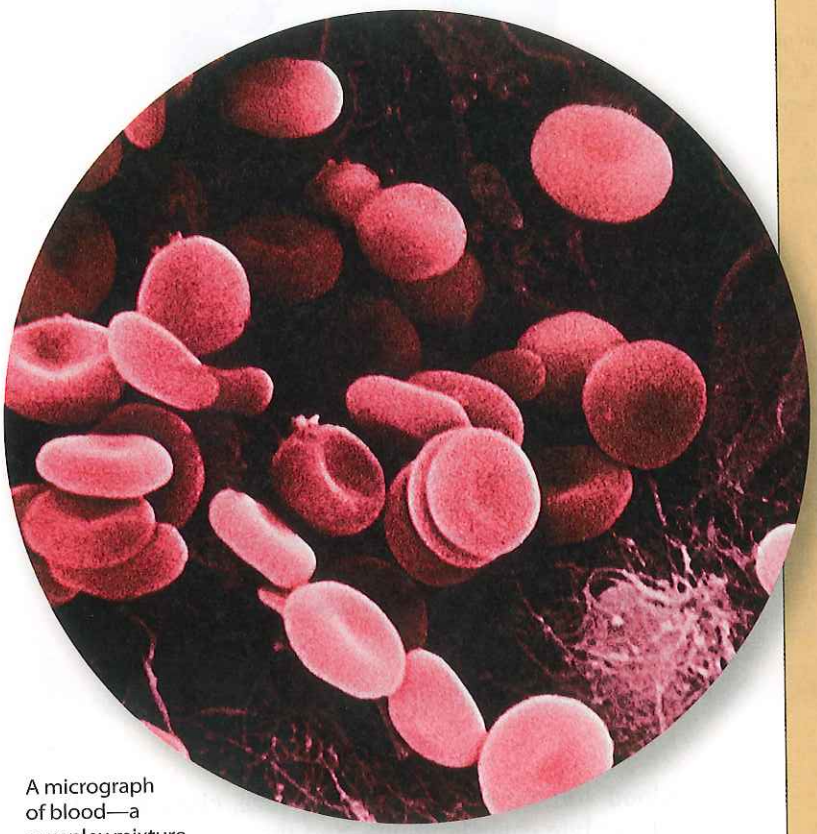
Unit IV

14 Blood



A micrograph of blood—a complex mixture of cells, cell fragments, and many types of dissolved biochemicals that provides nutrients, oxygen, and other vital substances to our cells (1,800×).

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Module 9: Cardiovascular System

Learning Outcomes

After you have studied this chapter, you should be able to:

14.1 Introduction

1 Describe the general characteristics of blood, and discuss its major functions. (p. 526)
2 Distinguish among the formed elements of blood and the liquid portion of blood. (p. 526)

14.2 Blood Cells

3 Describe the origin of blood cells. (p. 527)
4 Explain the significance of red blood cell counts and how they are used to diagnose disease. (p. 530)
5 Discuss the life cycle of a red blood cell. (p. 530)
6 Summarize the control of red blood cell production. (p. 530)
7 Distinguish among the five types of white blood cells, and give the function(s) of each type. (p. 534)
8 Describe a blood platelet, and explain its functions. (p. 537)

14.3 Blood Plasma

9 Describe the functions of each of the major components of plasma. (p. 538)

14.4 Hemostasis

10 Define *hemostasis,* and explain the mechanisms that help to achieve it. (p. 540)
11 Review the major steps in blood coagulation. (p. 541)
12 Explain how to prevent blood coagulation. (p. 544)

14.5 Blood Groups and Transfusions

13 Explain blood typing and how it is used to avoid adverse reactions following blood transfusions. (p. 545)
14 Describe how blood reactions may occur between fetal and maternal tissues. (p. 549)

LEARN PRACTICE ASSESS

Understanding Words

agglutin-, to glue together: *agglutin*ation—clumping of red blood cells.

bil-, bile: *bil*irubin—pigment excreted in the bile.

-crit, to separate: hemato*crit*—percentage by volume of red blood cells in a blood sample, determined by separating the red blood cells from the plasma.

embol-, stopper: *embol*ism—a mass lodging in and obstructing a blood vessel.

erythr-, red: *erythr*ocyte—red blood cell.

hema-, blood: *hema*tocrit—percentage of red blood cells in a given volume of blood.

hemo-, blood: *hemo*globin—red pigment responsible for the color of blood.

hepa-, liver: *hepa*rin—anticoagulant secreted by liver cells.

leuko-, white: *leuko*cyte—white blood cell.

-lys, to break up: fibrino*lys*in—protein-splitting enzyme that can digest fibrin.

macro-, large: *macro*phage—large phagocytic cell.

-osis, abnormal condition: leukocyto*sis*—condition in which white blood cells are overproduced.

-poie, make, produce: erythro*poie*tin—hormone that stimulates the production of red blood cells.

poly-, many: *poly*cythemia—overproduction of red blood cells.

-stasis, halt, make stand: hemo*stasis*—process that stops bleeding from damaged blood vessels.

thromb-, clot: *thromb*ocyte—blood platelet involved in the formation of a blood clot.

Universal Precautions

Blood can contain more than cells, nutrients, proteins, and water—a single drop from an infected individual can harbor billions of viruses. In the wake of the AIDS epidemic, in 1988 the U.S. Centers for Disease Control and Prevention (CDC) devised "universal precautions," which are specific measures that health-care workers should take to prevent transmission of bloodborne infectious agents in the workplace. The CDC singled out HIV and the hepatitis B virus. The guidelines grew out of earlier suggestions for handling patients suspected to have been exposed to viruses. The term *universal* refers to the assumption that *any* patient may have been exposed to a pathogen that can be transmitted in a body fluid.

Attention to safety in the health-care setting can prevent transmission of infectious diseases. The World Health Organization estimates that 4% to 7% of new infections worldwide are transmitted via unsafe injections. Specific recommendations include:

- use of personal protective equipment, such as gloves, goggles, and masks
- engineering controls, such as fume hoods and sharps containers
- work-practice controls, such as enforcing handwashing before and after performing procedures

Universal precautions were designed for, and work well in, preventing transmission of viral illnesses in settings already relatively safe, such as clinics. This isn't necessarily the case for outbreaks, natural disasters, and combat zones. For example, in 2005 several pediatric nurses who aided neighbors infected with the Marburg virus in the isolated town of Uige in Angola, in southwestern Africa, died from this hemorrhagic fever along with hundreds of other people.

Headache, fever, vomiting, and diarrhea begin three to nine days after exposure to the Marburg virus. Then the person bleeds from all body openings, internally and under the skin. Plummeting blood pressure kills most infected individuals within a week, and anyone contacting their blood is in danger of infection. Infected individuals must be isolated and not touched, but the scourge spreads because many family members become infected while tending to their loved ones.

In the 2005 outbreak, contaminated medical equipment caused the rapid and deadly spread of the infection. Untrained clinic workers reused needles, and some people reused needles and intravenous equipment in their homes. However, even universal precautions might not have contained this outbreak, because the infected body fluids were so copious. ■

Health-care workers wear personal protective equipment to shield themselves from body fluids containing disease-causing viruses.

Q: *Which protective gear is worn by this health-care worker?*

Answer can be found in Appendix G on page 938.

14.1 INTRODUCTION

Blood signifies life, and for good reason—it has many vital functions. This complex mixture of cells, cell fragments, and dissolved biochemicals transports nutrients, oxygen, wastes, and hormones; helps maintain the stability of the interstitial fluid; and distributes heat. The blood, heart, and blood vessels form the cardiovascular system and link the body's internal and external environments.

Blood is a type of connective tissue whose cells are suspended in a liquid extracellular matrix. Blood is vital in transporting substances between body cells and the external environment, thereby promoting homeostasis.

Whole blood is slightly heavier and three to four times more viscous than water. Its cells, which form mostly in red bone marrow, include red blood cells and white blood cells. Blood also contains cellular fragments called blood platelets (fig. 14.1). The cells and platelets are termed "formed elements" of the blood, in contrast to the liquid portion.

Blood volume varies with body size, changes in fluid and electrolyte concentrations, and the amount of adipose tissue. Blood volume is typically about 8% of body weight. An average-size adult has about 5 liters of blood.

If a blood sample stands in a tube for a while and is prevented from clotting, the cells separate from the liquid portion and settle to the bottom. Centrifuging the sample quickly packs the cells into the lower part of the centrifuge tube, as figure 14.2 shows. The percentages of cells and liquid in the blood sample can then be calculated.

Most blood samples are about 45% red blood cells by volume. This percentage is called the **hematocrit** (HCT), or **packed cell volume** (PCV). The white blood cells and platelets account for less than 1%. The remaining blood sample, about 55%, is the clear, straw-colored **plasma** (plaz'mah). Plasma is a complex mixture that includes water, amino acids, proteins, carbohydrates, lipids, vitamins, hormones, electrolytes, and cellular wastes (fig. 14.3). Appendix C, Laboratory Tests of Clinical Importance (pp. 928–930), lists values for the hematocrit and other blood tests commonly performed on healthy individuals.

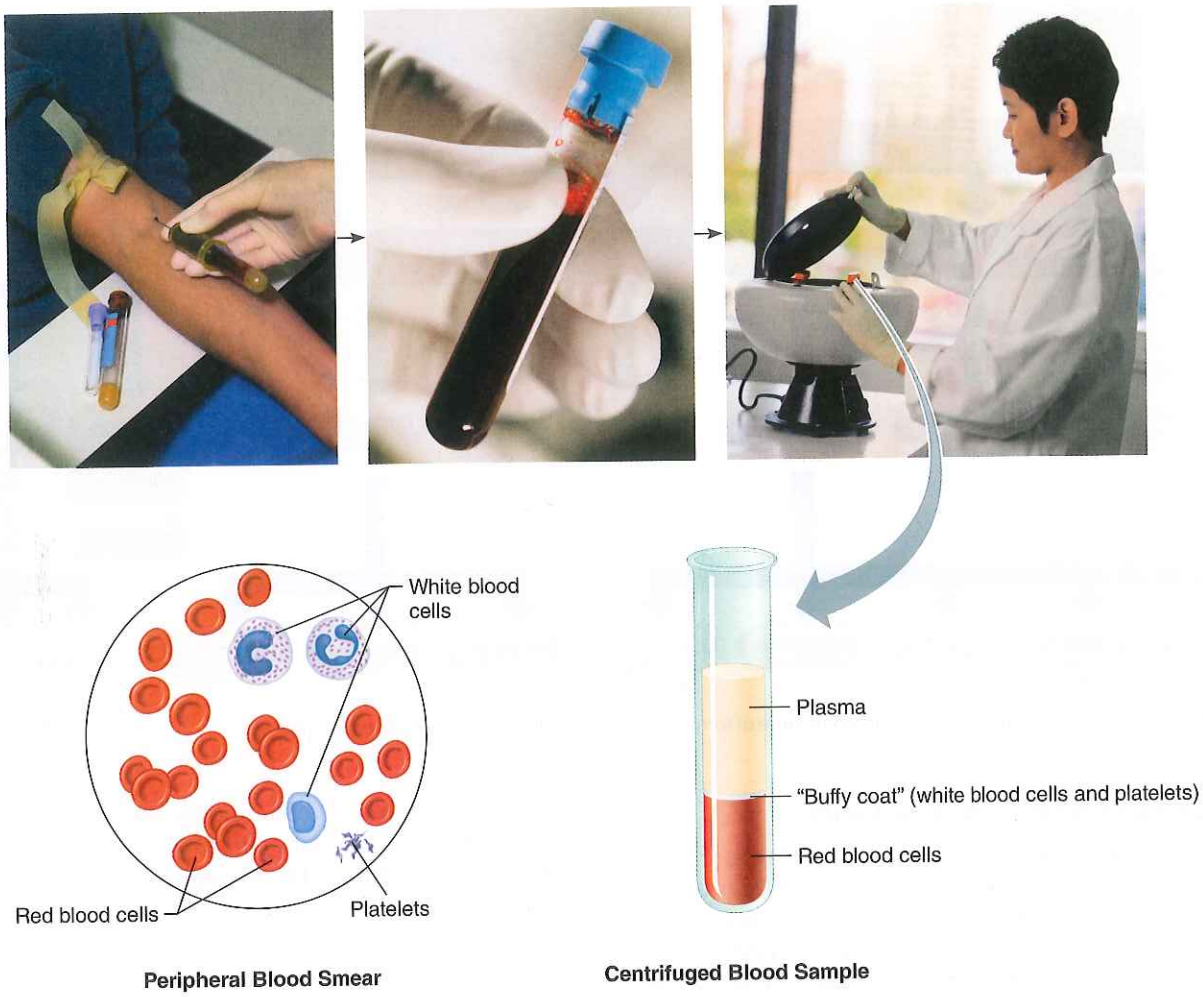


FIGURE 14.1 AP|R Blood consists of a liquid portion called plasma and a solid portion (the formed elements) that includes red blood cells, white blood cells, and platelets. (Note: When blood components are separated, the white blood cells and platelets form a thin layer, called the "buffy coat," between the plasma and the red blood cells.) Blood cells and platelets can be seen under a light microscope when a blood sample is smeared onto a glass slide.

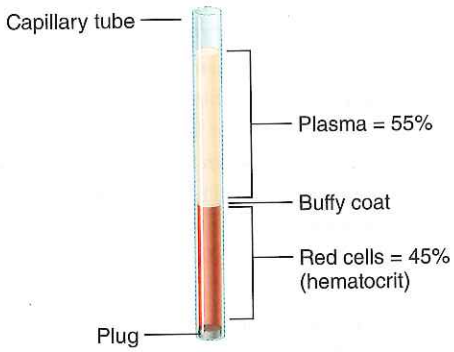


FIGURE 14.2 If a blood-filled capillary tube is centrifuged, the red cells pack in the lower portion and the percentage of red cells (hematocrit) can be determined. Values shown are within the normal range for healthy humans.

PRACTICE

1. What are the major components of blood?
2. What factors affect blood volume?
3. How is hematocrit determined?

14.2 BLOOD CELLS

The Origin of Blood Cells

Blood cells originate in red bone marrow from **hematopoietic** (he″mat-o-poi-et′ik) **stem cells** or **hemocytoblasts** (he″mo-si′to-blastz) (fig. 14.4). A stem cell can divide to give rise to specialized (more differentiated) cells as well as more stem cells. As hematopoietic stem cells divide, the new cells, myeloid and lymphoid stem cells, respond to different secreted growth factors, called **hematopoietic growth factors,** that turn on some genes and turn off others. This exposure to growth factors ultimately sculpts the distinctive formed elements of blood, including the cellular components of the immune system. A protein called *thrombopoietin* (TPO) stimulates large cells called **megakaryocytes** to proliferate. These cells eventually come apart, yielding platelets.

RECONNECT

To Chapter 3, Stem and Progenitor Cells, pages 113–114.

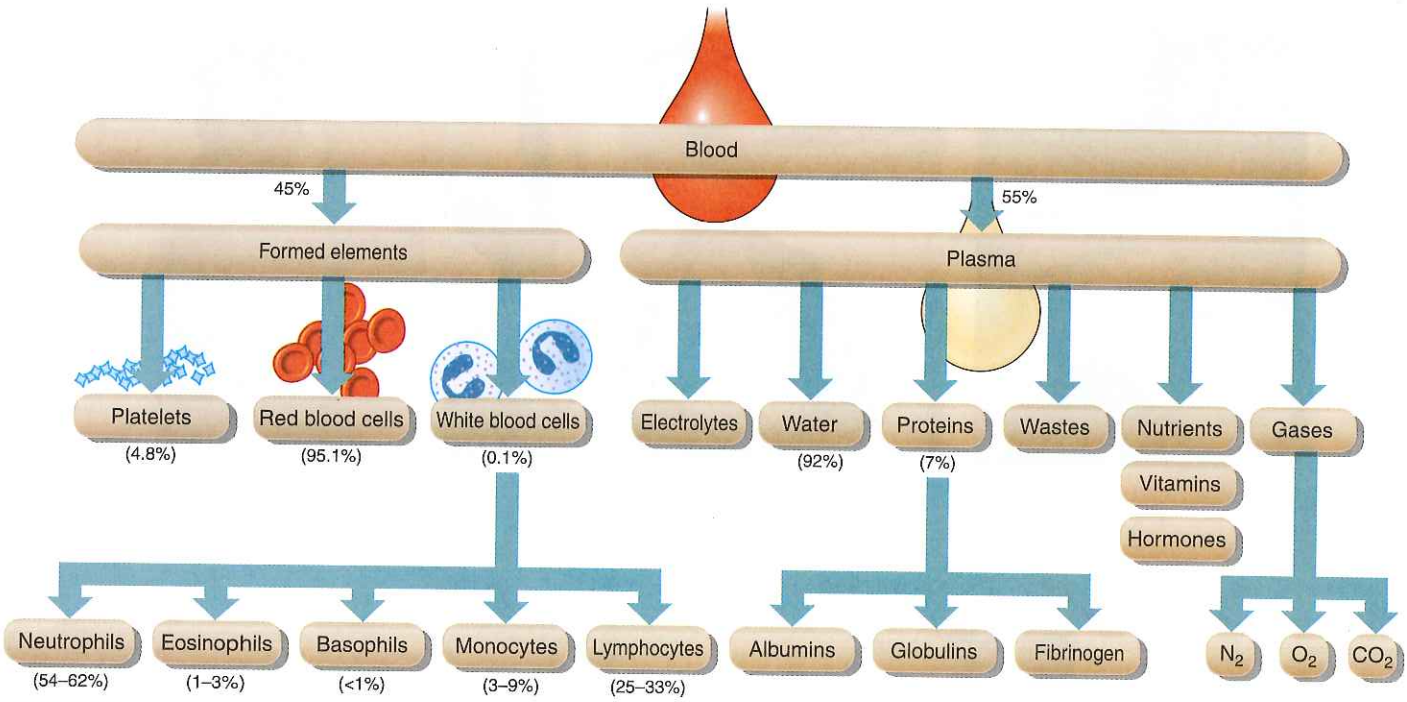


FIGURE 14.3 Blood composition. Blood is a complex mixture of formed elements in a liquid extracellular matrix, plasma.

Characteristics of Red Blood Cells

Red blood cells, or **erythrocytes** (ĕ-rith′ro-sīts), are tiny, approximately 7.5 µm in diameter. They are biconcave discs, thin near their centers and thicker around their rims (fig. 14.5). This distinctive shape is an adaptation for the red blood cell's function of transporting gases—it increases the surface area through which gases can diffuse. The shape also places the cell membrane closer to oxygen-carrying **hemoglobin** (he″mo-glo′bin) molecules in the cell. A red blood cell's shape and flexibility enable it to readily squeeze through the narrow capillaries.

Each red blood cell is about one-third hemoglobin by volume. This protein imparts the color of blood. The rest of the cell mainly consists of membrane, water, electrolytes, and enzymes. When hemoglobin combines with oxygen, the resulting *oxyhemoglobin* is bright red; when the oxygen is released, the resulting *deoxyhemoglobin* is darker. Blood rich in deoxyhemoglobin may appear bluish when it is viewed through blood vessel walls.

Prolonged oxygen deficiency (hypoxia) causes *cyanosis,* in which the skin and mucous membranes appear bluish due to an abnormally high blood concentration of deoxyhemoglobin. Exposure to low temperature may also result in cyanosis by constricting superficial blood vessels. This slows blood flow, allowing removal of more oxygen than usual from blood flowing through the vessels, increasing the amount of deoxyhemoglobin.

Red blood cells have nuclei during their early stages of development but extrude the nuclei as they mature, providing more space for hemoglobin. Because red blood cells lack nuclei, they cannot synthesize proteins or divide. Red blood cells produce ATP through glycolysis only and use none of the oxygen they carry because they also lack mitochondria. As long as cytoplasmic enzymes function, these cells can carry on vital energy-releasing processes. With time, however, red blood cells become less active, more rigid, and more likely to be damaged or worn. Eventually the spleen and liver remove older red blood cells from the circulation.

In *sickle cell disease,* a single DNA base mutation changes one amino acid in the protein part of hemoglobin, causing hemoglobin to crystallize in a low oxygen environment. This bends the red blood cells containing the abnormal hemoglobin into a sickle shape, which tend to get stuck and block flow in small blood vessels, causing excruciating joint pain and damaging many organs. As the spleen works harder to recycle the abnormally short-lived red blood cells, infection becomes likely.

Children with sickle cell disease are typically diagnosed at birth and receive antibiotics daily for years to prevent infection. Hospitalization for blood transfusions may be necessary for painful sickling "crises" of blocked circulation.

A drug, hydroxyurea, is used to activate production of a form of hemoglobin normally produced only in the fetus. The fetal hemoglobin slows sickling, which enables the red blood cells to reach the lungs—where fresh oxygen restores the cells' normal shapes. A bone marrow transplant or an umbilical cord stem cell transplant from a donor can completely cure sickle cell disease, but has a 15% risk of fatality.

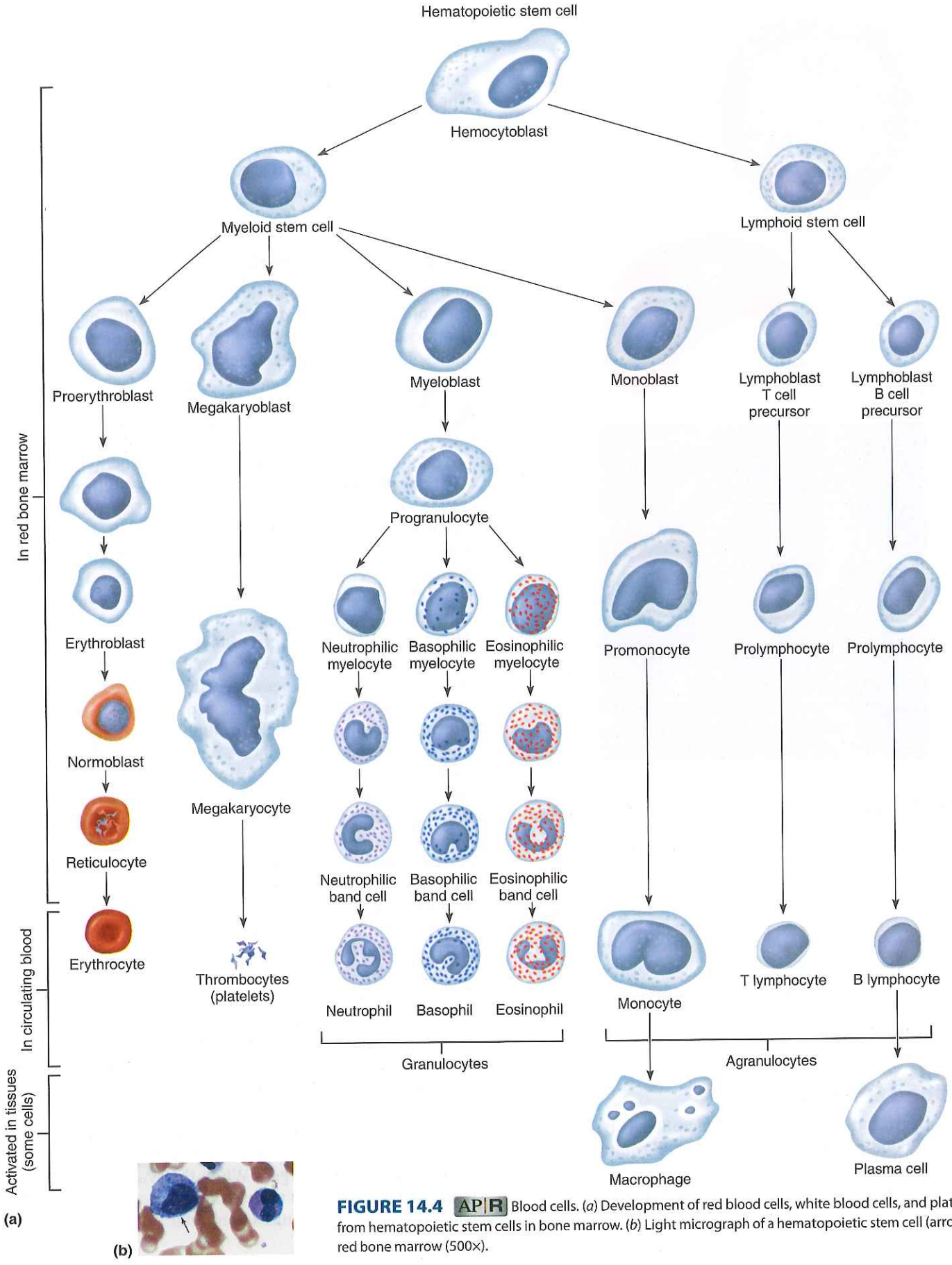
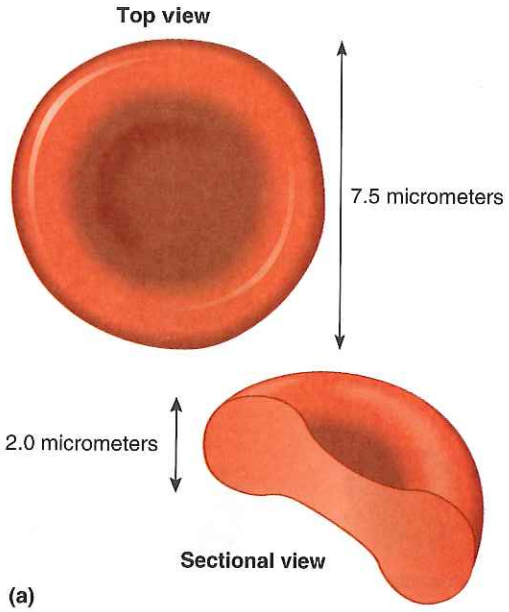


FIGURE 14.4 AP|R Blood cells. (*a*) Development of red blood cells, white blood cells, and platelets from hematopoietic stem cells in bone marrow. (*b*) Light micrograph of a hematopoietic stem cell (arrow) in red bone marrow (500×).



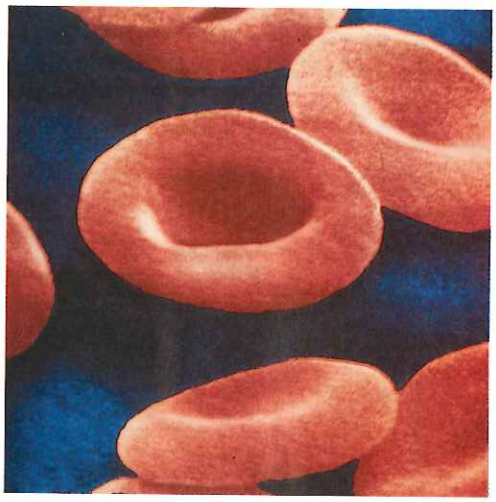


FIGURE 14.5 AP|R Red blood cells. (*a*) The biconcave shape of a red blood cell makes possible its function of transporting oxygen. (*b*) Falsely colored scanning electron micrograph of human red blood cells (5,000×).

