blood from the veins enters the right atrium. The amount of blood pumped by the two halves of the heart is normally balanced so that neither side pumps more than the other.

The heart also has its own circulation, called the *coronary circulation*. The aorta gives off two *coronary arteries* that course over the heart. The coronary arteries branch extensively, leading to dense capillary beds that serve the cardiac muscle cells. The blood from the capillary networks collects into veins that empty into the right atrium.

## The Heartbeat Is Produced by a Cycle of Contraction and Relaxation of the Atria and Ventricles

Average heart rates vary among mammals (and among vertebrates generally), depending on body size and the overall level of metabolic activity. A human heart beats 72 times each minute, on average, with each beat lasting about 0.8 second. The heart beat rate of a trained endurance athlete is typically much lower. The heart of a flying bat may beat 1200 times a minute, while that of an elephant beats only 30 times a minute. The period of contraction and emptying of the heart is called the **systole** and the period of relaxation and filling of the heart between contractions is called the **diastole.** The systole-diastole sequence of the heart is called the **cardiac cycle (Figure 42.11).** The following discussion goes through one cardiac cycle.

Starting when both the atria and ventricles are relaxed in diastole, the atria begin filling with blood (see Figure 42.11, step 1). At this point, the **atrioventricular valves (AV valves)** between each atrium and ventricle, and the **semilunar valves (SL valves)** between the ventricles and the aorta and pulmonary arteries, are closed. As the atria fill, the pressure pushes open the AV valves and begins to fill the relaxed ventricles (step 2). When the ventricles are about 80% full, the atria contract and completely fill the ventricles with blood (step 3). Although there are no valves where the veins open into the atria, the atrial contraction compresses the openings, sealing them so that little backflow occurs into the veins.

As the ventricles begin to contract, the rising pressure in the ventricular chambers forces the AV valves shut (step 4). As they continue to contract, the pressure in the ventricular chambers rises above that in the arteries leading away from the heart, forcing open the SL valves. Blood now rushes from the ventricles into the aorta and the pulmonary arteries (step 5).

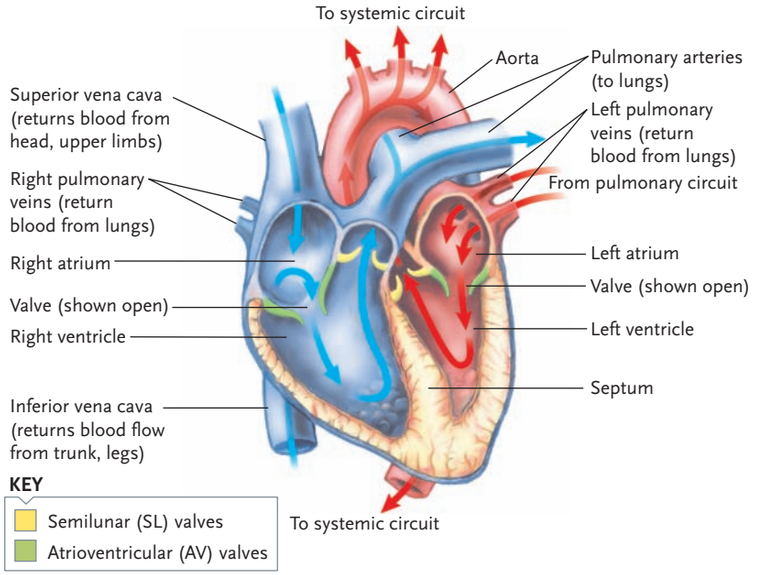



**Figure 42.9**
Cutaway view of the human heart showing its internal organization.

The completion of the contraction squeezes about two-thirds of the blood in the ventricles into the arteries. Now the ventricles relax, lowering the pressure in the ventricular chambers below that in the arteries. This reversal of the pressure gradient reverses the direction of blood flow in the regions of the SL valves, causing them to close. For about half a second, both the atria and ventricles remain in diastole and blood flows into the atria and ventricles. Then, the blood-filled atria contract, and the cycle repeats.

In an adult human at rest, each ventricle pumps roughly 5 liters of blood per minute—an amount roughly equivalent to the entire volume of blood in the body. At maximum rate and strength the human heart pumps about five times the resting amount, or more than 25 liters per minute.

The heart makes a "lub-dub" sound when it beats, which you can hear by placing an ear against a person's chest or listening to the heart through a stethoscope. The sound is produced mostly by vibrations created when the valves close. The "lub" sound occurs when the AV valves are pushed shut by the contraction of the ventricles; the "dub" sound is made when the SL valves are forced shut as the ventricles relax. *Heart murmurs* are abnormal sounds produced by turbulence created in the blood when one or more of the valves fails to open or close completely and blood flows backward.

## The Cardiac Cycle Is Initiated within the Heart

Contraction of cardiac muscle cells is triggered by action potentials that spread across the muscle cell membranes. Some crustaceans, such as crabs and lobsters,

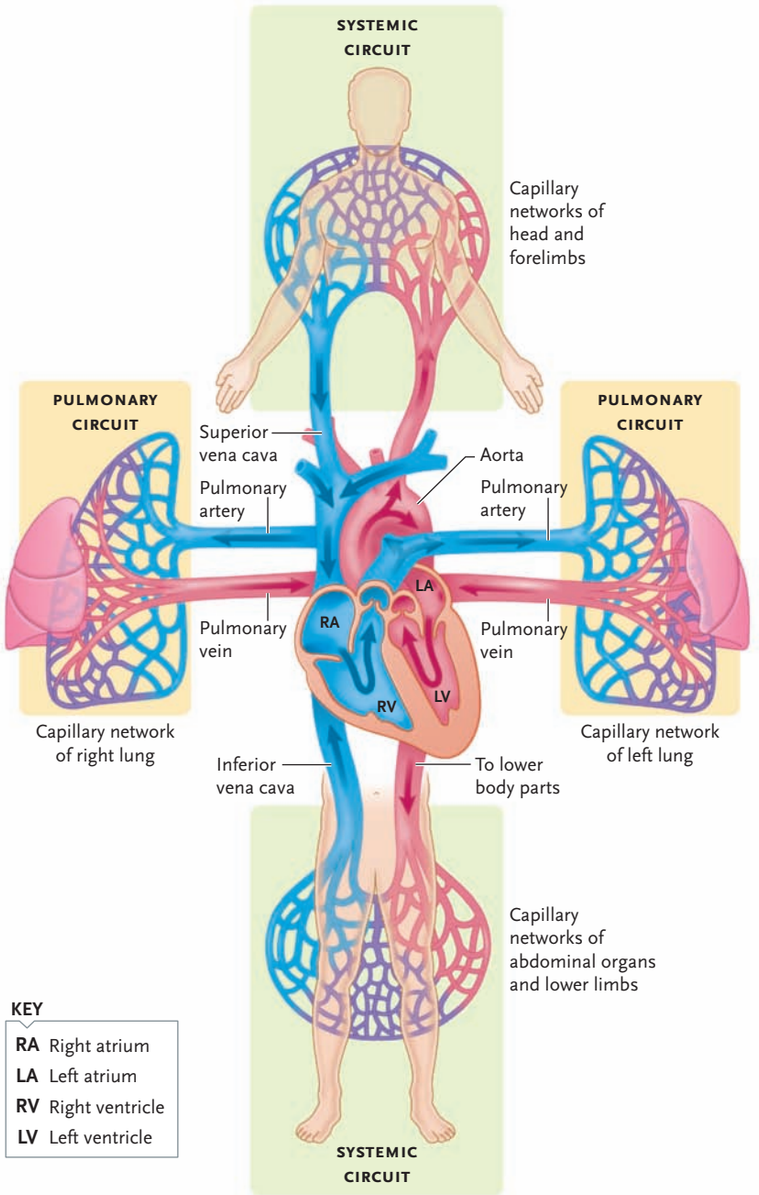



**Figure 42.10**

**The pulmonary and systemic circuits of mammals.** The right half of the heart pumps blood into the pulmonary circuit, and the left half of the heart pumps blood into the systemic circuit.

have **neurogenic hearts**, that is, hearts that beat under the control of signals from the nervous system. This type of heart contraction regulation allows for the heart to be stopped completely in these animals, which may not need continuous hemolymph circulation in some situations. Other animals, including all insects and all vertebrates, have **myogenic hearts**, that is, hearts that maintain their contraction rhythm with no requirement for signals from the nervous system. The advantage of a myogenic heart is that blood flow is ensured in the event of serious trauma to the nervous system.

The contraction of individual cardiac muscle cells in mammalian myogenic hearts is coordinated by a region of the heart called the **sinoatrial node (SA node)**, which controls the rate and timing of cardiac muscle cell contraction. The SA node consists of **pacemaker cells**, which are specialized cardiac muscle cells in the upper wall of the right atrium near where the blood enters the heart from the systemic circuit **(Figure 42.12).** Ion channels in these cells open in a cyclic, self-sustaining pattern that alternately depolarizes and repolarizes their plasma membranes. The regularly timed depolarizations initiate waves of contraction that travel over the heart (step 1). The first effect of a wave is to cause the cells of the atria to contract in unison and fill the ventricles with blood.

