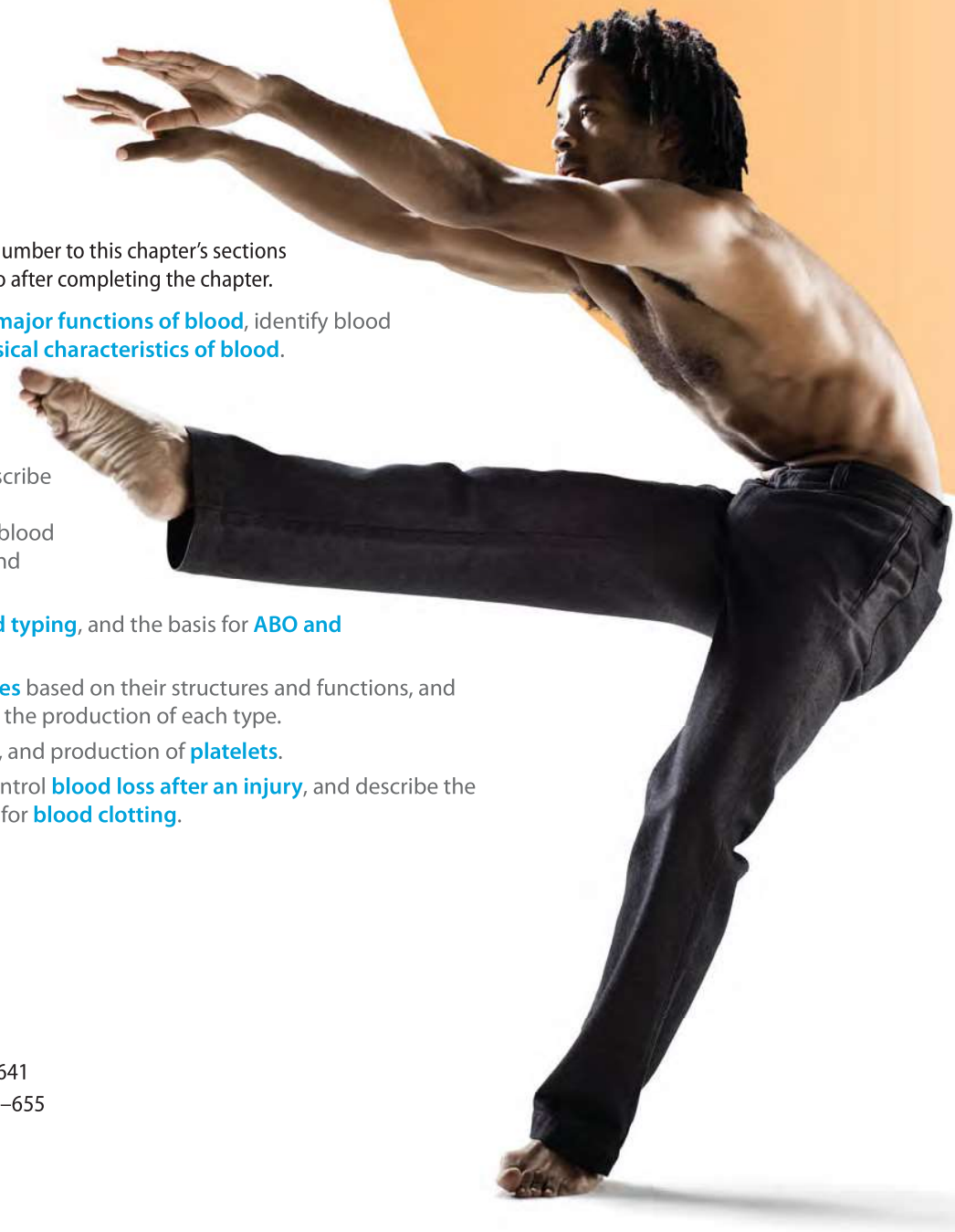
19

Blood



Learning Outcomes

These Learning Outcomes correspond by number to this chapter's sections and indicate what you should be able to do after completing the chapter.

19-1 Describe the **components and major functions of blood**, identify blood collection sites, and list the **physical characteristics of blood**.

19-2 Specify the composition and functions of **plasma**.

19-3 List the characteristics and functions of **red blood cells**, describe the structure and functions of **hemoglobin**, describe how red blood cell components are recycled, and explain **erythropoiesis**.

19-4 Explain the importance of **blood typing**, and the basis for **ABO and Rh incompatibilities**.

19-5 Categorize **white blood cell types** based on their structures and functions, and discuss the factors that regulate the production of each type.

19-6 Describe the structure, function, and production of **platelets**.

19-7 Discuss the mechanisms that control **blood loss after an injury**, and describe the reaction sequences responsible for **blood clotting**.

Clinical Notes

Spotlights

An Introduction to Blood and the Cardiovascular System

This chapter discusses the nature of blood, the fluid component of the **cardiovascular system.** This body system also includes a pump (the heart) that circulates the fluid and a series of conducting hoses (the blood vessels) that carry it throughout the body. In Chapter 18, we noted the importance of this system for transporting hormones, but that is only one of its many vital roles.

In adults, circulating blood provides each of the body's roughly 75 trillion cells a source of nutrients and oxygen, and a way of removing wastes. The blood also transports specialized cells that defend tissues from infection and disease. These services are essential—so much so that cells deprived of circulation may die in a matter of minutes. This chapter takes a close look at the structure and functions of blood, a fluid connective tissue with remarkable properties.

19-1 Blood has several important functions and unique physical characteristics

In this chapter, we examine the structure and functions of **blood,** a specialized fluid connective tissue that contains cells suspended in a fluid matrix. As you may recall, Chapter 4 introduced the components and properties of this connective tissue. ↩ p. 127

The functions of blood include the following:

- *Transporting Dissolved Gases, Nutrients, Hormones, and Metabolic Wastes.* Blood carries oxygen from the lungs to peripheral tissues, and carbon dioxide from those tissues back to the lungs. Blood distributes nutrients absorbed by the digestive tract or released from storage in adipose tissue or in the liver. It carries hormones from endocrine glands toward their target cells, and it absorbs and carries the wastes produced by tissue cells to the kidneys for excretion.
- *Regulating the pH and Ion Composition of Interstitial Fluids.* Diffusion between interstitial fluids and blood eliminates local deficiencies or excesses of ions, such as calcium or potassium. Blood also absorbs and neutralizes acids generated by active tissues, such as lactic acid produced by skeletal muscles.
- *Restricting Fluid Losses at Injury Sites.* Blood contains enzymes and other substances that respond to breaks in vessel walls by initiating the process of *clotting*. A blood clot acts as a temporary patch that prevents further blood loss.
- *Defending against Toxins and Pathogens.* Blood transports *white blood cells*, specialized cells that migrate into other tissues to fight infections or remove debris. Blood also delivers *antibodies*, proteins that specifically attack invading organisms or foreign compounds.
- *Stabilizing Body Temperature.* Blood absorbs the heat generated by active skeletal muscles and redistributes it to other tissues. If body temperature is already high, that heat will be lost across the surface of the skin. If body temperature is too low, the warm blood is directed to the brain and to other temperature-sensitive organs.

Spotlight Figure 19–1 describes the composition of whole blood, which is made up of plasma and formed elements.

The components of whole blood can be **fractionated,** or separated, for analytical or clinical purposes. We encounter examples of uses for fractionated blood later in the chapter.

Whole blood from any source—veins, capillaries, or arteries—has the same basic physical characteristics:

- Blood temperature is about 38°C (100.4°F), slightly above normal body temperature.
- Blood is five times as viscous as water—that is, five times as sticky, five times as cohesive, and five times as resistant to flow as water. The high viscosity results from interactions among dissolved proteins, formed elements, and water molecules in plasma.
- Blood is slightly alkaline, with a pH between 7.35 and 7.45 (average: 7.4).

Clinical Note

Collecting Blood for Analysis Fresh whole blood is generally collected from a superficial vein, such as the *median cubital vein* on the anterior surface of the elbow. The procedure is called **venipuncture** (VĒN-i-punk-chur; *vena*, vein + *punctura*, a piercing). It is a common sampling technique because (1) superficial veins are easy to locate, (2) the walls of veins are thinner than those of comparably sized arteries, and (3) blood pressure in the venous system is relatively low, so the puncture wound seals quickly. The most common clinical procedures examine venous blood.

A small drop of blood can be used to prepare a *blood smear*, a thin film of blood on a microscope slide. The blood smear is then stained with special dyes to show each type of formed element. Blood from peripheral capillaries can be obtained by puncturing the tip of a finger, an earlobe, or (in infants) the great toe or heel. Small amounts of capillary blood can also be used to test (among other items) glucose, cholesterol, and hemoglobin levels. This method is valuable when venous access is difficult.

An **arterial puncture,** or "arterial stick," can be used for checking the efficiency of gas exchange at the lungs. Samples are generally drawn from the *radial artery* at the wrist or the *brachial artery* at the elbow.

Spotlight

Figure 19–1
The Composition of Whole Blood

A Fluid Connective Tissue

Blood is a fluid connective tissue with a unique composition. It consists of a matrix called **plasma** (PLAZ-muh) and formed elements (cells and cell fragments). The term **whole blood** refers to the combination of plasma and the formed elements together. The cardiovascular system of an adult male contains 5–6 liters (5.3–6.4 quarts) of whole blood; that of an adult female contains 4–5 liters (4.2–5.3 quarts). The sex differences in blood volume primarily reflect differences in average body size.

The **hematocrit** (he-MAT-ō-krit) is the percentage of whole blood volume contributed by formed elements. The normal hematocrit, or **packed cell volume (PCV)**, in adult males is 46 and in adult females is 42. The sex difference in hematocrit primarily reflects the fact that androgens (male hormones) stimulate red blood cell production, whereas estrogens (female hormones) do not.

PLASMA

Plasma, the matrix of blood, makes up 46–63% of the volume of whole blood. In many respects, the composition of plasma resembles that of interstitial fluid. This similarity exists because water, ions, and small solutes are continuously exchanged between plasma and interstitial fluids across the walls of capillaries. The primary differences between plasma and interstitial fluid involve (1) the levels of respiratory gases (oxygen and carbon dioxide, due to the respiratory activities of tissue cells), and (2) the concentrations and types of dissolved proteins (because plasma proteins cannot cross capillary walls).

Formed elements are blood cells and cell fragments that are suspended in plasma. These elements account for 37–54% of the volume of whole blood. Three types of formed elements exist: platelets, white blood cells, and red blood cells. Formed elements are produced through the process of **hemopoiesis** (hēm-ō-poy-Ē-sis). Two populations of stem cells—myeloid stem cells and lymphoid stem cells—are responsible for the production of formed elements.

FORMED ELEMENTS

Plasma Proteins

Plasma proteins are in solution rather than forming insoluble fibers like those in other connective tissues, such as loose connective tissue or cartilage. On average, each 100 mL of plasma contains 7.6 g of protein, almost five times the concentration in interstitial fluid. The large size and globular shapes of most blood proteins prevent them from crossing capillary walls, so they remain trapped within the bloodstream. The liver synthesizes and releases more than 90% of the plasma proteins, including all albumins and fibrinogen, most globulins, and various prohormones.

Albumins (al-BŪ-minz) constitute roughly 60% of the plasma proteins. As the most abundant plasma proteins, they are major contributors to the osmotic pressure of plasma.

Globulins (GLOB-ū-linz) account for approximately 35% of the proteins in plasma. Important plasma globulins include antibodies and transport globulins. **Antibodies**, also called **immunoglobulins** (i-mū-no-GLOB-ū-linz), attack foreign proteins and pathogens. **Transport globulins** bind small ions, hormones, and other compounds.

Fibrinogen (fī-BRIN-ō-jen) functions in clotting, and normally accounts for roughly 4% of plasma proteins. Under certain conditions, fibrinogen molecules interact, forming large, insoluble strands of **fibrin** (Fī-brin) that form the basic framework for a blood clot.

Plasma also contains enzymes and hormones whose concentrations vary widely.

Other Solutes

Other solutes are generally present in concentrations similar to those in the interstitial fluids. However, because blood is a transport medium there may be differences in nutrient and waste product concentrations between arterial blood and venous blood.

Organic Nutrients: Organic nutrients are used for ATP production, growth, and maintenance of cells. This category includes lipids (fatty acids, cholesterol, glycerides), carbohydrates (primarily glucose), and amino acids.

Electrolytes: Normal extracellular ion composition is essential for vital cellular activities. The major plasma electrolytes are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, HPO_4^-, and SO_4^{2-}.

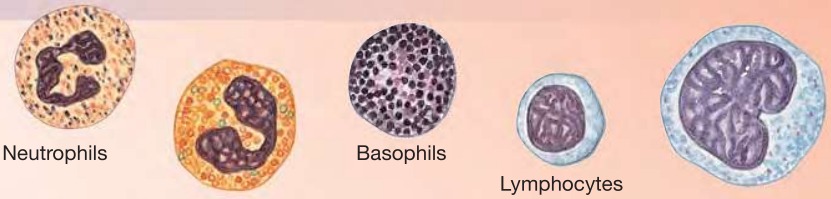
Organic Wastes: Waste products are carried to sites of breakdown or excretion. Examples of organic wastes include urea, uric acid, creatinine, bilirubin, and ammonium ions.

Platelets

Platelets are small, membrane-bound cell fragments that contain enzymes and other substances important to clotting.

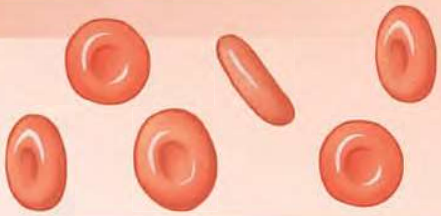
White Blood Cells

White blood cells (**WBCs**), or **leukocytes** (LOO-kō-sīts; *leukos*, white + *-cyte*, cell), participate in the body's defense mechanisms. There are five classes of leukocytes, each with slightly different functions that will be explored later in the chapter.



Red Blood Cells

Red blood cells (**RBCs**), or **erythrocytes** (e-RITH-rō-sits; *erythros*, red + *-cyte*, cell), are the most abundant blood cells. These specialized cells are essential for the transport of oxygen in the blood.



Adult males typically have more blood than do adult females. Blood volume in liters can be estimated for an individual of either sex by calculating 7 percent of the body weight in kilograms. For example, a 75-kg (165-lb) individual would have a blood volume of approximately 5.25 liters (5.4 quarts).

Checkpoint

1. **List five major functions of blood.**
2. **Identify the composition of the formed elements in blood.**
3. **What two components make up whole blood?**
4. **Why is venipuncture a common technique for obtaining a blood sample?**

See the blue Answers tab at the back of the book.

19-2 Plasma, the fluid portion of blood, contains significant quantities of plasma proteins

In this section we consider the composition of plasma and the kinds of proteins it contains.

The Composition of Plasma

As shown in **Spotlight Figure 19–1**, plasma makes up the greatest volume of whole blood. The components of plasma include plasma proteins, other solutes, and water.

19

Plasma Proteins

Plasma contains significant quantities of dissolved proteins, namely albumins, globulins, and fibrinogen. These three types make up more than 99 percent of the plasma proteins. The remainder consists of circulating enzymes, hormones, and prohormones.

Albumins

Albumins make up the majority of the plasma proteins. In addition to their functions highlighted in **Spotlight Figure 19–1**, albumins are also important for transporting fatty acids, thyroid hormones, some steroid hormones, and other substances.