PRACTICE

4 How do blood cells form?

5 Describe a red blood cell.

6 How does the biconcave shape of a red blood cell make possible its function?

7 What is the function of hemoglobin?

Red Blood Cell Counts

The number of red blood cells in a microliter (μL or mcL or 1 mm^3) of blood is called the *red blood cell count* (RBCC or RCC). Although this number varies from time to time even in healthy individuals, the typical range for adult males is 4,600,000–6,200,000 cells per microliter, and that for adult females is 4,200,000–5,400,000 cells per microliter. For children, the average range is 4,500,000–5,100,000 cells per microliter. These values may vary slightly with the hospital, physician, and type of equipment used to make blood cell counts. The number of red blood cells generally increases after several days following strenuous exercise or an increase in altitude.

Red blood cell counts are routinely consulted to help diagnose and evaluate the courses of various diseases. Changes in this number may affect health by altering the blood's *oxygen-carrying capacity.*

Red Blood Cell Production and Its Control

Red blood cell formation (erythropoiesis) initially occurs in the yolk sac, liver, and spleen. After birth, these cells are produced almost exclusively by tissue lining the spaces in bones, filled with red bone marrow.

RECONNECT
To Chapter 7, Blood Cell Formation, page 211.

In the red bone marrow, hemocytoblasts divide and give rise to **erythroblasts** (ĕ-rith'ro-blastz). The erythroblasts also divide and give rise to many new cells. The nuclei of these newly formed cells soon shrink and are extruded by being pinched off in thin coverings of cytoplasm and cell membrane. The resulting cells are erythrocytes. For a day or two, some of these young red cells may contain a netlike structure (reticulum) that is a remnant of the endoplasmic reticulum. These cells are called **reticulocytes** (rĕ-tik'u-lo-sitz). This is the stage that exits the bone marrow to enter the blood. When the reticulum degenerates, the cells are fully mature.

The average life span of a red blood cell is 120 days. During that time, it travels through the body about 75,000 times. Many red blood cells are removed from the circulation each day, yet the number in the circulating blood remains relatively stable. These numbers suggest a homeostatic control of the rate of red blood cell production.

A *negative feedback mechanism* using the hormone **erythropoietin** (e-rith"ro-poi'ĕ-tin) (EPO) controls the rate of red blood cell formation. In response to prolonged oxygen deficiency, EPO is released from the kidneys and to a lesser extent from the liver. (In a fetus, the liver is the main site of EPO production.) At high altitudes, for example, although the percentage of oxygen in the air remains the same, the atmospheric pressure decreases, reducing availability of oxygen. The amount of oxygen delivered to the tissues initially decreases. As figure 14.6 shows, this drop in oxygen triggers release of EPO, which travels via the blood to the red bone marrow and increases erythrocyte production.

After a few days, many newly formed red blood cells appear in the circulating blood. The increased rate of production continues until the number of erythrocytes is sufficient to supply tissues with oxygen. When the availability of oxygen returns to normal, EPO release decreases and the rate of red blood cell production returns to normal.

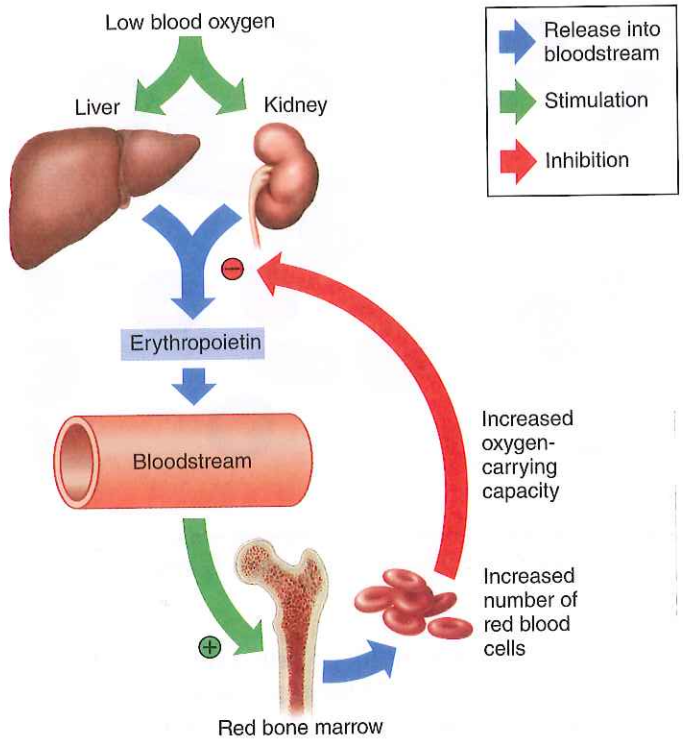


FIGURE 14.6 Low blood oxygen causes the kidneys and liver to release erythropoietin. Erythropoietin travels to red bone marrow and stimulates the production of red blood cells that carry oxygen to tissues.

RECONNECT
To Chapter 13, Abusing Hormones to Improve Athletic Performance, page 493.

Other conditions can lower oxygen levels and stimulate EPO release. These include loss of blood, which decreases the oxygen-carrying capacity of the cardiovascular system, and chronic lung diseases, which decrease the respiratory surface area available for gas exchange. An excessive increase in red blood cells is *polycythemia.* This increases blood viscosity, slowing blood flow and impairing circulation.

PRACTICE

8 What is the typical red blood cell count for an adult male? For an adult female?

9 Where are red blood cells produced?

10 How does a red blood cell change as it matures?

11 How is red blood cell production controlled?

Dietary Factors Affecting Red Blood Cell Production

Availability of B-complex vitamins B_{12} and folic acid significantly influences red blood cell production. These vitamins, required for DNA synthesis, are necessary for the growth and division of all cells. Because hematopoietic cells frequently divide, they are especially vulnerable to a deficiency of either of these vitamins. Lack of vitamin B_{12} is usually due to a disorder in the stomach lining rather than to a dietary deficiency, because parietal cells in the stomach secrete a substance called *intrinsic factor* required to absorb vitamin B_{12}.

In the absence of intrinsic factor, vitamin B_{12} absorption decreases, causing the red bone marrow to form abnormally large, irregularly shaped, thin-membraned fragile red blood cells resulting in a condition called *pernicious anemia.* B_{12} deficiency can also cause permanent brain damage if not treated promptly with vitamin B_{12} injections. Taking excess folic acid can mask a vitamin B_{12} deficiency by correcting the anemia, but will not prevent the neurological damage.

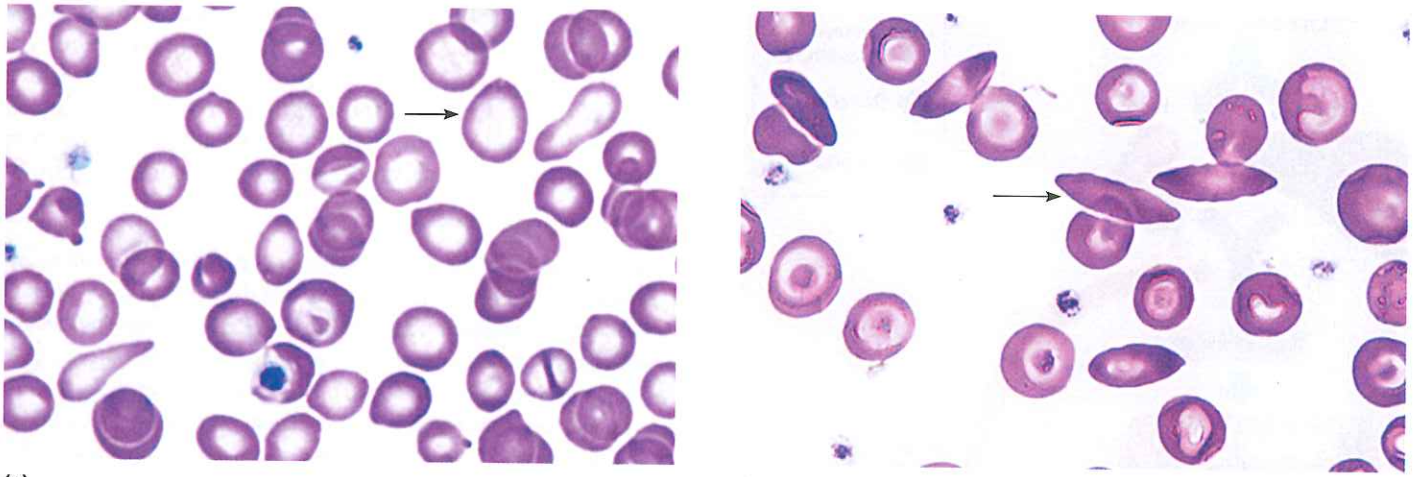
Iron is required for hemoglobin synthesis. Although much of the iron released during the decomposition of hemoglobin is available for reuse, some iron is lost each day and must be replaced. Only a small fraction of ingested iron is absorbed. Iron absorption is slow, but the rate varies with the total amount of iron in the body. When iron stores are low, absorption rate increases, and when the tissues are becoming saturated with iron, the rate greatly decreases. Table 14.1 summarizes the dietary factors that affect red blood cell production.

Vitamin C increases absorption of iron in the digestive tract. Drinking orange juice with a meal is a good way to boost iron absorption. Drinking tea with a meal reduces absorption of iron because tannic acid in tea binds dietary iron and prevents its absorption.

A deficiency of red blood cells or a reduction in the amount of hemoglobin they contain results in a condition called **anemia.** This reduces the oxygen-carrying capacity of the blood, and the affected person may appear pale and

TABLE 14.1 | Dietary Factors Affecting Red Blood Cell Production

Substance	Source	Function
Vitamin B_{12} (requires intrinsic factor for absorption via small intestine)	Absorbed from small intestine	DNA synthesis
Iron	Absorbed from small intestine; conserved during red blood cell destruction and made available for reuse	Hemoglobin synthesis
Folic acid	Absorbed from small intestine	DNA synthesis



(a) (b)

FIGURE 14.7 Abnormal red blood cells. (*a*) Light micrograph of erythrocytes with central pallor or paleness (arrow) as seen in iron-deficiency anemia (1,000×). (*b*) Light micrograph of sickled erythrocytes (arrow) from a person with sickle cell disease (1,000×). The purple color is due to the stain used in the preparation.

lack energy. Figure 14.7 shows red blood cells of someone who has iron-deficiency anemia (fig. 14.7*a*) and of someone with sickle cell disease (fig. 14.7*b*). A pregnant woman may become anemic if she doesn't eat iron-rich foods, because her blood volume increases due to fluid retention to accommodate the requirements of the fetus. This increased blood volume decreases the hematocrit. Table 14.2 describes some types of anemia,

PRACTICE

12 Which vitamins are necessary for red blood cell production?

13 Why is iron required for the formation of red blood cells?

Destruction of Red Blood Cells

Red blood cells are elastic and flexible, and they readily bend as they pass through small blood vessels. With age, however, these cells become more fragile, and may be damaged by passing through capillaries, particularly those in active muscles that must withstand contractile forces.

Damaged or worn red blood cells rupture as they pass through the spleen or liver. In these organs, macrophages (see chapter 5, p. 163) phagocytize and destroy damaged red blood cells and their contents. Hemoglobin molecules liberated from the red blood cells break down into their four component polypeptide "globin" chains, each surrounding a *heme* group (fig. 14.8*a*,*b*).

The heme further decomposes into iron and a greenish pigment called **biliverdin.** The iron, combined with a protein called *transferrin,* may be carried by the blood to the hematopoietic (red blood cell-forming) tissue in the red bone marrow and reused in synthesizing new hemoglobin. About 80% of the iron is stored in the liver cells in the form of an iron-protein complex called *ferritin.* In time, the biliverdin is converted to an orange pigment called **bilirubin.** Biliverdin and bilirubin are excreted in the bile as bile pigments (see fig. 14.8*c*,*d* and fig. 14.9).

The polypeptide globin chains break down into amino acids. The individual amino acids are metabolized by the macrophages or released into the blood. Table 14.3 summarizes the process of red blood cell destruction. Figure 14.9 summarizes the life cycle of a red blood cell.

TABLE 14.2 | Some Types of Anemia

Type	Cause	Defect
Aplastic anemia	Toxic chemicals, radiation	Damaged bone marrow
Hemolytic anemia	Toxic chemicals	Red blood cells destroyed
Iron deficiency anemia	Dietary lack of iron	Hemoglobin deficient
Pernicious anemia	Inability to absorb vitamin B_{12}	Excess of large, fragile cells
Sickle cell disease	Defective gene	Red blood cells abnormally shaped
Thalassemia	Defective gene	Hemoglobin deficient; red blood cells short-lived

TABLE 14.3 | Major Events in Red Blood Cell Destruction

1. Squeezing through the capillaries of active tissues damages red blood cells.
2. Macrophages in the spleen and liver phagocytize damaged red blood cells.
3. Hemoglobin from the red blood cells is decomposed into heme and globin.
4. Heme is decomposed into iron and biliverdin.
5. Iron is made available for reuse in the synthesis of new hemoglobin or is stored in the liver as ferritin.
6. Some biliverdin is converted into bilirubin.
7. Biliverdin and bilirubin are excreted in bile as bile pigments.
8. The globin is broken down into amino acids metabolized by macrophages or released into the plasma.

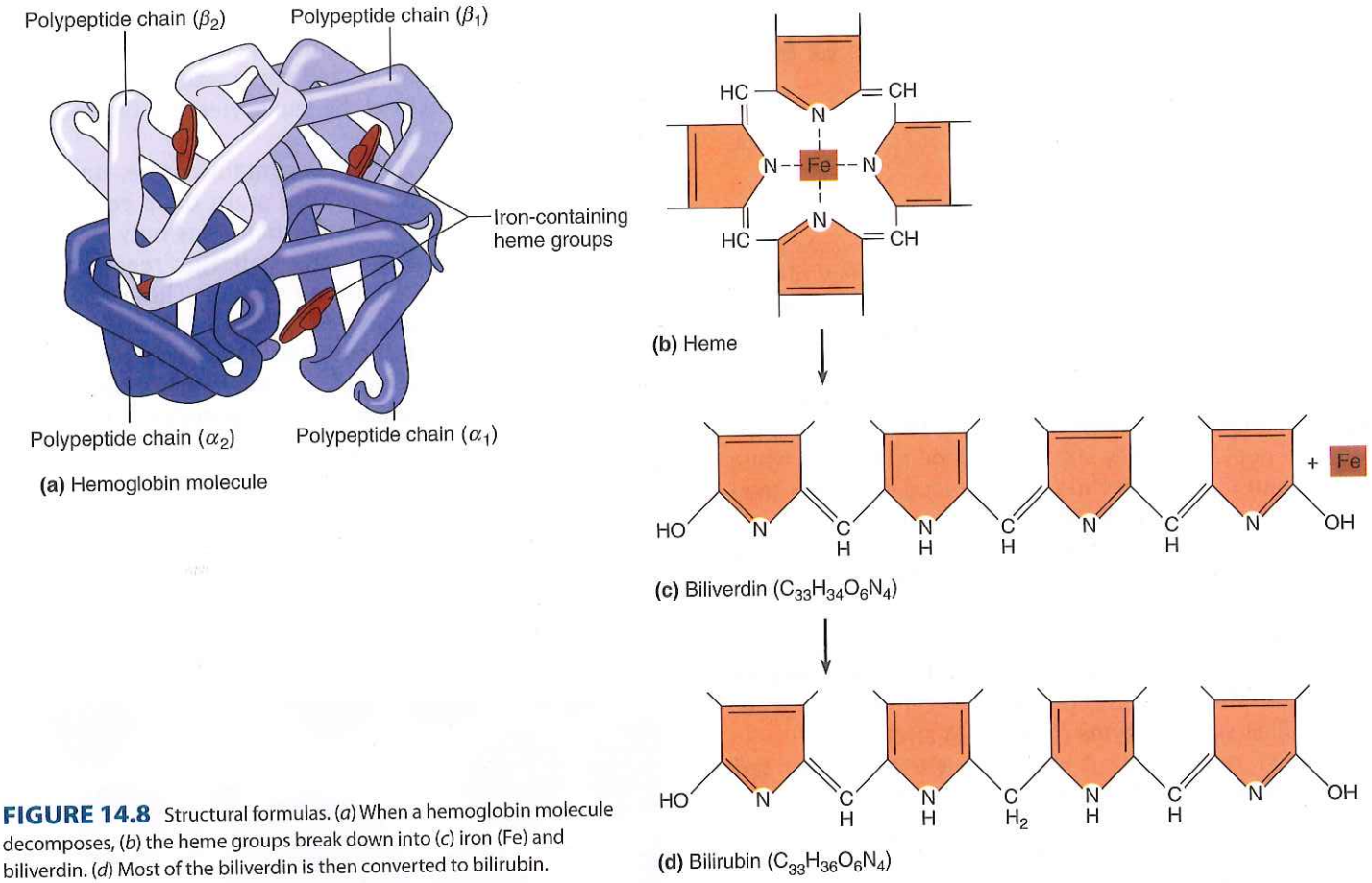


FIGURE 14.8 Structural formulas. (*a*) When a hemoglobin molecule decomposes, (*b*) the heme groups break down into (*c*) iron (Fe) and biliverdin. (*d*) Most of the biliverdin is then converted to bilirubin.

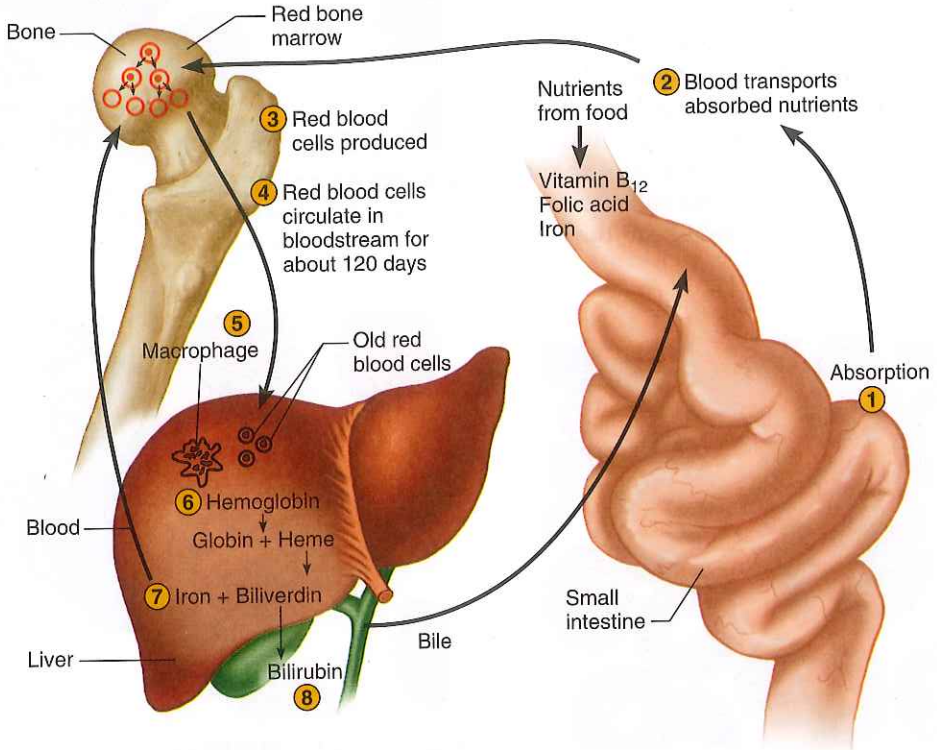


FIGURE 14.9 AP|R Life cycle of a red blood cell. (*1*) The small intestine absorbs essential nutrients. (*2*) Blood transports nutrients to red bone marrow. (*3*) In the red bone marrow, red blood cells arise from the division of less-specialized progenitor cells. (*4*) Mature red blood cells are released into the bloodstream, where they circulate for about 120 days. (*5*) Macrophages destroy old red blood cells in the liver and spleen. (*6*) Hemoglobin liberated from red blood cells is broken down into heme and globin. (*7*) Iron from heme returns to red bone marrow and is reused. (*8*) Biliverdin and bilirubin are excreted in bile.

PRACTICE

14 What happens to damaged red blood cells?

15 What are the products of hemoglobin breakdown?

Types of White Blood Cells

White blood cells, or **leukocytes** (lu'ko-sīts), protect against disease. Leukocytes develop from hemocytoblasts in the red bone marrow in response to hormones, much as red cells form from precursors upon stimulation from EPO. These hormones fall into two groups—**interleukins** (in"ter-lu-kinz) and **colony-stimulating factors** (CSFs). Interleukins are numbered, while most colony-stimulating factors are named for the cell population they stimulate. Blood transports white blood cells to sites of infection. White blood cells may then leave the bloodstream, as described later in this chapter.

Normally, five types of white cells are in circulating blood. They differ in size, the nature of their cytoplasm, the shape of the nucleus, and their staining characteristics, and they are named for these distinctions. For example, leukocytes with granular cytoplasm are called **granulocytes** (gran'u-lo-sīts"), whereas those without cytoplasmic granules are called **agranulocytes** (a-gran'u-lo-sīts).

A typical granulocyte is about twice the size of a red blood cell. Members of this group include neutrophils, eosinophils, and basophils. Granulocytes develop in red bone marrow, as do red blood cells. However, they have a short life span, averaging about twelve hours.

Neutrophils (nu'tro-filz) have fine cytoplasmic granules that appear light purple with a combination of acid and base stains. The nucleus of an older neutrophil is lobed and consists of two to five sections (segments, so these cells are sometimes called *segs*) connected by thin strands of chromatin (fig. 14.10). They are also called *polymorphonuclear leukocytes* (PMNs) due to the variation of nucleus shape from cell to cell. Younger neutrophils are also called *bands* because their nuclei are C-shaped. Neutrophils are the first white blood cells to arrive at an infection site. These cells phagocytize bacteria, fungi, and some viruses. Neutrophils account for 54% to 62% of the leukocytes in a typical blood sample from an adult.

Eosinophils (e"o-sin'o-filz) contain coarse, uniformly sized cytoplasmic granules that stain deep red in acid stain (fig. 14.11). The nucleus usually has only two lobes (bilobed). Eosinophils moderate allergic reactions and defend against parasitic worm infestation. These cells make up 1% to 3% of the total number of circulating leukocytes.

Basophils (ba'so-filz) are similar to eosinophils in size and in the shape of their nuclei. However, they have fewer, more irregularly shaped cytoplasmic granules than eosinophils, and these granules appear deep blue in basic stain (fig. 14.12). A basophil's granules can obscure a view of the nucleus. Basophils migrate to damaged tissues where they release *histamine,* which promotes inflammation, and *heparin,* which inhibits blood clotting, thus increasing blood flow to injured tissues. Basophils usually account for less than 1% of the leukocytes.

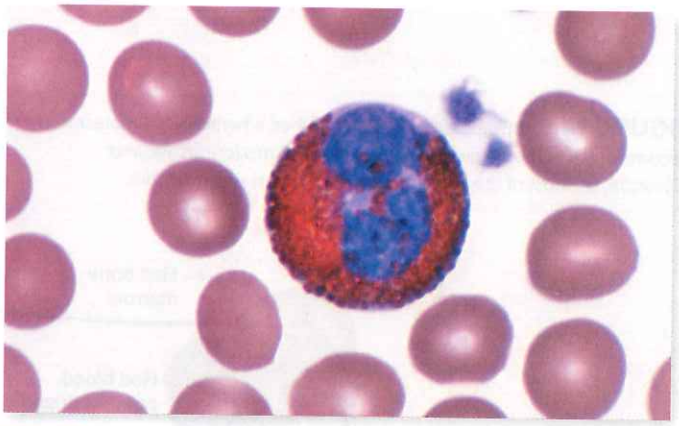


FIGURE 14.11 AP|R An eosinophil has red-staining cytoplasmic granules (2,000×). This type of white blood cell kills parasitic worms and helps to control allergic reactions.

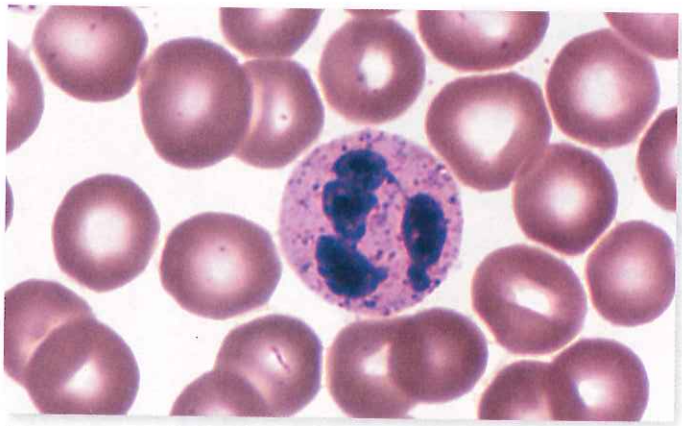


FIGURE 14.10 AP|R A neutrophil has a lobed nucleus with two to five segments (2,000×). This blood cell type has abundant lysosomes, which contain enzymes that break down parts of phagocytized bacteria.

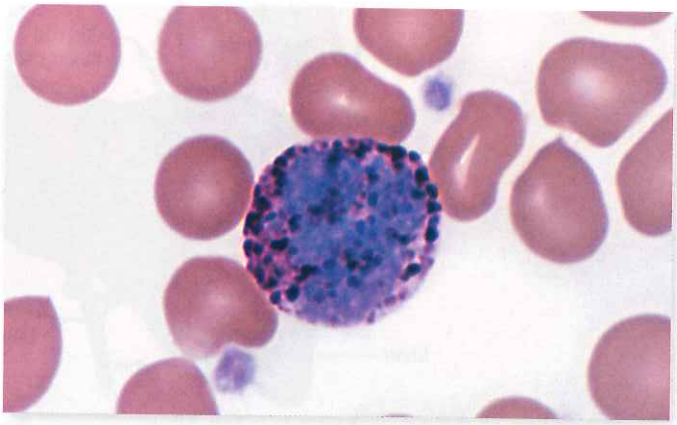


FIGURE 14.12 AP|R A basophil has cytoplasmic granules that stain deep blue (2,000×). This type of white blood cell produces heparin, which prevents inappropriate blood clotting, and histamines, which increase circulation to injured tissues.

The leukocytes of the agranulocyte group include monocytes and lymphocytes. Monocytes generally arise from red bone marrow. Lymphocytes form in the organs of the lymphatic system as well as in the red bone marrow.

Monocytes (mon'o-sītz), the largest blood cells, are two to three times greater in diameter than red blood cells. Their nuclei are spherical, kidney-shaped, oval, or lobed (fig. 14.13). Monocytes leave the bloodstream and become *macrophages* that phagocytize bacteria, dead cells, and other debris in the tissues. They usually make up 3% to 9% of the leukocytes in a blood sample and live for several weeks or even months.