A layer of connective tissue separates the atria from the ventricles, in effect placing a layer of electrical insulation between the top and bottom of the heart. The insulating layer keeps a contraction signal from the SA node from spreading directly from the atria to the ventricles (step 2). Instead, the atrial wave of contraction excites cells of the **atrioventricular node (AV node)**, located in the heart wall between the right atrium and right ventricle, just above the insulating layer of connective tissue. The signal produced travels from the AV node to the bottom of the heart via *Purkinje fibers* (step 3). These fibers follow a path downward through the insulating layer to the bottom of the heart, where they branch through the walls of the ventricles. The signal carried by the Purkinje fibers induces a wave of contraction that begins at the bottom of the heart and proceeds upward, squeezing the blood from the ventricles into the aorta and pulmonary arteries (step 4). The transmission of a signal from the AV node to the ventricles takes about 0.1 second; this delay gives the atria time to finish their contraction before the ventricles contract. Cardiac muscle cells have a relatively long refractory period, about 0.25 second, which keeps the signals or contractions from reversing at any point.

As Augustus Waller found, the electrical signals passing through the heart can be detected by attaching electrodes to different points on the surface of the body. The signals change in a regular pattern corresponding to the electrical signals that trigger the cardiac cycle, producing what is known as an **electrocardiogram** (**ECG**; also **EKG**, from German *elektrocardiogramm*). The highlighted region of the ECG under each stage of the cardiac cycle in Figure 42.12 indicates the electrical activity measured in those stages. Many malfunctions of the heart alter the ECG pattern in characteristic ways, providing clues to the location and type of heart disease.

The spontaneous, rhythmic signal set up by the SA node is the foundation of the normal heartbeat. Because of this internal signaling system, a myogenic heart will continue beating if all the nerves leading to the heart are severed.

The SA node normally dominates the AV node and other conductive regions of the heart, keeping the atria

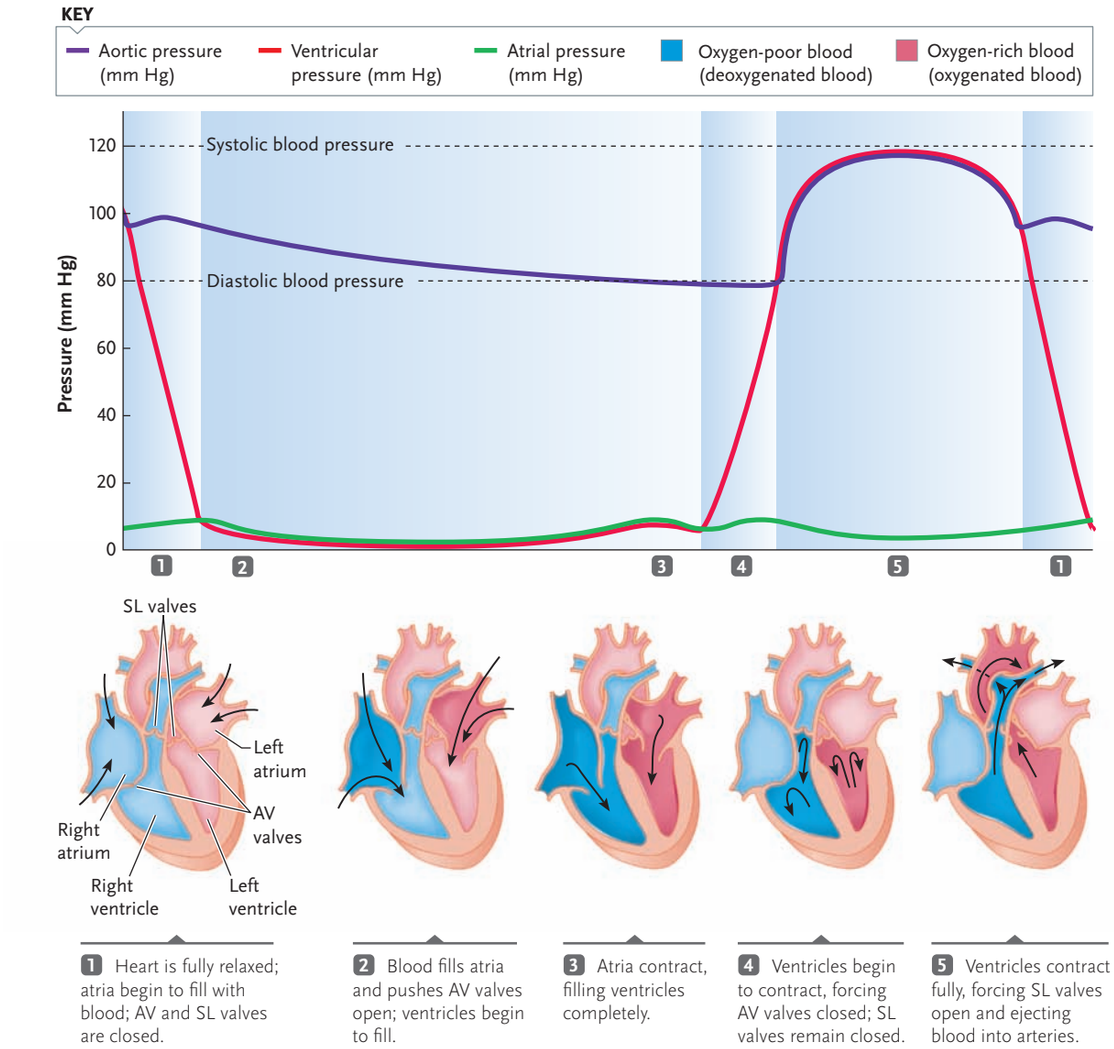


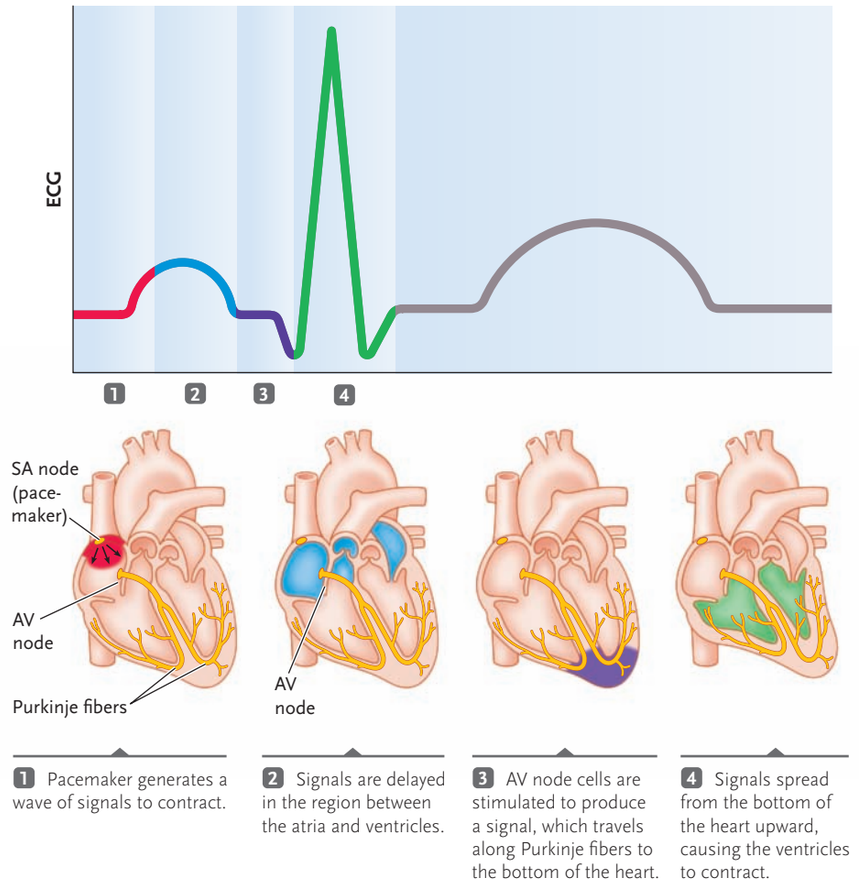

**Figure 42.11**
The cardiac cycle.

and ventricles beating in a fully coordinated fashion. At times, however, parts of the conductive system outside the SA node may generate signals independently and produce uncoordinated contractions known as *arrhythmias*. Depending on their source and characteristics, arrhythmias range from harmless to life threatening. Most commonly, the ventricles beat prematurely, and then fill more slowly for the next beat, which is proportionately more powerful. This arrhythmia, called a *premature ventricular contraction (PVC),* feels like a skipped beat but is usually harmless. Consumption of too much caffeine, chocolate, or alcohol can increase the frequency of PVCs. Other arrhythmias, such as those produced when the AV node becomes the dominant pacemaker, can be more dangerous. Some of the more threatening arrhythmias are corrected by surgically implanting an artificial pacemaker that produces an overriding, regular electrical impulse to keep the heart beating at a normal rhythm and rate.