Globulins

Globulins comprise the second most-abundant proteins in plasma. Transport globulins bind small ions, hormones, and compounds that might otherwise be removed by the kidneys or that have very low solubility in water. Important examples of transport globulins include the following:

- *Hormone-binding proteins*, which provide a reserve of hormones in the bloodstream. Examples include *thyroid-binding globulin* and *transthyretin*, which transport thyroid hormones, and *transcortin*, which transports ACTH. ↩ pp. 612, 616
- *Metalloproteins*, which transport metal ions. *Transferrin*, for example, is a metalloprotein that transports iron (Fe^{2+}).
- *Apolipoproteins* (ap-ō-lip-ō-PRŌ-tēnz), which carry triglycerides and other lipids in blood. When bound to lipids, an apolipoprotein becomes a **lipoprotein** (LĪ-pō-prō-tēn).
- *Steroid-binding proteins*, which transport steroid hormones in blood. For example, *testosterone-binding globulin* (*TeBG*) binds and transports testosterone.

Fibrinogen

The third major type of plasma protein, fibrinogen, functions in clotting. If steps are not taken to prevent clotting in a blood sample, the conversion of fibrinogen (a soluble protein) to fibrin (an insoluble protein) will occur. This conversion removes the clotting proteins, leaving a fluid known as **serum**. The clotting process also removes calcium ions and other materials from solution, so plasma and serum differ in several significant ways. (See Appendix.) Thus, the results of a blood test generally indicate whether the sample was plasma or serum.

Other Plasma Proteins

The remaining 1 percent of plasma proteins is composed of specialized proteins whose levels vary widely. Peptide hormones—including insulin, prolactin (PRL), and the glycoproteins thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)—are normally present in circulating blood. Their plasma concentrations rise and fall from day to day or even hour to hour.

Origins of the Plasma Proteins

The liver synthesizes and releases more than 90 percent of the plasma proteins, including all albumins and fibrinogen, most globulins, and various prohormones. Because the liver is the primary source of plasma proteins, liver disorders can alter the composition and functional properties of blood. For example, some forms of liver disease can lead to uncontrolled bleeding due to the inadequate synthesis of fibrinogen and other proteins involved in clotting.

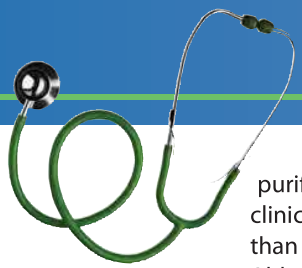
Checkpoint

5. **List the three major types of plasma proteins.**
6. **What would be the effects of a decrease in the amount of plasma proteins?**
7. **Which specific plasma protein would you expect to be elevated during a viral infection?**

See the blue Answers tab at the back of the book.

Clinical Note

Plasma Expanders



Expanding blood volume in a pinch

Plasma expanders can be used to increase blood volume temporarily, over a period of hours. They are often used to buy time for lab work to determine a person's blood type. (Transfusion of the wrong blood type can kill the recipient.) Isotonic electrolyte solutions such as normal (physiological) saline can be used as a plasma expander, but their effects are short-lived due to diffusion into interstitial fluid and cells. This fluid loss is slowed by the addition of solutes that cannot freely diffuse across plasma membranes. One example is lactated *Ringer's solution*, an isotonic saline also containing lactate, potassium chloride, and calcium chloride ions. The effects of Ringer's solution fade gradually as the liver, skeletal muscles, and other tissues absorb and metabolize the lactate ions. Another option is the administration of isotonic saline solution containing purified human albumin. However, the plasma expanders in clinical use often contain large carbohydrate molecules, rather than proteins, to maintain proper osmotic concentration. Although these carbohydrates are not metabolized, they are gradually removed from the bloodstream by phagocytes, and blood volume slowly declines.

Plasma expanders are easily stored, and their sterile preparation avoids viral or bacterial contamination, which can be a problem with donated plasma. Note that although they provide a temporary solution to low blood volume, plasma expanders do not increase the amount of oxygen carried by the blood; that function is performed by red blood cells.

19-3 Red blood cells, formed by erythropoiesis, contain hemoglobin that can be recycled

The most abundant blood cells are the red blood cells (RBCs), which account for 99.9 percent of the formed elements. These cells give whole blood its deep red color because they contain the red pigment *hemoglobin* (HĒ-mō-glō-bin), which binds and transports oxygen and carbon dioxide.

Abundance of RBCs

A standard blood test reports the number of RBCs per microliter (μL) of whole blood as the *red blood cell count*. In adult males, 1 microliter, or 1 *cubic millimeter* (mm^3), of whole blood contains 4.5–6.3 million RBCs; in adult females, 1 microliter contains 4.2–5.5 million. A single drop of whole blood contains approximately 260 million RBCs, and the blood of an average adult has 25 trillion RBCs. RBCs account for roughly one-third of all cells in the human body.

The percentage of a blood sample that consists of formed elements (most of which are red blood cells) is known as the hematocrit (**Spotlight Figure 19–1**). The hematocrit is determined by centrifuging a blood sample so that all the formed elements come out of suspension. Whole blood contains about 1000 red blood cells for each white blood cell. After centrifugation, the white blood cells and platelets form a very thin *buffy coat* above a thick layer of RBCs.

Many conditions can affect the hematocrit. For example, the hematocrit increases during dehydration, due to a reduction in plasma volume, or after *erythropoietin* (*EPO*) stimulation. ↩ p. 624 The hematocrit decreases as a result of internal bleeding or problems with RBC formation. So, the hematocrit alone does not provide specific diagnostic information. Still, an abnormal hematocrit is an indication that other, more specific tests are needed. (We consider some of those tests later in the chapter.)

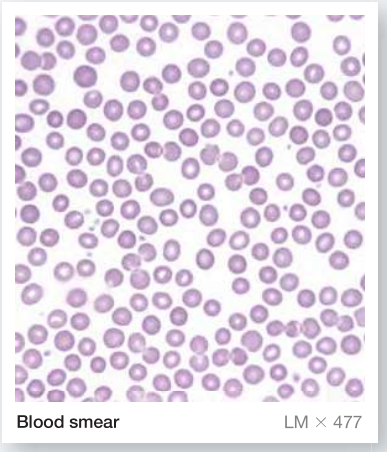
Structure of RBCs

Red blood cells are among the most specialized cells of the body. A red blood cell is very different from the "typical cell" we discussed in Chapter 3. Each RBC is a biconcave disc with a thin central region and a thicker outer margin (**Figure 19–2**). An average RBC has a diameter of 7.8 μm and a maximum thickness of 2.85 μm, although the center narrows to about 0.8 μm.

This unusual shape has three important effects on RBC function:

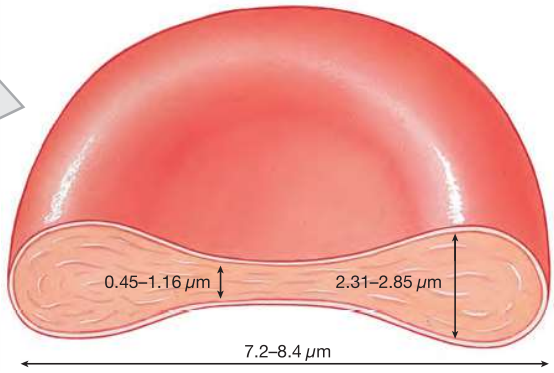
1. *Giving Each RBC a Large Surface-Area-to-Volume Ratio.* Each RBC carries oxygen bound to intracellular proteins. That oxygen must be absorbed or released quickly as the RBC passes through the capillaries of the lungs or peripheral tissues. The greater the surface area per unit volume, the faster the exchange between the RBC's interior and the surrounding plasma. The total surface area of all the RBCs in the blood of a typical adult is about 3800 square meters, (nearly 4600 square yards), some 2000 times the total surface area of the body.
2. *Enabling RBCs to Form Stacks, Like Dinner Plates, That Smooth the Flow through Narrow Blood Vessels.* These stacks, known as *rouleaux* (roo-LŌ; *rouleau*, singular), form and

Figure 19–2 The Anatomy of Red Blood Cells.



a When viewed in a standard blood smear, RBCs appear as two-dimensional objects, because they are flattened against the surface of the slide.

b The three-dimensional shape of RBCs



c A sectional view of a mature RBC, showing the normal ranges for its dimensions

d When traveling through relatively narrow capillaries, RBCs may stack like dinner plates.

dissociate repeatedly without affecting the cells involved. An entire stack can pass along a blood vessel that is only slightly larger than the diameter of a single RBC, whereas individual cells would bump the walls, bang together, and form logjams that could restrict or prevent blood flow. Such stacks are shown in **Figure 19–2d**.

3. *Enabling RBCs to Bend and Flex When Entering Small Capillaries and Branches.* Red blood cells are very flexible. By changing shape, individual RBCs can squeeze through capillaries as narrow as 4 μm.

During their differentiation, the RBCs of humans and other mammals lose most of their organelles, including nuclei. The cells retain only the cytoskeleton. (The RBCs of vertebrates other than mammals have nuclei.) Because they lack nuclei and ribosomes, circulating mammalian RBCs cannot divide or synthesize structural proteins or enzymes. As a result, the RBCs cannot perform repairs, so their life span is relatively short—normally less than 120 days. With few organelles and no ability to synthesize proteins, their energy demands are low. Without mitochondria, they obtain the energy they need through the anaerobic metabolism of glucose that is absorbed from the surrounding plasma. The lack of mitochondria ensures that absorbed oxygen will be carried to peripheral tissues, not "stolen" by mitochondria in the RBC.

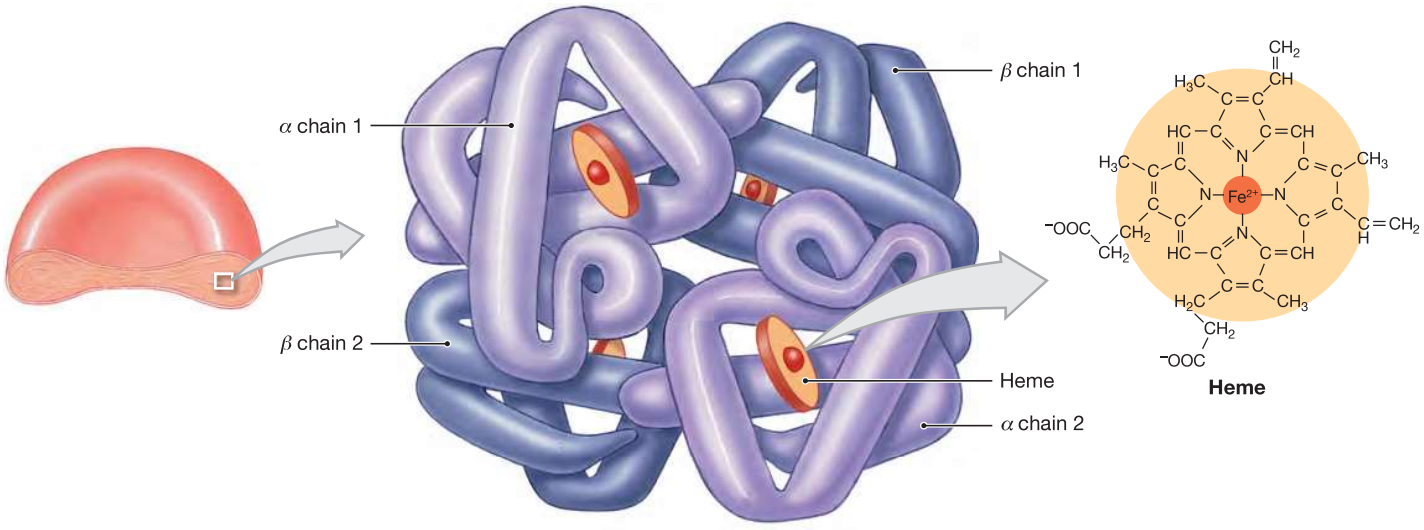
Hemoglobin

A developing red blood cell loses any organelle not directly associated with the cell's primary function: the transport of respiratory gases. Molecules of **hemoglobin (Hb)** account for more than 95 percent of its intracellular proteins. The hemoglobin content of whole blood is reported in grams of Hb per deciliter (100 mL) of whole blood (g/dL). Normal ranges are 14–18 g/dL in males and 12–16 g/dL in females. Hemoglobin is responsible for the cell's ability to transport oxygen and carbon dioxide.

Hemoglobin Structure

Hb molecules have complex quaternary structures. ↩ p. 51 Each Hb molecule has two *alpha* (α) *chains* and two *beta* (β) *chains* of polypeptides (**Figure 19–3**). Each chain is a globular protein subunit that resembles the myoglobin in skeletal and cardiac muscle cells. Like myoglobin, each Hb chain contains a single molecule of **heme,** a non-protein pigment complex.

Figure 19–3 The Structure of Hemoglobin. Hemoglobin consists of four globular protein subunits. Each subunit contains a single molecule of heme—a nonprotein ring surrounding a single ion of iron.



Each heme unit holds an iron ion in such a way that the iron can interact with an oxygen molecule, forming **oxyhemoglobin, HbO_2.** Blood that contains RBCs filled with oxyhemoglobin is bright red. The iron–oxygen interaction is very weak. The iron and oxygen can easily dissociate without damaging the heme unit or the oxygen molecule. The binding of an oxygen molecule to the iron in a heme unit is completely reversible. A hemoglobin molecule whose iron is not bound to oxygen is called **deoxyhemoglobin.** Blood containing RBCs filled with deoxyhemoglobin is dark red—almost burgundy.

The RBCs of an embryo or a fetus contain a different form of hemoglobin, known as *fetal hemoglobin*, which binds oxygen more readily than does the hemoglobin of adults. For this reason, a developing fetus can "steal" oxygen from the maternal bloodstream at the placenta. The conversion from fetal hemoglobin to the adult form begins shortly before birth and continues over the next year. The production of fetal hemoglobin can be stimulated in adults by the administration of drugs such as *hydroxyurea* or *butyrate*. This is one method of treatment for conditions, such as *sickle cell anemia* or *thalassemia*, that result from the production of abnormal forms of adult hemoglobin.

Hemoglobin Function

Each RBC contains about 280 million Hb molecules. Because an Hb molecule contains four heme units, each RBC can potentially carry more than a billion molecules of oxygen at a time. Roughly 98.5 percent of the oxygen carried by the blood travels through the bloodstream bound to Hb molecules inside RBCs.

The amount of oxygen bound to hemoglobin depends mostly on the oxygen content of the plasma. When plasma oxygen levels are low, hemoglobin releases oxygen. Under these conditions, typical of peripheral capillaries, plasma carbon dioxide levels are elevated. The alpha and beta chains of hemoglobin then bind carbon dioxide, forming **carbaminohemoglobin.** In the capillaries of the lungs, plasma oxygen levels are high and carbon dioxide levels are low. Upon reaching these capillaries, RBCs absorb oxygen (which is then bound to hemoglobin) and release carbon dioxide. We will revisit these processes in Chapter 23.

Normal activity levels can be sustained only when tissue oxygen levels are kept within normal limits. If the hematocrit is low or the Hb content of the RBCs is reduced, it results in **anemia.** Anemia interferes with oxygen delivery to peripheral tissues. Every system is affected as organ function deteriorates due to oxygen starvation. Anemic individuals become weak, lethargic, and often confused, because the brain is affected as well.

RBC Formation and Turnover

An RBC is exposed to severe mechanical stresses. A single round trip from the heart, through the peripheral tissues, and back to the heart usually takes less than a minute. In that time, the RBC gets pumped out of the heart and forced along vessels, where it bounces off the walls and collides with other RBCs. It forms stacks, contorts and squeezes through tiny capillaries, and then is rushed back to the heart to make another round trip.

With all this wear and tear and no repair mechanisms, a typical RBC has a short life span. After it travels about 700 miles in 120 days, either its plasma membrane ruptures or some other damage is detected by phagocytes, which engulf the RBC. The continuous elimination of RBCs usually goes unnoticed,

Clinical Note — Abnormal Hemoglobin

What happens when hemoglobin is abnormal?