Most **lymphocytes** (lim'fo-sītz) are only slightly larger than erythrocytes. A typical lymphocyte has a large, spherical nucleus surrounded by a thin layer of cytoplasm (fig. 14.14). The major types of lymphocytes are *T cells* and *B cells*, which are both important in *immunity*. T cells directly attack microorganisms, tumor cells, and transplanted cells (see chapter 16, p. 630). B cells produce *antibodies* (see chapter 16, p. 632), which are proteins that attack foreign molecules. Lymphocytes account for 25% to 33% of the circulating leukocytes. They may live for years.

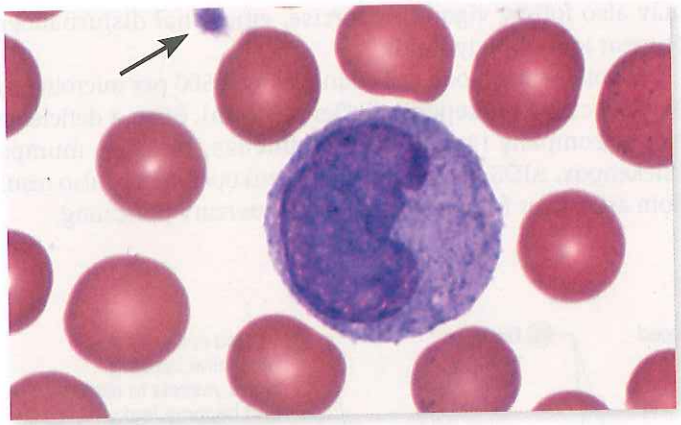


FIGURE 14.13 AP|R A monocyte is the largest of the blood cells (2,000×). It may leave the bloodstream and become a macrophage, which is a wandering phagocytic cell that destroys damaged red blood cells. Note the platelet indicated by the arrow. © R. G. Kessel/Visuals Unlimited

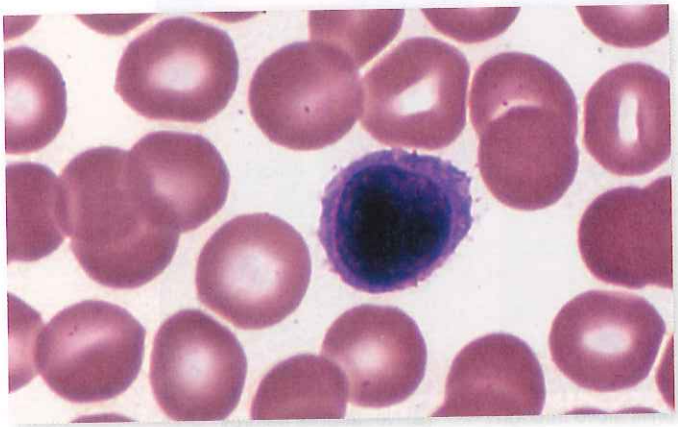


FIGURE 14.14 AP|R The lymphocyte, the smallest of the white blood cells, has a large, round nucleus (2,000×). Lymphocytes carry out the immune response and are discussed further in chapter 16.

PRACTICE

16 Which hormones are necessary for the differentiation of white blood cells from hematopoietic stem cells in red bone marrow?

17 Distinguish between granulocytes and agranulocytes.

18 List five types of white blood cells, and explain how they differ from one another.

19 Describe the function of each type of white blood cell.

Functions of White Blood Cells

Leukocytes can squeeze between the cells that form the walls of the smallest blood vessels. This movement, called **diapedesis** (di"ah-pĕ-de'sis), allows the white blood cells to leave the circulation (fig. 14.15). A series of proteins called cellular adhesion molecules help guide leukocytes to the site of injury. Once outside the blood, leukocytes move through interstitial spaces using a form of self-propulsion called *ameboid motion*.

RECONNECT
To Chapter 3, Cellular Adhesion Molecules, pages 89-90.

The most mobile and active phagocytic leukocytes are neutrophils and monocytes. Neutrophils cannot ingest particles much larger than bacterial cells, but monocytes can engulf larger structures. Monocytes contain many lysosomes, which are filled with digestive enzymes that break down organic molecules in captured bacteria. Neutrophils and monocytes can become so engorged with digestive products and bacterial toxins that they die.

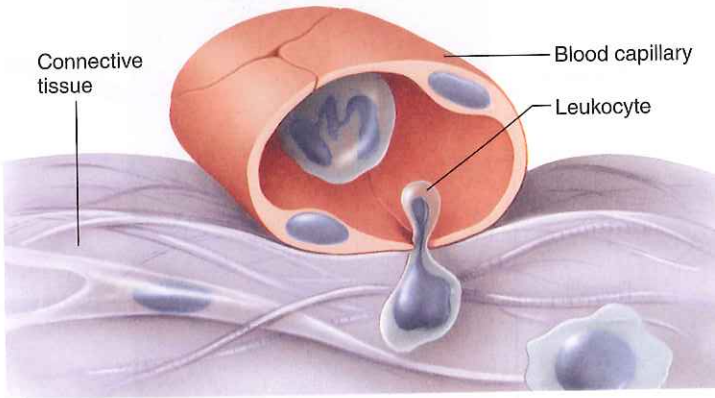


FIGURE 14.15 In a type of movement called diapedesis, leukocytes squeeze between the cells of a capillary wall and enter the tissue space outside the blood vessel.

Q: *What is a monocyte called once it has left the bloodstream and entered the tissues?*

Answer can be found in Appendix G on page 938.

When microorganisms invade human tissues, basophils respond by releasing biochemicals that dilate local blood vessels. For example, histamine dilates smaller blood vessels and makes the smallest vessels leaky. As more blood flows through the smallest vessels, the tissues redden and copious fluids leak into the interstitial spaces. This response, called an inflammatory reaction, produces swelling that delays the spread of invading microorganisms into other regions (see chapter 16, pp. 626–627). At the same time, damaged cells release chemicals that attract leukocytes. This phenomenon is called **positive chemotaxis** (poz′ĭ-tiv ke″mo-tak′sis) and, when combined with diapedesis, it quickly brings many white blood cells into inflamed areas (fig. 14.16).

As bacteria, leukocytes, and damaged cells accumulate in inflamed tissue, a thick fluid called *pus* forms and remains while the invading microorganisms are active. If the pus is not moved to the outside of the body or into a body cavity, it may remain trapped in the tissues for some time. Eventually, surrounding cells absorb it.

A GLIMPSE AHEAD | **To Chapter 16**

White blood cells protect against infection in various ways. Neutrophils and monocytes remove any foreign particles from the body as part of the innate (nonspecific) defense against disease. As part of the adaptive (specific) defense, lymphocytes participate in the formation of specific antibody proteins in the immune response.

PRACTICE

20 How do white blood cells reach microorganisms outside blood vessels?

21 Which white blood cells are the most active phagocytes?

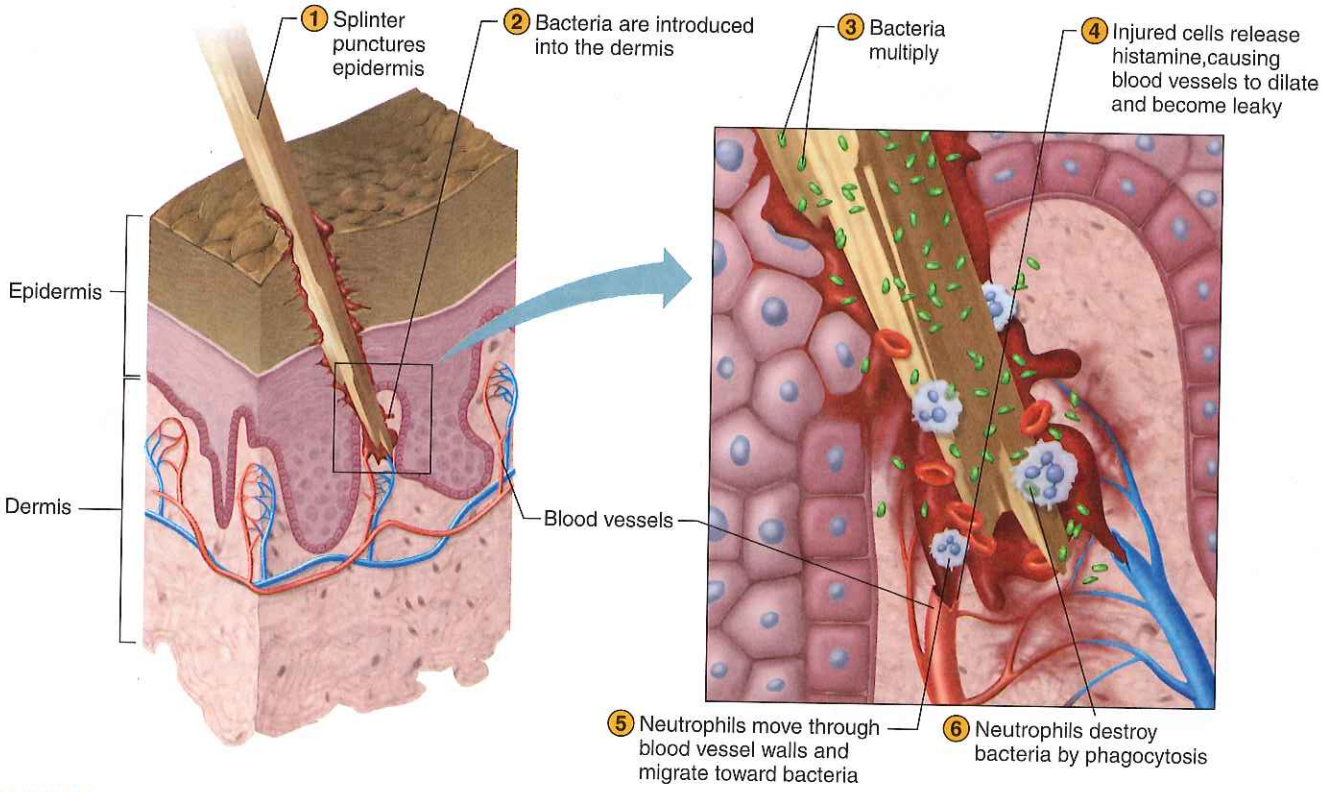
22 How do white blood cells fight infection?

White Blood Cell Counts

The procedure used to count white blood cells is similar to that used for counting red blood cells. However, before a *white blood cell count* (WBCC or WCC) is made, the red blood cells in the blood sample are destroyed so they will not be mistaken for white blood cells. Normally, a microliter of blood includes 4,500 to 10,000 white blood cells.

The total number and percentages of different white blood cell types are of clinical interest. A rise in the number of circulating white blood cells may indicate infection. A total number of white blood cells exceeding 10,000 per microliter of blood constitutes **leukocytosis** (lu″ko-si-to′sis), indicating acute infection, such as appendicitis. Leukocytosis may also follow vigorous exercise, emotional disturbances, or great loss of body fluids.

A total white blood cell count below 4,500 per microliter of blood is called **leukopenia** (lu″ko-pe′ne-ah). Such a deficiency may accompany typhoid fever, influenza, measles, mumps, chickenpox, AIDS, or poliomyelitis. Leukopenia may also result from anemia or from lead, arsenic, or mercury poisoning.



IGURE 14.16 When bacteria invade the tissues, leukocytes migrate into the region and destroy the microbes by phagocytosis.

A *differential white blood cell count* lists percentages of the various types of leukocytes in a blood sample. This test is useful because the relative proportions of white blood cells may change in particular diseases. The number of neutrophils, for instance, usually increases during bacterial infections, and eosinophils may become more abundant during certain parasitic infections and allergic reactions. In HIV infection and AIDS, the number of helper T cells, a type of lymphocyte, drops sharply.

Table 14.4 lists some disorders that alter the numbers of particular types of white blood cells. Clinical Application 14.1 examines leukemia, which is cancer of the white blood cells.

PRACTICE

23 What is the normal human white blood cell count?

24 Distinguish between leukocytosis and leukopenia.

25 What is a differential white blood cell count?

TABLE 14.4 | Abnormal White Blood Cell Numbers

White Blood Cell Population Change	Illness
Elevated lymphocytes	Hairy cell leukemia, whooping cough, mononucleosis
Elevated eosinophils	Tapeworm infestation, hookworm infestation, allergic reactions
Elevated monocytes	Typhoid fever, malaria, tuberculosis
Elevated neutrophils	Bacterial infections
Too few helper T cells (lymphocytes)	AIDS

Blood Platelets AP|R

Platelets (plāt'letz), or **thrombocytes** (throm'bo-sītz), are not complete cells. They arise from very large cells in the red bone marrow, called *megakaryocytes* (meg"ah-kar'o-sītz), that fragment like a shattered plate, releasing small sections of cytoplasm—platelets—into the circulation. The larger fragments of the megakaryocytes shrink and become platelets as they pass through the blood vessels in the lungs (see fig. 14.13). Megakaryocytes, and therefore platelets, develop from hemocytoblasts (see fig. 14.4) in response to the hormone **thrombopoietin** (throm"bo-poi'ĕ-tin).

Each platelet lacks a nucleus and is less than half the size of a red blood cell. It is capable of ameboid movement and may live for about ten days. In normal blood, the *platelet count* varies from 150,000 to 450,000 platelets per microliter.

Platelets help repair damaged blood vessels by sticking to broken surfaces. They release **serotonin,** which contracts smooth muscles in the vessel walls, reducing blood flow. Table 14.5 summarizes the characteristics of blood cells and platelets.

Thrombocytopenia (throm"bo-si"to-pe'ne-ah) occurs when the platelet count drops below 150,000 platelets per microliter of blood. Symptoms include bleeding easily; capillary hemorrhages throughout the body; and small, bruiselike spots on the skin called petechiae. Thrombocytopenia is a common side effect of cancer chemotherapy and radiation treatments and can be a complication of pregnancy, leukemia, bone marrow transplantation, infectious disease, cardiac surgery, or anemia. Conventional treatment is transfusion of platelets. Treatment with thrombopoietin (TPO) stimulates formation and maturation of megakaryocytes and thereby boosts platelet levels.

TABLE 14.5 | Cellular Components of Blood

Component	Description	Number Present	Function
Red blood cell (erythrocyte)	Biconcave disc without a nucleus, about one-third hemoglobin	4,200,000 to 6,200,000 per microliter	Transports oxygen and carbon dioxide
White blood cell (leukocyte)		4,500 to 10,000 per microliter	Destroys pathogenic microorganisms and parasites and removes worn cells
Granulocytes	About twice the size of red blood cells; cytoplasmic granules are present		
Neutrophil	Nucleus with two to five lobes; cytoplasmic granules stain light purple in combined acid and base stains	54%–62% of white blood cells present	Phagocytizes small particles
Eosinophil	Nucleus bilobed; cytoplasmic granules stain red in acid stain	1%–3% of white blood cells present	Kills parasites and moderates allergic reactions
Basophil	Nucleus lobed; cytoplasmic granules stain blue in basic stain	Less than 1% of white blood cells present	Releases heparin and histamine
Agranulocytes	Cytoplasmic granules are absent		
Monocyte	Two to three times larger than a red blood cell; nuclear shape varies from spherical to lobed	3%–9% of white blood cells present	Phagocytizes large particles
Lymphocyte	Only slightly larger than a red blood cell; its nucleus nearly fills cell	25%–33% of white blood cells present	Provides immunity
Platelet (thrombocyte)	Cytoplasmic fragment	150,000 to 450,000 per microliter	Helps control blood loss from broken vessels

14.1 CLINICAL APPLICATION

Leukemia

When the twenty-three-year-old had a routine physical examination, she expected reassurance that her healthy lifestyle had indeed been keeping her healthy. What she got, a few days later, was a shock. Instead of having 4,500 to 10,000 white blood cells per microliter of blood, she had more than ten times that number—and many of the cells were cancerous. She had chronic myeloid leukemia (CML). Her red bone marrow was flooding her circulation with too many granulocytes, most of them poorly differentiated (figure 14A).

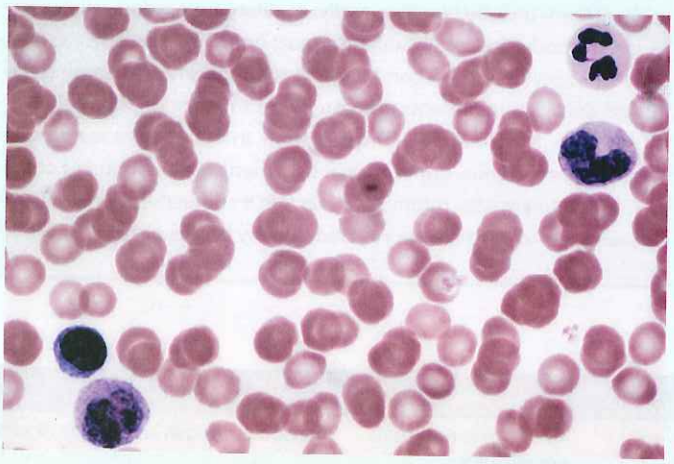
Another type of leukemia is lymphoid, in which the cancer cells are lymphocytes, produced in lymph nodes. Both myeloid and lymphoid leukemia can cause fatigue, headaches, nosebleeds and other bleeding, frequent respiratory infections, fever, bone pain, bruising, and other signs of slow blood clotting.

The symptoms arise from the disrupted proportions of the blood's formed elements and their malfunction. Immature white blood cells increase the risk of infection. Leukemic cells crowd out red blood cells and their precursors in the red marrow, causing anemia and the resulting fatigue. Platelet deficiency (thrombocytopenia) slows clotting time, causing bruises and bleeding.

Leukemia is also classified as acute or chronic. An acute condition appears suddenly, symptoms progress rapidly, and without treatment, death occurs in a few months. Chronic forms begin more slowly and may remain undetected for months or even years or, in rare cases, decades. Without treatment, life expectancy after symptoms develop is about three years.

Traditional cancer treatments destroy any cell that is actively dividing. A newer drug, Gleevec, specifically targets cancer cells by nestling into ATP-binding sites on a type of enzyme called a tyrosine kinase, which blocks the message to divide. If cancer cells become resistant to Gleevec, even newer drugs are available that target the cancer cells in different ways. People with leukemia have other options. Bone marrow and stem cell transplants may cure the condition.

Another way that leukemia treatment is improving is refining diagnosis, based on identifying the proteins that leukemia cells produce. This information is used to predict which drugs are most likely to be effective, and which will cause intolerable side effects, in particular individuals. For example, some people with acute lymphoblastic leukemia (ALL), diagnosed on the basis of the appearance of the cancer cells in a blood smear, do not respond to standard chemotherapy. However, DNA microarray (also called DNA chip) technology revealed that the cells of most patients who do not improve produce different proteins than the cancer cells of patients who do respond to the drugs used to treat ALL. The nonresponders actually have a different form of leukemia, called mixed-lineage leukemia. They respond to different drugs. ■



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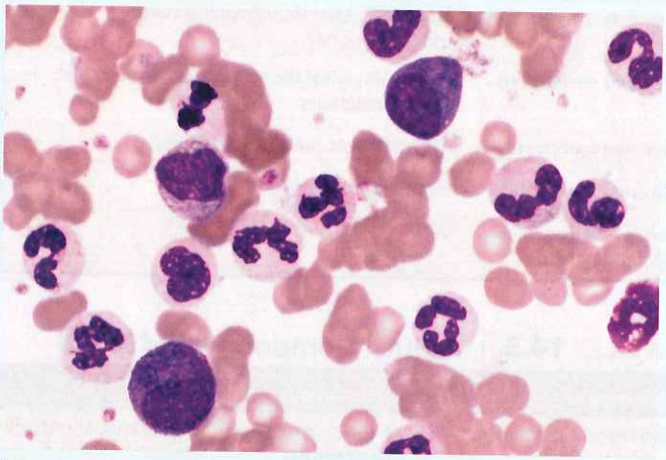


(b)

FIGURE 14A Leukemia and blood cells. (*a*) Normal blood cells (700×). (*b*) Blood cells from a person with granulocytic leukemia, a type of myeloid leukemia (700×). Note the increased number of leukocytes.

PRACTICE

26 What is the normal human blood platelet count?

27 What is the function of blood platelets?

14.3 BLOOD PLASMA

Plasma is the clear, straw-colored, liquid part of the blood in which the cells and platelets are suspended. It is approximately 92% water and contains a complex mixture of organic and inorganic biochemicals. Functions of plasma constituents include transporting nutrients, gases, and vitamins; helping to regulate fluid and electrolyte balance; and maintaining a favorable pH.

Plasma Proteins

By weight, **plasma proteins** are the most abundant dissolved substances (solutes) in plasma. These proteins remain in the blood and interstitial fluids and ordinarily are not used as energy sources. The three main types of plasma proteins

are albumins, globulins, and fibrinogen. The groups differ in composition and function.

Albumins (al-bu'minz) are the smallest of the plasma proteins, yet account for 60% of these proteins by weight. They are synthesized in the liver, and because they are so plentiful, albumins are an important determinant of the *osmotic pressure* of the plasma.

Recall from chapter 3 (p. 102) that the presence of an impermeant solute on one side of a selectively permeable membrane creates an osmotic pressure and that water always moves toward a greater osmotic pressure. Plasma proteins are too large to pass through the capillary walls, so they are impermeant, and they create an osmotic pressure that holds water in the capillaries despite blood pressure forcing water out of capillaries by filtration (see chapter 3, pp. 102–103). The term *colloid osmotic pressure* is used to describe this osmotic effect due to the plasma proteins.

By maintaining the colloid osmotic pressure of plasma, albumins and other plasma proteins help regulate water movement between the blood and the tissues. In doing so, they help control blood volume, which, in turn, directly affects blood pressure (see chapter 15, p. 585). For this reason, it is important that the concentration of plasma proteins remains relatively stable. Albumins also bind and transport certain molecules, such as bilirubin, free fatty acids, many hormones, and certain drugs.

If the concentration of plasma proteins falls, tissues swell, a condition called *edema*. This may result from starvation or a protein-deficient diet or from an impaired liver that cannot synthesize plasma proteins. As the concentration of plasma proteins drops, so does the colloid osmotic pressure, allowing fluids to accumulate in the interstitial spaces.

Globulins (glob'u-linz), which make up about 36% of the plasma proteins, can be further subdivided into *alpha, beta,* and *gamma globulins.* The liver synthesizes alpha and beta globulins, which have a variety of functions, including transport of lipids and fat-soluble vitamins. Lymphatic tissues produce the gamma globulins, which are the antibodies in the immune response (see chapter 16, p. 633).

Fibrinogen (fi-brin'o-jen), which constitutes about 4% of the plasma proteins, plays a primary role in blood coagulation. Synthesized in the liver, it is the largest of the plasma proteins. The function of fibrinogen is discussed later in this chapter under the section "Blood Coagulation" on page 541. Table 14.6 summarizes the characteristics of the plasma proteins.

TABLE 14.6 | Plasma Proteins

Protein	Percentage of Total	Origin	Function
Albumin	60%	Liver	Helps maintain colloid osmotic pressure
Globulin	36%		
Alpha globulins		Liver	Transport lipids and fat-soluble vitamins
Beta globulins		Liver	Transport lipids and fat-soluble vitamins
Gamma globulins		Lymphatic tissues	Constitute the antibodies of immunity
Fibrinogen	4%	Liver	Plays a key role in blood coagulation

PRACTICE

28 List three types of plasma proteins.

29 How do albumins help maintain water balance between the blood and the tissues?

30 Which of the globulins functions in immunity?

31 What is the role of fibrinogen?

Gases and Nutrients

The most important *blood gases* are oxygen and carbon dioxide. Plasma also contains a considerable amount of dissolved nitrogen, which ordinarily has no physiological function. Chapter 19 (pp. 756–760) discusses blood gases and their transport.

As a rule, blood gases are evaluated using a fresh sample of whole blood obtained from an artery. This blood is cooled to decrease the rates of metabolic reactions, and an anticoagulant is added to prevent clotting. In the laboratory, the levels of oxygen and carbon dioxide of the blood are determined, the blood pH is measured, and the plasma bicarbonate concentration is calculated. Such information is used to diagnose and treat disorders of circulation, respiration, and electrolyte balance. Appendix C (p. 929) lists average values for these laboratory tests.

The *plasma nutrients* include amino acids, simple sugars, nucleotides, and lipids absorbed from the digestive tract. For example, plasma transports glucose from the small intestine to the liver, where it may be stored as glycogen or converted to fat. If blood glucose concentration drops below the normal range, glycogen may be broken down into glucose, as chapter 13 describes (p. 514).

Recently absorbed amino acids are also carried to the liver. Here they may be used to manufacture proteins or deaminated and used as an energy source (see chapter 18, p. 700).

Plasma lipids include fats (triglycerides), phospholipids, and cholesterol. An analysis of all the different types of lipids in blood (called the lipidome) identified nearly 600! Because lipids are not water soluble and plasma is almost 92% water, the lipids in plasma are joined with proteins, forming soluble lipoprotein complexes.

PRACTICE

32 Which gases are in plasma?

33 Which nutrients are in plasma?

Nonprotein Nitrogenous Substances

Molecules that contain nitrogen atoms but are not proteins comprise a group called **nonprotein nitrogenous substances** (NPNs). In plasma, this group includes amino acids, urea, uric acid, creatine (kre′ah-tin), and creatinine (kre-at′ĭ-nin). Amino acids come from protein digestion and amino acid absorption. Urea and uric acid are products of protein and nucleic acid catabolism, respectively, and creatinine results from the metabolism of creatine. Creatine is present as **creatine phosphate** in muscle and brain tissues as well as in the blood, where it stores energy in phosphate bonds, much like those of ATP molecules. Creatine was discussed in chapter 9 (p. 302).

Normally, the concentration of nonprotein nitrogenous substances in plasma remains relatively stable because protein intake and use are balanced with excretion of nitrogenous wastes. Because about half of the NPN substances is urea, which the kidneys ordinarily excrete, a rise in the blood urea nitrogen (BUN) may suggest a kidney disorder. Excess protein catabolism or infection may also elevate BUN.

Plasma Electrolytes

Plasma contains a variety of *electrolytes* that are absorbed from the intestine or released as by-products of cellular metabolism. They include sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate, and sulfate ions. Of these, sodium and chloride ions are the most abundant. Bicarbonate ions are important in maintaining the osmotic pressure and the pH of plasma, and like other plasma constituents, they are regulated so that their blood concentrations remain relatively stable. These electrolytes are discussed in chapter 21 (pp. 807–811) in connection with water and electrolyte balance.

PRACTICE

34 What is a nonprotein nitrogenous substance?

35 Why does kidney disease increase the blood concentration of these substances?

36 What are the sources of plasma electrolytes?

14.4 HEMOSTASIS

Hemostasis (he″mo-sta′sis) refers to the process that stops bleeding, which is vitally important when blood vessels are damaged. Following an injury to the blood vessels, several actions may help to limit or prevent blood loss, including blood vessel spasm, platelet plug formation, and blood coagulation. These mechanisms are most effective in minimizing blood losses from small vessels. Injury to a larger vessel may result in a severe hemorrhage that requires special treatment.