## Arterial Blood Pressure Cycles between a High Systolic and a Low Diastolic Pressure

The pressure that a fluid in a confined space exerts is called *hydrostatic pressure*. That is, fluid in a container exerts some pressure on the wall of the container. Blood vessels are essentially tubular containers that are part of a closed system filled with fluid. Hence, the blood in vessels exerts hydrostatic pressure against the walls of the vessels. *Blood pressure* is the measurement of that hydrostatic pressure on the walls of the arteries as the heart pumps blood through the body. Blood pressure is determined by the force and amount of blood pumped by the heart and the size and flexibility of the arteries. In any person, blood pressure changes continually in response to activity, temperature, body position, emotional state, diet, and medications being taken.

**Figure 42.12**
**The electrical control of the cardiac cycle.** The top part of the figure shows how a signal originating at the SA node leads to ventricular contraction. The bottom part of the figure shows the electrical activity for each of the stages as seen in an ECG. The colors in the hearts show the location of the signal at each step and correspond to the colors in the ECG.




Two blood pressure measurements are typically made in clinical medicine, representing different parts of the cardiac cycle. As the ventricles contract, a surge of high-pressure blood moves outward through the arteries leading from the heart. This peak of high pressure, called the *systolic blood pressure,* can be felt as a *pulse* by pressing a finger against an artery that lies near the skin, such as the arteries of the neck or the artery that runs along the inside of the wrist. Between ventricular contractions, the arterial blood pressure reaches a low point called the *diastolic blood pressure.*

For most healthy adults at rest, the systolic pressure measured at the upper arm is between 90 and 120 mm Hg, and the diastolic pressure is between 60 and 80 mm Hg (**Figure 42.13** shows how these pressures are measured). The numbers, written in the form 120/80 mm Hg and stated verbally as "120 over 80," refer to the height of a column of mercury in millimeters that would be required to balance the pressure exactly. The systolic and diastolic blood pressures in the pulmonary arteries are typically much lower, about 24/8 mm Hg.

The blood pressure in the systemic and pulmonary circuits is highest in the arteries leaving the heart, and drops as the blood passes from the arteries into the capillaries. By the time the blood returns to the heart, its pressure has dropped to 2 to 5 mm Hg, with no differentiation between systolic and diastolic pressures. The reduction in pressure occurs because the blood encounters resistance as it moves through the vessels, produced primarily by the friction created when blood cells and plasma proteins move over each other and over vessel walls.

Some people have **hypertension,** commonly called high blood pressure, a medical condition in which blood pressure is chronically elevated above normal values; that is, at least 140/90. In some cases, no specific medical cause can be found to explain the hypertension. In other cases, the hypertension results from another medical condition, such as kidney disease, or diseases or cancers affecting the adrenal cortex. Hypertension can also be caused by certain medications, such as ibuprofen and steroids. Age is also a contributor to hypertension because over time the walls of blood vessels become stiffer as more collagen fibers are added, and this causes decreased elasticity of the arteries. During systole, these arteries cannot expand as much as they once could, and this results in a higher arterial blood pressure.

Hypertension is rarely severe enough to cause symptoms. However, in the long term, the increased pressure in the arteries can cause damage to organs. Hence, hypertension is treated because of the correlation with an increased risk for a number of medical conditions, including myocardial infarction (heart at-

tack), cardiovascular accident (stroke), chronic renal failure, and retinal damage. Treatments to reduce hypertension typically involve life style changes, such as weight loss and regular exercise; in the case of moderate to severe hypertension, drugs are also prescribed.

What happens to blood pressure during exercise? The answer depends on the type of exercise. During static exercise involving a sustained contraction of a muscle group or groups, such as weight lifting or Nautilus machine routines, both systolic and diastolic pressure increase. In elite weight lifters, for instance, blood pressure during lifts can reach 300/150 mm Hg. However, during dynamic exercise involving intermittent and rhythmical muscle contractions, such as running, bicycling, and swimming, only the systolic pressure increases.

### Study Break

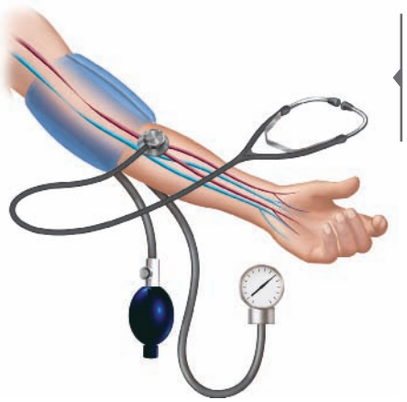
1. Explain the role of each of the four chambers of the mammalian heart in blood circulation.
2. Distinguish systole and diastole.
3. Distinguish neurogenic hearts and myogenic hearts.
4. Describe the electrical events that occur during the cardiac cycle in a mammalian myogenic heart.

## 42.4 Blood Vessels of the Circulatory System

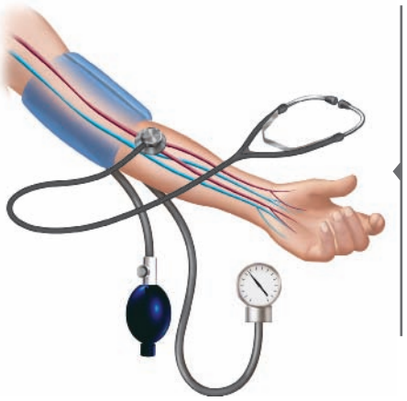
Both the systemic and pulmonary circuits consist of a continuum of different blood vessel types that begin and end at the heart **(Figure 42.14).** From the heart, large arteries carry blood and branch into progressively smaller arteries, which deliver the blood to the various parts of the body. When a small artery reaches the organ it supplies, it branches into yet smaller vessels, the **arterioles.** Within the organ, arterioles branch into capillaries, the smallest vessels of the circulatory system. The capillaries form a network in the organ that is used to exchange substances between the blood and the surrounding cells. Capillaries rejoin to form small **venules,** which merge into the small veins that leave the organ. The small veins progressively join to form larger veins that eventually become the large veins that enter the heart.

### Arteries Transport Blood Rapidly to the Tissues and Serve as a Pressure Reservoir

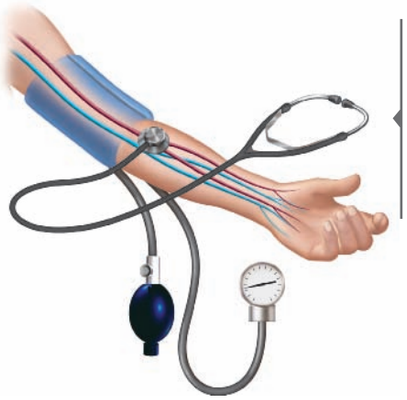
Arteries have relatively large diameters and, therefore, provide little resistance to blood flow. Structurally, they are adapted to the relatively high pressure of the blood passing through them. The walls of arteries consist of



**1** The cuff is pumped up until its pressure is higher than the arterial blood pressure, cutting off the flow of blood through the large artery serving the arm.



**2** A stethoscope is placed over the artery just below the cuff, and the pressure in the cuff is slowly released. When cuff pressure drops to the point that blood just begins to flow through the artery, a faint thumping sound is heard in the stethoscope. The sound is produced by turbulence created as spurts of blood pass through the narrowed artery. The pressure read on the meter when the thumping begins is the systolic pressure.



**3** The pressure in the cuff is released further until the thumping sound just disappears. At this point, there is no turbulence because the artery is fully open. The pressure read on the meter at this point is the diastolic pressure.

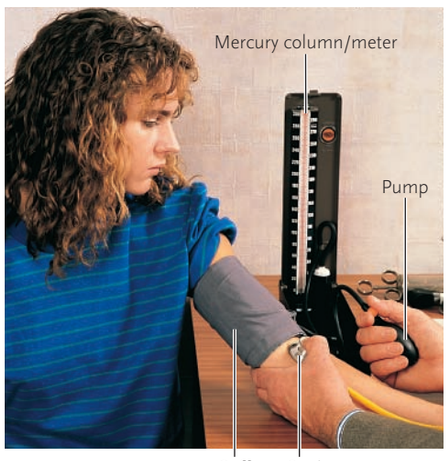





**Figure 42.13**
**Taking blood pressure with a sphygmomanometer.** The device consists of a rubber bladder (called a cuff) that is wrapped around an arm or leg and connected to an air pump and a mercury column, which records the pressure inside the bladder in millimeters of mercury (mm Hg).