Several inherited disorders are characterized by the production of abnormal hemoglobin. Two of the best known are thalassemia and sickle cell anemia (SCA).

The various forms of **thalassemia** (thal-ah-SĒ-mē-uh) result from an inability to produce adequate amounts of alpha or beta chains of hemoglobin. As a result, the rate of RBC production is slowed, and mature RBCs are fragile and short- lived. The scarcity of healthy RBCs reduces the oxygen-carrying capacity of the blood and leads to problems with the development and growth of systems throughout the body. Individuals with severe thalassemia must periodically undergo *transfusions*—the administration of blood components—to keep adequate numbers of RBCs in the bloodstream.

Sickle cell anemia results from a mutation affecting the amino acid sequence of the beta chains of the Hb molecule. When blood contains abundant oxygen, the Hb molecules and the RBCs that carry them appear normal. However, when the defective hemoglobin gives up enough of its bound oxygen, the adjacent Hb molecules interact and the cells become stiff and curved (**Figure 19–4**). This "sickling" makes the RBCs fragile and easily damaged. Moreover, an RBC that has folded to squeeze into a narrow capillary delivers its oxygen to the surrounding tissue, but the cell can become stuck as sickling occurs. A circulatory blockage results, and nearby tissues become starved for oxygen.

Figure 19–4 "Sickling" in Red Blood Cells. When fully oxygenated, the red blood cells of an individual with the sickling trait appear relatively normal. At lower oxygen concentrations, the RBCs change shape, becoming more rigid and sharply curved.

because new ones enter the bloodstream at a comparable rate. About 1 percent of the circulating RBCs are replaced each day, and in the process approximately 3 million new RBCs enter the bloodstream *each second*!

Hemoglobin Conservation and Recycling

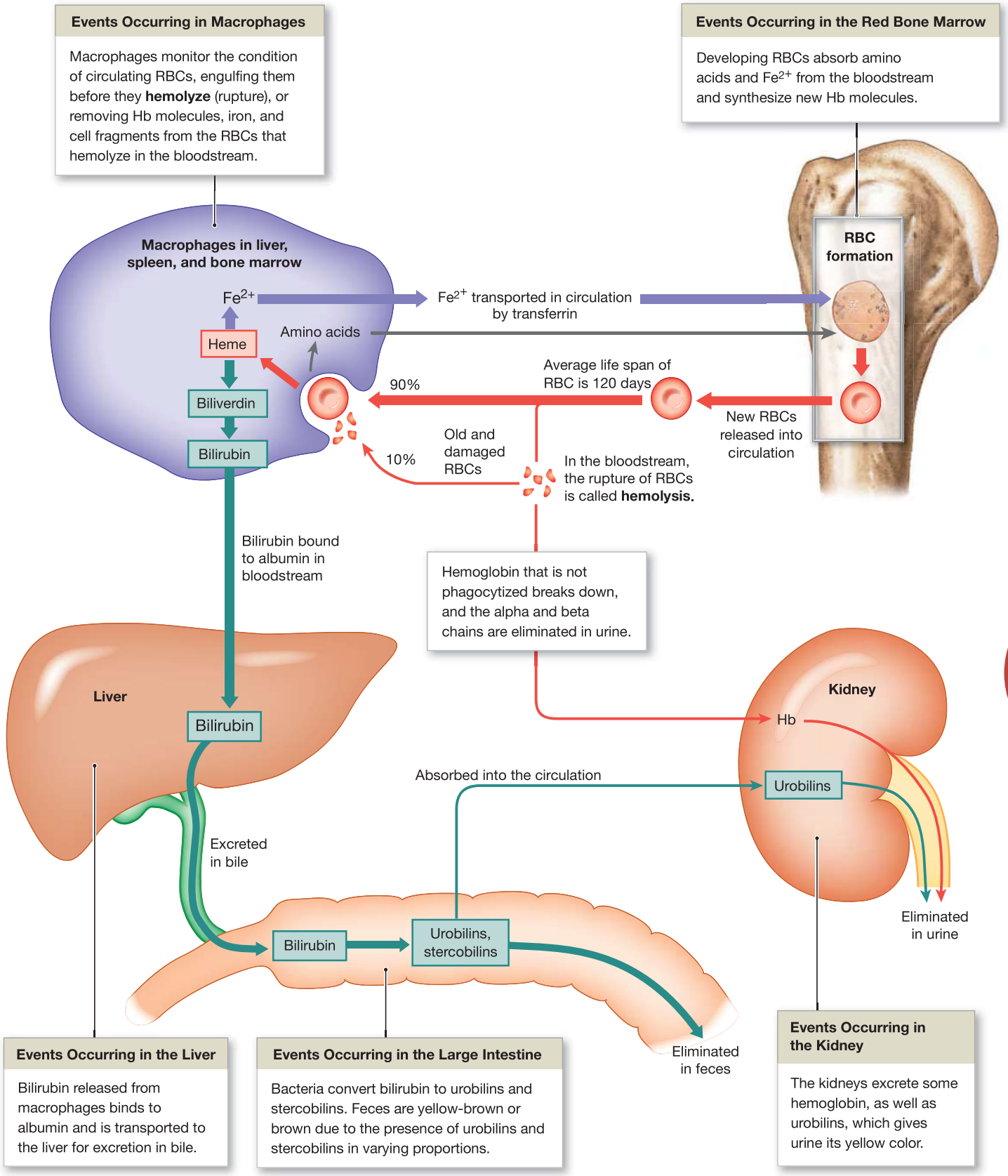
Macrophages of the liver, spleen, and bone marrow play a role in recycling red blood cell components. These phagocytes also detect and remove Hb molecules from hemolyzed (ruptured) red blood cells. If the Hb released by hemolysis is not phagocytized, its components will not be recycled. Hemoglobin remains intact only under the conditions inside RBCs. When hemolysis occurs, the Hb breaks down, and the alpha and beta chains are filtered by the kidneys and eliminated in urine. When abnormally large numbers of RBCs break down in the bloodstream, urine may turn red or brown. This condition is called **hemoglobinuria.** The presence of intact RBCs in urine—a sign called **hematuria** (hē-ma-TOO-rē-uh)—occurs only after kidney damage or damage to vessels along the urinary tract.

Once an RBC has been engulfed and broken down by a phagocytic cell, each component of the Hb molecule has a different fate (**Figure 19–5**). The globular proteins are broken apart into their component amino acids, which are then either metabolized by the cell or released into the bloodstream for use by other cells. Each heme unit is stripped of its iron and converted to **biliverdin** (bil-i-VER-din), an organic compound with a green color. (Bad bruises commonly develop a greenish tint due to biliverdin formation in the blood-filled tissues.) Biliverdin is then converted to **bilirubin** (bil-i-ROO-bin), an orange-yellow pigment, and released into the bloodstream. There, the bilirubin binds to albumin and is transported to the liver for excretion in bile.

If the bile ducts are blocked or the liver cannot absorb or excrete bilirubin, circulating levels of the compound climb rapidly. Bilirubin then diffuses into peripheral tissues, giving them a yellow color that is most apparent in the skin and over the sclera of the eyes. This combination of signs (yellow skin and eyes) is called **jaundice** (JAWN-dis).

In the large intestine, bacteria convert bilirubin to related pigments called *urobilinogens* (ūr-ō-bī-LIN-ō-jens) and *stercobilinogens* (ster-kō-bī-LIN-ō-jens). Some of the urobilinogens are absorbed into the bloodstream and are then excreted into urine. When exposed to oxygen, some of the urobilinogens and stercobilinogens are converted to **urobilins** (ūr-ō-BĪ-lins) and **stercobilins** (ster-kō-BĪ-lins).

Figure 19–5 Recycling of Red Blood Cell Components.



Iron

Large quantities of free iron are toxic to cells, so in the body iron is generally bound to transport or storage proteins. Iron extracted from heme molecules may be bound and stored in a phagocytic cell or released into the bloodstream, where it binds to **transferrin** (trans-FER-in), a plasma protein. Red blood cells developing in the red bone marrow absorb the amino acids and transferrins from the bloodstream and use them to synthesize new Hb molecules. Excess transferrins are removed in the liver and spleen, and the iron is stored in two special protein–iron complexes: **ferritin** (FER-i-tin) and **hemosiderin** (hē-mō-SID-e-rin).

This recycling system is remarkably efficient. Although roughly 26 mg of iron is incorporated into new Hb molecules each day, a dietary supply of 1–2 mg can keep pace with the incidental losses that occur at the kidneys and digestive tract.

Any impairment in iron uptake or metabolism can cause serious clinical problems, because RBC formation will be affected. *Iron-deficiency anemia*, which results from a lack of iron in the diet or from problems with iron absorption, is one example. Too much iron can also cause problems, due to excessive buildup in secondary storage sites, such as the liver and cardiac muscle tissue. Excessive iron deposition in cardiac muscle cells has been linked to heart disease.

RBC Production

Embryonic blood cells appear in the bloodstream during the third week of development. These cells divide repeatedly, rapidly increasing in number. The vessels of the embryonic *yolk sac* are the primary site of blood formation for the first eight weeks of development. As other organ systems appear, some of the embryonic blood cells move out of the bloodstream and into the liver, spleen, thymus, and bone marrow. These embryonic cells differentiate into stem cells that divide to produce blood cells.

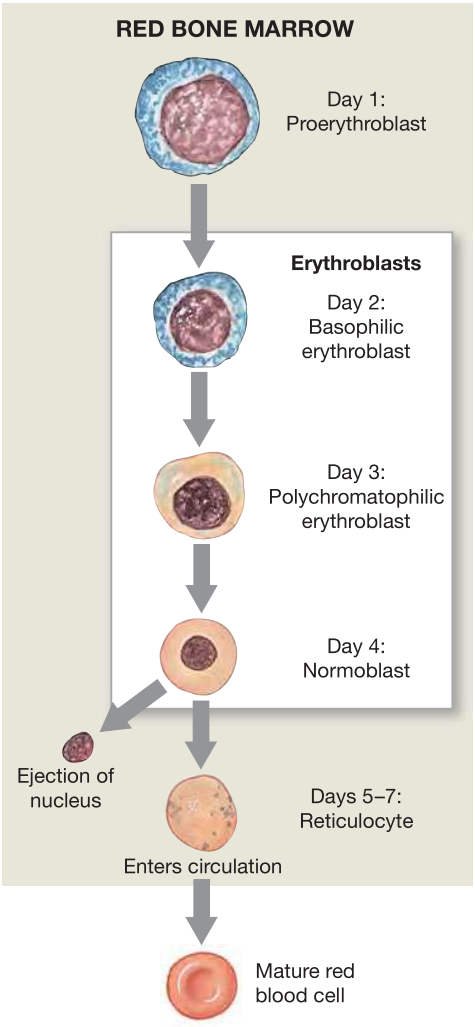
The liver and spleen are the primary sites of hemopoiesis from the second to fifth months of development, but as the skeleton enlarges, the bone marrow becomes increasingly important. In adults, red bone marrow is the only site of red blood cell production, as well as the primary site of white blood cell formation.

Red blood cell formation, or **erythropoiesis** (e-rith-rō-poy-Ē-sis), occurs only in *red bone marrow*, or **myeloid** (MĪ-e-loyd; *myelos*, marrow) **tissue.** This tissue is located in portions of the vertebrae, sternum, ribs, skull, scapulae, pelvis, and proximal limb bones. Other marrow areas contain a fatty tissue known as *yellow bone marrow*. ↩ p. 177 Under extreme stimulation, such as severe and sustained blood loss, areas of yellow marrow can convert to red marrow, increasing the rate of RBC formation.

Stages in RBC Maturation

During its maturation, a red blood cell passes through a series of stages. Blood specialists, known as **hematologists** (hē-ma-TOL-o-jists), have given specific names to key stages. Divisions of **hemocytoblasts** (*hemo-*, blood + *cyte*, cell + *blastos*, precursor), or *multipotent stem cells*, in red bone marrow produce (1) **myeloid stem cells,** which in turn divide to produce red blood cells and several classes of white blood cells, and (2) **lymphoid stem cells,** which divide to produce the various classes of lymphocytes. Cells destined to become RBCs first differentiate into **proerythroblasts** and then proceed through various **erythroblast** stages (**Figure 19–6**). Erythroblasts, which actively synthesize hemoglobin, are named based on total size, amount of hemoglobin present, and size and appearance of the nucleus.

Figure 19–6 Stages of RBC Maturation. Red blood cells are produced in the red bone marrow. The color density in the cytoplasm indicates the abundance of hemoglobin. Note the reductions in the sizes of the cell and nucleus leading up to the formation of a reticulocyte.



After roughly four days of differentiation, the erythroblast, now called a *normoblast*, sheds its nucleus and becomes a **reticulocyte** (re-TIK-ū-lō-sīt), which contains 80 percent of the Hb of a mature RBC. Hb synthesis then continues for two to three more days. During this period, while the cells are synthesizing hemoglobin and other proteins, their cytoplasm still contains RNA, which can be seen under the microscope with certain stains. After two days in the bone marrow, reticulocytes enter the bloodstream. At this time, reticulocytes normally account for about 0.8 percent of the RBC population in the blood and can still be detected by staining. After 24 hours in circulation, the reticulocytes complete their maturation and become indistinguishable from other mature RBCs.

Regulation of Erythropoiesis

For erythropoiesis to proceed normally, the red bone marrow must receive adequate supplies of amino acids, iron, and vitamins (including B_{12}, B_6, and folic acid) for protein synthesis. We obtain **vitamin B_{12}** from dairy products and meat. In order to absorb vitamin B_{12}, we need *intrinsic factor*, which is produced in the stomach. If vitamin B_{12} is not obtained from the diet, normal stem cell divisions cannot occur and *pernicious anemia* results. Thus, pernicious anemia is caused by either a vitamin B_{12} deficiency, a problem with the production of intrinsic factor, or a problem with the absorption of vitamin B_{12} bound to intrinsic factor.

Erythropoiesis is stimulated directly by the peptide hormone erythropoietin (↩ p. 624) and indirectly by several hormones, including thyroxine, androgens, and growth hormone. As noted earlier in the **Spotlight** on pp. 640–641, estrogens do not stimulate erythropoiesis, a fact that accounts for the differences in hematocrit values between males and females.

Erythropoietin (EPO), also called **erythropoiesis-stimulating hormone,** is a glycoprotein, formed by the kidneys and liver. EPO appears in the plasma when peripheral tissues, especially the kidneys, are exposed to low oxygen concentrations. A low oxygen level in tissues is called **hypoxia** (hī-POKS-ē-uh; *hypo-*, below + *oxy-*, presence of oxygen). Erythropoietin is released (1) during anemia; (2) when blood flow to the kidneys declines; (3) when the oxygen content of air in the lungs declines, due to disease or high altitude; and (4) when the respiratory surfaces of the lungs are damaged. Once in the bloodstream, EPO travels to the red bone marrow, where it stimulates stem cells and developing RBCs.

Erythropoietin has two major effects: (1) It stimulates cell division rates in erythroblasts and in the stem cells that produce erythroblasts, and (2) it speeds up the maturation of RBCs, mainly by accelerating Hb synthesis. Under maximum EPO stimulation, bone marrow can increase RBC formation tenfold, to about 30 million cells per second.

The ability to increase the rate of blood formation quickly and dramatically is important to a person recovering from a severe blood loss. But if EPO is administered to a healthy individual, as in the case of the cyclists mentioned in Chapter 18, the hematocrit may rise to 65 or more. ↩ p. 629 Such an increase can place an intolerable strain on the heart. Comparable problems can occur after **blood doping,** a practice in which athletes elevate their hematocrits by reinfusing packed RBCs that were removed and stored at an earlier date. The goal is to improve oxygen delivery to muscles, thereby enhancing performance. The strategy can be dangerous, however, because it elevates blood viscosity and increases the workload on the heart.