Blood Vessel Spasm

Cutting or breaking a small blood vessel stimulates the smooth muscles in its wall to contract, called *vasospasm*. Blood loss lessens almost immediately, and the ends of the severed vessel may close completely. This effect results from direct stimulation of the vessel wall as well as from reflexes elicited by pain receptors in the injured tissues.

Although the reflex response may last only a few minutes, the effect of the direct stimulation usually continues for about thirty minutes. By then, a blockage called a *platelet plug* has formed, and blood is coagulating. Also, platelets release serotonin, which contracts smooth muscles in the blood vessel walls. This vasoconstriction further helps to reduce blood loss.

Platelet Plug Formation

Platelets adhere to exposed ends of injured blood vessels. They adhere to any rough surface, particularly to the collagen in connective tissue underlying the endothelial lining of blood vessels.

When platelets contact collagen, their shapes change as many spiny processes begin to extend from their membranes. At the same time, platelets adhere to each other, forming a platelet plug in the vascular break. A plug may control blood loss from a small break, but a larger break may require a blood clot to halt bleeding. Figure 14.17 shows the steps in platelet plug formation.

PRACTICE

37 What is hemostasis?

38 How does a blood vessel spasm help control bleeding?

39 Describe the formation of a platelet plug.

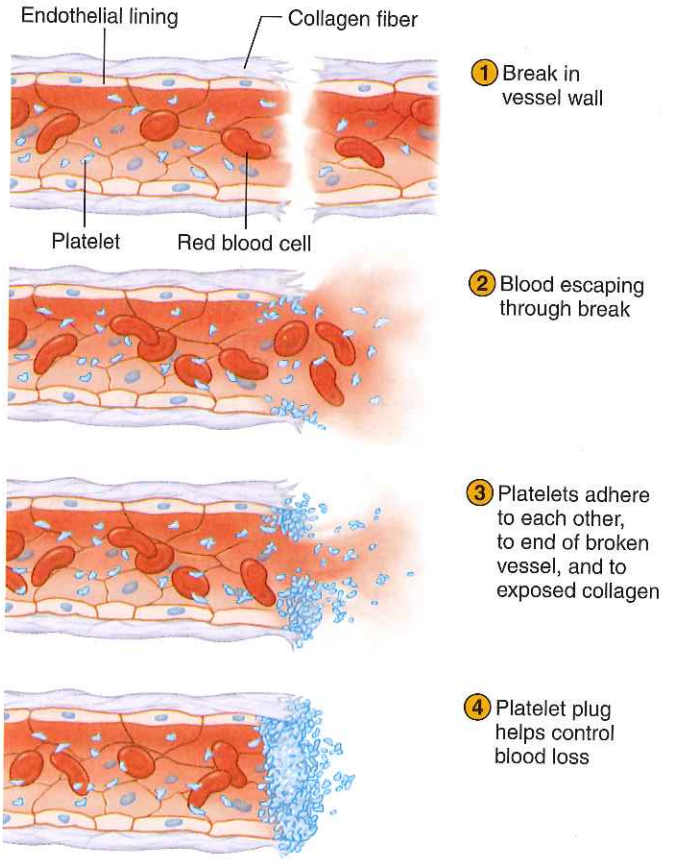


FIGURE 14.17 Steps in platelet plug formation.

Blood Coagulation

Coagulation (ko-ag″u-la′shun), the most effective hemostatic mechanism, forms a *blood clot* in a series of reactions, each one activating the next in a *cascade.* Coagulation may occur in two ways: extrinsically or intrinsically. Release of biochemicals from broken blood vessels or damaged tissues triggers the **extrinsic clotting mechanism.** Blood contact with foreign surfaces in the absence of tissue damage stimulates the **intrinsic clotting mechanism.** The following sections describe these responses.

Blood coagulation is complex and uses many biochemicals called *clotting factors.* They are designated by Roman numerals indicating the order of their discovery. Vitamin K is necessary for some clotting factors to function. Whether the blood coagulates depends on the balance between factors that promote coagulation (procoagulants) and others that inhibit it (anticoagulants). Normally, the anticoagulants prevail, and the blood does not clot. However, as a result of injury (trauma), biochemicals that favor coagulation may increase in concentration, and the blood may coagulate.

The major event in blood clot formation is conversion of the soluble plasma protein *fibrinogen* (factor I) into insoluble threads of the protein **fibrin** (fig. 14.18). Activation of certain plasma proteins by still other protein factors triggers conversion of fibrinogen to fibrin. Table 14.7 summarizes the three primary hemostatic mechanisms: blood vessel spasm, platelet plug formation, and blood coagulation.

Extrinsic Clotting Mechanism

The extrinsic clotting mechanism is triggered when blood contacts damaged blood vessel walls or tissues outside blood vessels. Such damaged tissues release *tissue thromboplastin* (factor III), that is associated with disrupted cell membranes. Tissue thromboplastin activates factor VII, which combines with and activates factor X. Further, factor X combines with and activates factor V. These reactions, which also require calcium ions (factor IV), lead the platelets to produce and release *prothrombin activator.*

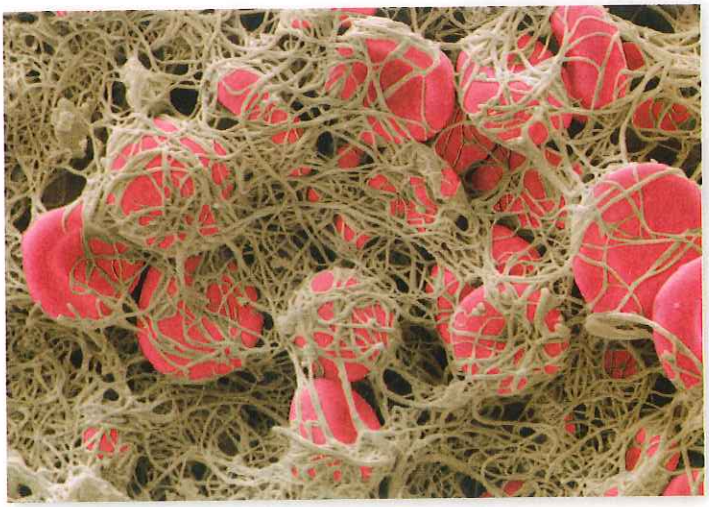


FIGURE 14.18 A scanning electron micrograph of red blood cells caught in a meshwork of fibrin threads (2,800×).

TABLE 14.7 | Hemostatic Mechanisms

Mechanism	Stimulus	Effect
Blood vessel spasm	Direct stimulus to vessel wall or to pain receptors; platelets release serotonin, a vasoconstrictor	Smooth muscles in vessel wall contract reflexly; vasoconstriction helps maintain prolonged vessel spasm
Platelet plug formation	Exposure of platelets to rough surfaces or to collagen of connective tissue	Platelets adhere to rough surfaces and to each other, forming a plug
Blood coagulation	Cellular damage and blood contact with foreign surfaces activate factors that favor coagulation	Blood clot forms as a result of a series of reactions, terminating in the conversion of fibrinogen into fibrin

Prothrombin (factor II) is an alpha globulin that the liver continually produces and is thus a normal constituent of plasma. In the presence of calcium ions, prothrombin activator converts prothrombin into **thrombin** (factor IIa). Thrombin, in turn, catalyzes a reaction that fragments fibrinogen (factor I). The fibrinogen fragments join, forming long threads of fibrin. Fibrinogen is a soluble plasma protein, but fibrin is insoluble. Thrombin also activates factor XIII, which strengthens and stabilizes fibrin threads (fig. 14.19).

Once fibrin threads form, they stick to exposed surfaces of damaged blood vessels, creating a meshwork that entraps blood cells and platelets. The resulting mass is a blood clot, which may block a vascular break and prevent further blood loss.

The amount of prothrombin activator in the blood is directly proportional to the degree of tissue damage. Once a blood clot begins to form, it promotes additional clotting, because thrombin also acts directly on blood clotting factors other than fibrinogen, causing prothrombin to form still more thrombin. This type of self-initiating action is an example of a **positive feedback system,** in which the original action stimulates more of the same type of action. Such a mechanism produces unstable conditions and can operate for only a short time in a living system, because life requires the maintenance of a stable internal environment (see chapter 1, p. 17).

Normally, blood flow throughout the body prevents formation of a massive clot in the cardiovascular system by rapidly carrying excess thrombin away and keeping its concentration too low to promote further clotting. In addition, a substance called *antithrombin,* in the blood and on the surfaces of endothelial cells that line blood vessels, limits thrombin formation. Consequently, blood coagulation usually happens only in blood that is standing still or moving slowly, and clotting ceases where a clot contacts circulating blood.

In *disseminated intravascular coagulation (DIC),* clotting is abnormally activated in several regions of the cardiovascular system. This condition is usually associated with bacterial infection or bacterial toxins in the blood or with a disorder causing widespread tissue damage. Many small clots form and obstruct blood flow into various tissues and organs, particularly the kidneys. As plasma clotting factors and platelets are depleted, severe bleeding occurs.

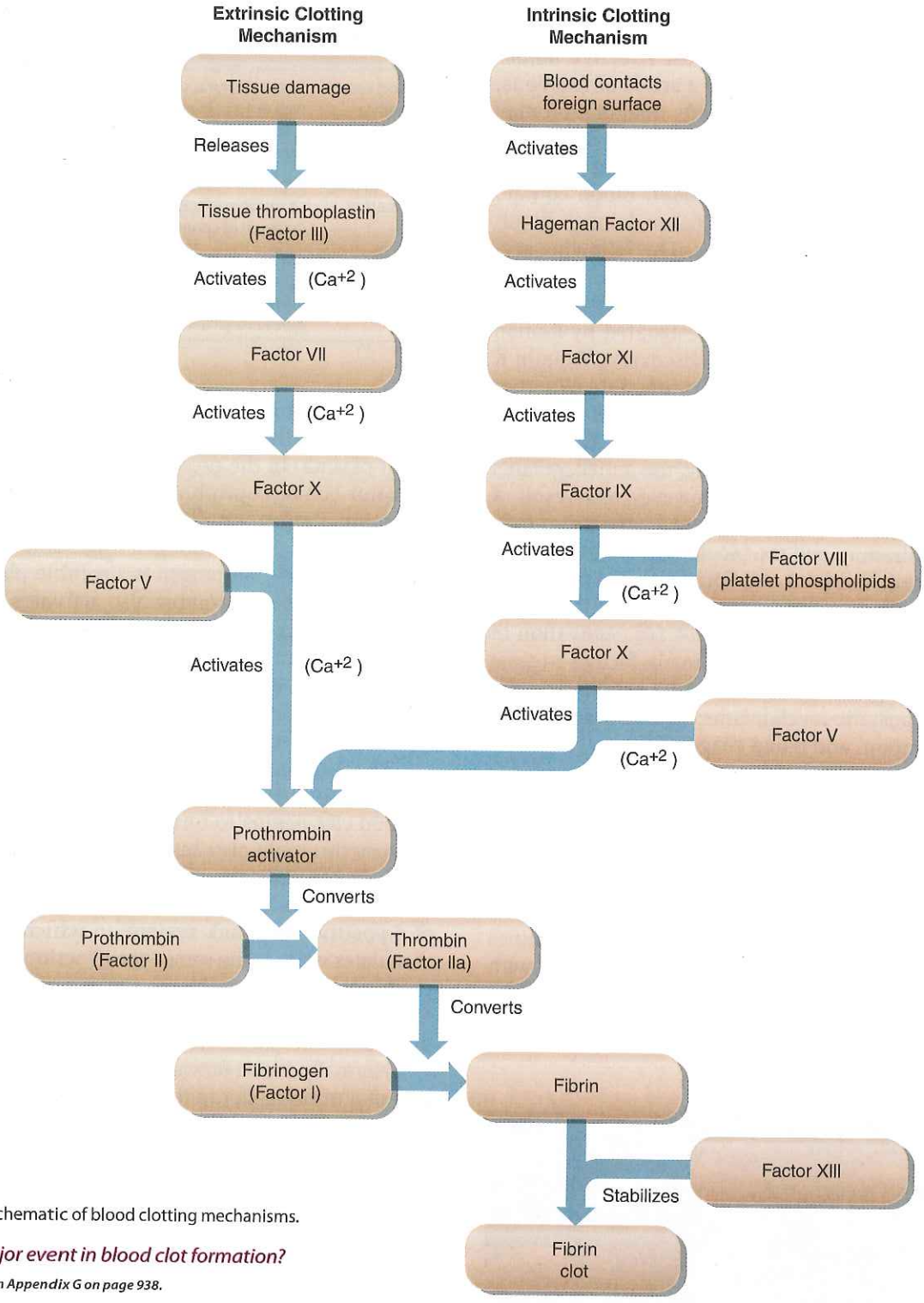


FIGURE 14.19 Schematic of blood clotting mechanisms.

Q: *Which is the major event in blood clot formation?*

Answer can be found in Appendix G on page 938.

Intrinsic Clotting Mechanism

Unlike extrinsic clotting, all of the components necessary for intrinsic clotting are in the blood. Activation of a substance called the *Hageman factor* (factor XII) initiates intrinsic clotting. This happens when blood is exposed to a foreign surface such as collagen in connective tissue instead of the smooth endothelial lining of intact blood vessels or when blood is stored in a glass container. Activated factor XII activates factor XI, which activates factor IX. Factor IX then joins with factor VIII and platelet phospholipids to activate factor X. These reactions, which also require calcium ions, lead to the production of prothrombin activator. The

subsequent steps of blood clot formation are the same as those described for the extrinsic mechanism (fig. 14.19). Table 14.8 compares extrinsic and intrinsic clotting mechanisms. Table 14.9 lists the clotting factors, their sources, and clotting mechanisms.

Laboratory tests commonly used to evaluate blood coagulation mechanisms include *prothrombin time* (PT) and *partial thromboplastin time* (PTT). These tests measure the time it takes for fibrin threads to form in a sample of blood plasma. The prothrombin time test checks the extrinsic clotting mechanism, whereas the partial thromboplastin test evaluates intrinsic clotting.

Fate of Blood Clots

A newly formed blood clot soon begins to retract as the tiny extensions from the platelet membranes adhere to strands of fibrin within the clot and contract. The blood clot shrinks, pulling the edges of the broken vessel closer together and squeezing a fluid called **serum** from the clot. Serum is essentially plasma minus all of its fibrinogen and most other clotting factors. Platelets associated with a blood clot also release *platelet-derived growth factor* (PDGF), which stimulates smooth muscle cells and fibroblasts to repair damaged blood vessel walls.

Fibroblasts (see chapter 5, p. 163) invade blood clots that form in ruptured vessels, producing fibrous connective tissue throughout the clots, which helps strengthen and seal vascular breaks. Many clots, including those that form in tissues as a result of blood leakage (hematomas), disappear in time. In clot dissolution, fibrin threads absorb a plasma protein called *plasminogen* (profibrinolysin). Then a substance called plasminogen activator released from the lysosomes of damaged tissue cells converts plasminogen to *plasmin*. Plasmin is a protein-splitting enzyme that can digest fibrin threads and other proteins associated with blood clots. Plasmin formation may dissolve a whole

TABLE 14.8 | Blood Coagulation

Steps	Extrinsic Clotting Mechanism	Intrinsic Clotting Mechanism
Trigger	Damage to vessel or tissue	Blood contacts foreign surface
Initiation	Tissue thromboplastin	Hageman factor
Series of reactions involving several clotting factors and calcium ions (Ca^{+2}) lead to the production of:	Prothrombin activator	Prothrombin activator
Prothrombin activator and calcium ions cause the conversion of:	Prothrombin to thrombin	Prothrombin to thrombin
Thrombin causes fragmentation, then joining of:	Fibrinogen to fibrin	Fibrinogen to fibrin

TABLE 14.9 | Clotting Factors

Clotting Factor		Source	Mechanism(s)
I	(fibrinogen)	Synthesized in liver	Extrinsic and intrinsic
II	(prothrombin)	Synthesized in liver, requires vitamin K	Extrinsic and intrinsic
III	(tissue thromboplastin)	Damaged tissue	Extrinsic
IV	(calcium ions)	Plasma electrolyte	Extrinsic and intrinsic
V	(proaccelerin)	Synthesized in liver, released by platelets	Extrinsic and intrinsic
VII	(serum prothrombin conversion accelerator)	Synthesized in liver, requires vitamin K	Extrinsic
VIII	(antihemophilic factor)	Released by platelets and endothelial cells	Intrinsic
IX	(plasma thromboplastin component)	Synthesized in liver, requires vitamin K	Intrinsic
X	(Stuart-Prower factor)	Synthesized in liver, requires vitamin K	Extrinsic and intrinsic
XI	(plasma thromboplastin antecedent)	Synthesized in liver	Intrinsic
XII	(Hageman factor)	Synthesized in liver	Intrinsic
XIII	(fibrin-stabilizing factor)	Synthesized in liver, released by platelets	Extrinsic and intrinsic

There is no clotting factor VI. The chemical once thought to be factor VI is apparently a combination of activated factors V and X.

clot. However, clots that fill large blood vessels are seldom removed naturally.

A blood clot abnormally forming in a vessel is a **thrombus** (throm'bus). A clot that dislodges, or a fragment of a clot that breaks loose and is carried away by the blood flow, is called an **embolus** (em'bo-lus). Generally, emboli continue to move until they reach narrow places in vessels where they may lodge and block blood flow, causing an **embolism.** (Other than a blood clot, an embolus could be an air bubble, a fat globule, or plaque—any obstructive object in the bloodstream.)

A blood clot forming in a vessel that supplies a vital organ, such as the heart (coronary thrombosis) or the brain (cerebral thrombosis), blocks blood flow and kills tissues the vessel serves *(infarction)* and may be fatal. A blood clot that travels and then blocks a vessel that supplies a vital organ, such as the lungs (pulmonary embolism), affects the portion of the organ that the blocked blood vessel supplies.

Drugs based on "clot-busting" biochemicals can be lifesavers. *Tissue plasminogen activator* (tPA) may restore blocked coronary or cerebral circulation if given within an hour of a heart attack or within three hours of a stroke. A drug derived from bacteria, called *streptokinase,* may also be successful, for a fraction of the cost. Another plasminogen activator used as a drug is *urokinase,* an enzyme produced by certain kidney cells.

Abnormal clot formations are often associated with conditions that change the endothelial linings of vessels. For example, in *atherosclerosis* (ath"er-o"skle-ro'sis), accumulations of fatty deposits change arterial linings, sometimes initiating inappropriate clotting. This is the most common cause of thrombosis in medium-sized arteries (fig. 14.20).

Coagulation may also occur in blood flowing too slowly. The concentration of clot-promoting substances may increase to a critical level instead of being carried away by more rapidly moving blood, and a clot may form. This imbalance is the usual cause of thrombosis in veins. Clinical Application 14.2 discusses deep vein thrombosis.

PRACTICE

40 Distinguish between extrinsic and intrinsic clotting mechanisms.

41 What factors initiate the formation of fibrin?

42 What prevents the formation of massive clots throughout the cardiovascular system?

43 Distinguish between a thrombus and an embolus.

44 How might atherosclerosis promote the formation of blood clots?

Prevention of Coagulation

In a healthy cardiovascular system, the endothelium of the blood vessels partly prevents spontaneous blood clot formation. This smooth lining lowers the risk of platelets and clotting factors accumulating. Endothelial cells also produce a prostaglandin (see chapter 13, pp. 495–496) called *prostacyclin* (PGI_2), which inhibits the adherence of platelets to the inner surface of healthy blood vessel walls.

Several mechanisms confine clotting to the area where it is needed. When a clot is forming, fibrin threads latch onto or *adsorb* thrombin, thus helping prevent the spread of the clotting reaction. A plasma alpha globulin, *antithrombin,* inactivates additional thrombin by binding to it and blocking its action on fibrinogen. In addition, basophils and mast cells in the connective tissue surrounding capillaries secrete the anticoagulant *heparin.* This substance interferes with formation of prothrombin activator, prevents the action of thrombin on fibrinogen, and promotes removal of thrombin by antithrombin

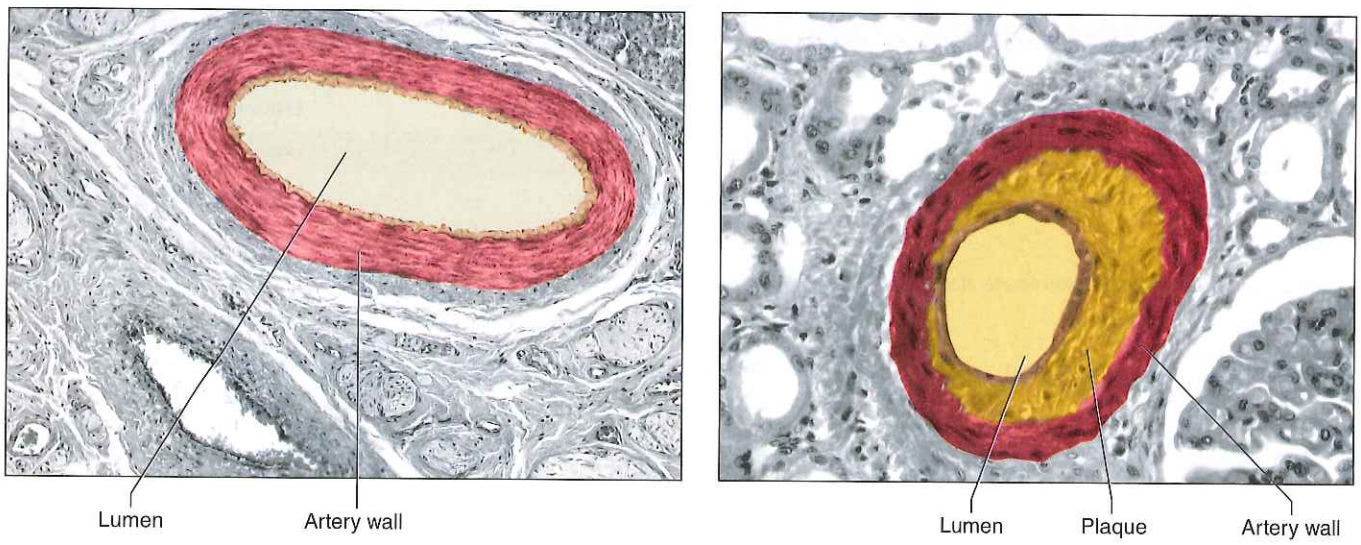


FIGURE 14.20 Artery cross sections. (*a*) Light micrograph of a normal artery (50×). (*b*) The inner wall of an artery changed as a result of atherosclerosis (100×).

14.2 CLINICAL APPLICATION

Deep Vein Thrombosis

After a transcontinental flight, a man complained of cramps behind his knees. He mentioned the unfamiliar sensations to his traveling companion, who urged him to call his doctor. The nurse who took the call told the man to seek immediate medical attention, but because he was already starting to feel better, he didn't take her advice. Instead, he continued his trip, reaching his destination after a short bus ride. Three days later, the man suddenly collapsed and died from a pulmonary embolism, the result of a condition called deep vein thrombosis (DVT). He had several risk factors for DVT: prolonged periods of immobility on flights; dehydration; and an inherited clotting disorder that he had not known about called factor V Leiden. Other risk factors for DVT are prolonged immobility due to surgery; oral contraceptive use; hormone replacement therapy (estrogen); surgery (of the abdomen, pelvis, or limbs); and cancer (of the ovaries, pancreas, colon, liver, stomach, or lymphoma).

In DVT, stagnant blood pools, leading to clot formation, typically in the femoral or popliteal veins or in the deep veins of the pelvis. Symptoms occur in half of all affected individuals. These include deep muscle pain, redness, swelling, and possibly discoloration and dilation of surface veins (phlebitis). Part of the clot may break off hours or days after it forms and follow the path of circulation, lodging in the pulmonary arteries. This is a pulmonary embolism, and it is life threatening. Symptoms include chest pain, anxiety, racing pulse, sweating, cough with bloody sputum, and loss of consciousness. In the United States, approximately 2 million people a year develop DVT, and 200,000 die from pulmonary embolism.

Measures to prevent DVT include taking anticoagulants if immobilization is expected; wearing compression stockings that keep blood flowing in the legs; and doing exercises while immobilized during travel. Some airlines advise passengers on how to exercise on cramped flights, such as by curling the toes up and down (figure 14B). DVT is sometimes called "traveler's thrombosis" for good reason. ■

FIGURE 14B Exercising the toes and ankles on a long flight can lower the risk of deep vein thrombosis.

and fibrin adsorption. Heparin and another compound, coumadin (warfarin), are used as drugs to prevent abnormal clotting.

Heparin-secreting cells are particularly abundant in the liver and lungs, where capillaries trap small blood clots that commonly form in the slow-moving blood of veins. These cells continually secrete heparin, preventing additional clotting in the cardiovascular system. Table 14.10 summarizes clot-inhibiting factors.

PRACTICE

45 How does the lining of a blood vessel help prevent blood clot formation?

46 What is the function of antithrombin?

47 How does heparin help prevent blood clot formation?

14.5 BLOOD GROUPS AND TRANSFUSIONS

Early blood transfusion experiments, which date from the late 1600s, used lamb blood. By the 1800s, human blood was being used with unpredictable results—some recipients were cured, but some were killed when their kidneys failed under the strain of handling clumping red blood cells when blood types were incompatible. So poor was the success rate that, by the late 1800s, many nations banned transfusions.

Around this time, Austrian physician Karl Landsteiner began investigating why transfusions sometimes worked and sometimes did not. In 1900, he determined that blood was of differing types and that only certain combinations of them were compatible. In 1910, identification of the ABO blood

TABLE 14.10 | Factors That Inhibit Blood Clot Formation

Factor	Action	Factor	Action
Smooth lining of blood vessel	Prevents activation of intrinsic blood clotting mechanism	Antithrombin in plasma	Interferes with the action of thrombin
Prostacyclin	Inhibits adherence of platelets to blood vessel wall	Heparin from mast cells and basophils	Interferes with the formation of prothrombin activator
Fibrin threads	Adsorbs thrombin		

14.1 FROM SCIENCE TO TECHNOLOGY

Blood Typing and Matching: From Serology to DNA Chips

Typing and matching blood is essential to minimize the chance that the immune response of a blood transfusion recipient will reject the blood. The popular view of blood types is that it is a simple matter of A, B, AB, or O. Rh blood types become important in pregnancy, when woman and offspring may be incompatible. However, human blood can be classified into twenty-nine major types based on protein and carbohydrate molecules (antigens) on the surfaces of red blood cells. Each of these types includes many subtypes, generating hundreds of ways that the topographies of our red blood cells differ from individual to individual.