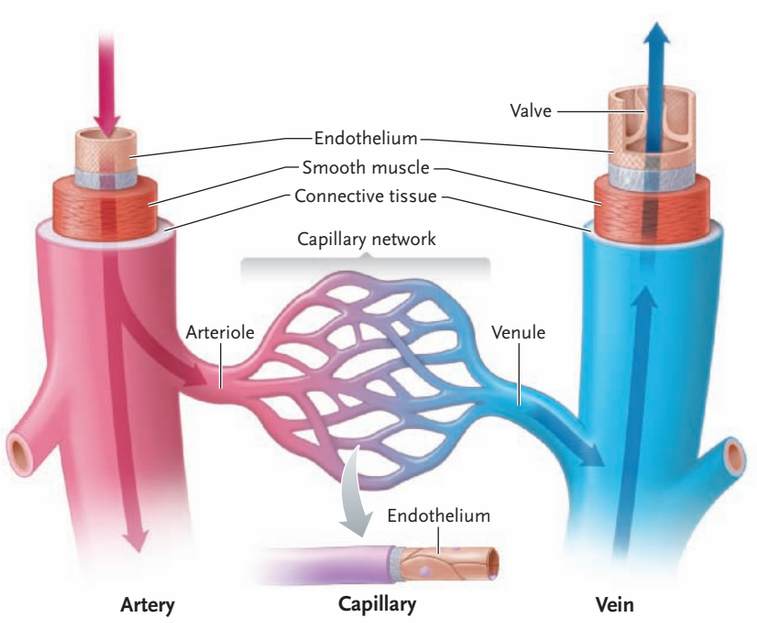



**Figure 42.14**
The structure of arteries, capillaries, and veins and their relationship in blood circuits.

three major tissue layers: (1) an outer layer of connective tissue containing collagen fibers mixed with fibers of the protein elastin, which gives the vessel recoil ability; (2) a relatively thick middle layer of vascular smooth muscle cells also mixed with elastin fibers; and (3) a one-cell-thick inner layer of flattened cells that forms an *endothelium,* a specialized type of epithelial tissue that lines the entire circulatory system (see Figure 42.14).

In addition to being the conduits for blood traveling to the tissues, arteries also act as a pressure reservoir to generate the force for blood movement when the heart is relaxing. When contraction of the ventricles pumps blood into the arteries, the amount of blood flowing into the arteries is greater than the amount flowing out into the smaller vessels downstream because of the higher resistance to blood flow in those smaller vessels. The arteries can accommodate the excess volume of blood because their elastic walls allow the arteries to expand in diameter. When the heart then relaxes and blood is no longer being pumped into the arteries, the arterial walls recoil passively back to their original state. The recoil pushes the excess blood from the arteries into the smaller downstream vessels. As a result, blood flow to tissues is continuous during systole and diastole.

## Capillaries Are the Sites of Exchange between the Blood and Interstitial Fluid

Capillaries thread through nearly every tissue in the body, arranged in networks that bring them within 10 μm of most body cells. They form an estimated 2600 $km^2$ of total surface area for the exchange of gases, nutrients, and wastes with the interstitial fluid. Capillary walls consist of a single layer of endothelial cells.

**Control of Blood Flow through Capillaries.** Blood flow through the capillary networks is controlled by contraction of smooth muscle in the arterioles **(Figure 42.15).** The capillaries themselves do not have smooth muscle but, in many cases, a small ring of smooth muscle called a *precapillary sphincter* is present at the junction between an arteriole and a capillary.

When the sphincter is relaxed, blood flows readily through the arterioles and capillary networks (see Figure 42.15a). In the most contracted state, blood flow

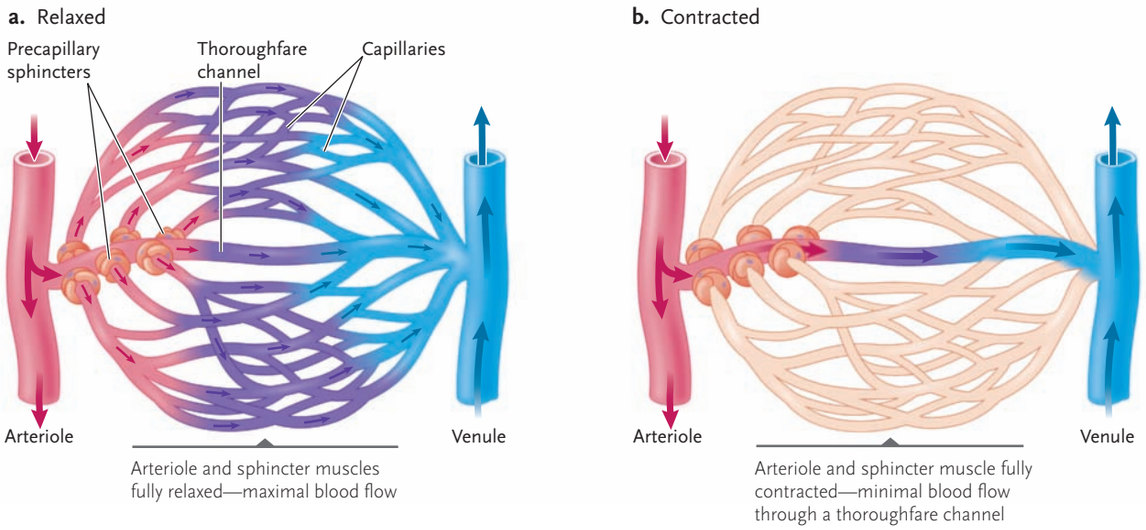



**Figure 42.15**
Control of blood flow through capillary networks. **(a)** Maximal blood flow when arteriole and sphincter muscles are fully relaxed. **(b)** Minimal blood flow when the arteriole and sphincter muscles are fully contracted.

through the arterioles and capillary networks is limited (see Figure 42.15b). Variation in the contraction of arteriole and sphincter smooth muscles adjusts the rate of flow through the capillary networks between the two flow limits. For example, during exercise, flow of blood through the capillary networks is increased severalfold over the resting state by relaxation of the precapillary sphincters.

**Control of Blood Volume to Capillaries by Arterioles.** The volume of blood flowing through an organ is adjusted by regulating the internal diameter of the arterioles of the organ. The blood leaving the arterioles enters the capillaries that branch from them. Although their total surface area is astoundingly large, the diameter of individual capillaries is so small that red blood cells must squeeze through most of them in single file **(Figure 42.16).** As a result, each capillary presents a high resistance to blood flow. Yet there are so many billions of capillaries in the networks that their combined diameter is about 1300 times greater than the cross-sectional area of the aorta. As a result, blood slows considerably as it moves through the capillaries **(Figure 42.17).** This is analogous to the slowing that occurs when a narrow, swiftly running streams widens into a broad pool. The slow movement of blood through the capillaries maximizes the time for exchange of substances between blood and tissues. As they leave the tissues, the capillaries rejoin to form veins. Veins have a reduced total cross-sectional area compared with capillaries, so the rate of flow increases as blood returns to the heart (see Figure 42.17).

**Exchange of Substances across Capillary Walls.** In most body tissues, narrow spaces between the capillary endothelial cells allow water, ions, and small molecules such as glucose to pass freely between the blood and interstitial fluid. Erythrocytes, platelets, and most plasma proteins are too large to pass between the cells and are retained inside the capillaries, except for molecules that are transported through the epithelial cells by specific carriers. Leukocytes, however, are able to squeeze actively between the cells and pass from the blood to the interstitial fluid.

There are exceptions to these general properties in some tissues; in the brain, for example, the capillary endothelial cells are tightly sealed together, preventing essentially all molecules and even ions from passing between them. The tight seals set up the *blood–brain barrier,* which limits the exchange between capillaries and brain tissues to molecules and ions that are specifically transported through the capillary endothelial cells (see Section 38.3 for additional discussion of the blood–brain barrier).

**Forces Driving the Exchange.** Two major mechanisms drive the exchange of molecules and ions between the capillaries and the interstitial fluid: (1) diffusion along concentration gradients and (2) bulk flow.