Blood tests provide information about the general health of an individual, usually with a minimum of trouble and expense. Several common blood tests focus on RBCs. These *RBC tests* assess the number, size, shape, and maturity of circulating RBCs, indicating the erythropoietic activities under way. The tests can also be useful in detecting problems, such as internal bleeding, that may not produce other obvious signs or symptoms. **Table 19–1** lists examples of important blood tests and related terms.

Table 19–1 RBC Tests and Related Terminology

Test	Determines	Terms Associated with Abnormal Values: Elevated	Terms Associated with Abnormal Values: Depressed
Hematocrit (Hct)	Percentage of formed elements in whole blood Normal = 37–54%	Polycythemia (may reflect erythrocytosis or leukocytosis)	Anemia
Reticulocyte count (Retic.)	Percentage of circulating reticulocytes Normal = 0.8%	Reticulocytosis	
Hemoglobin concentration (Hb)	Concentration of hemoglobin in blood Normal =12–18 g/dL		Anemia
RBC count	Number of RBCs per µL of whole blood Normal = 4.2–6.3 million/μL	Erythrocytosis/polycythemia	Anemia
Mean corpuscular volume (MCV)	Average volume of single RBC Normal = 82–101 μm^3 (normocytic)	Macrocytic	Microcytic
Mean corpuscular hemoglobin concentration (MCHC)	Average amount of Hb in one RBC Normal = 27–34 pg/μL (normochromic)	Hyperchromic	Hypochromic

Checkpoint

8. Describe hemoglobin.
9. How would the hematocrit change after an individual suffered a significant blood loss?
10. Dave develops a blockage in his renal arteries that restricts blood flow to the kidneys. What effect will this have on his hematocrit?
11. In what way would a disease that causes damage to the liver affect the level of bilirubin in the blood?

See the blue Answers tab at the back of the book.

19-4 The ABO blood types and Rh system are based on antigen–antibody responses

Antigens are substances that can trigger a protective defense mechanism called an *immune response.* Most antigens are proteins, although some other types of organic molecules are antigens as well. Your plasma membranes contain **surface antigens,** substances that your immune system recognizes as "normal." In other words, your immune system ignores these substances rather than attacking them as "foreign."

Your **blood type** is determined by the presence or absence of specific surface antigens in RBC plasma membranes. The surface antigens involved are integral membrane glycoproteins or glycolipids whose characteristics are genetically determined. Although red blood cells have at least 50 kinds of surface antigens, three surface antigens are of particular importance: **A, B,** and **Rh** (or **D**).

Based on RBC surface antigens, there are four blood types (**Figure 19–7a**): **Type A** blood has surface antigen A only, **Type B** has surface antigen B only, **Type AB** has both A and B, and **Type O** has neither A nor B. Individuals with these blood types are not evenly distributed throughout the world. The average values for various populations are given in **Table 19–2**.

The term **Rh positive (Rh^+)** indicates the presence of the Rh surface antigen, commonly called the *Rh factor*. The absence of this antigen is indicated as **Rh negative (Rh^-).** When the complete blood type is recorded, the term *Rh* is usually omitted, and a positive or negative sign is used. For example, the data are reported as O negative (O^-), A positive (A^+), and so on. As in the distribution of A and B surface antigens, Rh type differs by ethnic group and by region (**Table 19–2**).

Your immune system ignores these surface antigens—called **agglutinogens** (a-gloo-TIN-ō-jenz)—on your own RBCs. However, your plasma contains antibodies, sometimes called *agglutinins* (a-GLOO-ti-ninz), that will attack the antigens on "foreign" RBCs. When these antibodies attack, the foreign cells **agglutinate,** or clump together. This process is called **agglutination.** If you have Type A blood, your plasma contains anti-B antibodies, which will attack Type B surface antigens. If you have Type B blood, your plasma contains anti-A antibodies. The RBCs of an individual with Type O blood have neither A nor B surface antigens, and that person's plasma contains both anti-A and anti-B antibodies. A Type AB individual has RBCs with both A and B surface antigens, and the plasma does not contain anti-A or anti-B antibodies. The presence of anti-A and/or anti-B antibodies is genetically determined and they are present throughout life, regardless of whether the individual has ever been exposed to foreign RBCs.

In contrast, the plasma of an Rh-negative individual does not contain anti-Rh antibodies. These antibodies are present only if the individual has been **sensitized** by previous exposure to Rh^+ RBCs. Such exposure can occur accidentally during a transfusion, but it can also accompany a seemingly normal pregnancy involving an Rh^- mother and an Rh^+ fetus. (See **Spotlight Figure 19–9** on pp. 654–655.)

Cross-Reactions in Transfusions

When an antibody meets its specific surface antigen, the RBCs agglutinate and may also hemolyze. This reaction is called a **cross-reaction** (**Figure 19–7b**). For instance, an anti-A antibody that encounters A surface antigens will cause the RBCs bearing the surface antigens to clump or even break up. Clumps and fragments of RBCs under attack form drifting masses that can plug small blood vessels in the kidneys, lungs, heart, or brain, damaging or destroying affected tissues. Such cross-reactions, or *transfusion reactions*, can be prevented by ensuring that the blood types of the donor and the recipient are **compatible**—that is, that the donor's blood cells and the recipient's plasma will not cross-react.

In practice, the surface antigens on the donor's cells are more important in determining compatibility than are the antibodies in the donor's plasma. Unless large volumes of whole blood or plasma are transferred, cross-reactions between the donor's plasma and the recipient's blood cells will not produce significant agglutination. This is because the donated plasma is diluted quickly through mixing with the large plasma volume of the recipient. (One unit of whole blood, 500 mL, contains roughly 275 mL of plasma, only about 10 percent of normal plasma volume.) When the goal is to increase the blood's oxygen- carrying capacity rather than its plasma volume, packed RBCs, with a minimal amount of plasma, are often transfused. This practice minimizes the risk of a cross-reaction.

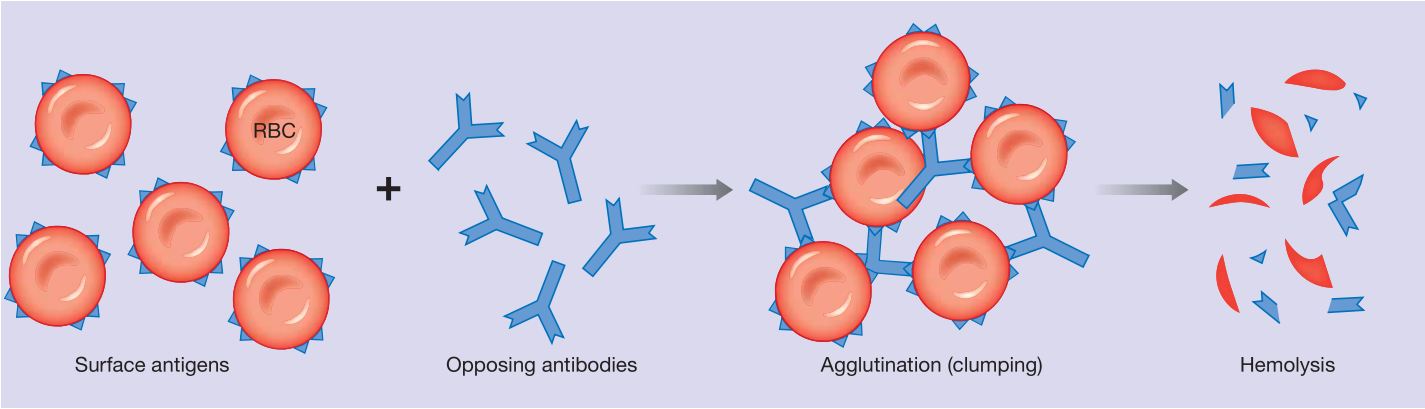
Testing for Transfusion Compatibility

Extra care must be taken to avoid potentially life-threatening cross-reactions between the donor's cells and the recipient's plasma. As a result, a compatibility test is usually performed in advance. This process normally involves two steps: (1) a determination of blood type and (2) a cross-match test.

Figure 19–7 Blood Types and Cross-Reactions.

Type A	Type B	Type AB	Type O
Type A blood has RBCs with surface antigen A only.	**Type B** blood has RBCs with surface antigen B only.	**Type AB** blood has RBCs with both A and B surface antigens.	**Type O** blood has RBCs lacking both A and B surface antigens.
Surface antigen A	Surface antigen B		
If you have Type A blood, your plasma contains anti-B antibodies, which will attack Type B surface antigens.	If you have Type B blood, your plasma contains anti-A antibodies, which will attack Type A surface antigens.	If you have Type AB blood, your plasma has neither anti-A nor anti-B antibodies.	If you have Type O blood, your plasma contains both anti-A and anti-B antibodies.

a Blood type depends on the presence of surface antigens (agglutinogens) on RBC surfaces. The plasma contains antibodies (agglutinins) that will react with foreign surface antigens.



b In a cross-reaction, antibodies react with their target antigens causing agglutination and hemolysis of the affected RBCs.

Table 19–2 Differences in Blood Group Distribution

Population	Percentage with Each Blood Type				
	O	A	B	AB	Rh^+
U.S. (AVERAGE)	46	40	10	4	85
African American	49	27	20	4	95
Caucasian	45	40	11	4	85
Chinese American	42	27	25	6	100
Filipino American	44	22	29	6	100
Hawaiian	46	46	5	3	100
Japanese American	31	39	21	10	100
Korean American	32	28	30	10	100
NATIVE NORTH AMERICAN	79	16	4	1	100
NATIVE SOUTH AMERICAN	100	0	0	0	100
AUSTRALIAN ABORIGINE	44	56	0	0	100

The standard test for blood type considers only the three surface antigens most likely to produce dangerous cross-reactions: A, B, and Rh (**Figure 19–8**). The test involves taking drops of blood and mixing them separately with solutions containing anti-A, anti-B, and anti-Rh (anti-D) antibodies. Any cross-reactions are then recorded. For example, if an individual's RBCs clump together when exposed to anti-A and to anti-B antibodies, the individual has Type AB blood. If no reactions occur after exposure, that person must have Type O blood. The presence or absence of the Rh surface antigen is also noted, and the individual is classified as Rh positive or Rh negative on that basis. Type O^+ is the most common blood type. The RBCs of Type O^+ individuals lack surface antigens A and B but have the Rh antigen.

Spotlight Figure 19–9 describes a situation known as hemolytic disease of the newborn. Hemolytic disease of the newborn is a serious condition involving Rh incompatibility between a pregnant mother and her developing baby.

Standard blood-typing of both donor and recipient can be completed in a matter of minutes. However, in an emergency, there may not be time for preliminary testing. For example, a person with a severe gunshot wound may require 5 *liters* or more of blood before the damage can be repaired. Under these circumstances, Type O blood (preferably O^-) will be administered. Because the donated RBCs lack both A and B surface antigens, the recipient's blood can have anti-A antibodies, anti-B antibodies, or both and still not cross-react with the donor's blood. Because cross-reactions with Type O blood are very unlikely, Type O individuals are sometimes called *universal donors*. Type AB individuals were once called *universal recipients*, because they lack anti-A or anti-B antibodies that would attack donated RBCs, and so can safely receive blood of any type. However, now that blood supplies are adequate and compatibility testing is regularly performed, the term has largely been dropped. If the recipient's blood type is known to be AB, Type AB blood will be administered.

It is now possible to use enzymes to strip off the A or B surface antigens from RBCs and create Type O blood in the laboratory. The procedure is expensive and time-consuming and has limited use in emergency treatment. Still, cross-reactions can occur, even to Type O^- blood, because at least 48 other surface antigens are present. As a result, whenever time and facilities permit, further testing is performed to ensure complete compatibility between donor blood and recipient blood. **Cross-match testing** involves exposing the donor's RBCs to a sample of the recipient's plasma under controlled conditions. This procedure reveals significant cross-reactions involving surface antigens other than A, B, or Rh. Another way to avoid compatibility problems is to replace lost blood with synthetic blood substitutes, which do not contain surface antigens that can trigger a cross-reaction.

Because blood groups are inherited, blood tests are also used as paternity tests and in crime detection. The blood collected cannot prove that a particular individual *is* a certain child's father or *is* guilty of a specific crime, but it can prove that the individual is *not* involved. It is impossible, for example, for an adult with Type AB blood to be the parent of an infant with Type O blood. Testing for additional surface antigens, other than the standard ABO groups, can increase the accuracy of the conclusions. When available, DNA identity testing, which has nearly 100% accuracy, has replaced blood type identity testing.

19

Figure 19–8 Blood Type Testing. Test results for blood samples from four individuals. Drops are mixed with solutions containing antibodies to the surface antigens A, B, AB, and D (Rh). Clumping occurs when the sample contains the corresponding surface antigen(s). The individuals' blood types are shown at right.

Anti-A	Anti-B	Anti-D	Blood type
			A^+
			B^+
			AB^+
			O^-

Checkpoint

12. **What is the function of surface antigens on RBCs?**
13. **Which blood type can be safely transfused into a person with Type O blood?**
14. **Why can't a person with Type A blood safely receive blood from a person with Type B blood?**

See the blue Answers tab at the back of the book.

19-5 The various types of white blood cells contribute to the body's defenses

Unlike red blood cells, white blood cells (WBCs) have nuclei and other organelles, and they lack hemoglobin. White blood cells, or leukocytes, help defend the body against invasion by pathogens, and they remove toxins, wastes, and abnormal or damaged cells. Several types of WBCs can be distinguished microscopically in a blood smear by using either of two standard stains: *Wright's stain* or *Giemsa stain*. Traditionally, WBCs have

been divided into two groups based on their appearance after staining: (1) *granular leukocytes*, or *granulocytes* (with abundant stained granules)—the *neutrophils*, *eosinophils*, and *basophils*; and (2) *agranular leukocytes*, or *agranulocytes* (with few, if any, stained granules)—the *monocytes* and *lymphocytes*. This categorization is convenient but somewhat misleading, because the granules in "granular leukocytes" are secretory vesicles and lysosomes, and the "agranular leukocytes" also contain vesicles and lysosomes; they are just smaller and difficult to see with the light microscope.

A typical microliter of blood contains 5000 to 10,000 WBCs, compared with 4.2 to 6.3 million RBCs. Most of the WBCs in the body at any moment are in connective tissue proper or in organs of the lymphatic system. Circulating WBCs represent only a small fraction of the total WBC population.

WBC Circulation and Movement

Unlike RBCs, WBCs circulate for only a short time of their life span. White blood cells migrate through the loose and dense connective tissues of the body, using the bloodstream to travel from one organ to another and for rapid transportation to areas of infection or injury. As they travel along the miles of capillaries, WBCs can detect the chemical signs of damage to surrounding tissues. When problems are detected, these cells leave the bloodstream and enter the damaged area.

Circulating WBCs have four characteristics:

1. *All Can Migrate Out of the Bloodstream.* When WBCs in the bloodstream are activated, they contact and adhere to the vessel walls in a process called *margination*. After further interaction with endothelial cells, the activated WBCs squeeze between adjacent endothelial cells and enter the surrounding tissue. This process is called *emigration*, or *diapedesis* (*dia*, through + *pedesis*, a leaping).
2. *All Are Capable of Amoeboid Movement. Amoeboid movement* is a gliding motion made possible by the flow of cytoplasm into slender cellular processes extended in the direction of movement. (The movement is so named because it is similar to that of an *amoeba*, a type of protozoan.) The mechanism is not fully understood, but it involves the continuous rearrangement of bonds between actin filaments in the cytoskeleton, and it requires calcium ions and ATP. This mobility allows WBCs to move through the endothelial lining and into peripheral tissues.
3. *All Are Attracted to Specific Chemical Stimuli.* This characteristic, called **positive chemotaxis** (kē-mō-TAK-sis), guides WBCs to invading pathogens, damaged tissues, and other active WBCs.
4. *Neutrophils, Eosinophils, and Monocytes Are Capable of Phagocytosis.* These cells may engulf pathogens, cell debris, or other materials. Neutrophils and eosinophils are sometimes called *microphages*, to distinguish them from the larger macrophages in connective tissues. Macrophages are monocytes that have moved out of the bloodstream and have become actively phagocytic. ↩ p. 122

Types of WBCs

Neutrophils, eosinophils, basophils, and monocytes are part of the body's *nonspecific defenses*. Such defenses are activated by a variety of stimuli, but they do not discriminate between one type of threat and another. Lymphocytes, in contrast, are responsible for *specific defenses*: the mounting of a counterattack against specific types of invading pathogens or foreign proteins. We discuss the interactions among WBCs and the relationships between specific and nonspecific defenses in Chapter 22.