For more than a century, an approach called serology has been used to type blood into major groups by identifying red blood cell antigens. Different reagents are required to detect different antigens, and so typing by serology beyond a few blood groups is costly and time consuming. It can also miss variants of antigens that are small or hidden among the embedded proteins and emanating carbohydrate chains of the cell surface. A more informative way to type blood is to identify the *instructions* for the cell-surface antigens—the genes that encode these proteins. This approach, termed genotyping, is being tested in Europe and Canada.

A consortium of European blood banks and universities, called Bloodgen, is using a tiny device called a BLOODchip that detects, with one test, 128 distinct DNA "signatures" (fig. 14C). These represent some of the gene variant combinations that underlie blood types traditionally defined by serology. So far the BLOODchip is able to accurately type 99.8% of samples; serology can accurately type 97%. Another device called BeadChip tests for a different group of antigens. Other variations on the DNA chip theme are in development.

Accurate blood matching for many blood groups may not be of great importance for the average person who may require just one or two transfusions in a lifetime. But for a person who has a chronic disorder that requires multiple transfusions—such as leukemia or sickle cell disease—greater specificity in typing and matching blood can be lifesaving. Such individuals produce so many antibodies (immune system proteins) against so many types of donor blood that it is often difficult to determine, by serology, the blood types that can safely be given them. DNA typing, however, can tell. DNA blood typing is being used in some diagnostic laboratories in cases in which serology is not sufficient, and may become routine within ten years. ■

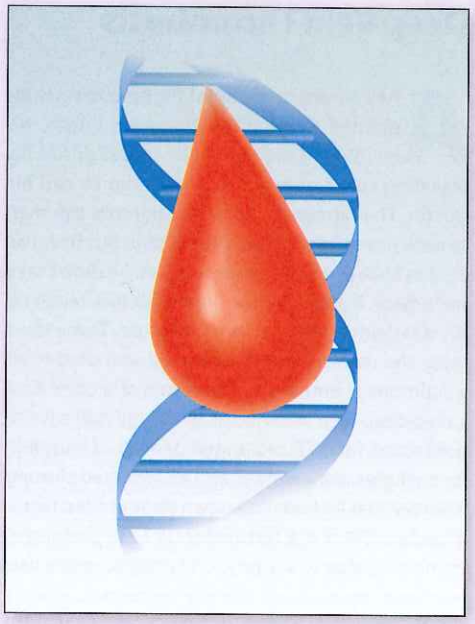


FIGURE 14C Bloodgen is a consortium of European blood banks and universities investigating the use of DNA microarrays ("chips") to type blood. Their logo is a drop of blood superimposed on a DNA double helix.

antigen gene explained the observed blood type incompatibilities. Today, thirty-one different genes are known to contribute to the surface features of red blood cells, which determine compatibility between blood types.

Antigens and Antibodies

The clumping of red blood cells when testing blood compatibility or resulting from a transfusion reaction is called **agglutination** (ah-gloo″tĭn-a′shun). This phenomenon is due to a reaction between red blood cell surface molecules called **antigens** (an′ti-jenz), formerly called *agglutinogens*, and protein **antibodies** (an′ti-bod″ez), formerly called *agglutinins*, carried in the plasma. Antibodies are called *anti-* because they are "against" specific antigens. Although human erythrocytes have many different antigens, only a few types are likely to produce serious transfusion reactions. These include the antigens of the ABO group and those of the Rh group. Avoiding the mixture of certain types of antigens and antibodies prevents adverse transfusion reactions. From Science to Technology 14.1 discusses a DNA chip that prevents transfusion mismatches.

A mismatched blood transfusion quickly produces telltale signs of agglutination—anxiety; breathing difficulty; facial flushing; headache; and severe pain in the neck, chest, and lumbar area. Red blood cells burst, releasing free hemoglobin. Macrophages phagocytize the hemoglobin, breaking it down into heme and globin. Some of the heme is recycled. The rest of the heme is converted to bilirubin, which may sufficiently accumulate to cause the yellow skin of jaundice. Free hemoglobin in the plasma may ultimately cause the kidneys to fail.

ABO Blood Group

The *ABO blood group* is based on the presence (or absence) of two major antigens on red blood cell membranes—*antigen A* and *antigen B.* A person's erythrocytes have one of four antigen combinations: only A, only B, both A and B, or neither A nor B. An individual with only antigen A has *type A blood;* a person with only antigen B has *type B blood;* one with both antigen A and antigen B has *type AB blood;* and one with neither antigen A nor antigen B has *type O blood.*

TABLE 14.11 | Some ABO Blood Type Frequencies (%) in the United States

Population	Type O	Type A	Type B	Type AB
Caucasian	45	40	11	4
African American	49	27	20	4
Native American	79	16	4	1
Hispanic	63	14	20	3
Chinese American	42	27	25	6
Japanese American	31	38	21	10
Korean American	32	28	30	10

Table 14.11 indicates some of the frequencies of ABO blood types in the diverse population of the United States.

ABO blood group antibodies are synthesized in the plasma about two to eight months following birth. The stimulus for their synthesis has not clearly been established. However, we know that whenever antigen A is absent in the red blood cells, an antibody called *anti-A* is produced, and whenever antigen B is absent, an antibody called *anti-B* is manufactured. Therefore, persons with type A blood have anti-B antibody in their plasma; those with type B blood have anti-A antibody; those with type AB blood have neither antibody; and those with type O blood have both anti-A and anti-B antibodies (fig. 14.21 and table 14.12). The anti-A and anti-B antibodies are too large to cross the placenta. If a pregnant woman and her fetus are of different ABO blood types, agglutination in the fetus will not occur.

TABLE 14.12 | Antigens and Antibodies of the ABO Blood Group

Blood Type	Antigen	Antibody
A	A	anti-B
B	B	anti-A
AB	A and B	Neither anti-A nor anti-B
O	Neither A nor B	Both anti-A and anti-B

The major concern in blood transfusion procedures is that the cells in donated blood not clump due to antibodies in the recipient's plasma. For example, a person with type A blood makes anti-B antibodies and therefore must not receive blood of type B or AB, either of which would clump (fig. 14.22). Likewise, a person with type B blood must not be given type A or AB blood, and a person with type O blood must not be given type A, B, or AB blood.

Type AB blood lacks both anti-A and anti-B antibodies, so an AB person can receive a transfusion of blood of any other type. For this reason, type AB persons are sometimes called *universal recipients*. However, type A blood, type B blood, and type O blood still contain antibodies (either anti-A and/or anti-B) that could agglutinate type AB cells. Consequently, even for AB individuals, it is always best to use donor blood of the same type as the recipient blood. If the matching type is not available and type A, B, or O is used, it should be transfused slowly and in limited amounts so that the recipient's larger blood volume dilutes the donor blood. This precaution usually avoids serious reactions between the donor's antibodies and the recipient's antigens.

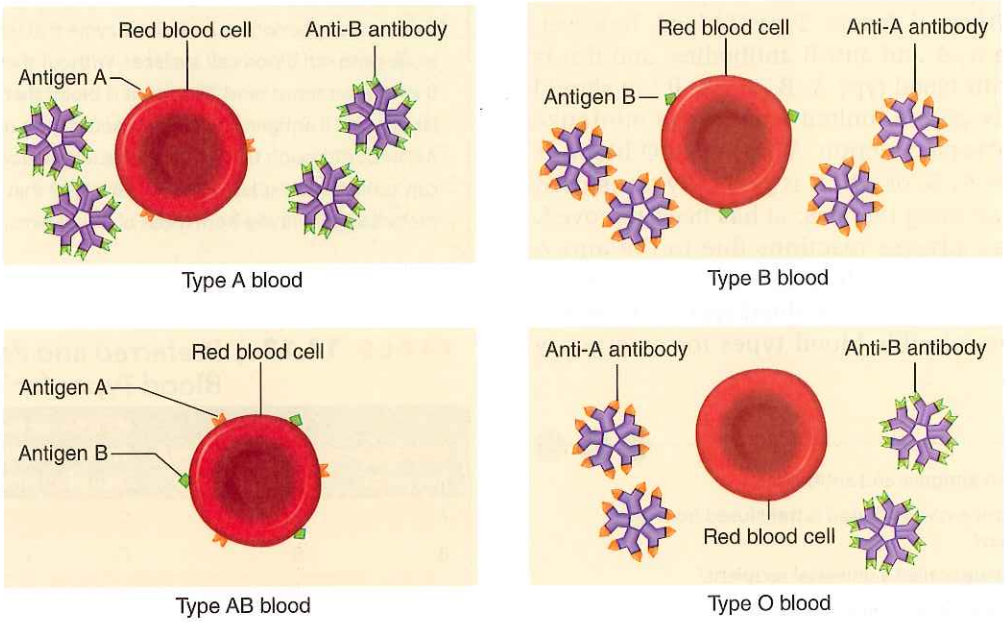


FIGURE 14.21 Different combinations of antigens and antibodies distinguish blood types. (Cells and antibodies not drawn to scale.)

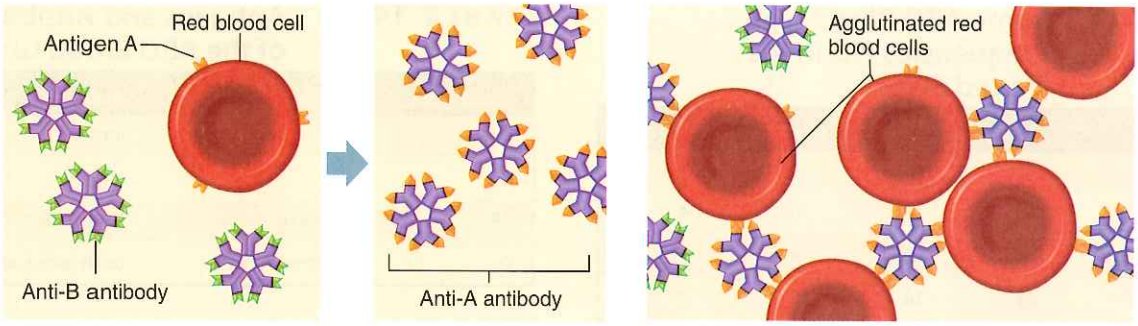


FIGURE 14.22 Agglutination. (*a*) If red blood cells with antigen A are added to blood containing anti-A antibody, (*b*) the antigens react with the antibodies, causing clumping (agglutination). (*c*) Nonagglutinated blood (210×). (*d*) Agglutinated blood (220×). (Cells and antibodies in *a* and *b* not drawn to scale.)

Type O blood lacks antigens A and B. Therefore, theoretically this type could be transfused into persons with blood of any other type. Individuals with type O blood are sometimes called *universal donors.* Type O blood, however, does contain both anti-A and anti-B antibodies, and if it is given to a person with blood type A, B, or AB, it too should be transfused slowly and in limited amounts to minimize the chance of an adverse reaction. When type O blood is given to blood types A, B, or AB, it is generally transfused as "packed cells," meaning the plasma has been removed. This also minimizes adverse reactions due to the anti-A and anti-B antibodies found in the plasma of type O blood. Table 14.13 summarizes preferred blood types for normal transfusions and permissible blood types for emergency transfusions.

PRACTICE

48 Distinguish between antigens and antibodies.

49 What is the main concern when blood is transfused from one individual to another?

50 Why is a type AB person called a universal recipient?

51 Why is a type O person called a universal donor?

When is type O blood not really type O blood? This occurs when a certain mutation is present. A person with a rare genetic condition called the Bombay phenotype lacks an enzyme that inserts a particular molecule onto red blood cell surfaces. Without that molecule, the A and B antigens cannot bind. The result is blood that tests as O (because it lacks A and B antigens) but can genetically be of any ABO type—A, B, AB, or O. Although the Bombay phenotype does not affect health, it can sometimes explain a child's ABO type that cannot otherwise be predicted genetically from those of the parents.

TABLE 14.13 | Preferred and Permissible Blood Types for Transfusions

Blood Type of Recipient	Preferred Blood Type of Donor	If Preferred Blood Type Unavailable, Permissible Blood Type of Donor (In an Extreme Emergency)
A	A	O
B	B	O
AB	AB	A, B, O
O	O	No alternate types

Rh Blood Group

The *Rh blood group* was named after the rhesus monkey in which it was first studied. In humans, this group includes several Rh antigens (factors). The most prevalent of these is *antigen D*. If antigen D or other Rh antigens are present on red blood cell membranes, the blood is said to be *Rh-positive.* Conversely, if red blood cells lack Rh antigens, the blood is called *Rh-negative.* About 15% of Caucasians and 5% of African Americans in the U.S. population are Rh-negative. The remaining ethnic groups are all Rh-positive.

The presence or absence of Rh antigens is an inherited trait, as is the case for antigens A and B. *Anti-Rh antibodies (anti-Rh)* form only in Rh-negative individuals in response to the presence of red blood cells with Rh antigens. This happens, for example, if an Rh-negative person receives a transfusion of Rh-positive blood. The Rh antigens stimulate the recipient's antibody-producing cells to make anti-Rh antibodies. Generally, no serious consequences result from the first transfusion, but if the Rh-negative person—now sensitized to Rh-positive blood—receives another transfusion of Rh-positive blood some months later, the donated red blood cells are likely to agglutinate.

A similar situation of Rh incompatibility arises when an Rh-negative woman is pregnant with an Rh-positive fetus. Her first pregnancy with an Rh-positive fetus would probably be uneventful. However, if at the time of this infant's birth there is a tearing of the placental membranes that separated the maternal blood from the fetal blood during the pregnancy, and some of the infant's Rh-positive blood cells enter the maternal circulation, these cells may stimulate the maternal tissues to produce anti-Rh antibodies (fig. 14.23). This situation may also arise if the pregnancy ends before the birth or fetal cells enter the maternal circulation during an invasive prenatal test such as amniocentesis. If a woman who has already developed anti-Rh antibodies becomes pregnant with a second Rh-positive fetus, these anti-Rh antibodies, called hemolysins, can cross the placental membrane and destroy the fetal red cells. The fetus then develops a condition called *erythroblastosis fetalis* (ĕrith″ro-blas-to′sis fe′tal-iz), or hemolytic disease of the newborn (fig. 14.23).

Erythroblastosis fetalis is extremely rare today because obstetricians carefully track Rh status. An Rh^- woman who might carry an Rh^+ fetus is given an injection of a drug called RhoGAM at week 28 of her pregnancy and after delivery of an Rh+ baby. RhoGam is a preparation of anti-Rh antibodies, which bind to and shield any Rh^+ fetal cells that might enter the woman's bloodstream and sensitize her immune system. RhoGAM must be given within 72 hours of possible contact with Rh^+ cells—including giving birth, terminating a pregnancy, miscarrying, or undergoing amniocentesis (a prenatal test in which a needle is inserted into the uterus).

PRACTICE

52 What is the Rh blood group?

53 What are two ways that Rh incompatibility can arise?

Table 14.14 describes a few of the many and diverse inherited disorders that affect the blood.

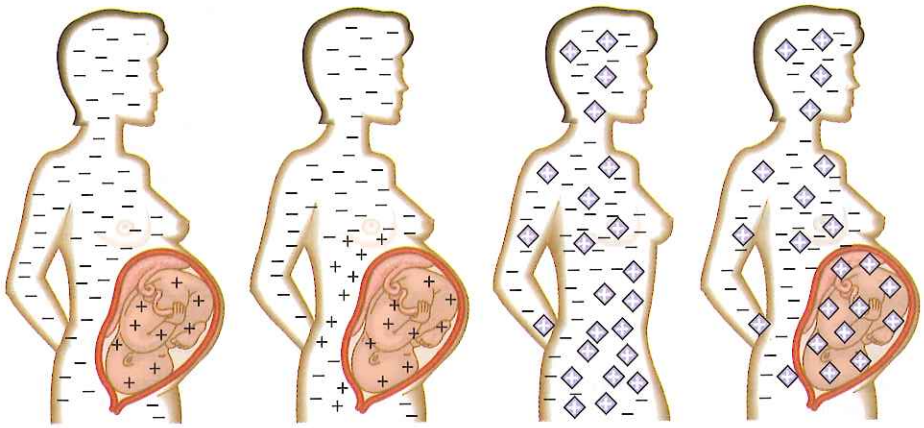


FIGURE 14.23 Rh incompatibility. If a man who is Rh-positive and a woman who is Rh-negative conceive a child who is Rh-positive, the woman's body may manufacture antibodies that attack future Rh-positive offspring.

TABLE 14.14 | Some Inherited Disorders of Blood

Disorder	Abnormality
Chronic granulomatous disease	Granulocytes cannot produce superoxide, which kills pathogenic bacteria
Erythrocytosis	Reticulocytes have extra EPO receptors, enhancing stamina
Factor V Leiden	Increases risk of abnormal clotting; elevates risk of deep vein thrombosis
Hemophilia (several types)	Lack of specific clotting factor causes bleeding
Hereditary hemochromatosis	Excess absorption of dietary iron into bloodstream deposits iron in various organs
Porphyria variegata	Enzyme deficiency excretes porphyrin ring of hemoglobin into urine; metabolic blockage causes sequence of varied symptoms
Sickle cell disease	Abnormal hemoglobin crystallizes under low-oxygen conditions, sickling red blood cells, which block circulation causing anemia, pain, and other symptoms
Von Willebrand disease	Lack of clotting factor (von Willebrand factor), which stabilizes factor VIII, causes bleeding; less severe than hemophilia

CHAPTER SUMMARY

14.1 INTRODUCTION (PAGE 526)

Blood is a type of connective tissue in which cells are suspended in a liquid extracellular matrix. It transports substances between the body cells and the external environment and helps maintain a stable internal environment. Blood volume varies with body size, fluid and electrolyte balance, and adipose tissue content. Blood can be separated into formed elements (mostly red blood cells) and liquid portions—plasma.

14.2 BLOOD CELLS (PAGE 527)

1. The origin of blood cells
   a. Blood cells develop from hematopoietic stem cells, or hemocytoblasts, in red bone marrow.
   b. Blood cells descended from stem cells respond to hematopoietic growth factors to specialize.
   c. Thrombopoietin stimulates megakaryocytes to give rise to platelets.
2. Characteristics of red blood cells
   a. Red blood cells are biconcave discs with shapes that provide increased surface area and place their cell membranes close to oxygen-carrying hemoglobin.
   b. Red blood cells contain hemoglobin, which combines loosely with oxygen.
   c. The mature form lacks nuclei and mitochondria, but contains enzymes needed for glycolysis.
3. Red blood cell counts
   a. The red blood cell count equals the number of cells per microliter of blood.
   b. The average count may range from approximately 4,000,000 to 6,000,000 cells per microliter.
   c. Red blood cell count determines the oxygen-carrying capacity of the blood and is used in diagnosing and evaluating the courses of certain diseases.
4. Red blood cell production and its control
   a. During fetal development, red blood cells form in the yolk sac, liver, and spleen; after birth, red blood cells are produced by the red bone marrow.
   b. In a person in good health, the number of red blood cells remains relatively stable.
   c. A negative feedback mechanism involving erythropoietin from the kidneys and liver controls rate of red blood cell production.
      (1) Erythropoietin is released in response to low oxygen levels.
      (2) High altitude, loss of blood, or chronic lung disease can lower oxygen concentration in the blood.
5. Dietary factors affecting red blood cell production
   a. The availability of vitamin B_{12}, iron, and folic acid affects red blood cell production.
   b. The rate of iron absorption, needed for hemoglobin synthesis, varies with the amount of iron in the body.
6. Destruction of red blood cells
   a. Red blood cells are fragile and are damaged while moving through capillaries.
   b. Macrophages in the spleen and liver phagocytize damaged red blood cells.
   c. Hemoglobin molecules are decomposed, and nearly all of the iron from the heme portion is recycled.
   d. Biliverdin and bilirubin are pigments, released from the heme portion, excreted in bile.
   e. The globin portion is broken down into amino acids metabolized by macrophages or released into the blood.
7. Types of white blood cells
   a. Granulocytes include neutrophils, eosinophils, and basophils.
   b. Agranulocytes include monocytes and lymphocytes.
8. Functions of white blood cells
   a. Neutrophils and monocytes phagocytize foreign particles.
   b. Basophils release biochemicals that dilate local blood vessels.
   c. Chemicals released by damaged cells attract and stimulate leukocytes.
9. White blood cell counts
   a. Normal total white blood cell counts vary from 4,500 to 10,000 cells per microliter of blood.

b. The number of white blood cells may change in abnormal conditions such as infections, emotional disturbances, or excessive loss of body fluids.
c. Because relative proportions of white blood cells may change in particular diseases, the differential white blood cell count, which indicates the percentages of various types of leukocytes, is a useful test.

10. Blood platelets
    a. Blood platelets are fragments of megakaryocytes that enter the circulation.
    b. The normal count varies from 150,000 to 450,000 platelets per microliter.
    c. Platelets help close breaks in blood vessels.

14.3 BLOOD PLASMA (PAGE 538)

Plasma is the liquid part of the blood that is composed of water and a mixture of organic and inorganic substances. It transports nutrients and gases, helps regulate fluid and electrolyte balance, and helps maintain stable pH.

1. Plasma proteins
    a. Plasma proteins remain in the blood and interstitial fluids and are not normally used as energy sources.
    b. Three major types exist.
        (1) Albumins help maintain the colloid osmotic pressure.
        (2) Globulins transport lipids and fat-soluble vitamins and include antibodies that provide immunity.
        (3) Fibrinogen functions in blood clotting.
2. Gases and nutrients
    a. Gases in plasma include oxygen, carbon dioxide, and nitrogen.
    b. Plasma nutrients include simple sugars, amino acids, and lipids.
        (1) Glucose is stored in the liver as glycogen and is released whenever the blood glucose concentration falls.
        (2) Amino acids are used to synthesize proteins and are deaminated for use as energy sources.
        (3) Lipoproteins transport lipids.
3. Nonprotein nitrogenous substances
    a. Nonprotein nitrogenous substances are composed of molecules that contain nitrogen atoms but are not proteins.
    b. They include amino acids, urea, uric acid, creatine, and creatinine.
        (1) Urea and uric acid are products of catabolism.
        (2) Creatinine results from the metabolism of creatine.
    c. Levels of these substances usually remain stable; an increase may indicate a kidney disorder.
4. Plasma electrolytes
    a. Plasma electrolytes are absorbed from the intestines and are released as by-products of cellular metabolism.
    b. They include ions of sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate, and sulfate.
    c. They are important in maintaining the osmotic pressure and pH of plasma.

14.4 HEMOSTASIS (PAGE 540)

Hemostasis refers to the stoppage of bleeding. Hemostatic mechanisms are most effective in controlling blood loss from small vessels.

1. Blood vessel spasm (vasospasm)
    a. Smooth muscles in the walls of smaller blood vessels reflexly contract following injury.
    b. Platelets release serotonin that stimulates vasoconstriction and helps maintain blood vessel spasm.
2. Platelet plug formation
    a. Platelets adhere to rough surfaces and exposed collagen.
    b. Platelets adhere together at the sites of injuries and form platelet plugs in broken vessels.
3. Blood coagulation
    a. Blood clotting, the most effective means of hemostasis, is a series of reactions wherein each reaction stimulates the next (cascade), which may be initiated by extrinsic or intrinsic mechanisms.
    b. The major event of coagulation is the conversion of soluble fibrinogen into insoluble fibrin.
    c. The extrinsic clotting mechanism is triggered when blood contacts damaged tissue.
    d. The intrinsic clotting mechanism is triggered when blood contacts a foreign surface.
    e. Clot formation reflects balance between clotting factors that promote or inhibit clotting.
    f. A formed clot retracts and pulls the edges of a broken blood vessel closer together.
    g. A thrombus is an abnormal blood clot in a blood vessel; an embolus is a clot or fragment of a clot that moves in a blood vessel.
    h. Fibroblasts invade a clot, forming connective tissue throughout.
    i. Protein-splitting enzymes may eventually destroy a clot.
4. Prevention of coagulation
    a. The smooth inner lining of blood vessels discourages the accumulation of platelets.
    b. As a clot forms, fibrin adsorbs thrombin and prevents the reaction from spreading.
    c. Antithrombin interferes with the action of excess thrombin.
    d. Some cells secrete heparin, an anticoagulant.

14.5 BLOOD GROUPS AND TRANSFUSIONS (PAGE 545)

Blood can be typed on the basis of the surface structures of its cells.

1. Antigens and antibodies
    a. Red blood cell membranes may display specific antigens.
    b. Blood plasma may contain antibodies against certain of these antigens.
2. ABO blood group
    a. Blood can be grouped according to the presence or absence of antigens A and B.
    b. Wherever antigen A is absent, anti-A antibody is present; wherever antigen B is absent, anti-B antibody is present.

c. Preventing the mixing of red blood cells that have an antigen with plasma that contains the corresponding antibody avoids a transfusion reaction.
d. Adverse reactions are due to agglutination (clumping) of the red blood cells.

3. Rh blood group
   a. Rh antigens are present on the red blood cell membranes of Rh-positive blood; they are absent in Rh-negative blood.
   b. An Rh-negative person exposed to Rh-positive blood produces anti-Rh antibodies in response.
   c. Mixing Rh-positive red cells with plasma that contains anti-Rh antibodies agglutinates the positive cells.
   d. If an Rh-negative female is pregnant with an Rh-positive fetus, some of the positive cells may enter the maternal blood at the time of birth and stimulate the maternal tissues to produce anti-Rh antibodies.
   e. Anti-Rh antibodies in maternal blood may pass through the placental tissues and react with the red blood cells of an Rh-positive fetus.