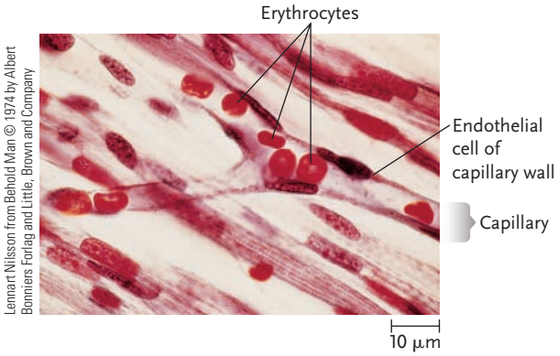



**Figure 42.16**
Erythrocytes moving through a capillary that is just wide enough to admit the cells in single file.

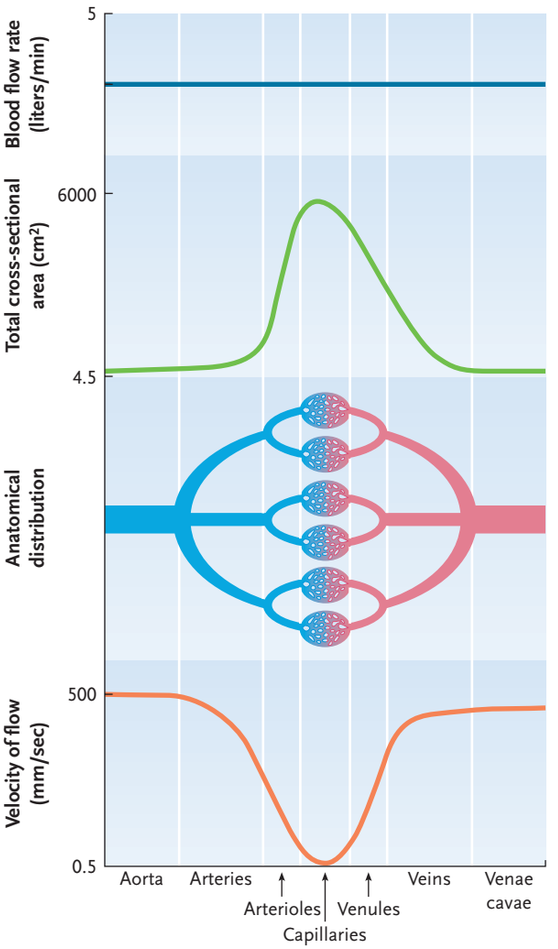



**Figure 42.17**
**Blood flow rate and velocity of flow in relation to total cross-sectional area of the blood vessels.** The blood flow rate is identical throughout the circulatory system and is equal to the cardiac output. The velocity of flow in the different types of blood vessels is inversely related to the total cross-sectional area of all the vessels of a particular type: for example, the velocity is highest in the aorta, which has the smallest cross-sectional area, and lowest in the capillaries, which collectively have the largest total cross-sectional area.

Diffusion along concentration gradients occurs both through the spaces between the capillary endothelial cells and through their plasma membranes. Ions or molecules such as $O_2$ and glucose, which are more concentrated inside the capillaries, diffuse outward along their gradients; other ions or molecules that are more concentrated outside, such as $CO_2$, diffuse inward. Some molecules, such as $O_2$ and $CO_2$, diffuse directly through the lipid bilayer of the endothelial cell plasma membranes; others, such as glucose, pass by facilitated diffusion through transport proteins. The total diffusion is greatest at the ends of capillaries nearest the arterioles, where the concentration differences between blood plasma and interstitial fluid are highest, and lowest at the ends nearest the venules, where the inside/outside concentrations of diffusible substances are almost equal.

Bulk flow, which carries water, ions, and molecules out of the capillaries, occurs through the spaces between capillary endothelial cells. The flow is driven by the pressure of the blood, which is higher than the pressure of the interstitial fluid. Like diffusion, bulk flow is greatest in the ends of the capillaries nearest the arterioles, where the pressure difference is highest, and drops off steadily as the blood moves through the capillaries and the pressure difference becomes smaller.

## Venules and Veins Serve as Blood Reservoirs in Addition to Conduits to the Heart

The walls of venules and veins are thinner than those of arteries and contain little elastin. Many veins have flaps of connective tissue that extend inward from their walls. These flaps form one-way valves that keep blood flowing toward the heart (see Figure 42.14).

Rather than stretching and contracting elastically, like arteries, the relatively thin walls of venules and veins can expand and contract over a relatively wide range, allowing them to act as blood reservoirs as well as conduits. At times, the venules and veins may contain from 60% to 80% of the total blood volume of the body. The stored volume is adjusted by skeletal muscle contraction and by the valves, in response to metabolic conditions and signals carried by hormones and neurotransmitters.

Although blood pressure in the venous system is relatively low, several mechanisms assist the movement of blood back to the heart. As skeletal muscles contract, they compress nearby veins, increasing their internal pressure **(Figure 42.18).** The one-way valves in the veins, especially numerous in the larger veins of the limbs, keep the blood from flowing backward when the muscles relax.

When you sit without moving for long periods of time, as you might during an airline flight, the lack of skeletal muscular activity greatly reduces the return of venous blood to the heart. As a result, the blood pools in the veins of the body below the heart, making the hands, legs, and feet swell. The motionless blood can also form clots, particularly in the veins of the legs, a condition called *deep vein thrombosis*. Deep vein thrombosis often does not cause symptoms, but can cause serious medical problems if a clot breaks loose and moves elsewhere in the body, such as to the lungs. Raising the arms and getting up at intervals to exercise or contracting and relaxing the leg muscles as you sit can relieve this condition.

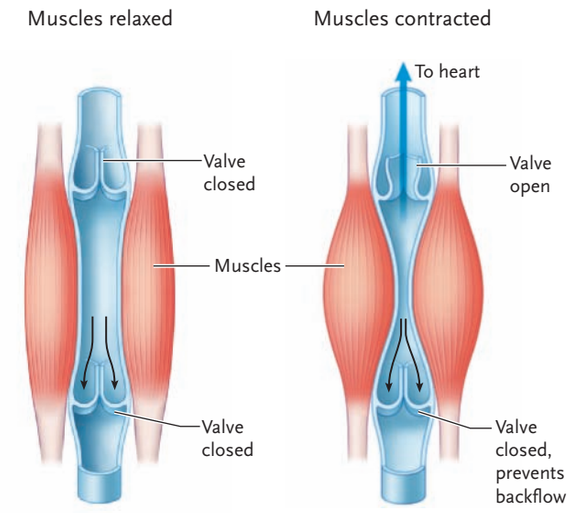



**Figure 42.18**
How skeletal muscle contraction, and the valves inside veins, help move blood toward the heart.

## Disorders of the Circulatory System Are Major Sources of Human Disease

The layer of endothelial cells lining the arteries and veins is normally smooth and does not impede blood flow. However, several conditions, including bacterial and viral infections, chronic hypertension, smoking, and a diet high in fats, can damage the endothelial cells, exposing the underlying smooth muscle tissue, which begins a cycle of injury and repair leading to lesions. (*Focus on Research* in Chapter 3 discussed the relationship between fats and cholesterol and coronary artery disease.) Thickened deposits of material called *atherosclerotic plaques* may form at the damaged sites **(Figure 42.19).** The plaques, which consist of cholesterol-rich fatty substances, smooth muscle cells, and collagen deposits, reduce the diameter of the blood vessel and impede blood flow. Worse, the damaged endothelial lining may stimulate platelets to adhere and trigger the formation of blood clots. The clots further reduce the vessel diameter and flow and may break loose, along with segments of plaque material, to block finer vessels in other regions of the body.

Atherosclerosis has its most serious effects in the smaller arteries of the body, particularly in the fine coronary arteries that serve the heart muscle. Here, the plaques and clots reduce or block the flow of blood to the heart muscle cells. Serious blockage can cause a heart attack—the death of cardiac muscle cells de-

prived of blood flow. The blockage of arteries in the brain by plaque material or blood clots released from atherosclerotic arteries is also a common cause of stroke—a loss of critical brain functions due to the death of nerve cells in the brain. Heart attacks and strokes are the most common causes of death in North America and in Europe.

The risk of heart attacks and stroke can be reduced by avoiding the conditions that damage the blood vessel endothelium. A diet low in fats and cholesterol, avoidance of cigarette smoke, and a program of exercise can reduce epithelial damage and plaque deposition. Medication and exercise, or exercise alone, can also reduce the effects of hypertension. There are good indications that these preventive programs can also reduce the size of existing atherosclerotic plaques.

### Study Break

1. How is blood flow through capillary networks controlled?
2. Explain how, in contrast to most body tissues, the brain does not allow exchange of molecules and ions with blood.
3. Describe the two major mechanisms that drive the exchange of molecules and ions between the capillaries and the interstitial fluid.
4. What are atherosclerotic plaques? Indicate, in general, how they form, and provide some examples of factors contributing to their formation.

## 42.5 Maintaining Blood Flow and Pressure

Arterial blood pressure is the principal force moving blood to the tissues. Blood pressure must be regulated carefully so that the brain and other tissues receive adequate blood flow, but not so high that the heart is overburdened, risking damage to blood vessels. The three main mechanisms for regulating blood pressure are controlling *cardiac output* (the pressure and amount of blood pumped by the left and right ventricles), the degree of constriction of the blood vessels (primarily the arterioles), and the total blood volume. The sympathetic division of the autonomic nervous system and the endocrine system interact to coordinate these mechanisms. The system is effective in counteracting the effects of constantly changing internal and external conditions, such as movement from rest to physical activity or ending a period of fasting by eating a large meal. For example, the heart responds to the initiation of moderate physical activity by increasing blood flow to the heart itself by 367%, to the muscles of the skin by 370%, and to the skeletal muscle by 1066%, while decreasing flow to the digestive tract and liver by 56%, to the kidneys by 45%, and to the bone and most other tissues by 30%. Only the blood flow to the brain remains unchanged.