Neutrophils

Fifty to 70 percent of the circulating WBCs are **neutrophils** (NOO-trō-filz). This name reflects the fact that the granules of these WBCs are chemically neutral and thus are difficult to stain with either acidic or basic (alkaline) dyes. A mature neutrophil has a very dense, segmented nucleus with two to five lobes resembling beads on a string (**Figure 19–10a**). This structure has given neutrophils another name: **polymorphonuclear** (pol-ē-mor-fō-NOO-klē-ar) **leukocytes** (*poly*, many + *morphe*, form), or *PMNs*. "Polymorphs," or "polys," as they are often called, are roughly 12 μm in diameter. Their cytoplasm is packed with pale granules containing lysosomal enzymes and bactericidal (bacteria-killing) compounds.

Neutrophils are highly mobile, and are generally the first of the WBCs to arrive at the site of an injury. These very active cells specialize in attacking and digesting bacteria that have been "marked" with antibodies or with *complement proteins*—plasma proteins involved in tissue defenses. (We discuss the complement system in Chapter 22.)

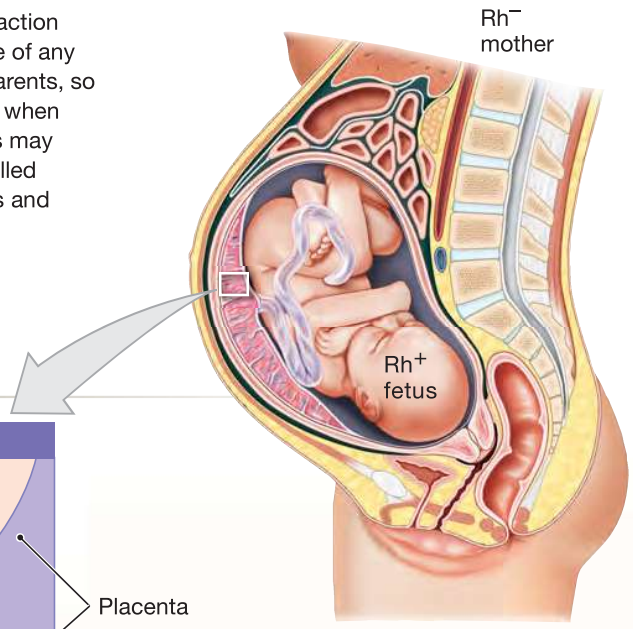
Upon encountering a bacterium, a neutrophil quickly engulfs it, and the metabolic rate of the neutrophil increases dramatically. This *respiratory burst* accompanies the production of highly reactive, destructive chemical agents, including *hydrogen peroxide* (H_2O_2) and *superoxide anions* (O_2^-), which can kill bacteria.

Meanwhile, the vesicle containing the engulfed pathogen fuses with lysosomes that contain digestive enzymes and small peptides called **defensins.** This process, which reduces the number of granules in the cytoplasm, is called **degranulation.** Defensins kill a variety of pathogens, including bacteria, fungi, and enveloped viruses, by combining to form large channels in their plasma membranes. The digestive enzymes then break down the bacterial remains. While actively engaged in attacking bacteria, a neutrophil releases prostaglandins and leukotrienes. ↩ p. 598 The prostaglandins increase capillary permeability in the affected region, thereby contributing to local inflammation and restricting the spread of injury and infection. Leukotrienes are

Spotlight

Figure 19–9
Hemolytic Disease of the Newborn

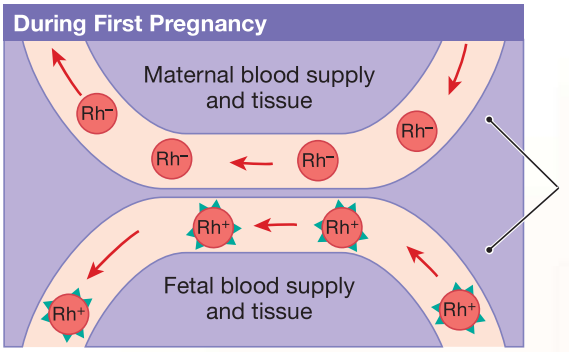
Hemolytic disease of the newborn is an RBC-related disorder caused by a cross-reaction between fetal and maternal blood types. Genes controlling the presence or absence of any surface antigen in the plasma membrane of a red blood cell are provided by both parents, so a child can have a blood type different from that of either parent. During pregnancy, when fetal and maternal vascular systems are closely intertwined, the mother's antibodies may cross the placenta, attacking and destroying fetal RBCs. The resulting condition, called **hemolytic disease of the newborn (HDN)**, has many forms, some quite dangerous and others so mild as to remain undetected.



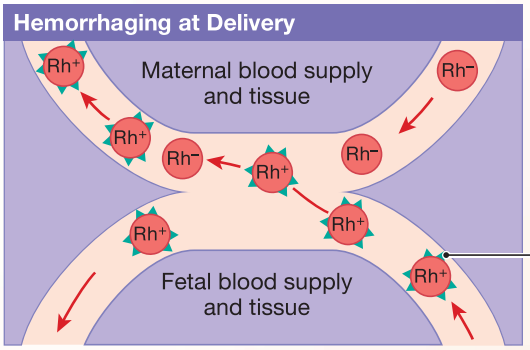
The most common form of hemolytic disease of the newborn develops after an Rh⁻ woman has carried an Rh⁺ fetus.

FIRST PREGNANCY

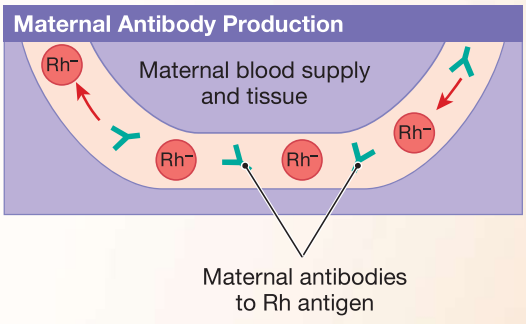
1 Problems seldom develop during a first pregnancy, because very few fetal cells enter the maternal circulation then, and thus the mother's immune system is not stimulated to produce anti-Rh antibodies.



2 Exposure to fetal red blood cell antigens generally occurs during delivery, when bleeding takes place at the placenta and uterus. Such mixing of fetal and maternal blood can stimulate the mother's immune system to produce anti-Rh antibodies, leading to sensitization.



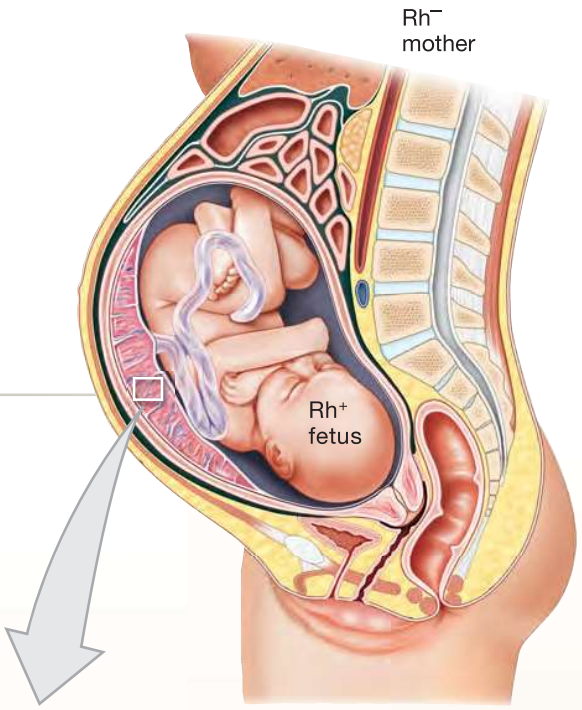
3 Roughly 20% of Rh^- mothers who carried Rh^+ children become sensitized within 6 months of delivery. Because the anti-Rh antibodies are not produced in significant amounts until after delivery, a woman's first infant is not affected.



SECOND PREGNANCY

4

If a subsequent pregnancy involves an Rh^+ fetus, maternal anti-Rh antibodies produced after the first delivery cross the placenta and enter the fetal bloodstream. These antibodies destroy fetal RBCs, producing a dangerous anemia. The fetal demand for blood cells increases, and they begin leaving the bone marrow and entering the bloodstream before completing their development. Because these immature RBCs are erythroblasts, HDN is also known as **erythroblastosis fetalis** (e-rith-rō-blas-TŌ-sis fē-TAL-is). Without treatment, the fetus will probably die before delivery or shortly thereafter. A newborn with severe HDN is anemic, and the high concentration of circulating bilirubin produces jaundice. Because the maternal antibodies remain active in the newborn for 1 to 2 months after delivery, the infant's entire blood volume may require replacement to remove the maternal anti-Rh antibodies, as well as the damaged RBCs. Fortunately, the mother's anti-Rh antibody production can be prevented if such antibodies (available under the name RhoGAM) are administered to the mother in weeks 26–28 of pregnancy and during and after delivery. These antibodies destroy any fetal RBCs that cross the placenta before they can stimulate a maternal immune response. Because maternal sensitization does not occur, no anti-Rh antibodies are produced. In the United States, this relatively simple procedure has almost entirely eliminated HDN mortality caused by Rh incompatibilities.



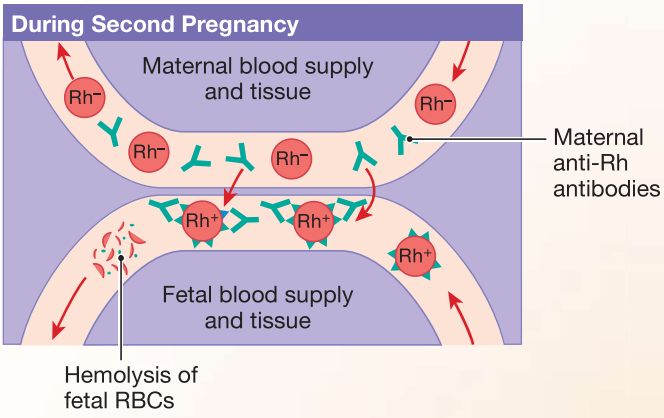
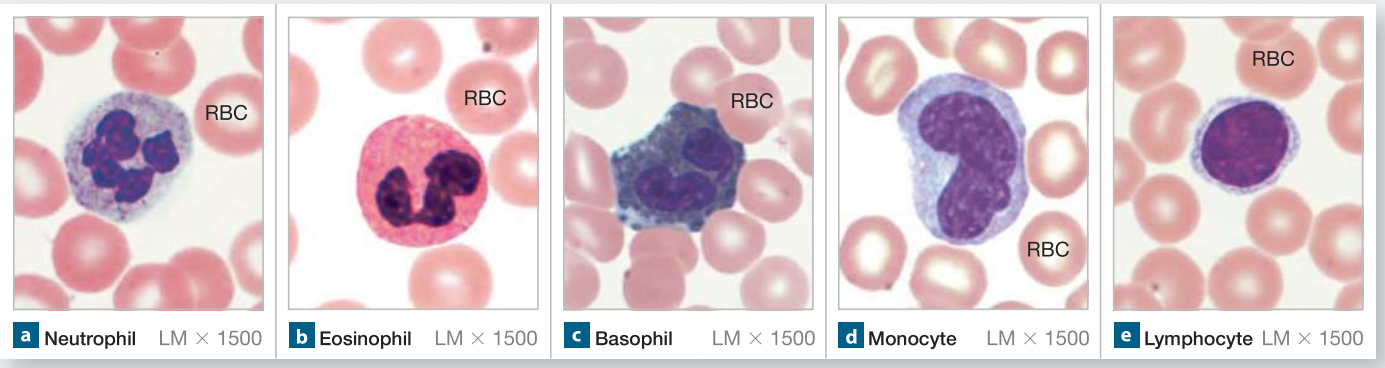


Figure 19–10 White Blood Cells.



hormones that attract other phagocytes and help coordinate the immune response.

Most neutrophils have a short life span, surviving in the bloodstream for only about 10 hours. When actively engulfing debris or pathogens, they may last 30 minutes or less. A neutrophil dies after engulfing one to two dozen bacteria, but its breakdown releases chemicals that attract other neutrophils to the site. A mixture of dead neutrophils, cellular debris, and other waste products form the *pus* associated with infected wounds.

Tips & Tricks

Remember that ***neu***trophils are the most ***nu***merous of the white blood cells.

19

Eosinophils

Eosinophils (ē-ō-SIN-ō-filz) were so named because their granules stain darkly with *eosin*, a red dye. The granules also stain with other acid dyes, so the name **acidophils** (a-SID-ō-filz) applies as well. Eosinophils, which generally represent 2–4 percent of the circulating WBCs, are similar in size to neutrophils. However, the combination of deep red granules and a typically bilobed (two-lobed) nucleus makes eosinophils easy to identify (**Figure 19–10b**).

Eosinophils attack objects that are coated with antibodies. Although they will engulf antibody-marked bacteria, protozoa, or cellular debris, their primary mode of attack is the exocytosis of toxic compounds, including nitric oxide and cytotoxic enzymes. This is particularly effective against multicellular parasites, such as flukes or parasitic roundworms, that are too big to engulf. The number of circulating eosinophils increases dramatically during a parasitic infection.

Because they are sensitive to circulating *allergens* (materials that trigger allergies), eosinophils increase in number during allergic reactions as well. Eosinophils are also attracted to sites of injury, where they release enzymes that reduce inflammation produced by mast cells and neutrophils. This will control the spread of inflammation to adjacent tissues.

Basophils

Basophils (BĀ-sō-filz; *baso-*, base+ *phileo*, to love) have numerous granules that stain darkly with basic dyes. In a standard blood smear, the inclusions are deep purple or blue (**Figure 19–10c**). Measuring 8–10 μm in diameter, basophils are smaller than neutrophils or eosinophils. They are also relatively rare, accounting for less than 1 percent of the circulating WBC population.

Basophils migrate to injury sites and cross the capillary endothelium to accumulate in the damaged tissues, where they discharge their granules into the interstitial fluids. The granules contain *histamine*, which dilates blood vessels, and *heparin*, a compound that prevents blood clotting. Stimulated basophils release these chemicals into the interstitial fluids to enhance the local inflammation initiated by mast cells. ↩ p. 138 Although the same compounds are released by mast cells in damaged connective tissues, mast cells and basophils are distinct populations with separate origins. Other chemicals released by stimulated basophils attract eosinophils and other basophils to the area.

Monocytes

Monocytes (MON-ō-sīts) are spherical cells that may exceed 15 μm in diameter, nearly twice the diameter of a typical RBC. When flattened in a blood smear, they look even larger, so monocytes are fairly easy to identify. The nucleus is large and tends to be oval or kidney bean–shaped rather than lobed (**Figure 19–10d**). Monocytes normally account for 2–8 percent of circulating WBCs.