CHAPTER ASSESSMENTS

14.1 Introduction

1 Major functions of blood include _____. (p. 526)
   a. nutrient, hormone, and oxygen transport
   b. helping maintain the stability of interstitial fluid
   c. heat distribution
   d. waste transport
   e. all of the above
2 Formed elements in blood are _____, _____, and _____. (p. 526)
3 Define *hematocrit,* and explain how it is determined. (p. 526)
4 The liquid portion of the blood is called _____. (p. 526)

14.2 Blood Cells

5 Indicate where blood cells differentiate, and explain the process. (p. 527)
6 Describe a red blood cell. (p. 528)
7 Contrast oxyhemoglobin and deoxyhemoglobin. (p. 528)
8 Explain the significance of red blood cell counts. (p. 530)
9 Describe the life cycle of a red blood cell from production through destruction. (p. 530)
10 Define *erythropoietin,* and explain its function. (p. 530)
11 Explain how vitamin B_{12} and folic acid deficiencies affect red blood cell production. (p. 531)
12 List two sources of iron that can be used for the synthesis of hemoglobin. (p. 531)
13 Distinguish between biliverdin and bilirubin. (p. 532)
14 Distinguish between granulocytes and agranulocytes. (p. 534)
15 Name five types of leukocytes, and list the major functions of each type. (p. 534)
16 Explain the significance of white blood cell counts as aids to diagnosing disease. (p. 536)
17 _____ are fragments of megakaryocytes that function in _____. (p. 537)

14.3 Blood Plasma

18 The most abundant component of plasma is _____. (p. 538)
   a. vitamins
   b. oxygen
   c. proteins
   d. water
   e. electrolytes
19 Name three types of plasma proteins, and indicate the function of each type. (p. 539)
20 Name the gases and nutrients in plasma. (p. 539)
21 Define *nonprotein nitrogenous substances,* and name those commonly present in plasma. (p. 540)
22 The most abundant plasma electrolytes are _____ and _____. (p. 540)
23 Name several plasma electrolytes. (p. 540)

14.4 Hemostasis

24 _____ is the term for stoppage of bleeding. (p. 540)
25 Explain how blood vessel spasm is stimulated following an injury. (p. 540)
26 Platelets adhering to form a plug may control blood loss from a _____ break, but a larger break may require a _____ to halt bleeding. (p. 540)
27 Name a vitamin required for blood clotting. (p. 541)
28 Distinguish between fibrinogen and fibrin. (p. 541)
29 Indicate the trigger and outline the steps for extrinsic clotting and for intrinsic clotting. (pp. 541–542)
30 Describe the major steps leading to the formation of a blood clot. (p. 541)
31 Describe a positive feedback system that operates during blood clotting. (p. 541)
32 Define *serum.* (p. 543)
33 Explain how a blood clot may be removed naturally from a blood vessel. (p. 543)
34 Distinguish between a thrombus and an embolus. (p. 544)
35 Describe how blood coagulation may be prevented. (p. 544)

14.5 Blood Groups and Transfusions

36 Distinguish between an antigen and an antibody. (p. 546)
37 Explain the basis of ABO blood types. (p. 546)
38 Explain why a person with blood type AB is sometimes called a universal recipient. (p. 547)
39 Explain why a person with blood type O is sometimes called a universal donor. (p. 548)
40 Distinguish between Rh-positive and Rh-negative blood. (p. 549)
41 Describe how a person may become sensitized to Rh-positive blood. (p. 549)
42 Describe *erythroblastosis fetalis,* and explain how this condition may develop. (p. 549)

INTEGRATIVE ASSESSMENTS/CRITICAL THINKING

OUTCOMES 3.4, 3.6,14.2

1. If a patient with inoperable cancer is treated using a drug that reduces the rate of cell division, how might the patient's white blood cell count change? How might the patient's environment be modified to compensate for the effects of these changes?

OUTCOMES 4.5, 9.3, 13.3, 14.2

2. Erythropoietin is available as a drug, as are drugs that mimic the effects of erythropoietin. Why would athletes abuse these drugs? Why is it difficult to detect erythropoietin that has been taken as a drug?
3. Some athletes have been accused of performing "blood doping" to improve their athletic performance. Why would removing blood a month or so prior to performance, then reinfusing the blood shortly before a competition, boost performance?

OUTCOME 14.2

4. Hypochromic (iron-deficiency) anemia is common among aging persons admitted to hospitals for other conditions. What environmental and sociological factors might promote this form of anemia?
5. How would you explain to a patient with leukemia, who has a greatly elevated white blood cell count, the importance of avoiding bacterial infections?

OUTCOMES 14.2, 14.4

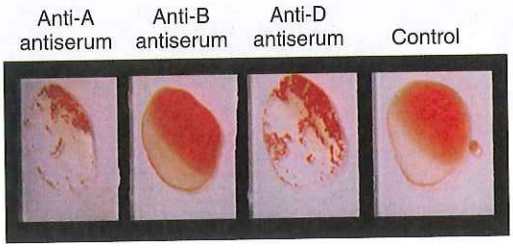
6. In the United States between 1977 and 1985, more than 10,000 men contracted the human immunodeficiency virus (HIV) from contaminated factor VIII that they received to treat hemophilia. What are two abnormalities in the blood of these men?

OUTCOMES 14.3, 14.4

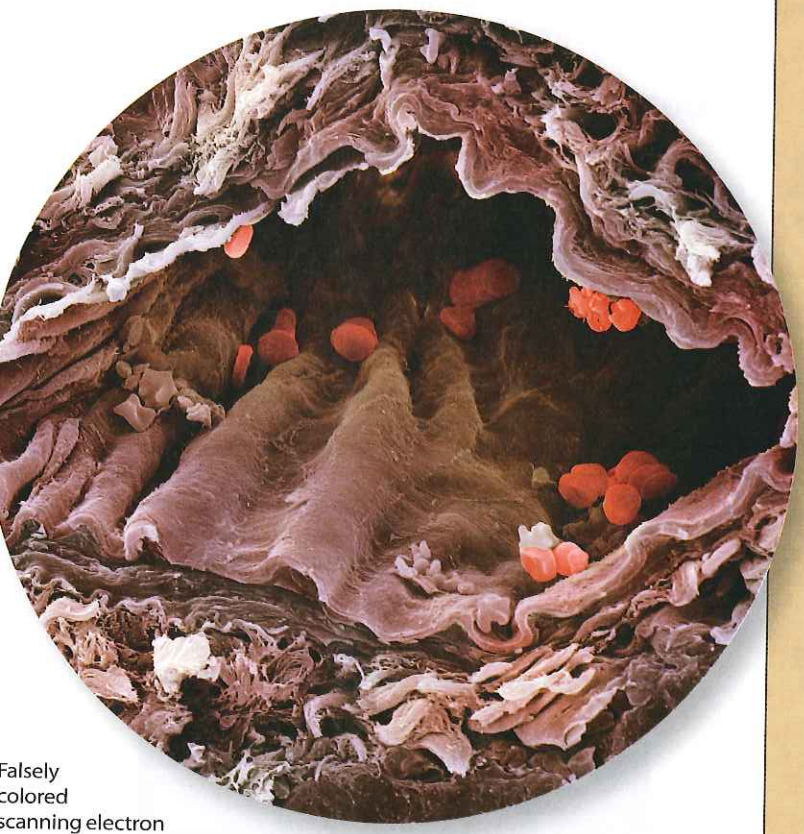
7. Why do patients with liver diseases commonly develop blood clotting disorders?

OUTCOME 14.5

8. Commercially available antiserum samples containing antibodies for antigens A, B, and D are used to determine the type of a particular patient's blood. The antiserum is mixed with the sample of blood, and if agglutination (clumping) occurs, that means that the antigen with the same name as the antiserum is present on those RBCs.Indicate the blood type (both ABO and Rh) of this individual: What blood type(s) could safely receive blood from this individual? What blood type(s) could this individual safely receive? (Note: The control indicates the absence of aggultination, or clumping.)



15 Cardiovascular System



Falsely colored scanning electron micrograph of a cross-section through an artery containing red blood cells. The typical thick wall (pink/brown) is adapted to withstand the high pressure of blood that the beating heart pumps throughout the body.

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Module 9: Cardiovascular System

Learning Outcomes

After you have studied this chapter, you should be able to:

15.1 Introduction

1 Discuss the functions of the organs of the cardiovascular system. (p. 555)

15.2 Structure of the Heart

2 Distinguish between the coverings of the heart and the layers that compose the wall of the heart. (p. 556)

3 Identify and locate the major parts of the heart and discuss the function of each part. (p. 559)

4 Trace the pathway of the blood through the heart and the vessels of coronary circulation. (p. 562)

15.3 Heart Actions

5 Describe the cardiac cycle and explain how heart sounds are produced. (p. 566)

6 Identify the parts of a normal ECG pattern and discuss the significance of this pattern. (p. 570)

7 Explain control of the cardiac cycle. (p. 570)

15.4 Blood Vessels

8 Compare the structures and functions of the major types of blood vessels. (p. 576)

9 Describe how substances are exchanged between blood in capillaries and the tissue fluid surrounding body cells. (p. 580)

15.5 Blood Pressure

10 Explain how blood pressure is produced and controlled. (p. 582)

11 Describe the mechanisms that aid in returning venous blood to the heart. (p. 588)

15.6 Paths of Circulation

12 Compare the pulmonary and systemic circuits of the cardiovascular system. (p. 591)

15.7–15.8 Arterial System–Venous System

13 Identify and locate the major arteries and veins. (p. 593)

15.9 Life-Span Changes

14 Describe life-span changes in the cardiovascular system. (p. 607)

LEARN PRACTICE ASSESS

Understanding Words

angio-, vessel: *angio*tensin—substance that constricts blood vessels.

ather-, porridge: *ather*osclerosis—deposits of plaque in arteries.

brady-, slow: *brady*cardia—abnormally slow heartbeat.

diastol-, dilation: *diastol*ic pressure—blood pressure when the ventricle of the heart is relaxed.

edem-, swelling: *edema*—accumulation of fluids in the tissues that causes them to swell.

-gram, something written: electrocardio*gram*—recording of the electrical changes in the myocardium during a cardiac cycle.

lun-, moon: semi*lun*ar valve—valve with crescent-shaped flaps.

myo-, muscle: *myo*cardium—muscle tissue within the wall of the heart.

papill-, nipple: *papill*ary muscle—small mound of muscle projecting into a ventricle of the heart.

phleb-, vein: *phleb*itis—inflammation of a vein.

scler-, hard: arterio*scler*osis—loss of elasticity and hardening of a blood vessel wall.

syn-, together: *syn*cytium—mass of merging cells that act together.

systol-, contraction: *systol*ic pressure—blood pressure resulting from a single ventricular contraction.

tachy-, rapid: *tachy*cardia—abnormally fast heartbeat.

The base of the aorta, which includes the aortic valve, protrudes somewhat into the interatrial septum close to the AV bundle. Consequently, inflammatory conditions, such as bacterial endocarditis affecting the aortic valve (aortic valvulitis), may also affect the AV bundle.

If a portion of the bundle is damaged, it may no longer conduct impulses normally. As a result, cardiac impulses may reach the two ventricles at different times so that they fail to contract together. This condition is called a *bundle branch block*.

The Purkinje fibers spread from the interventricular septum into the papillary muscles, which project inward from the ventricular walls, and then continue downward to the apex of the heart. There they curve around the tips of the ventricles and pass upward over the lateral walls of these chambers. Along the way, the Purkinje fibers give off many small branches, which become continuous with cardiac muscle fibers. Figure 15.18 shows the parts of the conduction system and figure 15.19 summarizes them.

The muscle fibers in the ventricular walls form irregular whorls. When impulses on the Purkinje fibers stimulate these muscle fibers, the ventricular walls contract with a twisting motion (fig. 15.20). This action squeezes blood out of the ventricular chambers and forces it into the aorta and pulmonary trunk.

Another property of the conduction system is that the Purkinje fibers transmit the impulse to the apex of the heart first. As a result, contraction begins at the apex and pushes the blood superiorly toward the aortic and pulmonary semilunar valves, rather than originating the impulse superiorly and pushing blood toward the apex, as it would if the impulse traveled from cell to cell.

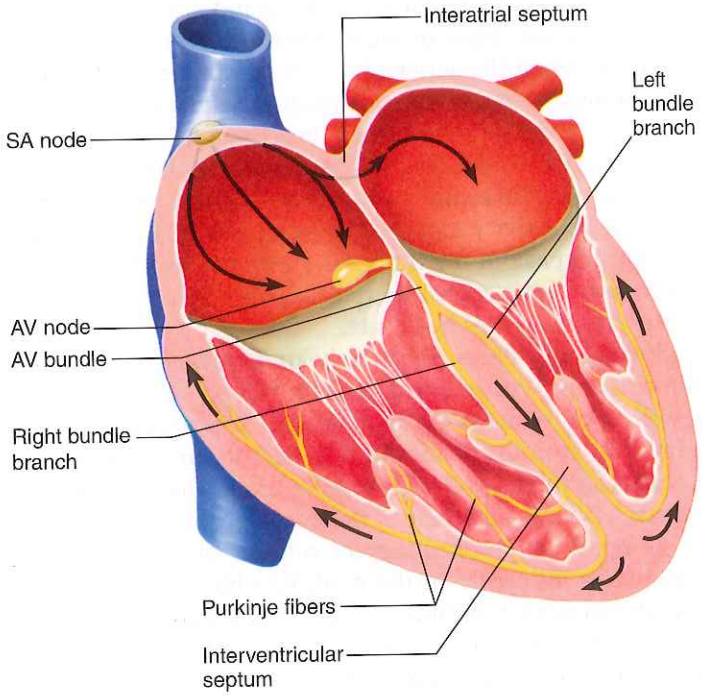


FIGURE 15.18 AP|R The cardiac conduction system coordinates the cardiac cycle.

PRACTICE

22 What is the function of the cardiac conduction system?

23 What types of tissues make up the cardiac conduction system?

24 How is a cardiac impulse initiated?

25 How is a cardiac impulse transmitted from the right atrium to the other heart chambers?

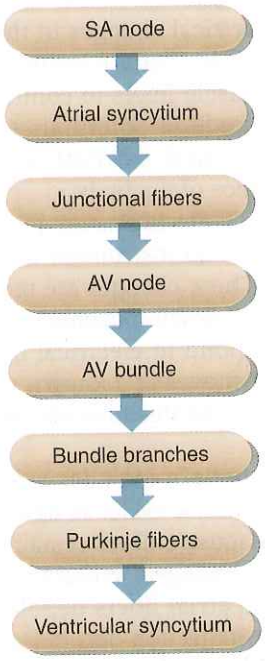


FIGURE 15.19 Components of the cardiac conduction system.

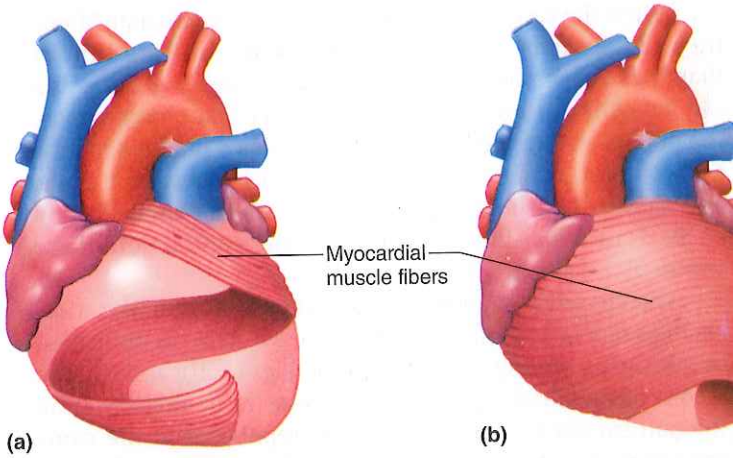


FIGURE 15.20 The muscle fibers within the ventricular walls form whorled patterns. The fibers of groups (*a*) and (*b*) surround both ventricles in these anterior views of the heart.

A significant percentage of cases of heart failure in adults of African descent may be due to an inherited condition called familial amyloidosis. A protein called amyloid forms deposits in the heart, causing angina (chest pain), failure of cardiac muscle function (cardiomyopathy), blockage of conduction of electrical impulses, and disturbed heart rhythm (arrhythmia). Echocardiography can detect the amyloid deposits that thicken the ventricular walls. It is important to distinguish amyloidosis from other forms of arrhythmias, because drug treatments are different.

Electrocardiogram

An **electrocardiogram** (e-lek"tro-kar'de-o-gram") (ECG) is a recording of the electrical changes in the myocardium during a cardiac cycle. (This pattern occurs as action potentials stimulate cardiac muscle fibers to contract, but it is not the same as individual action potentials.) Because body fluids can conduct electrical currents, such changes can be detected on the surface of the body.

To record an ECG, electrodes are placed on the skin and connected by wires to an instrument that responds to weak electrical changes. These changes are recorded on a moving strip of paper. Up-and-down movements, or deflections from the baseline, correspond to electrical changes in the myocardium. The paper moves at a known rate, so the distance between deflections indicates time elapsing between phases of the cardiac cycle.

A normal ECG pattern includes several deflections, or *waves*, during each cardiac cycle, as figure 15.21*a* illustrates. Between cycles, the muscle fibers remain polarized, with no detectable electrical changes. When the SA node triggers a cardiac impulse, the atrial fibers depolarize, producing an electrical change. A deflection occurs, and at the end of the electrical change the recording returns to the baseline. This first deflection produces a *P wave,* corresponding to a depolarization of the atrial fibers that will lead to contraction of the atria (fig. 15.21*b–d*).

When the cardiac impulse reaches the ventricular fibers, they rapidly depolarize. The ventricular walls are thicker than those of the atria, so the electrical change is greater, and the deflection is greater. When the electrical change ends, the pen returns to the baseline. This leaves a mark called the *QRS complex,* which usually consists of a *Q wave,* an *R wave,* and an *S wave.* The complex appears due to depolarization of the ventricular fibers just prior to the contraction of the ventricular walls (fig. 15.21*e* and *f*).

The electrical changes that accompany ventricular muscle fiber repolarization slowly produce a *T wave* as deflection occurs again, ending the ECG pattern (fig. 15.21*g* and *h*). The record of the atrial repolarization seems to be missing from the pattern because the atrial fibers repolarize at the same time that the ventricular fibers depolarize. Thus, the QRS complex obscures the recording of the atrial repolarization.

The graph in figure 15.22 summarizes some of the changes that occur during a cardiac cycle with corresponding ECG patterns and heart sounds.

Physicians use ECG patterns to assess the heart's ability to conduct impulses. For example, the period between the beginning of a P wave and the beginning of a QRS complex called the *PQ interval* (or if the initial portion of the QRS complex is upright, the *PR interval*) indicates the time for the cardiac impulse to travel from the SA node through the AV node. Ischemia or other problems affecting the fibers of the AV conduction pathways can prolong this PQ interval. Similarly, injury to the AV bundle can extend the QRS complex, because it may take longer for an impulse to spread throughout the ventricular walls (fig. 15.23).

PRACTICE

26 What is an electrocardiogram?

27 Which cardiac events do the P wave, QRS complex, and T wave represent?

Regulation of the Cardiac Cycle

The volume of blood pumped changes to accommodate cellular requirements. For example, during strenuous exercise, skeletal muscles require more blood, and heart rate increases in response. Because the SA node normally controls heart rate, changes in this rate often involve factors that affect the pacemaker, such as the motor impulses carried on the parasympathetic and sympathetic nerve fibers (see figs. 11.38 p. 433, 11.39 p. 434, fig. 15.24, and figs.15.37, 15.38).

The parasympathetic fibers that innervate the heart arise from neurons in the medulla oblongata and make up parts of the *vagus nerves.* Most of these fibers branch to the SA and AV nodes. When the series of action potentials reach nerve fiber endings, they secrete acetylcholine, which decreases SA and AV nodal activity. As a result, heart rate decreases.

The vagus nerves continually carry impulses to the SA and AV nodes, "braking" heart action. Consequently, parasympathetic activity can change heart rate in either direction. An increase in the impulses slows the heart rate, and a decrease in the impulses releases the parasympathetic "brake" and increases heart rate.

Sympathetic fibers reach the heart by means of the *accelerator nerves,* whose branches join the SA and AV nodes as well as other areas of the atrial and ventricular myocardium. The endings of these fibers secrete norepinephrine in response to series of action potentials. Norepinephrine increases the rate and force of myocardial contractions.

Reflexes called *baroreceptor reflexes* arising from the *cardiac control center* of the medulla oblongata maintain balance between inhibitory effects of the parasympathetic fibers and excitatory effects of the sympathetic fibers. In this region of the brain, masses of neurons function as *cardioinhibitor* and *cardioaccelerator reflex centers.* These

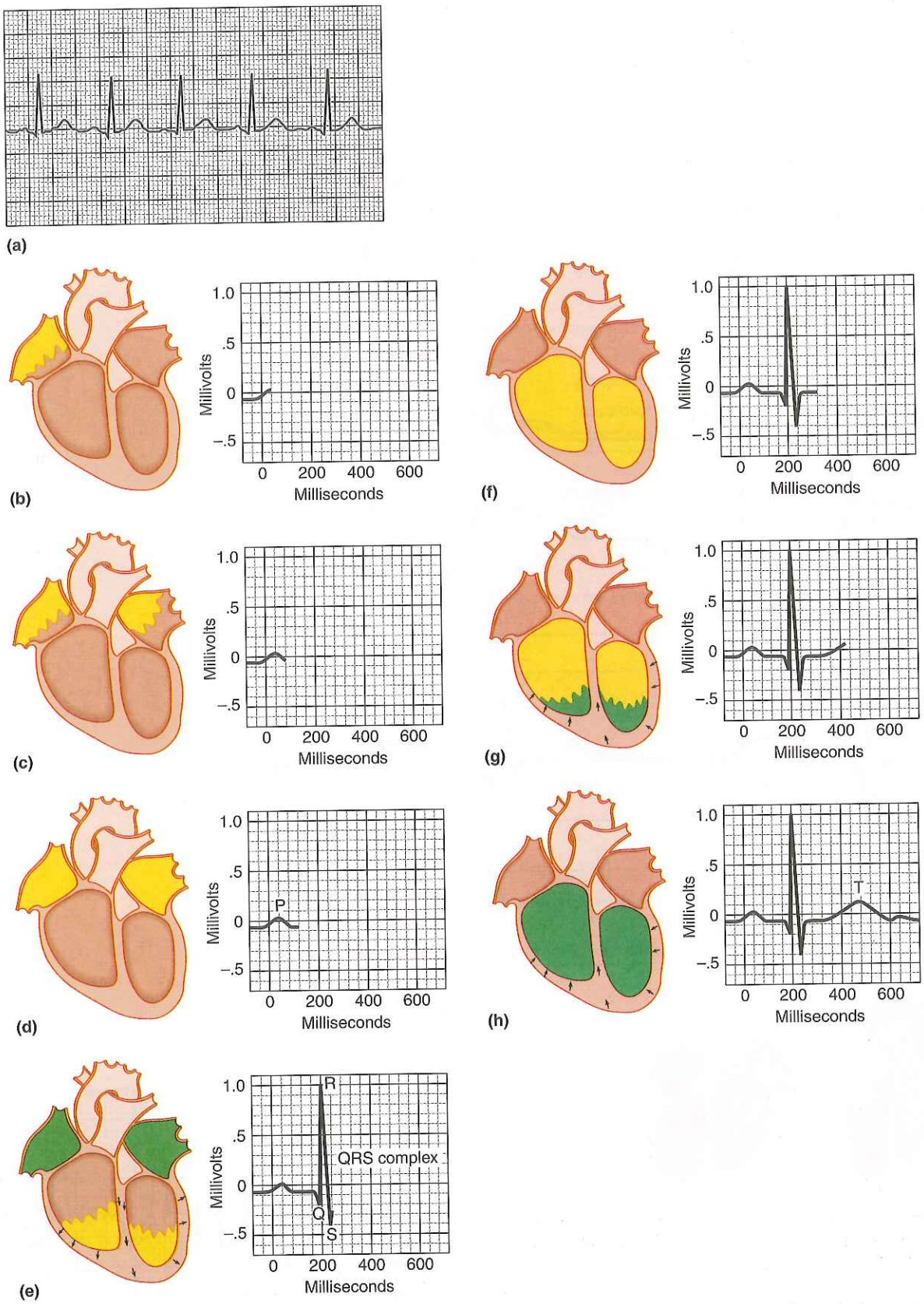
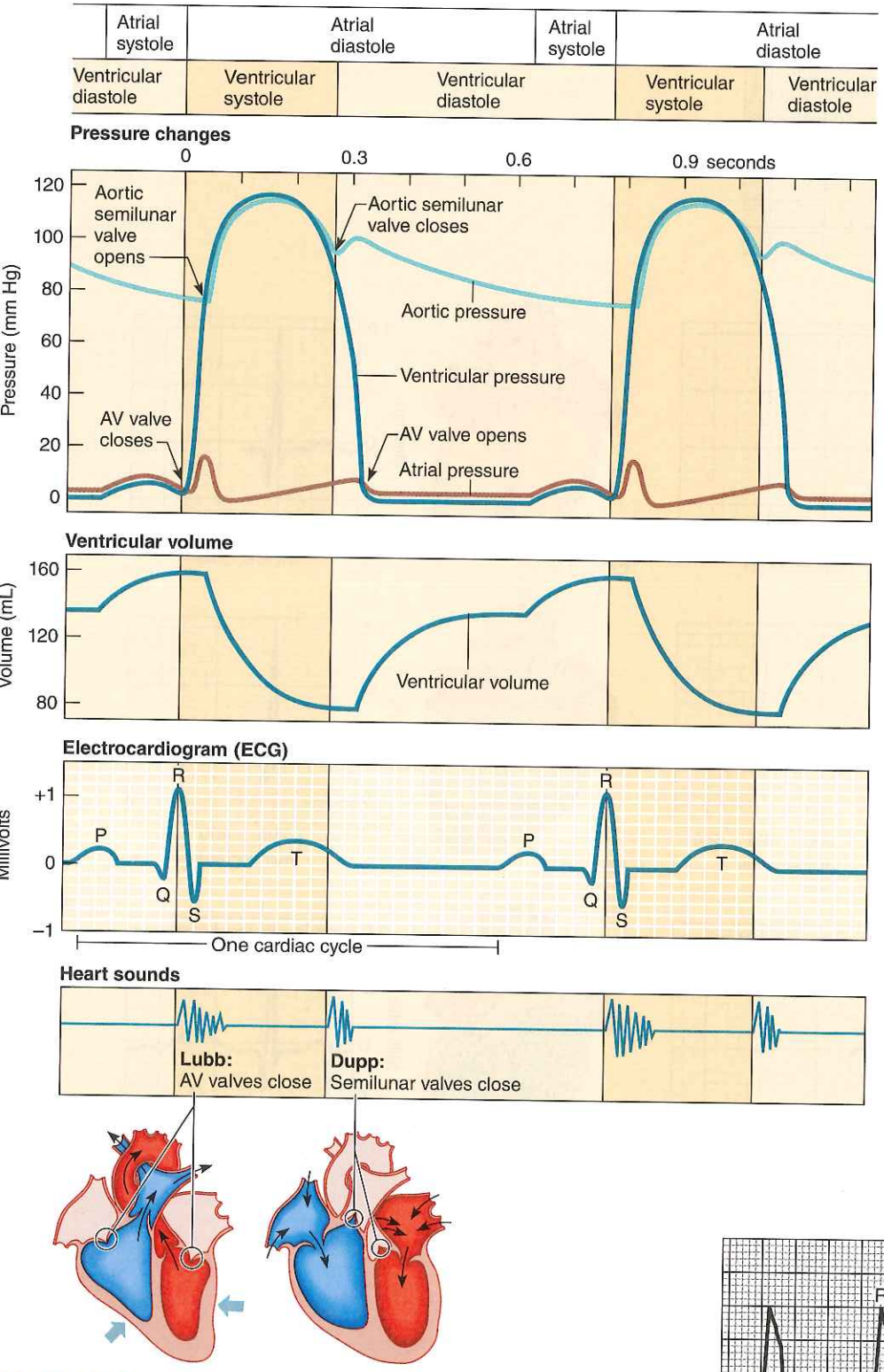


FIGURE 15.21 ECG pattern. (*a*) A normal ECG. In this set of drawings (*b–h*), the yellow areas of the hearts indicate where depolarization is occurring, and the green areas indicate where tissues are repolarizing; the portion of the ECG pattern produced at each step is shown by the continuation of the line on the graph paper.