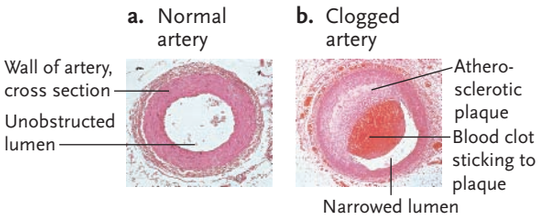



**Figure 42.19** Atherosclerosis. **(a)** A normal coronary artery. **(b)** A coronary artery that is partially clogged by an atherosclerotic plaque. (a: Ed Reschke; b: © Biophoto Associates/Photo Researchers, Inc.)

### Cardiac Output Is Controlled by Regulating the Rate and Strength of the Heartbeat

Regulation of the strength and rate of the heartbeat starts at stretch receptors called *baroreceptors* (a type of mechanoreceptor; see Section 39.2), located in the walls of blood vessels. By detecting the amount of stretch of the vessel walls, baroreceptors constantly provide information about blood pressure. The baroreceptors in the cardiac muscle, the aorta, and the carotid arteries (which supply blood to the brain), are the most crucial. Signals sent by the baroreceptors go to the medulla within the brain stem. In response, the brain stem sends signals via the autonomic nervous system that adjust the rate and force of the heartbeat: the heart beats more slowly and contracts less forcefully when arterial pressure is above normal levels, and it beats faster and contracts more forcefully when arterial pressure is below normal levels.

The $O_2$ content of the blood, detected by chemoreceptors in the aorta and carotid arteries, also influences cardiac output. If the $O_2$ concentration falls below normal levels, the brain stem integrates this information with the signals sent from baroreceptors and issues signals that increase the rate and force of the heartbeat. Too much $O_2$ in the blood has the opposite effect, reducing the cardiac output.

### Hormones Regulate both Cardiac Output and Arteriole Diameter

Hormones secreted by several glands contribute to the regulation of blood pressure and flow. As part of the stress response, the adrenal medulla reinforces the action of the sympathetic nervous system by secreting epinephrine and norepinephrine into the bloodstream (see Section 40.4). Epinephrine in particular raises the blood pressure by increasing the strength and rate of the heartbeat and stimulating vasoconstriction of arterioles in some parts of the body, including the skin, gut, and kidneys. At the same time, by inducing the vasodilation of arterioles that deliver blood to the heart, skeletal muscles, and lungs, epinephrine increases the blood flow to these structures. *Insights from the Molecular Revolution* shows how gene manipulation experi-

## Insights from the Molecular Revolution

### Identifying the Role of a Hormone Receptor in Blood Pressure Regulation Using Knockout Mice

The sympathetic division of the autonomic nervous system brings about a temporary increase in blood pressure when the body experiences stress. That is, the sympathetic nervous system stimulates the adrenal medulla to release the catecholamines epinephrine and norepinephrine. These hormones stimulate the strength and rate of the heartbeat and change arteriole diameter. Epinephrine and norepinephrine exert their effects by binding to specific membrane-embedded receptors on target cells, activating them and triggering a cellular response via a signal transduction pathway. The receptors, which are G-protein–coupled receptors (see Section 7.4), are known as *adrenergic receptors* because of the adrenal origin of the hormones that bind to them.

Different types of adrenergic receptors are responsible for different responses to epinephrine and norepinephrine. With respect to blood pressure regulation, two key receptors are the $\alpha_1$ receptor and the $\beta_2$ receptor. $\alpha_1$ Receptors are found on cells of all arteriolar smooth muscle, but not in the brain, whereas $\beta_2$ receptors are found only on cells of arteriolar smooth muscle in the heart and skeletal muscles. Norepinephrine has strong affinity for the $\alpha_1$ receptors, while epinephrine has less affinity for this type of receptor. Binding of norepinephrine, and to a lesser extent, epinephrine, to $\alpha_1$ receptors on arteriolar smooth muscle causes vasoconstriction of arterioles, thereby contributing to an increase in blood pressure.

Researchers have identified three subtypes of $\alpha_1$-adrenergic receptors: $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$. Tissues that express $\alpha_1$ receptors can express all subtypes. Each of the subtypes responds to catecholamines, but the contribution of each subtype to the physiological responses caused by the hormones has not been characterized well. For example, despite attempts, scientists have not been able to develop drugs that are completely specific for inhibiting one subtype, making it impossible to use that approach to look at the effects of loss of activity of one subtype. Now, Gozoh Tsujimoto and colleagues at the Tokyo University of Pharmacy and Life Sciences, and the National Children's Medical Research Center, Tokyo, Japan, have used a different approach—making a gene knockout for the gene that encodes the $\alpha_{1D}$ receptor (the technique for making a gene knockout is described in Section 18.2). Using molecular techniques, the researchers showed that, in the knockout mice, no mRNA transcripts of the $\alpha_{1D}$ receptor gene was produced in any of the tissues examined, and there was no change in the expression of the $\alpha_{1A}$ and $\alpha_{1B}$ receptor subtypes. These results indicated that these mice were a highly useful model system for their physiological studies.

Next, the researchers compared the $\alpha_{1D}$ receptor knockout mice with normal mice to determine what had changed in the knockout mice with respect to cardiovascular function. They found that the knockout mice were modestly hypotensive (had slightly lower-than-normal blood pressure) but had a normal heart rate. They also had normal levels of circulating catecholamines. The investigators tested whether norepinephrine would stimulate an increase in blood pressure. They found that increasing doses of norepinephrine progressively increased blood pressure in both knockout and normal mice but that the response was markedly reduced in the knockout mice. Then, to determine whether the $\alpha_{1D}$ receptor is directly involved in vascular smooth muscle contraction, the researchers measured the effect of norepinephrine on contraction of segments of the aortas isolated from knockout and normal mice. Their results showed that norepinephrine induced concentration-dependent contraction of aortal segments from both types of mice but that the contraction response was considerably reduced in the knockout mice. The researchers concluded from their results that the $\alpha_{1D}$-adrenergic receptor participates directly in sympathetic nervous system–driven regulation of blood pressure by vasoconstriction.

ments illuminated the role of a receptor for these hormones in regulating blood pressure.

The adrenal cortex and the posterior pituitary also release hormones that regulate blood pressure. Those hormones and their effects are described in Chapter 46.

## Local Controls Also Regulate Arteriole Diameter

Several automated mechanisms also operate locally to increase the flow of blood to body regions engaged in increased metabolic activity, such as the muscles of your legs during an extended uphill bike ride. Low $O_2$ and high $CO_2$ concentrations, produced by the increased oxidation of glucose and other fuels, induce vasodilation of the arterioles serving muscles. The vasodilation increases the flow of blood and the $O_2$ supply. Nitric oxide (NO) released by arterial endothelial cells in body regions engaged in increased metabolic activity also works as a potent vasodilator. NO is broken down quickly after its release, ensuring that its effects are local.

## Study Break

1. Why is it important to regulate arterial blood pressure?
2. What are the three main mechanisms for regulating blood pressure?
3. How does epinephrine affect blood pressure?

## 42.6 The Lymphatic System

Under normal conditions, a little more fluid from the blood plasma in the capillaries enters the tissues than is reabsorbed from the interstitial fluid into the plasma. The **lymphatic system** is an extensive network of vessels that collect the excess interstitial fluid and return it to the venous blood **(Figure 42.20).** The interstitial fluid picked up by the lymphatic system is called **lymph.** This system also collects fats that have been absorbed from the small intestine and delivers them to the blood circulation (see Chapter 45). The lymphatic system is also a key component of the immune system.

### Vessels of the Lymphatic System Extend throughout Most of the Body

Vessels of the lymphatic system collect the lymph and transport it to *lymph ducts* that empty into veins of the circulatory system. The *lymph capillaries,* the smallest vessels of the lymphatic system, are distributed throughout the body, intermixed intimately with the capillaries of the circulatory system. Although they are several times larger in diameter than the blood capillaries, the walls of lymph capillaries also consist of a single layer of endothelial cells surrounded by a thin network of collagen fibers. Interstitial fluid enters the lymph capillaries—becoming lymph—at sites in their walls where the endothelial cells overlap, forming a flap that is forced open by the higher pressure of the interstitial fluid. The openings are wide enough to admit all components of the interstitial fluid, including infecting bacteria, damaged cells, cellular debris, and lymphocytes.

The lymph capillaries merge into *lymph vessels,* which contain one-way valves that prevent the lymph from flowing backward. The lymph vessels lead to the thoracic duct and the right lymphatic duct (see Figure 42.20), which empty the lymph into a vein beneath the clavicles (collarbones), adding it to the plasma in the vein.

Movements of the skeletal muscles adjacent to the lymph vessels and breathing movements help move the lymph through the vessels, just as they help move the blood through veins. Over a day's time, the lymphatic system returns about 3 to 4 liters of fluid to the bloodstream.

### Lymphoid Tissues and Organs Act as Filters and Participate in the Immune Response

The tissues and organs of the lymphatic system include the *lymph nodes,* the *spleen,* the *thymus,* and the *tonsils.* They play primary roles in filtering viruses, bacteria, damaged cells, and cellular debris from the lymph and bloodstream, and in defending the body against infection and cancer. Patches of lymphoid tissue are also scattered in other regions of the body, such as the small intestine and the appendix.