An individual monocyte is transported in the bloodstream, remaining in circulation for only about 24 hours before entering peripheral tissues to become a tissue macrophage. Macrophages are aggressive phagocytes, often attempting to en-

gulf items as large as or larger than themselves. While phagocytically active, they release chemicals that attract and stimulate neutrophils, monocytes, and other phagocytic cells. Active macrophages also secrete substances that draw fibroblasts into the region. The fibroblasts then begin producing scar tissue, which will wall off the injured area.

Tips & Tricks

A ***mon***ocyte is the ***mon***ster cell that engulfs debris and pathogens.

Lymphocytes

Typical **lymphocytes** (LIM-fō-sīts) are slightly larger than RBCs and lack abundant, deeply stained granules. In blood smears, lymphocytes typically have a large, round nucleus surrounded by a thin halo of cytoplasm (**Figure 19–10e**).

Lymphocytes account for 20–30 percent of the circulating WBC population. Lymphocytes continuously migrate from the bloodstream, through peripheral tissues, and back to the bloodstream. Circulating lymphocytes represent only a small fraction of all lymphocytes. At any moment, most of your body's lymphocytes are in other connective tissues and in organs of the lymphatic system.

The circulating blood contains three functional classes of lymphocytes, which cannot be distinguished with a light microscope:

1. **T cells** are responsible for *cell-mediated immunity*, a specific defense mechanism against invading foreign cells, and for the coordination of the immune response. T cells either enter peripheral tissues and attack foreign cells directly, or they control the activities of other lymphocytes.
2. **B cells** are responsible for *humoral immunity*, a specific defense mechanism that involves the production of antibodies. These antibodies are distributed by blood, lymph, and interstitial fluid and are capable of attacking foreign antigens throughout the body. Activated B cells differentiate into **plasma cells,** which are specialized to synthesize and secrete antibodies. Whereas the T cells responsible for cellular immunity must migrate to their targets, the antibodies produced by plasma cells in one location can destroy antigens almost anywhere in the body.
3. **Natural killer (NK) cells** are responsible for *immune surveillance*—the detection and subsequent destruction of abnormal cells. NK cells, sometimes known as *large granular lymphocytes*, are important in preventing cancer.

Tips & Tricks

To remember the various white blood cell populations, think "Never let monkeys eat bananas" for neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

The Differential Count and Changes in WBC Profiles

A variety of conditions, including infection, inflammation, and allergic reactions, cause characteristic changes in circulating populations of WBCs. By examining a stained blood smear, we can obtain a **differential count** of the WBC population. The values reported indicate the number of each type of cell in a sample of 100 WBCs.

The normal range of abundance for each type of WBC is shown in **Table 19–3**. The term **leukopenia** (loo-kō-PĒ-nē-uh; *penia*, poverty) indicates inadequate numbers of WBCs. **Leukocytosis** (loo-kō-sī-TŌ-sis) refers to excessive numbers of WBCs. A modest leukocytosis is normal during an infection. Extreme leukocytosis (100,000/μL or more) generally indicates the presence of some form of **leukemia** (loo-KĒ-mē-uh). The endings *-penia* and *-osis* can also indicate low or high numbers of specific types of WBCs. For example, *lymphopenia* means too few lymphocytes, and *lymphocytosis* means too many.

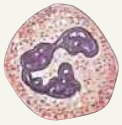
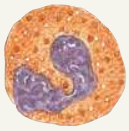
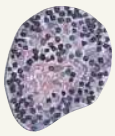
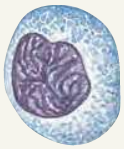
WBC Production

Stem cells responsible for the production of WBCs originate in the red bone marrow, with the divisions of hemocytoblasts (**Figure 19–11**). As previously noted, hemocytoblast divisions produce myeloid stem cells and lymphoid stem cells. Myeloid stem cell division creates **progenitor cells,** which give rise to all the formed elements except lymphocytes. One type of progenitor cell produces daughter cells that mature into RBCs; a second type produces cells that manufacture platelets. Neutrophils, eosinophils, basophils, and monocytes develop from daughter cells produced by a third type of progenitor cell.

Granulocytes (basophils, eosinophils, and neutrophils) complete their development in the red bone marrow. These WBCs go through a series of maturational stages, proceeding from *blast cells* to *myelocytes* to *band cells* before becoming mature WBCs. For example, a cell differentiating into a neutrophil goes from a myeloblast to a *neutrophilic myelocyte* and then becomes a *neutrophilic band cell*. Some band cells enter the bloodstream before completing their maturation. Normally, 3–5 percent of all circulating WBCs are band cells.

Monocytes begin their differentiation in the red bone marrow, enter the bloodstream, and complete development when they become free macrophages in peripheral tissues. Some lymphocytes are derived from lymphoid stem cells that remain in red bone marrow; these lymphocytes differentiate into either B cells or natural killer cells. Many of the lymphoid stem cells responsible for the production of lymphocytes migrate from the red bone marrow to peripheral **lymphatic tissues,** including the thymus, spleen, and lymph nodes. As a result, lymphocytes are produced in these organs as well as in the red bone marrow. Lymphoid stem cells migrating to the thymus mature into T cells. The process of

Table 19–3 Formed Elements of the Blood

Cell	Abundance (average number per μL)	Appearance in a Stained Blood Smear	Functions	Remarks
RED BLOOD CELLS 	5.2 million (range: 4.4–6.0 million)	Flattened, circular cell; no nucleus, mitochondria, or ribosomes; red	Transport oxygen from lungs to tissues and carbon dioxide from tissues to lungs	Remain in bloodstream; 120-day life expectancy; amino acids and iron recycled; produced in red bone marrow
WHITE BLOOD CELLS	7000 (range: 5000–10,000)			
Neutrophils 	4150 (range: 1800–7300) Differential count: 50–70%	Round cell; nucleus lobed and may resemble a string of beads; cytoplasm contains large, pale inclusions	Phagocytic: Engulf pathogens or debris in tissues, release cytotoxic enzymes and chemicals	Move into tissues after several hours; may survive minutes to days, depending on tissue activity; produced in red bone marrow
Eosinophils 	165 (range: 0–700) Differential count: 2–4%	Round cell; nucleus generally in two lobes; cytoplasm contains large granules that generally stain bright red	Phagocytic: Engulf antibody-labeled materials, release cytotoxic enzymes, reduce inflammation; increase in allergic and parasitic situations	Move into tissues after several hours; survive minutes to days, depending on tissue activity; produced in red bone marrow
Basophils 	44 (range: 0–150) Differential count: <1%	Round cell; nucleus generally cannot be seen through dense, blue-stained granules in cytoplasm	Enter damaged tissues and release histamine and other chemicals that promote inflammation	Survival time unknown; assist mast cells of tissues in producing inflammation; produced in red bone marrow
Monocytes 	456 (range: 200–950) Differential count: 2–8%	Very large cell; kidney bean–shaped nucleus; abundant pale cytoplasm	Enter tissues to become macrophages; engulf pathogens or debris	Move into tissues after 1–2 days; survive for months or longer; produced primarily in red bone marrow
Lymphocytes 	2185 (range: 1500–4000) Differential count: 20–30%	Generally round cell, slightly larger than RBC; round nucleus; very little cytoplasm	Cells of lymphatic system, providing defense against specific pathogens or toxins	Survive for months to decades; circulate from blood to tissues and back; produced in red bone marrow and lymphatic tissues
PLATELETS 	350,000 (range: 150,000–500,000)	Round to spindle-shaped cytoplasmic fragment; contain enzymes, proenzymes, actin, and myosin; no nucleus	Hemostasis: Clump together and stick to vessel wall (platelet phase); activate intrinsic pathway of coagulation phase	Remain in bloodstream or in vascular organs; remain intact for 7–12 days; produced by megakaryocytes in red bone marrow

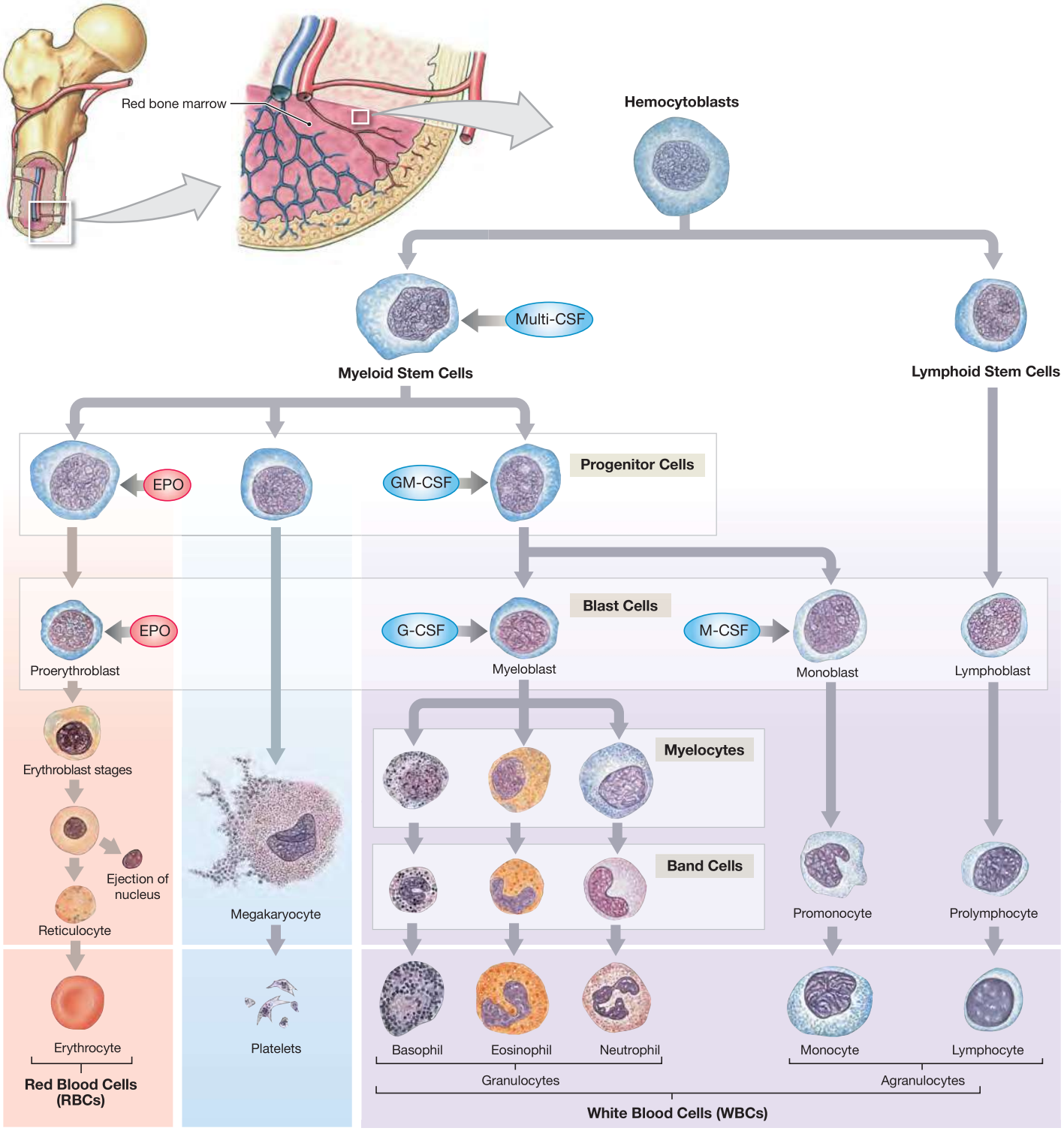
lymphocyte production is called **lymphopoiesis.** Lymphocytes are further discussed in Chapter 22.

Regulation of WBC Production

Factors that regulate lymphocyte maturation remain incompletely understood. Until adulthood, hormones produced by the thymus promote the differentiation and maintenance of T cell populations. The importance of the thymus in adults, especially with respect to aging, remains controversial. In adults, the production of B and T lymphocytes is regulated primarily by exposure to antigens (foreign proteins, cells, or toxins). When antigens appear, lymphocyte production escalates. We describe the control mechanisms in Chapter 22.

Several hormones are involved in the regulation of other WBC populations. The targets of these hormones, called **colony-stimulating factors (CSFs),** are shown in **Figure 19–11**. Four

Figure 19–11 The Origins and Differentiation of Formed Elements. Hemocytoblast divisions give rise to myeloid stem cells or lymphoid stem cells. Lymphoid stem cells produce the various lymphocytes. Myeloid stem cells produce progenitor cells that divide to produce the other classes of formed elements. The targets of EPO and the four colony-stimulating factors (CSFs) are indicated.



CSFs have been identified, each stimulating the formation of WBCs or both WBCs and RBCs. The designation for each factor indicates its target:

1. **M-CSF** stimulates the production of monocytes.
2. **G-CSF** stimulates the production of granulocytes (neutrophils, eosinophils, and basophils).
3. **GM-CSF** stimulates the production of both granulocytes and monocytes.
4. **Multi-CSF** accelerates the production of granulocytes, monocytes, platelets, and RBCs.

Chemical communication between lymphocytes and other WBCs assists the coordination of the immune response. For example, active macrophages release chemicals that make lymphocytes more sensitive to antigens and that accelerate the development of specific immunity. In turn, active lymphocytes release multi-CSF and GM-CSF, reinforcing nonspecific defenses. Immune system hormones are currently being studied intensively because of their potential clinical importance. The molecular structures of many of the stimulating factors have been identified, and several can be produced by genetic engineering. The U.S. Food and Drug Administration approved the administration of synthesized forms of EPO, G-CSF, and GM-CSF to stimulate the production of specific blood cell lines. For instance, a genetically engineered form of G-CSF, sold under the name *filgrastim* (*Neupogen*), is used to stimulate the production of neutrophils in patients undergoing cancer chemotherapy.

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Checkpoint

15. **Identify the five types of white blood cells.**
16. **Which type of white blood cell would you find in the greatest numbers in an infected cut?**
17. **Which type of cell would you find in elevated numbers in a person who is producing large amounts of circulating antibodies to combat a virus?**
18. **How do basophils respond during inflammation?**

See the blue Answers tab at the back of the book.

19-6 Platelets, disc-shaped structures formed from megakaryocytes, function in the clotting process

In a blood smear, platelets (PLĀT-lets) appear as spindle-shaped cell fragments. They average about 4 μm in diameter and are roughly 1 μm thick. Platelets in nonmammalian vertebrates are nucleated cells called **thrombocytes** (THROM-bō-sīts; *thrombos*, clot). Because in humans they are cell fragments rather than individual cells, the term *platelet* is preferred when referring to our blood. Platelets are a major participant in a vascular *clotting system* that also includes plasma proteins and the cells and tissues of the blood vessels.

Platelets are continuously replaced. Each platelet circulates for 9–12 days before being removed by phagocytes, mainly in the spleen. Each microliter of circulating blood contains 150,000–500,000 platelets; 350,000/μL is the average concentration. About one-third of the platelets in the body at any moment are in the spleen and other vascular organs, rather than in the bloodstream. These reserves are mobilized during a circulatory crisis, such as severe bleeding.

An abnormally low platelet count (80,000/μL or less) is known as **thrombocytopenia** (throm-bō-sī-tō-PĒ-nē-uh). Thrombocytopenia generally indicates excessive platelet destruction or inadequate platelet production. Signs include bleeding along the digestive tract, within the skin, and occasionally inside the CNS. In **thrombocytosis** (throm-bō-sī-TŌ-sis), platelet counts can exceed 1,000,000/μL. Thrombocytosis usually results from accelerated platelet formation in response to infection, inflammation, or cancer.

Platelet Functions

The functions of platelets include:

- *Releasing Chemicals Important to the Clotting Process.* By releasing enzymes and other factors at the appropriate times, platelets help initiate and control the clotting process.
- *Forming a Temporary Patch in the Walls of Damaged Blood Vessels.* Platelets clump together at an injury site, forming a *platelet plug*, which can slow blood loss while clotting occurs.
- *Reducing the Size of a Break in the Vessel Wall.* Platelets contain filaments of actin and myosin. After a blood clot has formed, platelet filaments contract to shrink the clot and reduce the size of the break in the vessel wall.