Q: *Which two electrical events occur during the QRS complex?*

Answer can be found in Appendix G on page 938.



IGURE 15.22 A graph of some of the changes that occur in the heart uring a cardiac cycle with corresponding ECG pattern and heart sounds.

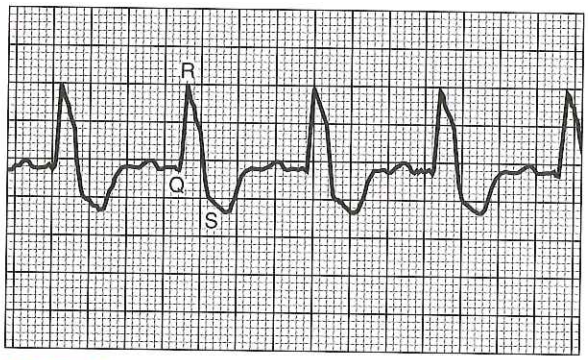


FIGURE 15.23 A prolonged QRS complex may result from damage to the AV bundle fibers.

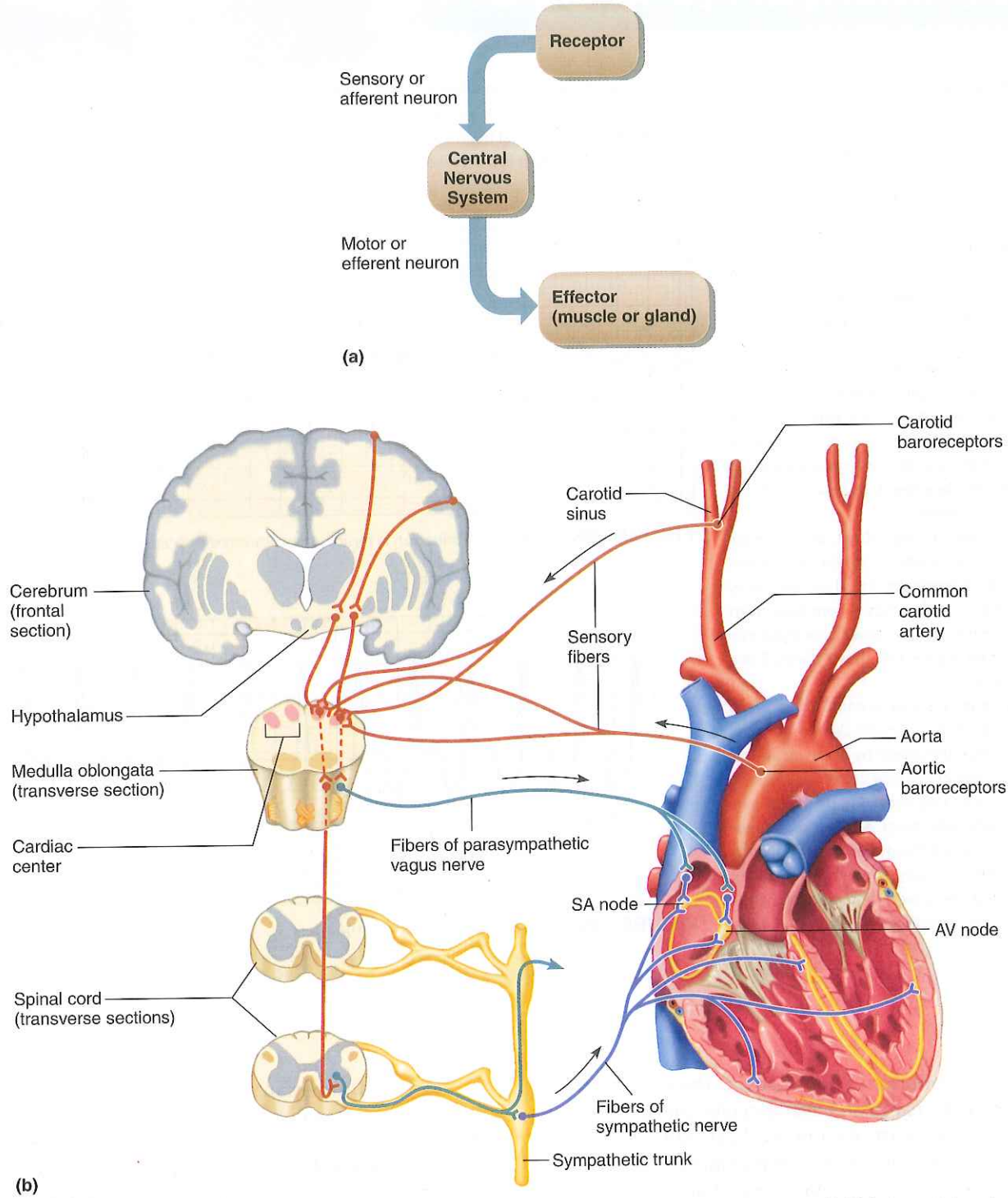


FIGURE 15.24 AP|R Baroreceptor reflex. (*a*) Schematic of a general reflex arc. Note the similarity to figure 1.6 on page 18. (*b*) Autonomic impulses alter the activities of the SA and AV nodes.

centers receive sensory impulses from throughout the cardiovascular system and relay motor impulses to the heart in response. For example, receptors sensitive to stretch are located in certain regions of the aorta (aortic arch) and in the carotid arteries (carotid sinuses). These receptors, called *baroreceptors* (pressoreceptors), can detect changes in blood pressure (fig. 15.24). Rising pressure stretches the receptors, and they signal the cardioinhibitor center in the medulla. In response, the medulla sends parasympathetic motor impulses to the heart via the vagus nerve, decreasing the heart rate. This action helps lower blood pressure toward normal.

Another regulatory reflex uses stretch receptors in the venae cavae near the entrances to the right atrium. If venous

15.1 CLINICAL APPLICATION

Arrhythmias

Each year, thousands of people die from fast or irregular heartbeats. These altered heart rhythms are called *arrhythmias*. There are several types.

In *fibrillation*, small areas of the myocardium contract in an uncoordinated, chaotic fashion (fig. 15B). As a result, the myocardium fails to contract as a whole, and blood is no longer pumped. Atrial fibrillation is not life threatening, because the ventricles still pump blood, but ventricular fibrillation is often deadly. Ventricular fibrillation can be caused by an obstructed coronary artery, toxic drug exposure, electric shock, or traumatic injury to the heart or chest wall. A defibrillator device can deliver a shock to restore a normal heartbeat, as described in the chapter-opening vignette.

An abnormally fast heartbeat, usually more than 100 beats per minute, is called *tachycardia*. Increase in body temperature, nodal stimulation by sympathetic fibers, certain drugs or hormones, heart disease, excitement, exercise, anemia, or shock can cause tachycardia. Figure 15C shows the ECG of a tachycardic heart.

Bradycardia means a slow heart rate, usually fewer than 60 beats per minute. Decreased body temperature, nodal stimulation by parasympathetic impulses, or certain drugs may cause bradycardia. It also may occur during sleep. Figure 15D shows the ECG of a bradycardic heart. Athletes sometimes have unusually slow heartbeats because their hearts pump a greater-than-average volume of blood with each beat. The slowest heartbeat recorded in a healthy athlete was 25 beats per minute!

A heart chamber *flutters* when it contracts regularly, but very rapidly, such as 250–350 times per minute. Although normal hearts may flutter occasionally, this condition is more likely to be due to damage to the myocardium (fig. 15E).

A *premature beat* occurs before it is expected in a normal series of cardiac cycles. Cardiac impulses originating from unusual (ectopic) regions of the

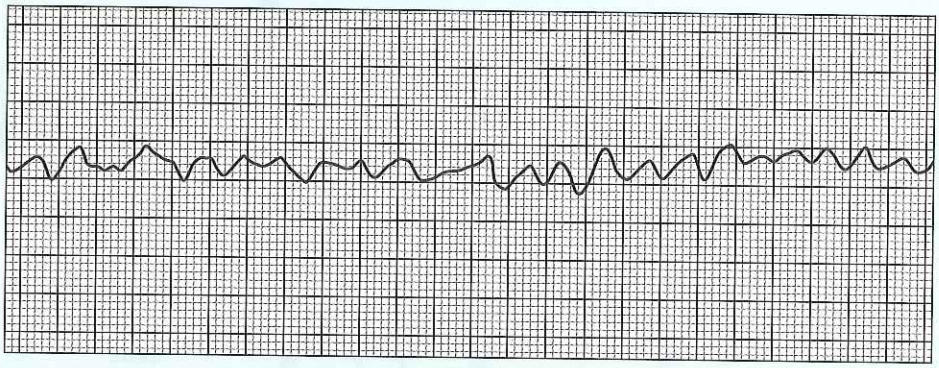


FIGURE 15B Ventricular fibrillation is rapid, uncoordinated depolarization of the ventricles.

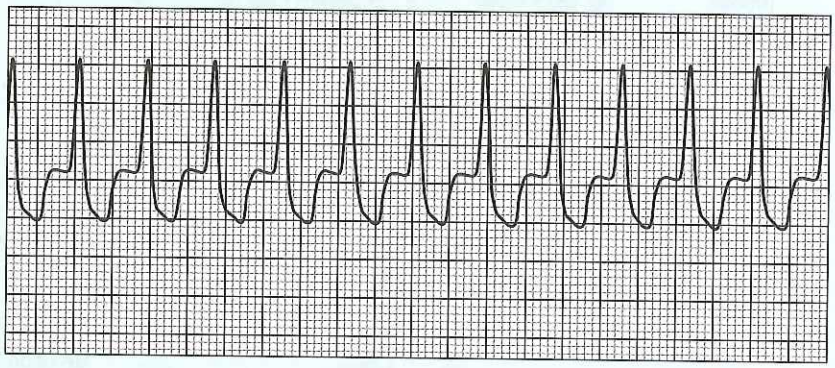


FIGURE 15C Tachycardia is a rapid heartbeat.

blood pressure abnormally increases in these vessels, the receptors signal the cardioaccelerator center, and sympathetic impulses reach the heart. As a result, heart rate and force of contraction increase, and the venous pressure is reduced.

Impulses from the cerebrum or hypothalamus also influence the cardiac control center. These impulses may decrease heart rate, such as occurs when a person faints following an emotional upset, or they may increase heart rate during a period of anxiety.

Two other factors that influence heart rate are temperature change and certain ions. Rising body temperature increases heart action, which is why heart rate usually increases during fever. Abnormally low body temperature decreases heart action.

The most important ions that influence heart action are potassium (K^+) and calcium (Ca^{+2}). Potassium affects the electrical potential of the cell membrane, altering its ability to reach the threshold for conducting an impulse (see chapter 10, p. 375). Some calcium ions cross the cell membrane of cardiac muscle cells and bind to the sarcoplasmic reticulum, causing the release of many calcium ions into the sarcoplasm. These calcium ions bind to troponin, resulting in cardiac muscle cell contraction much like skeletal muscle cell contraction. Although homeostatic mechanisms normally maintain the concentrations of these ions within narrow ranges, these mechanisms sometimes fail, and the consequences can be serious or even fatal. Clinical Application 15.1 examines abnormal heart rhythms.

Continued—

heart probably cause a premature beat. That is, the impulse originates from a site other than the SA node. Cardiac impulses may arise from ischemic tissues or from muscle fibers irritated by disease or drugs.

Any interference or block in cardiac impulse conduction may cause arrhythmia, the type varying with the location and extent of the block. Such arrhythmias may arise from ectopic pacemakers (pacemakers outside the SA node).

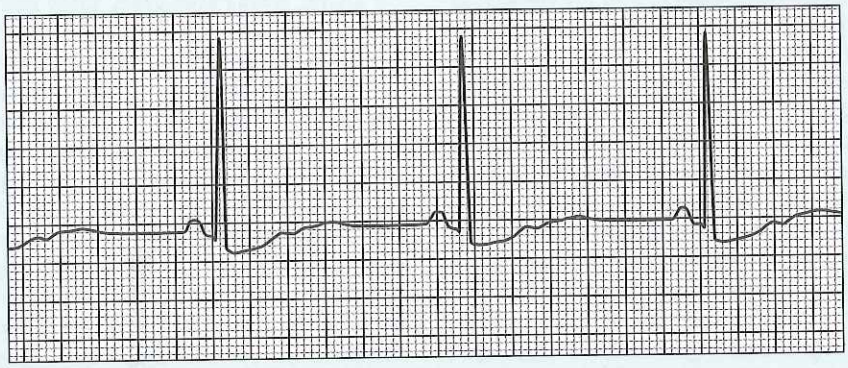


FIGURE 15D Bradycardia is a slow heartbeat.

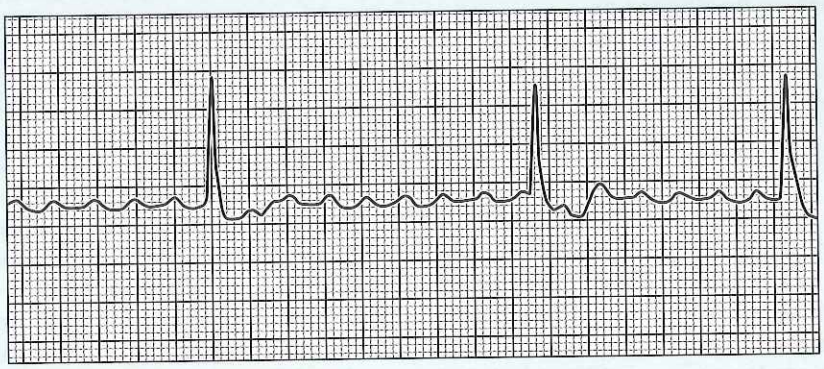


FIGURE 15E Atrial flutter is an abnormally rapid rate of atrial depolarization.

The SA node usually initiates 70–80 heartbeats per minute, called a sinus rhythm. If the SA node is damaged, impulses originating in the AV node may take over and travel upward into the atrial myocardium and downward into the ventricular walls, stimulating them to contract. Under the influence of the AV node acting as a *secondary pacemaker,* the heart may continue to pump blood, but at a rate of 40–60 beats per minute, called a nodal rhythm. Similarly, the Purkinje fibers can initiate cardiac impulses, contracting the heart 15–40 times per minute.

An *artificial pacemaker* can treat a disorder of the cardiac conduction system. This device includes an electrical pulse generator and a lead wire that communicates with a portion of the myocardium. The pulse generator contains a permanent battery that provides energy and a microprocessor that can sense the cardiac rhythm and signal the heart to alter its contraction rate.

An artificial pacemaker is surgically implanted beneath the patient's skin in the shoulder. A programmer adjusts its functions from the outside. The first pacemakers, made in 1958, were crude. Today, thanks to telecommunications advances, a physician can check a patient's pacemaker over the phone. A device called a pacemaker-cardioverter-defibrillator attempts to correct ventricular fibrillation should it occur. ■

Excess potassium ions in the blood (hyperkalemia) alter the usual polarized state of the cardiac muscle fibers, decreasing the rate and force of contractions. A high potassium ion concentration may block conduction of cardiac impulses, and heart action may suddenly stop (cardiac arrest). Conversely, if the potassium concentration drops below normal (hypokalemia), the heart may develop a potentially life-threatening abnormal rhythm (arrhythmia).

An excess of calcium ions in the blood (hypercalcemia) increases heart action, which can result in dangerously extended heart contractions. Conversely, a low calcium ion concentration (hypocalcemia) depresses heart action because these ions are needed to initiate heart muscle contraction.

PRACTICE

28 Which nerves supply parasympathetic fibers to the heart? Which nerves supply sympathetic fibers?

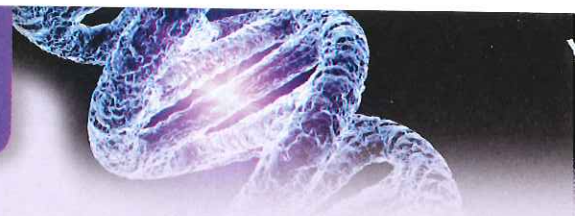
29 How do parasympathetic and sympathetic impulses help control heart rate?

30 How do changes in body temperature affect heart rate?

15.4 BLOOD VESSELS

The blood vessels are organs of the cardiovascular system. They form a closed circuit of tubes that carries blood from the heart to the body cells and back again. These vessels

15.2 FROM SCIENCE TO TECHNOLOGY



Altering Angiogenesis

Angiogenesis is the formation of new blood vessels. Under the influence of vascular endothelial growth factor (VEGF), endothelial cells divide and assemble into the tubules that form capillaries as well as the innermost linings of larger blood vessels. In normal development, angiogenesis is crucial to build a blood supply to serve a growing body. New blood vessels deliver nutrients, hormones, and growth factors to tissues and remove wastes. Angiogenesis is also essential for healing. After a heart attack, for example, new vessels form in the remaining healthy cardiac muscle.

As with most biological processes, angiogenesis must be highly controlled. Drugs that increase or decrease the activity of VEGF are used to target several common diseases caused by excess, deficient, or inappropriate angiogenesis. Two specific applications are healing hearts and removing extra capillaries in tumors and in eyes.

Promoting Angiogenesis

A clot blocks a coronary artery. Within seconds, the localized lack of oxygen stimulates muscle cells to release hypoxia-inducible factor (HIF-1). This protein activates several genes whose products restore homeostasis by stimulating glycolysis (anaerobic respiration); signaling the kidneys to produce erythropoietin, which boosts the red blood cell supply and turns on production of VEGF. Capillaries extend and restore some blood flow to the blocked cardiac muscle. Fibroblast growth factor also assists in angiogenesis.

When natural angiogenesis isn't sufficient, part of the heart dies. Coronary bypass surgery and angioplasty are treatments that restore blood flow, but for patients who cannot undergo these procedures or whose blockages are in vessels too narrow or difficult to reach, targeting angiogenesis may help to save starved heart parts. One approach is to package growth factors in time-release capsules implanted near small vessels while large ones are being surgically bypassed. Another strategy is gene therapy, which delivers the genes that encode VEGF to oxygen-starved areas of the heart.

Preventing Angiogenesis

Once a tumor reaches the size of a pinhead, it secretes VEGF, which stimulates nearby capillaries to branch and extend toward it. At the same time, endothelial cells that are part of the tumor assemble into sheets, roll into tubules, and snake out of the tumor as new capillaries. Other cancer cells wrap around the capillaries, spreading out on this scaffolding into nearby tissues. Some cancer cells enter blood vessels and travel to other parts of the body. For a time, maybe even years, these secondary tumors stay small, adhering to the outsides of the blood vessels that delivered them.

From the observation by many surgeons that when a primary tumor is removed, secondary tumors grow, Harvard researcher, Judah Folkman hypothesized that the primary tumor secretes antiangiogenesis factors that keep the secondary tumors small. Once factors that promote or block angiogenesis were discovered in the 1980s, researchers began to study the antiangiogenesis factors that keep secondary tumors small, to develop them as cancer treatments. The first antiangiogenesis drug to treat cancer became available in 2004, for colorectal cancer that has spread to other organs. Today it is also used to treat age-related macular degeneration, in which extra capillaries extend into the retina and block central vision. ■

include arteries, arterioles, capillaries, venules, and veins. The arteries and arterioles conduct blood away from the ventricles of the heart and lead to the capillaries, where substances are exchanged between blood and the body cells. Venules and veins return blood from the capillaries to the atria. From Science to Technology 15.2 describes angiogenesis, the formation of new blood vessels in the body.

Researchers create replacement blood vessels from cells and their products plus synthetic materials. One such blood vessel consists of smooth muscle cells seeded onto tubes of a biodegradable polymer. The cells secrete collagen and extracellular matrix, which replace the polymer, and then detergent is applied to remove the cells. The tubes can be stored for long periods of time. Another approach uses rubber tubing and a nutrient solution that prompts the cells to produce extra elastin, which makes the replacement vessels more flexible.

Arteries and Arterioles

Arteries (ar′-te-rēz) are strong, elastic vessels adapted for carrying blood away from the heart under relatively high pressure. These vessels subdivide into progressively thinner tubes and eventually give rise to the finer, branched **arterioles** (ar-te′re-olz).

The wall of an artery consists of three distinct layers, or *tunics*, shown in figure 15.25*a*. The innermost tunic, tunica interna (intima), is composed of a layer of simple squamous epithelium, called *endothelium*, that rests on a connective tissue membrane rich in elastic and collagenous fibers.

The endothelial lining of an artery provides a smooth surface that allows blood cells and platelets to flow through without being damaged. Additionally, endothelium helps prevent blood clotting by secreting biochemicals that inhibit platelet aggregation (see chapter 14, p. 540). Endothelium also may help regulate local blood flow by secreting substances that dilate or constrict blood vessels. For example, endothelium releases the gas nitric oxide, which relaxes the smooth muscle of the vessel.

The middle layer, tunica media, makes up the bulk of the arterial wall. It includes smooth muscle fibers, which encircle the tube, and a thick layer of elastic connective tissue. The connective tissue gives the vessel a tough elasticity that enables it to withstand the force of blood pressure and, at the same time, to stretch and accommodate the sudden increase in blood volume that accompanies ventricular contraction.

The outer layer, tunica externa (adventitia), is relatively thin and chiefly consists of connective tissue with irregular elastic and collagenous fibers. This layer attaches the artery to the surrounding tissues. It also contains minute vessels (vasa vasorum) that give rise to capillaries and provide blood to the more external cells of the artery wall.

The sympathetic branches of the autonomic nervous system innervate smooth muscle in artery and arteriole walls.

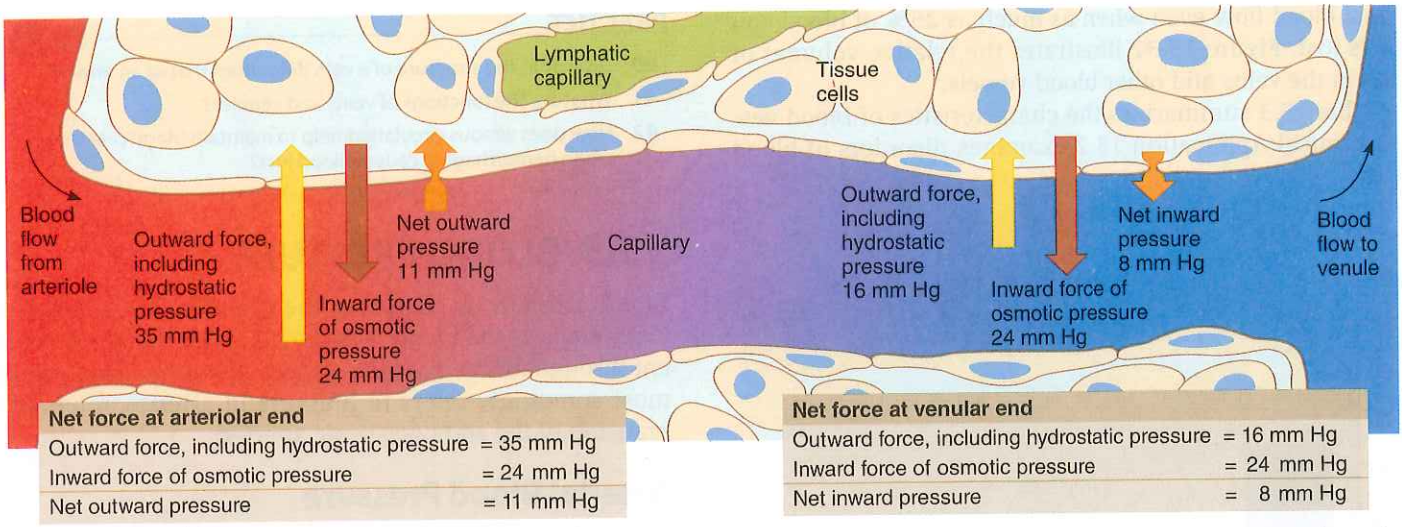


FIGURE 15.30 AP|R Water and other substances leave capillaries because of a net outward pressure at the capillaries' arteriolar ends. Water enters at the capillaries' venular ends because of a net inward pressure. Substances move in and out along the length of the capillaries according to their respective concentration gradients.

Q: *Which substances do not leave the blood at the arteriolar end of the capillary and whose presence at the venular end of the capillary draw water back into the capillary by osmosis?*

Answer can be found in Appendix G on page 938.

leak out of the capillaries to overwhelm lymphatic drainage. Affected tissues become swollen (edematous) and painful.

PRACTICE

37 Which forces affect the exchange of substances between blood and tissue fluid?

38 Why is the fluid movement out of a capillary greater at its arteriolar end than at its venular end?

39 More fluid leaves the capillary than returns to it, so how is the remainder returned to the vascular system?

If the right ventricle of the heart is unable to pump blood out as rapidly as it enters, other parts of the body may develop edema because the blood backs up into the veins, venules, and capillaries, increasing blood pressure in these vessels. As a result of this increased *back pressure*, osmotic pressure of the blood in the venular ends of the capillaries is less effective at balancing filtration, and the tissues swell. This is true particularly in the lower extremities if the person is upright, or in the back if the person is supine. In the terminal stages of heart failure, edema is widespread, and fluid accumulates in the peritoneal cavity of the abdomen. This painful condition is called *ascites*.

Venules and Veins

Venules (ven'ūlz) are the microscopic vessels that continue from the capillaries and merge to form **veins** (vānz). The veins, which carry blood back to the atria, follow pathways that roughly parallel those of the arteries.

The walls of veins are similar to those of arteries in that they are composed of three distinct layers. However, the middle layer of the venous wall is poorly developed compared to that of the arterial wall. Consequently, veins have thinner walls that have less smooth muscle and less elastic connective tissue than those of comparable arteries, but their lumens have a greater diameter (see fig. 15.25*b*).

Many veins, particularly those in the upper and lower limbs, have flaplike *valves* (called semilunar valves), which project inward from their linings. Valves, shown in figure 15.31, are usually composed of two leaflets that close if blood begins to back up in a vein. These valves aid in returning blood to the heart because they are open as long as the blood flow is toward the heart but close if flow is in the opposite direction.

Veins also function as *blood reservoirs*, which are useful in times of blood loss. For example, in hemorrhage accompanied by a drop in arterial blood pressure, sympathetic nerve impulses reflexly stimulate the muscular walls of the veins to constrict, which helps maintain blood pressure by returning more blood to the heart. This mechanism ensures a nearly

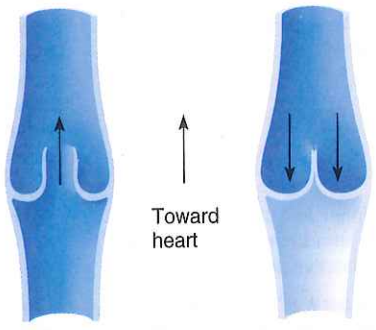


FIGURE 15.31 Venous valves. (*a*) allow blood to move toward the heart, but (*b*) prevent blood from moving backward away from the heart.

normal blood flow even when as much as 25% of blood volume is lost. Figure 15.32 illustrates the relative volumes of blood in the veins and other blood vessels.