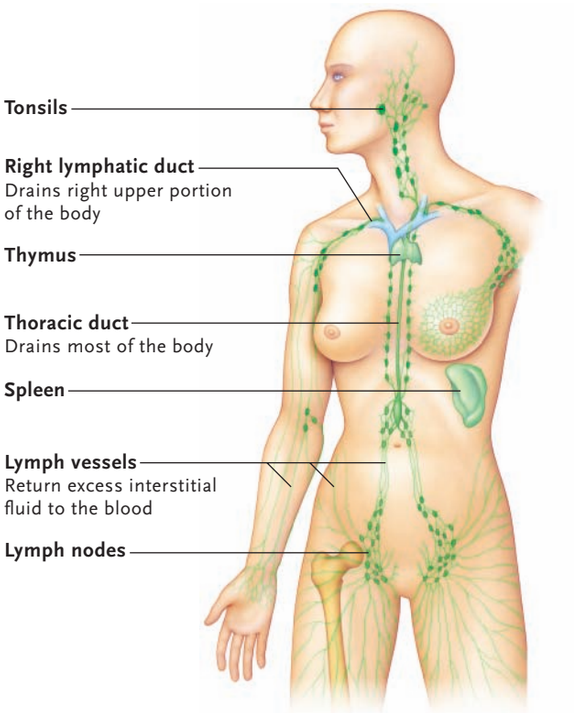



**Figure 42.20** The human lymphatic system. Patches of lymphoid tissue in the small intestine and in the appendix also are part of the lymphatic system.

The **lymph nodes** are small, bean-shaped organs spaced along the lymph vessels and clustered along the sides of the neck, in the armpits and groin, and in the center of the abdomen and chest cavity (see Figure 42.20). Spaces in the nodes contain macrophages, a type of leukocyte that engulfs and destroys cellular debris and infecting bacteria and viruses in the lymph. The lymph nodes also contain other leukocytes, which produce antibodies that aid in the destruction of invading pathogens (discussed more in Chapter 43). Cancer cells that lodge in the nodes may be destroyed or may remain to grow and divide, forming new tumors within the nodes. Therefore, to reduce the risk of cancer spread, lymph nodes near a tumor typically are inspected and may be removed during surgery to excise that tumor.

The lymph nodes may become enlarged and painful if large numbers of bacteria or viruses carried by the lymph become trapped inside them. A doctor usually checks for swollen nodes, particularly in the neck, armpits, and groin, as indicators of an infection in the region of the body served by the nodes.

### Study Break

What is lymph, and how does it enter the lymph capillaries?

## Unanswered Questions

**How did vertebrate blood clotting evolve?**

Vertebrate blood clotting is a complex process involving about two dozen different proteins found in the blood plasma. The system has the properties of a biochemical amplifier in that the exposure of a tiny amount of tissue initiates a series of proteolytic events, one protease activating another successively, with the climax being a large amount of localized thrombin that transforms fibrinogen into a fibrin clot.

Many years ago when I was a graduate student working in a laboratory devoted to blood proteins, I asked myself the question, How could blood clotting ever have evolved? The process seemed much too complicated to have been concocted in one fell swoop, so, I reasoned, it must have begun in a simpler fashion and gradually become more complicated. Certainly, other people had been asking similar questions about complex organs—the evolution of the eye, for example, had been considered by many scientists, including Charles Darwin—but facts about the evolution of individual proteins were just beginning to emerge.

In particular, Vernon Ingram, a scientist working at MIT, had just determined the amino acid sequences of the alpha and beta chains of hemoglobin and found that these two proteins were about 45% identical. They must be the products of a gene duplication, he reported. Given his observation, it seemed to me that the proteases involved in blood clotting ought also to be the products of gene duplication. At the time, none of their amino acid sequences was known, but several had unique properties that distinguished them from other proteases, so it stood to reason that they were related. Yet, some nonproteolytic proteins were also involved, and they must have been added to the process independently.

So where to start? I decided to compare the blood clotting process in a wide range of animals. As it happens, most animals, invertebrate and vertebrate alike, have a kind of blood (see Section 42.2), and in most cases it can be coagulated by various stressful events. But the vertebrate process looked unique to me and must have evolved independently of the system that occurs in lobsters (Crustacea), for example. Among the vertebrates, the most primitive (early diverging) creature I could get my hands on was the lamprey (see Section 30.4, where its place in the vertebrate lineage is discussed).

Because I was hoping to find a simple, predecessor scheme, I was a little disappointed to find that lampreys have a rather sophisticated coagulation process that involved many of the proteins observed in mammals. Certainly, a small amount of tissue factor provoked a thrombin generation that converted fibrinogen to fibrin, just as in humans, at least in a general way. At the time there was no way to determine whether lampreys use the equivalent of *all* the clotting factors on the way to generating thrombin. Some of the most important proteins in the human system occur in minute amounts, and there was no possibility of ever isolating them from the lamprey, short of collecting several barrels of lamprey blood.

Many years later, after the sequences for many of the clotting factors had been reported for humans, my colleague Da-Fei Feng and I were able to align the sequences with a computer and make a phylogenetic tree. It fit the notion of a series of gene duplications very well. Moreover, it implied that most of the duplications had occurred a long time ago, at the very dawn of the vertebrates.

In 2003, the complete genomic sequence of a modern bony fish, the pufferfish, was determined, and one could scan through it and see what genes it has. It has all but a few of the more peripheral clotting proteins found in humans, the central theme being the same. However, the amount of sequence difference between human and pufferfish proteins compared with the degree of difference observed between the duplicated genes suggested some of the gene duplications had occurred not long before the appearance of bony fish. Why not look at the lamprey genome, which diverged 50 million to 100 million years before the appearance of bony fish, to see if the preduplication genes were there? The reason is that the lamprey genome has not been totally sequenced.

Recently, various genome centers around the world have begun maintaining "trace databases." These are uncurated collections of raw DNA sequences determined by random shotgun methods and robotized sequencers. The data are not assembled in any way, and each entry is at best a fragment of a gene. Several hundred organisms, from bacteria to monkeys, are being logged automatically. Among them is the lamprey! So now one can get a glimpse of what genes the lamprey has. We have been scrutinizing this database, even while recognizing its limitations. The reason is that I am getting on in years and can't wait for some mammoth operation with the resources to assemble all the lamprey DNA fragments into a complete genome.

At this point it looks like the lamprey may lack at least two of the mainline clotting factors (Factors VIII and IX), each of which in other vertebrates is the result of a gene duplication. Although the step-by-step evolution of vertebrate blood clotting factors is still technically an "unanswered question," I'm hoping our efforts with the limited trace database will spur others to go for a more convincing, fully assembled lamprey genome.

Russell Doolittle is professor emeritus at the University of California at San Diego. Finding out how blood clotting evolved is one of his major research interests. To learn more about Dr. Doolittle, go to http://www-biology.ucsd.edu/faculty/doolittle.html.

## Review

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### 42.1 Animal Circulatory Systems: An Introduction

- Only the simplest invertebrates—the sponges, cnidarians, and flatworms—have no circulatory systems (Figure 42.2).
- Animals with circulatory systems have a muscular heart that pumps a specialized fluid, such as blood, from one body region to another through tubular vessels. The blood carries $O_2$ and nutrients to body tissues, and carries away $CO_2$ and wastes.
- Most invertebrates have an open circulatory system, in which the heart pumps hemolymph into vessels that empty into body

spaces called sinuses before returning to the heart. Some invertebrates and all vertebrates have a closed system, in which the blood is confined in blood vessels throughout the body and does not mix directly with the interstitial fluid (Figure 42.3).

- In invertebrates, open circulatory systems occur in arthropods and most mollusks, while closed circulatory systems occur in annelids and in mollusks such as squids and octopuses. In vertebrates, the circulatory system has evolved from a heart with a single series of chambers, pumping blood through a single circuit, to a double heart that pumps blood through separate pulmonary and systemic circuits (Figures 42.4 and 42.5).

**Animation: Types of circulatory systems**

**Animation: Circulatory systems**

## 42.2 Blood and Its Components

- Mammalian blood is a fluid connective tissue consisting of erythrocytes, leukocytes, and platelets, suspended in a fluid matrix, the plasma (Figure 42.6).
- Plasma contains water, ions, dissolved gases, glucose, amino acids, lipids, vitamins, hormones, and plasma proteins. The plasma proteins include albumins, globulins, and fibrinogen.
- Erythrocytes contain hemoglobin, which transports $O_2$ between the lungs and all body regions (Figure 42.7).
- Leukocytes defend the body against infecting pathogens.
- Platelets are functional cell fragments that trigger clotting reactions at sites of damage to the circulatory system.