Platelet Production

Platelet production, or **thrombocytopoiesis,** occurs in the red bone marrow. Normal red bone marrow contains **megakaryocytes** (meg-a-KAR-ē-ō-sīts; *mega-*, big + *karyon*, nucleus + *-cyte*, cell), enormous cells (up to 160 μm in diameter) with large nuclei (**Figure 19–11**). During their development and growth, megakaryocytes manufacture structural proteins, enzymes, and membranes. They then begin shedding cytoplasm in small membrane-enclosed packets. These packets are the platelets that enter the bloodstream. A mature megakaryocyte gradually loses all of its cytoplasm, producing about 4000

platelets before the nucleus is engulfed by phagocytes and broken down for recycling.

The rate of megakaryocyte activity and platelet formation is influenced by (1) *thrombopoietin* (TPO), or *thrombocyte-stimulating factor*, a peptide hormone produced in the kidneys (and perhaps other sites) that accelerates platelet formation and stimulates the production of megakaryocytes; (2) *interleukin-6* (IL-6), a hormone that stimulates platelet formation; and (3) multi-CSF, which stimulates platelet production by promoting the formation and growth of megakaryocytes.

Checkpoint

19. **Define thrombocytopoiesis.**
20. **Explain the difference between platelets and thrombocytes.**
21. **List the three primary functions of platelets.**

See the blue Answers tab at the back of the book.

19-7 Hemostasis involves vascular spasm, platelet plug formation, and blood coagulation

The process of **hemostasis** (*haima*, blood + *stasis*, halt), the stopping of bleeding, halts the loss of blood through the walls of damaged vessels. At the same time, it establishes a framework for tissue repairs. Hemostasis consists of three phases: the *vascular phase*, the *platelet phase*, and the *coagulation phase*. However, the boundaries of these phases are somewhat arbitrary. In reality, hemostasis is a complex cascade in which many things happen at once, and all of them interact to some degree.

The Vascular Phase

Cutting the wall of a blood vessel triggers a contraction in the smooth muscle fibers of the vessel wall (**Figure 19–12**). This local contraction of the vessel is a **vascular spasm,** which decreases the diameter of the vessel at the site of injury. Such a constriction can slow or even stop the loss of blood through the wall of a small vessel. The vascular spasm lasts about 30 minutes, a period called the **vascular phase** of hemostasis.

During the vascular phase, changes occur in the endothelium of the vessel at the injury site:

- *The Endothelial Cells Contract and Expose the Underlying Basement Membrane to the Bloodstream.*
- *The Endothelial Cells Begin Releasing Chemical Factors and Local Hormones.* We will discuss several of these factors, including *ADP*, *tissue factor*, and *prostacyclin*, in later sections. Endothelial cells also release **endothelins,** peptide hormones that (1) stimulate smooth muscle contraction and promote vascular spasms and (2) stimulate the division of endothelial cells, smooth muscle cells, and fibroblasts to accelerate the repair process.
- *The Endothelial Plasma Membranes Become "Sticky."* A tear in the wall of a small artery or vein may be partially sealed off by the attachment of endothelial cells on either side of the break. In small capillaries, endothelial cells on opposite sides of the vessel may stick together and prevent blood flow along the damaged vessel. The stickiness is also important because it facilitates the attachment of platelets as the platelet phase gets under way.

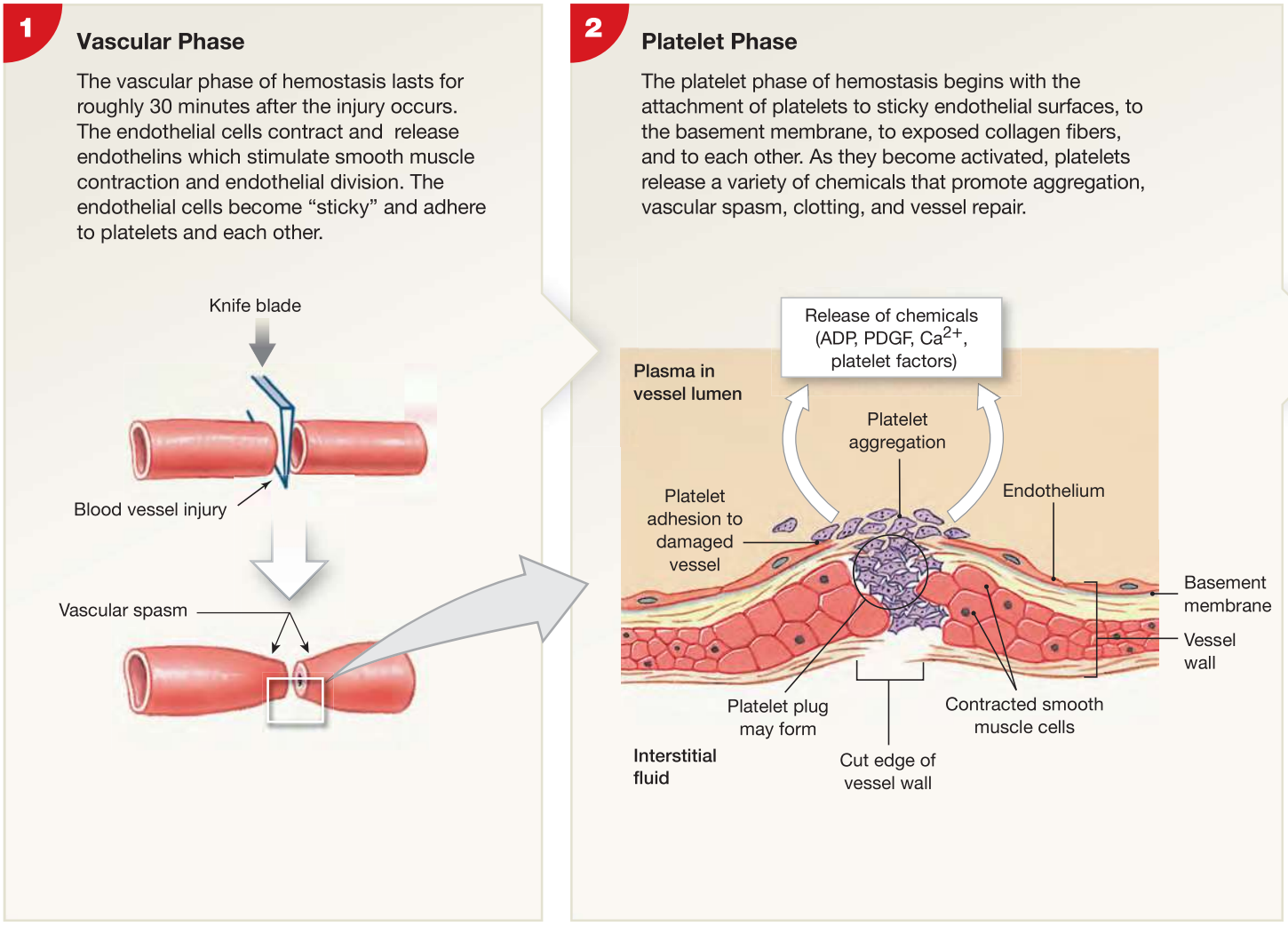
The Platelet Phase

The attachment of platelets to sticky endothelial surfaces, to the basement membrane, and to exposed collagen fibers marks the start of the **platelet phase** of hemostasis (**Figure 19–12**). The attachment of platelets to exposed surfaces is called **platelet adhesion.** As more and more platelets arrive, they begin sticking to one another as well. This process, called **platelet aggregation,** forms a **platelet plug** that may close the break in the vessel wall if the damage is not severe or the vessel is relatively small. Platelet aggregation begins within 15 seconds after an injury occurs.

As they arrive at the injury site, the platelets become activated. The first sign of activation is that they become more spherical and develop cytoplasmic processes that extend toward nearby platelets. At this time, the platelets begin releasing a wide variety of compounds, including (1) *adenosine diphosphate (ADP)*, which stimulates platelet aggregation and secretion; (2) *thromboxane* A_2 and *serotonin*, which stimulate vascular spasms; (3) *clotting factors*, proteins that play a role in blood clotting; (4) *platelet-derived growth factor* (*PDGF*), a peptide that promotes vessel repair; and (5) calcium ions, which are required for platelet aggregation and in several steps in the clotting process.

The platelet phase proceeds quickly, because ADP, thromboxane, and calcium ions released from each arriving platelet stimulate further aggregation. This positive feedback loop ultimately produces a platelet plug that will be reinforced as clotting occurs. However, platelet aggregation must be controlled and restricted to the injury site. Several key factors limit the growth of the platelet plug: (1) **prostacyclin,** a prostaglandin that inhibits platelet aggregation and is released by endothelial cells; (2) inhibitory compounds released by WBCs entering the area; (3) circulating plasma enzymes that break down ADP near the plug; (4) compounds that, when abundant, inhibit plug formation (for example, serotonin, which at high concentrations blocks the action of ADP); and (5) the development of a

Figure 19–12 The Vascular, Platelet, and Coagulation Phases of Hemostasis and Clot Retraction.



blood clot, which reinforces the platelet plug, but isolates it from the general circulation.

The Coagulation Phase

The vascular and platelet phases begin within a few seconds after the injury. The **coagulation** (cō-ag-ū-LĀ-shun) **phase** does not start until 30 seconds or more after the vessel has been damaged. **Figure 19–12** shows the formation and structure of a blood clot.

Clotting Factors

Normal blood clotting depends on the presence of **clotting factors,** or **procoagulants,** in the plasma. Important clotting factors include Ca^{2+} and 11 different proteins (**Table 19–4**).

Many of the proteins are **proenzymes,** which, when converted to active enzymes, direct essential reactions in the clotting response. The activation of one proenzyme commonly creates an enzyme that activates a second proenzyme, and so on in a chain reaction, or *cascade*. During the coagulation phase, enzymes and proenzymes interact.

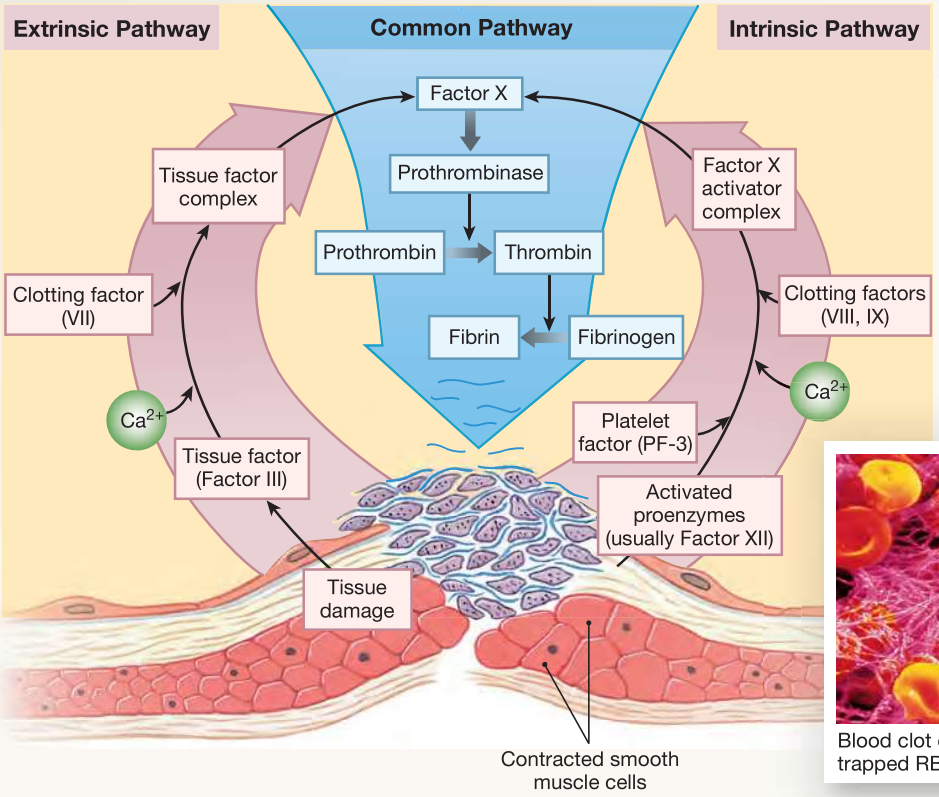
Figure 19–12 shows the cascades involved in the *extrinsic*, *intrinsic*, and *common pathways*. The extrinsic pathway begins outside the bloodstream, in the vessel wall; the intrinsic pathway begins inside the bloodstream, with the activation of a circulating proenzyme. These two pathways converge at the common pathway.

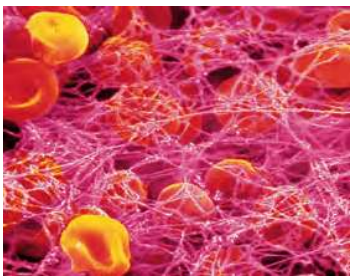
The Extrinsic Pathway

The **extrinsic pathway** begins with the release of **Factor III,** also known as **tissue factor (TF),** by damaged endothelial cells or peripheral tissues. The greater the damage, the more tissue factor is released and the faster clotting occurs. Tissue factor then combines with Ca^{2+} and another clotting factor (Factor VII) to form an enzyme complex capable of activating Factor X, the first step in the common pathway.

3 Coagulation Phase

Coagulation, or blood clotting, involves a complex sequence of steps leading to the conversion of circulating fibrinogen into the insoluble protein fibrin. As the fibrin network grows, blood cells and additional platelets are trapped in the fibrous tangle, forming a **blood clot** that seals off the damaged portion of the vessel.





Blood clot containing trapped RBCs SEM × 1200

4 Clot Retraction

Once the fibrin meshwork has formed, platelets and red blood cells stick to the fibrin strands. The platelets then contract, and the entire clot begins to undergo clot retraction, a process that continues over 30–60 minutes.

Table 19–4 Clotting Factors

Factor	Structure	Name	Source	Concentration in Plasma (μg/mL)	Pathway
I	Protein	Fibrinogen	Liver	2500–3500	Common
II	Protein	Prothrombin	Liver, requires vitamin K	100	Common
III	Lipoprotein	Tissue factor (TF)	Damaged tissue, activated platelets	0	Extrinsic
IV	Ion	Calcium ions	Bone, diet, platelets	100	Entire process
V	Protein	Proaccelerin	Liver, platelets	10	Extrinsic and intrinsic
VI	(No longer used)				
VII	Protein	Proconvertin	Liver, requires vitamin K	0.5	Extrinsic
VIII	Protein factor (AHF)	Antihemophilic	Platelets, endothelial cells	15	Intrinsic
IX	Protein factor	Plasma thromboplastin	Liver, requires vitamin K	3	Intrinsic
X	Protein	Stuart–Prower factor	Liver, requires vitamin K	10	Extrinsic and intrinsic
XI	Protein antecedent (PTA)	Plasma thromboplastin	Liver	<5	Intrinsic
XII	Protein	Hageman factor	Liver	<5	Intrinsic; also activates plasmin
XIII	Protein factor (FSF)	Fibrin-stabilizing	Liver, platelets	20	Stabilizes fibrin, slows fibrinolysis

The Intrinsic Pathway

The **intrinsic pathway** begins with the activation of proenzymes (usually Factor XII) exposed to collagen fibers at the injury site (or to a glass surface of a slide or collection tube). This pathway proceeds with the assistance of **PF-3,** a platelet factor released by aggregating platelets. Platelets also release a variety of other factors that accelerate the reactions of the intrinsic pathway. After a series of linked reactions, activated Factors VIII and IX combine to form an enzyme complex capable of activating Factor X.