Table 15.3 summarizes the characteristics of blood vessels. Clinical Application 15.2 examines disorders of blood vessels.

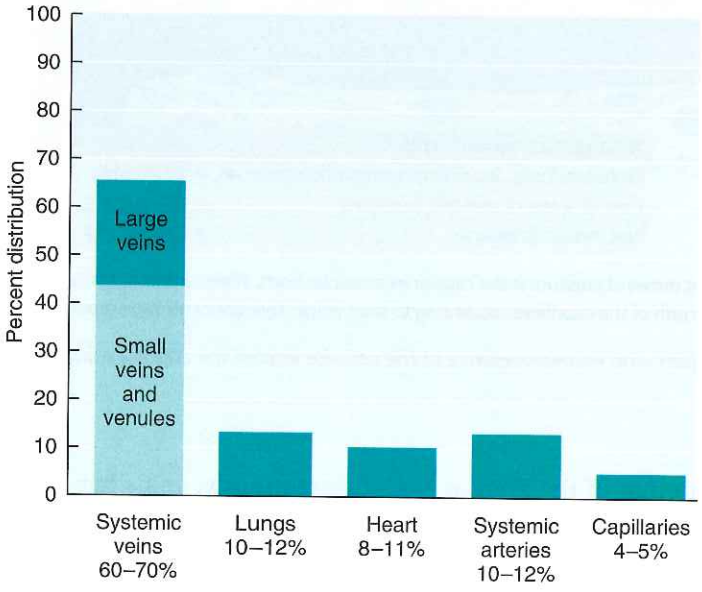


FIGURE 15.32 Most blood is in the veins and venules.

TABLE 15.3 | Characteristics of Blood Vessels

Vessel	Type of Wall	Function
Artery	Thick, strong wall with three layers—an endothelial lining, a middle layer of smooth muscle and elastic connective tissue, and an outer layer of connective tissue	Carries blood under relatively high pressure from the heart to arterioles
Arteriole	Thinner wall than an artery but with three layers; smaller arterioles have an endothelial lining, some smooth muscle tissue, and a small amount of connective tissue	Connects an artery to a capillary, helps control the blood flow into a capillary by vasoconstricting or vasodilating
Capillary	Single layer of squamous epithelium	Allows nutrients, gases, and wastes to be exchanged between the blood and tissue fluid; connects an arteriole to a venule
Venule	Thinner wall than an arteriole, less smooth muscle and elastic connective tissue	Connects a capillary to a vein
Vein	Thinner wall than an artery but with similar layers; the middle layer is more poorly developed; some have flaplike valves	Carries blood under relatively low pressure from a venule to the heart; valves prevent a backflow of blood; serves as a blood reservoir

PRACTICE

40 How does the structure of a vein differ from that of an artery?

41 What are the functions of veins and venules?

42 How does venous circulation help to maintain blood pressure when hemorrhaging causes blood loss?

15.5 BLOOD PRESSURE

Blood pressure is the force the blood exerts against the inner walls of the blood vessels. Although this force is present throughout the vascular system, the term *blood pressure* most commonly refers to pressure in arteries supplied by branches of the aorta (systemic arteries).

Arterial Blood Pressure

Arterial blood pressure rises and falls in a pattern corresponding to the phases of the cardiac cycle. That is, when the ventricles contract (ventricular systole), their walls squeeze the blood inside their chambers and force it into the pulmonary trunk and aorta. As a result, the pressures in these arteries sharply increase. The maximum pressure achieved during ventricular contraction is called the **systolic pressure.** When the ventricles relax (ventricular diastole), the arterial pressure drops, and the lowest pressure that remains in the arteries before the next ventricular contraction is termed the **diastolic pressure.**

The surge of blood entering the arterial system during ventricular systole distends the elastic arterial walls, but the pressure begins to drop almost immediately as the contraction ends, and the arterial walls recoil. This alternate expanding and recoiling of the arterial wall can be felt as a *pulse* in an artery that runs close to the body surface. Figure 15.33 shows

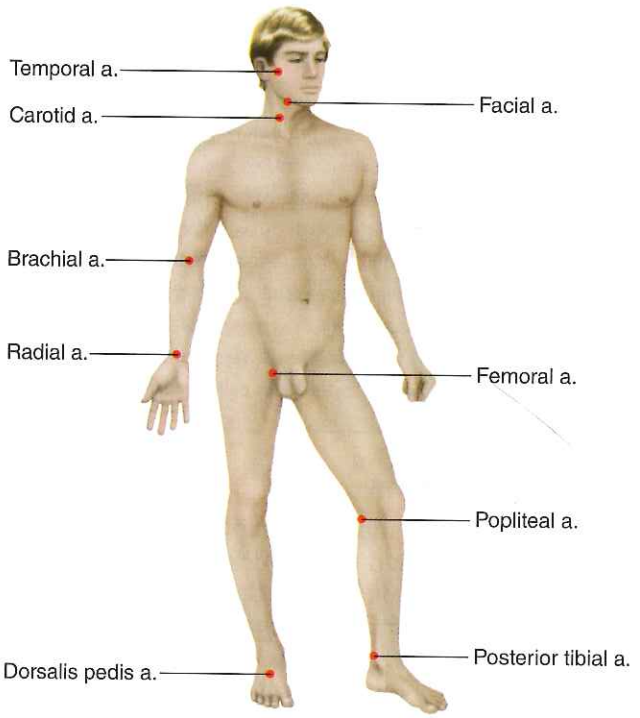


FIGURE 15.33 Sites where an arterial pulse is most easily detected. (*a.* stands for artery.)

15.2 CLINICAL APPLICATION

Blood Vessel Disorders

In the arterial disease *atherosclerosis* (ath"er-o-sklĕ-ro'sis), deposits of fatty materials, particularly cholesterol, form within and on the inner lining of the arterial walls. Such deposits, called *plaque,* protrude into the lumens of the vessels and interfere with blood flow (fig. 15F). Furthermore, plaque often forms a surface texture that can initiate formation of a blood clot, increasing the risk of developing thrombi or emboli that decrease blood flow *(ischemia),* causing tissue death *(necrosis)* downstream from the obstruction. In addition, the walls of diseased arteries may degenerate, losing their elasticity and becoming hardened or *sclerotic.* In this stage of the disease, a sclerotic vessel may rupture under the force of blood pressure.

Risk factors for developing atherosclerosis include a fatty diet, elevated blood pressure, tobacco smoking, obesity, and lack of physical exercise (see chapter 18, pp. 704–705). Genetic factors may increase the risk of developing atherosclerosis.

If atherosclerosis so weakens the wall of an artery that blood pressure dilates a region of it, a pulsating sac called an *aneurysm* may form. Aneurysms tend to grow. If the resulting sac develops by a longitudinal splitting of the middle layer of the arterial wall, it is called a *dissecting aneurysm.* An aneurysm may cause symptoms by pressing on nearby organs, or it may rupture, producing great blood loss and death.

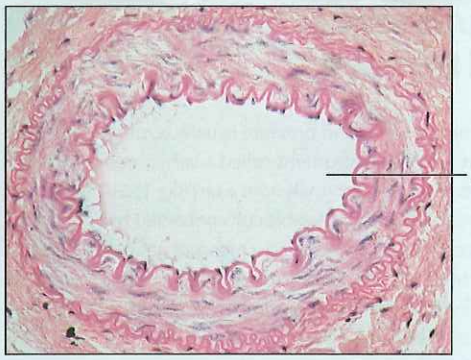
Aneurysms may also result from trauma, high blood pressure, infections, inherited disorders such as Marfan syndrome, or congenital defects in blood vessels. Common sites of aneurysms include the thoracic and abdominal aorta and an arterial circle at the base of the brain (circle of Willis).

Phlebitis, or inflammation of a vein, is relatively common. It may occur in association with an injury or infection or after surgery, or it may develop for no apparent reason. If inflammation is restricted to a superficial vein, such as the greater or lesser saphenous veins, blood flow may be rechanneled through other vessels. But if it occurs in a deep vein, such as the tibial, peroneal, popliteal, or femoral veins, the consequences can be serious, particularly if the blood in the affected vessel clots and blocks normal circulation (see Clinical Application 14.2, p. 545). This condition, called *thrombophlebitis,* introduces a risk that a blood clot in a vein will detach, move with the venous blood, pass through the heart, and lodge in the pulmonary arterial system in a lung (pulmonary embolism).

Varicose veins are abnormal and irregular dilations in superficial veins, particularly in the legs. This condition is usually associated with prolonged, increased back pressure in the affected vessels due to gravity, such as when a person stands. Crossing the legs or sitting in a chair so that its edge presses against the area behind the knee can obstruct venous blood flow and aggravate varicose veins.

Increased venous back pressure stretches and widens the veins. The valves in these vessels do not change size, so they lose their abilities to block the backflow of blood, and blood accumulates in the enlarged regions. Increased venous pressure is also accompanied by rising pressure in the venules and capillaries that supply the veins. Consequently, tissues in affected regions typically become edematous and painful.

Genetics, pregnancy, obesity, and standing for long periods raise the risk of developing varicose veins. Elevating the legs above the level of the heart or putting on support hosiery before arising in the morning can relieve discomfort. Intravenous injection of a substance that destroys veins (a sclerosing agent) or surgical removal of the affected veins may be necessary. ■



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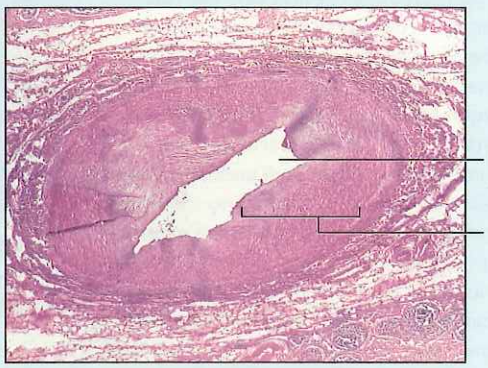

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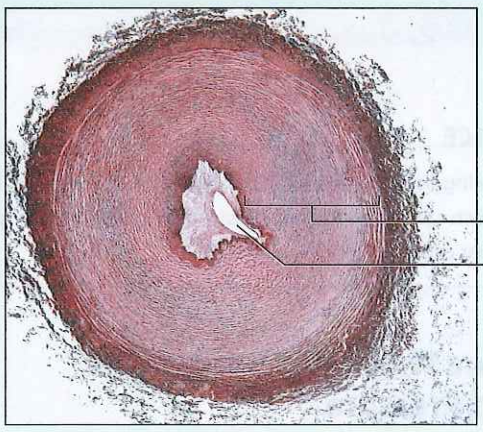


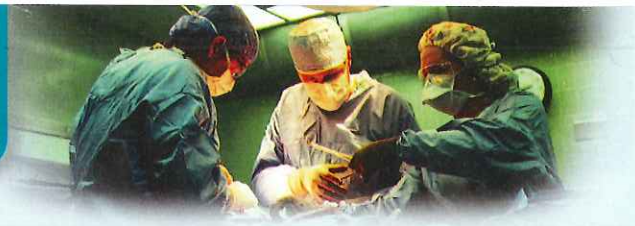
(c)

FIGURE 15F Development of atherosclerosis. (*a*) Normal arteriole (100×). (*b, c*) Accumulation of plaque on the inner wall of the arteriole (*b* and *c* 100×).

several sites where a pulse can be detected. The radial artery, for example, courses near the surface at the wrist and is commonly used to sense a person's radial pulse.

The radial pulse rate is equal to the rate at which the left ventricle contracts, and for this reason, it can be used to determine heart rate. A pulse can also reflect blood pressure, because an elevated pressure produces a pulse that feels strong and full, whereas a low pressure produces a pulse that is weak and easily compressed. Clinical Application 15.3 describes how to measure arterial blood pressure.

15.3 CLINICAL APPLICATION



Measurement of Arterial Blood Pressure

Systemic arterial blood pressure usually is measured using an instrument called a sphygmomanometer (sfig"mo-mah-nom'ĕ-ter) (fig. 15G). This device consists of an inflatable cuff connected by tubing to a compressible bulb and a pressure gauge. The bulb is used to pump air into the cuff, and a rise in pressure is indicated on the pressure gauge. The pressure in the cuff is expressed in millimeters of mercury (mm Hg) based on older equipment that used a glass tube containing a column of mercury in place of a pressure gauge. The older devices have been discontinued because of the danger of exposure to mercury, though the units have been retained.

To measure arterial blood pressure, the cuff of the sphygmomanometer is wrapped around the arm so that it surrounds the brachial artery. Air is pumped into the cuff until the cuff pressure exceeds the pressure in that artery, squeezing the vessel closed and stopping its blood flow. At this moment, if the diaphragm of a stethoscope is placed over the brachial artery at the distal border of the cuff, no sounds can be heard from the vessel because the blood flow is interrupted. As air is slowly released from the cuff, the air pressure inside it decreases. When the cuff pressure is just slightly lower than

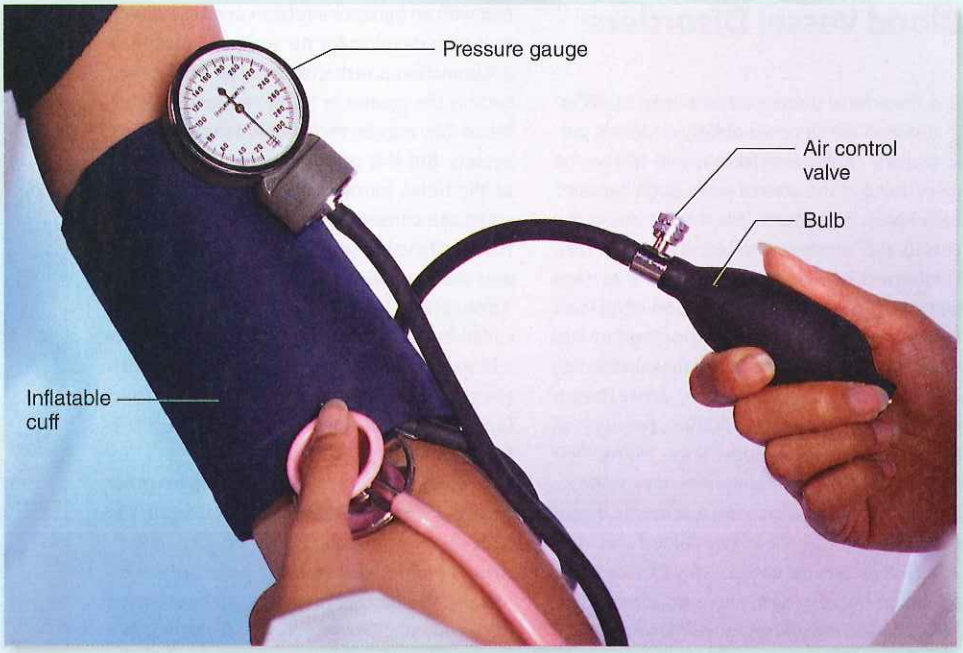


FIGURE 15G A sphygmomanometer is used to measure arterial blood pressure. The use of the column of mercury is the most accurate measurement, but due to environmental concerns, it has been replaced by alternative gauges and digital readouts.

PRACTICE

43 Distinguish between systolic and diastolic blood pressure.

44 Which cardiac event causes systolic pressure? Diastolic pressure?

45 What causes a pulse in an artery?

Factors That Influence Arterial Blood Pressure

Arterial pressure depends on a variety of factors. These include cardiac output, blood volume, peripheral resistance, and blood viscosity (fig. 15.34).

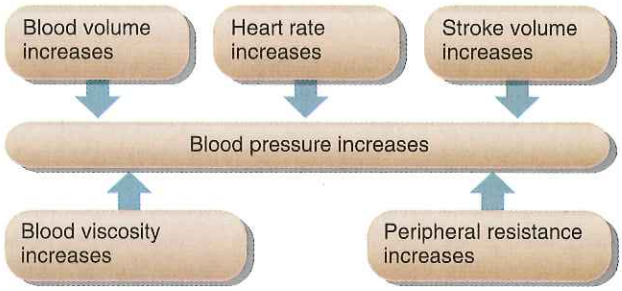


FIGURE 15.34 Some of the factors that influence arterial blood pressure.

Cardiac Output AP|R

Each ventricular contraction determines the volume of blood that enters the arterial system, which is called the **stroke volume.** In an average-weight male at rest, the stroke volume equals about 70 milliliters. The volume discharged from the ventricle per minute, called the **cardiac output,** is the stroke volume multiplied by the heart rate, expressed in beats per minute. (Cardiac output = stroke volume × heart rate.) For example, if the stroke volume is 70 milliliters and the heart rate is 72 beats per minute, the cardiac output is 5,040 milliliters per minute.

Blood pressure varies with the cardiac output. If either the stroke volume or the heart rate increases, so does the cardiac output, and, blood pressure initially rises. Conversely, if the stroke volume or the heart rate decreases, the cardiac output decreases, and blood pressure also initially decreases.

Blood Volume

Blood volume equals the sum of the formed elements and plasma volumes in the vascular system. Although the blood

Continued—

the systolic blood pressure in the brachial artery, the artery opens enough for a small volume of blood to spurt through, producing a sharp sound (Korotkoff's sound) heard through the stethoscope. Turbulence in the narrowed artery causes the sound. The pressure indicated on the pressure gauge when this first tapping sound is heard represents a good estimate of the *arterial systolic pressure* (SP).

As the cuff pressure continues to drop, increasingly louder sounds are heard. Then, when the cuff pressure is just slightly lower than that within the fully opened artery, the sounds become abruptly muffled and disappear. The pressure indicated on the pressure gauge when this happens represents a good estimate of the *arterial diastolic pressure* (DP).

The results of a blood pressure measurement are reported as a fraction, such as 120/80. The upper number indicates the systolic pressure in mm Hg (SP), and the lower number indicates the diastolic pressure in mm Hg (DP). Figure 15H shows how these pressures decrease as distance from the left ventricle increases. The difference between the systolic and diastolic pressures (SP - DP), called the *pulse pressure* (PP), is about 40 mm Hg.

The average pressure in the arterial system is also of interest because it represents the force effective throughout the cardiac cycle for driving blood to the tissues. To approximate this force, called the *mean arterial pressure,* add the diastolic pressure to one-third of the pulse pressure (DP + 1/3PP). ■

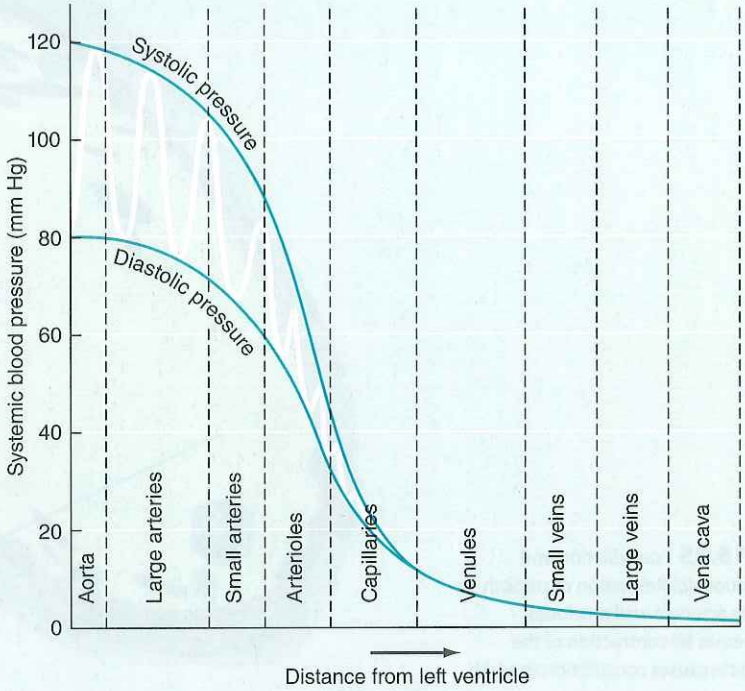


FIGURE 15H Blood pressure decreases as the distance from the left ventricle increases. Systolic pressure occurs during maximal ventricular contraction. Diastolic pressure occurs when the ventricles relax.

volume varies somewhat with age, body size, and sex, it is usually about 5 liters for adults or 8% of body weight in kilograms (1 kilogram of water equals 1 liter).

Normally blood pressure is directly proportional to the volume of the blood in the cardiovascular system. Thus, any changes in the blood volume can initially alter the blood pressure. For example, if a hemorrhage reduces blood volume, blood pressure at first drops. If a transfusion restores normal blood volume, normal pressure may be reestablished. Blood volume can also fall if the fluid balance is upset, as happens in dehydration. Fluid replacement can reestablish normal blood volume and pressure.

Muscle cells of the atria secrete a peptide hormone called *atrial natriuretic peptide* (ANP) when increasing blood volume stretches them. ANP inhibits release of renin from the kidneys and of aldosterone from the adrenal cortex. The result is increased excretion of sodium ions and water from the kidneys and lowered blood volume and blood pressure. Researchers are investigating drugs that increase ANP to treat the excess volume associated with congestive heart failure.

Peripheral Resistance

Friction between the blood and the walls of the blood vessels produces a force called **peripheral resistance** (pĕ-rif'er-al re-zis'tans), which hinders blood flow. Blood pressure must overcome peripheral resistance if the blood is to continue flowing. Factors that alter the peripheral resistance change blood pressure. For example, when smooth muscles in arteriolar walls contract, this increases the peripheral resistance by constricting these vessels. Blood backs up into the arteries supplying the arterioles, and the arterial pressure rises. Dilation of the arterioles has the opposite effect—peripheral resistance decreases, and the arterial blood pressure drops in response (fig. 15.35).

Arterial walls are elastic, so when the ventricles discharge a surge of blood, arteries swell. Almost immediately, the elastic tissues recoil, and the vessel walls press against the blood inside. This action helps force the blood onward against the peripheral resistance in arterioles and capillaries. Recoiling of the arteries maintains blood pressure during diastole. If there were no elasticity in the arterial walls, blood pressure would fall to zero between ventricular contractions. Elastic recoil also converts the intermittent flow of blood, characteristic of the arterial system, into a more continuous movement through the capillaries.

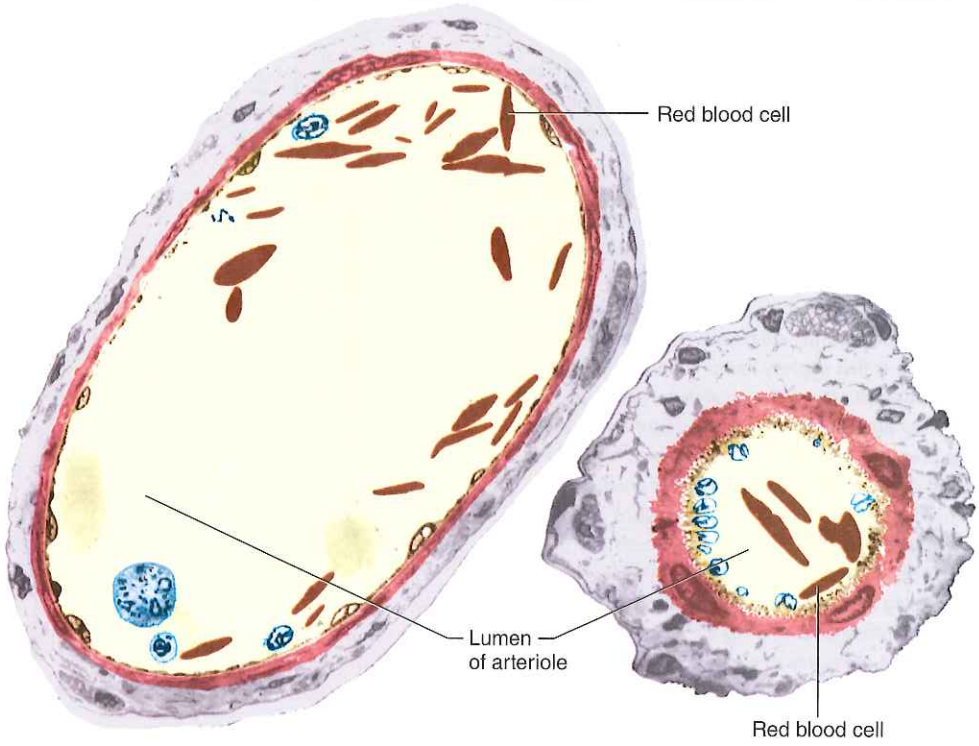


FIGURE 15.35 Vasodilation and vasoconstriction. (*a*) Relaxation of smooth muscle in the arteriole wall produces dilation, whereas (*b*) contraction of the smooth muscle causes constriction (*a* and *b* 1,500×).

Viscosity

Viscosity (vis-kos′ĭ-te) is the difficulty with which the molecules of a fluid flow past one another. The greater the viscosity, the greater the resistance to flow.

Blood cells and plasma proteins increase blood viscosity. The greater the blood's resistance to flowing, the greater the force needed to move it through the vascular system, so blood pressure rises as blood viscosity increases and drops as blood viscosity decreases.

The viscosity of blood normally remains stable. However, any condition that alters the concentrations of blood cells or plasma proteins may alter blood viscosity. For example, anemia may decrease viscosity and consequently lower blood pressure. Excess red blood cells increase viscosity and blood pressure.

PRACTICE

46 How is cardiac output calculated?

47 How are cardiac output and blood pressure related?

48 How does blood volume affect blood pressure?

49 What is the relationship between peripheral resistance and blood pressure? between blood viscosity and blood pressure?

Control of Blood Pressure

Blood pressure (BP) is determined by cardiac output (CO) and peripheral resistance (PR) according to this relationship: BP = CO × PR. Maintenance of normal blood pressure therefore requires regulation of these two factors (fig. 15.36).

Cardiac output depends on the stroke volume and heart rate. Stroke volume, the amount of blood pumped in a single beat, is reflected by the difference between **end-diastolic volume** (EDV), the volume of blood in each ventricle at the end of ventricular diastole, and **end-systolic volume** (ESV), the volume of blood in each ventricle at the end of ventricular systole. Mechanical, neural, and chemical factors affect stroke volume and heart rate.

Cardiac output is limited by the amount of blood returning to the ventricles, called the *venous return*. Usually, however, stroke volume can be increased by sympathetic stimulation, which increases the force of ventricular contraction. Because only about 60% of the end-diastolic volume is pumped out in a normal contraction, increasing the force of ventricular contraction may increase that fraction and help maintain stroke volume if venous return should decrease.

RECONNECT
To Chapter 9, Recording a Muscle Contraction, pages 304–305.

Another mechanism increases stroke volume independently of sympathetic stimulation. As blood enters the ventricles, myocardial fibers are mechanically stretched. This constitutes the **preload.** The greater the EDV, the greater the preload. Within limits, the longer these fibers, the greater the force with which they contract. This relationship between fiber length (due to stretching of the cardiac muscle cell just before contraction) and force of contraction is called the **Frank-Starling law of the heart,** or Starling's law of