**Animation: White blood cells**

**Animation: ABO compatibilities**

**Animation: Rh factor and pregnancy**

**Animation: Hemostasis**

## 42.3 The Heart

- The mammalian heart is a four-chambered pump. Two atria at the top of the heart pump the blood into two ventricles at the bottom of the heart, which pump blood into two separate pulmonary and systemic circuits of blood vessels (Figures 42.9 and 42.10).
- In both circuits, the blood leaves the heart in large arteries, which branch into smaller arteries, the arterioles. The arterioles deliver the blood to capillary networks, where substances are exchanged between the blood and the interstitial fluid. Blood is collected from the capillaries in small veins, the venules, which join into larger veins that return the blood to the heart (Figure 42.10).
- Contraction of the ventricles pushes blood into the arteries at a peak (systolic) pressure. Between contractions, the blood pressure in the arteries falls to a minimum (diastolic) pressure. The systole–diastole sequence is the cardiac cycle (Figure 42.11).
- Contraction of the atria and ventricles is initiated by signals from the SA node (pacemaker) of the heart (Figure 42.12).

**Animation: Human blood circulation**

**Animation: Major human blood vessels**

**Animation: The human heart**

**Animation: Cardiac cycle**

**Animation: Cardiac conduction**

**Animation: Examples of ECGs**

## 42.4 Blood Vessels of the Circulatory System

- Blood is carried from the heart to body tissues in arteries; small branches of arteries, the arterioles, deliver blood to the capillaries, where substances are exchanged with the interstitial fluid. The blood is collected from the capillaries in venules and then returned to the heart in veins (Figure 42.14).
- The walls of arteries consist of an inner endothelial layer, a middle layer of smooth muscle, and an outer layer of elastic fibers. The smallest arteries, the arterioles, constrict and dilate to regulate blood flow and pressure into the capillaries.
- Capillary walls consist of a single layer of endothelial cells. Blood flow through capillaries is controlled by variation in contraction of the smooth muscles of arterioles and precapillary sphincters (Figure 42.15).
- In the capillary networks, the rate of blood flow is considerably slower than that in arteries and veins. This maximizes the time for exchange of substances between blood and tissues. Diffusion along concentration gradients and bulk flow drive the exchange of substances (Figure 42.17).
- Venules and veins have thinner walls than arteries, allowing the vessels to expand and contract over a wide range. As a result, they act as blood reservoirs as well as conduits.
- The return of blood to the heart is aided by pressure exerted on the veins when surrounding skeletal muscles contract and by respiratory movements. One-way valves in the veins prevent the blood from flowing backward (Figure 42.18).

**Animation: Capillary forces**

**Animation: Vessel anatomy**

## 42.5 Maintaining Blood Flow and Pressure

- Blood pressure and flow are regulated by controlling cardiac output, the degree of blood vessel constriction (primarily arterioles), and the total blood volume. The autonomic nervous system and the endocrine system coordinate these mechanisms.
- Regulation of cardiac output starts with baroreceptors, which detect blood pressure changes and send signals to the medulla. In response, the brain stem sends signals via the autonomic nervous system that alter the rate and force of the heartbeat.
- Hormones secreted by several glands contribute to the regulation of blood pressure and flow.
- Local controls respond primarily to $O_2$ and $CO_2$ concentrations in tissues. Low $O_2$ and high $CO_2$ concentration cause dilation of arteriole walls, increasing the arteriole diameter and blood flow. High $O_2$ and low $CO_2$ concentrations have the opposite effects. NO released by arterial endothelial cells acts locally to increase arteriole diameter and blood flow.

**Animation: Measuring blood pressure**

**Animation: Vein function**

## 42.6 The Lymphatic System

- The lymphatic system, a key component of the immune system, is an extensive network of vessels that collect excess interstitial fluid—which becomes lymph—and returns it to the venous blood (Figure 42.20).
- The tissues and organs of the lymphatic system include the lymph nodes, the spleen, the thymus, and the tonsils. They remove viruses, bacteria, damaged cells, and cellular debris from the lymph and bloodstream, and defend the body against infection and cancer.

**Animation: Human lymphatic system**

**Animation: Lymph vascular system**

# Questions

## Self-Test Questions

1. Compared with vertebrates, most invertebrates:
   a. lead more mobile lives.
   b. require a higher level of oxygen.
   c. have more complex layers of cells.
   d. have slower distribution of blood.
   e. require faster delivery and greater quantities of nutrients.
2. Which circulatory system best describes the animal?
   a. Squids and octopuses have open circulatory systems with ventricles that pump blood away from the heart.
   b. Fishes have a single-chambered heart with an atrium that pumps blood through gills for oxygen exchange.
   c. Amphibians have the most oxygenated blood in the pulmocutaneous circuit and the most deoxygenated blood in the systemic circuit.
   d. Amphibians and reptiles use a two-chambered heart to separate oxygenated and deoxygenated blood.
   e. Birds and mammals pump blood to separate pulmonary and systemic systems from two separate ventricles in a four-chambered heart.
3. A healthy student from the coastal city of Boston enrolls at a college in Boulder, Colorado, a mile above sea level. An analysis of her blood in her first months at college would show:
   a. decreased macrophage activity.
   b. increased secretion of erythropoietin by the kidneys.
   c. increased signaling ability of platelets.
   d. anemia caused by malfunctioning erythrocytes.
   e. increased mitosis of leukocytes.
4. A characteristic of blood circulation through or to the heart is that:
   a. the superior vena cava conveys blood to the head.
   b. the inferior vena cava conveys blood to the right atrium.
   c. the pulmonary arteries convey blood from the lungs to the left atrium.
   d. the pulmonary veins convey blood into the left ventricle.
   e. the aorta branches into two coronary arteries that convey blood from heart muscle.
5. The heartbeat includes:
   a. the systole when the heart fills.
   b. the diastole when the heart muscle contracts.
   c. pressure that causes the AV valves to open, filling the ventricles.
   d. rising pressure in the ventricles to open the AV valves and close the SL valves.
   e. the "lub" sound when the SL valves open and the "dub" sound when the AV valves close.
6. Keeping the mammalian cardiac cycle balanced is/are:
   a. an AV node between the right atria and right ventricle, which signals the Purkinje fibers.
   b. pacemaker cells, which compose the AV node and signal the SA node.
   c. an insulating layer that isolates the SA node from the right atrium.
   d. ion channels in pacemaker cells, which close to depolarize their plasma membranes.
   e. neurogenic stimuli from the nervous system.
7. Hydrostatic pressure is best described as:
   a. the uncoordinated contractions that occur during heart attacks.
   b. a premature ventricular contraction that signifies a skipped beat.
   c. a high point of pressure called diastolic blood pressure.
   d. hypertension, which decreases with age.
   e. the pressure of blood on the walls of arteries.
8. Characteristics of veins and venules are:
   a. thick walls.
   b. large muscle mass in walls.
   c. a large quantity of elastin in the walls.
   d. low blood volume compared with arteries.
   e. one-way valves to prevent backflow of blood.
9. When capillaries exchange substances:
   a. red blood cells move through the capillary lumens in double file.
   b. blood flow resistance is lower than it is in arteries and veins.
   c. water, ions, glucose, and erythrocytes pass freely between blood and tissues.
   d. diffusion along a concentration gradient and bulk flow are operating.
   e. diffusion is greatest closest to the arterioles.
10. To increase cardiac output:
    a. the adrenal medulla and sympathetic nervous system secrete epinephrine and norepinephrine.
    b. baroreceptors in the brain signal the sympathetic nerves.
    c. the brain stem signals the baroreceptors, causing the heart to beat faster.
    d. the autonomic nervous system responds to low oxygen on chemoreceptors and decreases the force of the heartbeat.
    e. chemoreceptors, stimulated by excessive blood oxygen, increase the rate of the heartbeat.

## Questions for Discussion

1. *Aplastic anemia* develops when certain drugs or radiation destroy red bone marrow, including the stem cells that give rise to erythrocytes, leukocytes, and platelets. Predict some symptoms a person with aplastic anemia would be likely to develop. Include at least one symptom related to each type of blood cell.
2. In addition to the engine exhaust of boats and cars, carbon monoxide is also a component of cigarette smoke. What might be the impact of this phenomenon on a smoker's health?
3. In some people, the pressure of the blood pooling in the legs leads to a condition called *varicose veins,* in which the veins stand out like swollen, purple knots. Explain why this might happen, and why veins closer to the leg surface are more susceptible to the condition than those in deeper leg tissues.

## Experimental Analysis

Mice in which the apolipoprotein E gene has been knocked out (deleted) by genetic engineering methods have high levels of plasma cholesterol and readily develop atherosclerosis, particularly on diets high in cholesterol. The immunosuppressant drug rapamycin is being touted also to be a drug that can affect atherosclerosis. Design an experiment to determine whether and at what dose rapamycin is effective in reducing atherosclerosis caused by dietary cholesterol.

## Evolution Link

What is the evolutionary advantage of closure of the septum between the two ventricles to create a double circulatory system?

## How Would You Vote?

Cardiopulmonary resuscitation (CPR) can make the difference between life and death after a cardiac arrest or a heart attack. Should public high schools in your state require all students to take a course in CPR? Is such a course worth diverting time and resources from the basic curriculum? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.