The Common Pathway

The **common pathway** begins when enzymes from either the extrinsic or intrinsic pathway activate Factor X, forming the enzyme **prothrombinase.** Prothrombinase converts the proenzyme prothrombin into the enzyme **thrombin** (THROM-bin). Thrombin then completes the clotting process by converting fibrinogen, a soluble plasma protein, to insoluble strands of fibrin.

Interactions among the Pathways

When a blood vessel is damaged, both the extrinsic and the intrinsic pathways respond. The extrinsic pathway is shorter and faster than the intrinsic pathway, and it is usually the first to initiate clotting. In essence, the extrinsic pathway produces a small amount of thrombin very quickly. This quick patch is reinforced by the intrinsic pathway, which later produces more thrombin.

The time required to complete clot formation varies with the site and the nature of the injury. In tests of the clotting system, blood held in fine glass tubes normally clots in 8–18 minutes (the *coagulation time*), and a small puncture wound typically stops bleeding in 1–4 minutes (the *bleeding time*).

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Feedback Control of Blood Clotting

Thrombin generated in the common pathway stimulates blood clotting by (1) stimulating the formation of tissue factor and (2) stimulating the release of PF-3 by platelets. Thus, the activity of the common pathway stimulates both the intrinsic and extrinsic pathways. This positive feedback loop accelerates the clotting process, and speed can be very important in reducing blood loss after a severe injury.

Blood clotting is restricted by substances that either deactivate or remove clotting factors and other stimulatory agents from the blood. Examples include the following:

- Normal plasma contains several **anticoagulants**—enzymes that inhibit clotting. One, **antithrombin-III,** inhibits several clotting factors, including thrombin.
- **Heparin,** a compound released by basophils and mast cells, is a cofactor that accelerates the activation of antithrombin-III. Heparin is used clinically to impede or prevent clotting.
- **Aspirin** is an agent that inhibits the production of thromboxane A_2 and prostaglandins. This action prevents platelet aggregation and subsequent clot formation. It also prolongs bleeding time.
- **Thrombomodulin** is released by endothelial cells. This protein binds to thrombin and converts it to an enzyme that activates protein C. **Protein C** is a plasma protein that inactivates several clotting factors and stimulates the formation of *plasmin*, an enzyme that gradually breaks down fibrin strands.
- Prostacyclin released during the platelet phase inhibits platelet aggregation and opposes the stimulatory action of thrombin, ADP, and other factors.
- Other plasma proteins with anticoagulant properties include *alpha-2-macroglobulin*, which inhibits thrombin, and C_1 *inactivator*, which inhibits several clotting factors involved in the intrinsic pathway.

The clotting process involves a complex chain of events, and disorders that affect any individual clotting factor can disrupt the entire process. As a result, managing many clinical conditions involves controlling or manipulating the clotting response.

Calcium Ions, Vitamin K, and Blood Clotting

Calcium ions and **vitamin K** affect almost every aspect of the clotting process. All three pathways (intrinsic, extrinsic, and common) require Ca^{2+}, so any disorder that lowers plasma Ca^{2+} concentrations will impair blood clotting.

Adequate amounts of vitamin K must be present for the liver to synthesize four of the clotting factors, including prothrombin. Vitamin K is a fat-soluble vitamin, present in green vegetables, grain, and organ meats, that is absorbed with dietary lipids. Roughly half of the daily requirement is obtained from the diet, and the other half is manufactured by bacteria in the large intestine. A diet inadequate in fats or in vitamin K, or a disorder that affects fat digestion and absorption (such as problems with bile production), or prolonged use of antibiotics that kill normal intestinal bacteria may lead to a vitamin K deficiency. This condition will cause the eventual breakdown of the common pathway due to a lack of clotting factors and, ultimately, deactivation of the entire clotting system.

Clot Retraction

Clot retraction, or *syneresis* (si-NER-e-sis; "a drawing together"), (1) pulls the torn edges of the vessel closer together, reducing residual bleeding and stabilizing the injury site, and (2) reduces the size of the damaged area, making it easier for fibrocytes, smooth muscle cells, and endothelial cells to complete repairs (**Figure 19–12**).

Fibrinolysis

As the repairs proceed, the clot gradually dissolves. This process, called **fibrinolysis** (fī-bri-NOL-i-sis), begins with the activation of the proenzyme **plasminogen** by two enzymes: thrombin, produced by the common pathway, and **tissue plasminogen activator** (t-PA), released by damaged tissues at the site of injury. The activation of plasminogen produces the enzyme **plasmin** (PLAZ-min), which begins digesting the fibrin strands and eroding the clot.

To perform its vital functions, blood must be kept in motion. On average, an RBC completes two circuits around the cardiovascular system each minute. The circulation of blood begins in the third week of embryonic development and continues throughout life. If the blood supply is cut off, dependent tissues may die in a matter of minutes. In Chapter 20, we examine the structure and function of the heart—the pump that maintains this vital blood flow.

Checkpoint

22. **A sample of red bone marrow has unusually few megakaryocytes. What body process would you expect to be impaired as a result?**
23. **Vitamin K is fat soluble, and some dietary fat is required for its absorption. How could a diet of fruit juice and water have an effect on blood clotting?**
24. **Unless chemically treated, blood will coagulate in a test tube. This clotting process begins when Factor XII becomes activated. Which clotting pathway is involved in this process?**

See the blue Answers tab at the back of the book.

Related Clinical Terms

arterial stick: The taking of a blood sample from an artery rather than a vein. It is usually more painful due to arteries being deeper, having more nerves, and having thicker walls.
blood bank: Place where blood is collected, typed, separated into components, stored, and prepared for transfusion to recipients.
bone marrow biopsy: The removal of a small piece of bone marrow for either laboratory analysis, to diagnose and stage some forms of cancer, to diagnose other blood disorders, to find the source of unexplained fever, or to diagnose fibrosis of bone marrow or myeloma, a tumor composed of cells normally found in the bone marrow.
disseminated intravascular coagulation: A serious disorder in which the proteins that control blood clotting become abnormally active, causing small blood clots to form, which can prevent blood from reaching vital organs.
dyscrasia: An abnormal condition, especially of the blood.
ecchymosis: Skin discoloration caused by the escape of blood into tissues from ruptured blood vessels.
embolism: A condition in which a drifting blood clot (an embolus) becomes stuck in a blood vessel, blocking circulation to the area downstream.
hematology: The science concerned with the medical study of blood and blood-producing organs.
hemochromatosis: A rare metabolic disorder wherein the skin has a bronze coloration; accompanied by cirrhosis and severe diabetes mellitus; caused by the deposit of hemosiderin in tissues.
hemophilia: Inherited disorders characterized by the inadequate production of clotting factors.
hemopoietic growth factor: A group of proteins that cause blood cells to grow and mature.
hemosiderosis: An increase in tissue iron stores without any associated damage.
hypervolemic: Having an excessive blood volume.
hypovolemic: Having a low blood volume.
iron overload: Pathology in which iron accumulates in the tissues; characterized by bronzed skin, enlarged liver, diabetes mellitus, and abnormalities of the pancreas.
myeloproliferative disorder: A group of slow-growing blood cancers, including chronic myelogenous leukemia, characterized by large numbers of abnormal RBCs, WBCs, or platelets growing and spreading in the bone marrow and the peripheral blood.
normovolemic: Referring to a normal blood volume.
phlebotomist: Medical technician who extracts blood via venipuncture for treatment or for laboratory analysis.
plaque: An abnormal accumulation of large quantities of lipids within a blood vessel wall.
plasmapheresis: A procedure consisting of the removal of blood from a person, separating the blood cells from plasma, and returning these blood cells to the person's circulation, diluted with fresh plasma or a substitute. Used to treat autoimmune disorders.
Schilling test: The test to determine whether the body absorbs vitamin B_{12} normally.
septicemia: Systemic toxic illness due to bacterial invasion of the bloodstream from a local infection. Signs and symptoms include chills, fever, and exhaustion. The disorder is treated with massive doses of antibiotics. Also known as blood poisoning.
thrombolytic: An agent that causes the breakup of a thrombus (clot).
thrombus: A blood clot attached to the luminal (inner) surface of a blood vessel.

Chapter Review

Study Outline

An Introduction to Blood and the Cardiovascular System p. 639

1. The **cardiovascular system** enables the rapid transport of nutrients, respiratory gases, waste products, and cells within the body.

19-1 Blood has several important functions and unique physical characteristics p. 639

2. **Blood** is a specialized fluid connective tissue. Its functions include (1) transporting dissolved gases, nutrients, hormones, and metabolic wastes; (2) regulating the pH and ion composition of interstitial fluids; (3) restricting fluid losses at injury sites; (4) defending the body against toxins and pathogens; and (5) regulating body temperature by absorbing and redistributing heat.
3. Blood contains **plasma** and **formed elements—red blood cells (RBCs), white blood cells (WBCs),** and **platelets.** The plasma and formed elements make up **whole blood,** which can be **fractionated** for analytical or clinical purposes. *(Spotlight Figure 19–1)*
4. **Hemopoiesis** is the process of blood cell formation. Circulating stem cells divide to form all types of blood cells.
5. Whole blood from any region of the body has roughly the same temperature, viscosity, and pH.

19-2 Plasma, the fluid portion of blood, contains significant quantities of plasma proteins p. 642

6. Plasma accounts for 46–63 percent of the volume of blood; roughly 92 percent of plasma is water. *(Spotlight Figure 19–1)*
7. Plasma differs from interstitial fluid in terms of its oxygen and carbon dioxide levels and the concentrations and types of dissolved proteins.
8. The three major types of plasma proteins are *albumins, globulins,* and *fibrinogen*.
9. **Albumins** make up about 60 percent of plasma proteins. **Globulins** constitute roughly 35 percent of plasma proteins; they include **antibodies (immunoglobulins),** which attack foreign proteins and pathogens, and **transport globulins,** which bind ions, hormones, and other compounds. **Fibrinogen** molecules are converted to **fibrin** in the clotting process. **Serum** is plasma without fibrinogen.
10. The liver synthesizes and releases more than 90 percent of the plasma proteins.

19-3 Red blood cells, formed by erythropoiesis, contain hemoglobin that can be recycled p. 643

11. Red blood cells account for slightly less than half of the blood volume and 99.9 percent of the formed elements. The **hematocrit** value indicates the percentage of formed elements within whole blood. It is commonly reported as the *volume of packed red cells (VPRC)* or the *packed cell volume (PCV)*. *(Spotlight Figure 19–1; Table 19–1)*
12. Each RBC is a biconcave disc, providing a large surface-to-volume ratio. This shape allows RBCs to stack, bend, and flex. *(Figure 19–2)*
13. Red blood cells lack most organelles, including mitochondria and nuclei, retaining only the cytoskeleton. They typically degenerate after about 120 days in the bloodstream.
14. Molecules of **hemoglobin (Hb)** account for more than 95 percent of the proteins in RBCs. Hemoglobin is a globular protein formed from two pairs of polypeptide subunits. Each subunit contains a single molecule of **heme,** which also has an iron atom that can reversibly bind an oxygen molecule. Phagocytes recycle damaged or dead RBCs. *(Figures 19–3, 19–5)*
15. Damaged RBCs are continuously replaced at a rate of approximately 3 million new RBCs entering the bloodstream per second. They are replaced before they **hemolyze.**
16. The components of hemoglobin are individually recycled. The heme is stripped of its iron and converted to **biliverdin,** which is converted to **bilirubin.** If bile ducts are blocked, bilirubin builds up in skin and eyes, resulting in **jaundice.** *(Figure 19–5)*
17. Iron is recycled by being stored in phagocytic cells or transported through the bloodstream, bound to **transferrin**.
18. **Erythropoiesis,** the formation of red blood cells, occurs only in *red bone marrow* **(myeloid tissue).** The process speeds up under stimulation by erythropoietin (EPO or **erythropoiesis-stimulating hormone).** Stages in RBC development include **erythroblasts** and **reticulocytes.** *(Figure 19–6)*

19-4 The ABO blood types and Rh system are based on antigen–antibody responses p. 650

19. **Blood type** is determined by the presence or absence of specific **surface antigens** (*agglutinogens*) in the RBC plasma membranes: antigens **A, B,** and **Rh (D).** Antibodies (*agglutinins*) in the plasma will react with RBCs that have different surface antigens. When an antibody meets its specific surface antigen, a **cross-reaction** results. *(Figures 19–7 to Spotlight Figure 19–9; Table 19–2)*

19-5 The various types of white blood cells contribute to the body's defenses p. 652

20. White blood cells **(leukocytes)** have nuclei and other organelles. They defend the body against pathogens and remove toxins, wastes, and abnormal or damaged cells.
21. White blood cells are capable of *margination*, amoeboid movement, and **positive chemotaxis.** Some WBCs are also capable of *phagocytosis*.
22. *Granular leukocytes* (*granulocytes*) are subdivided into **neutrophils, eosinophils,** and **basophils.** Fifty to 70 percent of circulating WBCs are neutrophils, which are highly mobile phagocytes. The much less common eosinophils are phagocytes attracted to foreign compounds that have reacted with circulating antibodies. The fairly rare basophils migrate to damaged tissues and release *histamine* and *heparin*, aiding the inflammatory response. *(Figure 19–10)*
23. *Agranular leukocytes* (*agranulocytes*) include **monocytes** and **lymphocytes.** Monocytes that migrate into peripheral tissues become tissue macrophages. Lymphocytes, the primary cells of the lymphatic system, include **T cells** (which enter peripheral tissues and attack foreign cells directly, or affect the activities of other lymphocytes), **B cells** (which produce antibodies), and **natural killer (NK) cells** (which destroy abnormal cells). *(Figure 19–10; Table 19–3)*

24. A **differential count** of the WBC population can indicate a variety of disorders. **Leukemia** is indicated by extreme **leukocytosis**—that is, excessive numbers of WBCs. *(Table 19–3)*
25. Granulocytes and monocytes are produced by myeloid stem cells in the red bone marrow that divide to create **progenitor cells.** Lymphoid stem cells also originate in the red bone marrow, but many migrate to peripheral **lymphatic tissues.** *(Figure 19–11)*
26. Factors that regulate lymphocyte maturation are not completely understood. Several **colony-stimulating factors** (CSFs) are involved in regulating other WBC populations and in coordinating RBC and WBC production. *(Figure 19–11)*

19-6 Platelets, disc-shaped structures formed from megakaryocytes, function in the clotting process p. 660

27. Platelets are spindle-shaped cell fragments. They circulate for 9–12 days before being removed by phagocytes. *(Figure 19–10)*
28. The functions of platelets include (1) transporting and releasing chemicals important to the clotting process, (2) forming a temporary patch in the walls of damaged blood vessels, and (3) reducing the size of a break in the vessel wall.
29. During **thrombocytopoiesis, megakaryocytes** in the red bone marrow release packets of cytoplasm (platelets) into the circulating blood. The rate of platelet formation is stimulated by thrombopoietin or thrombocyte-stimulating factor, interleukin-6, and multi-CSF.

19-7 Hemostasis involves vascular spasm, platelet plug formation, and blood coagulation p. 661

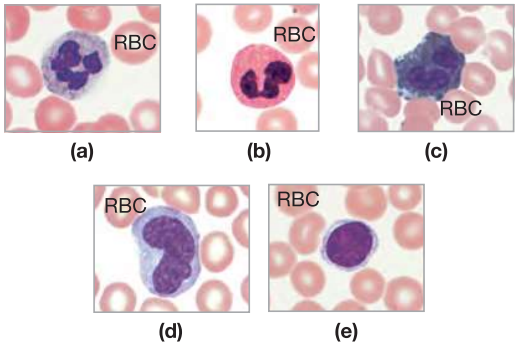
30. **Hemostasis** halts the loss of blood through the walls of damaged vessels. It consists of three phases: the *vascular phase*, the *platelet phase*, and the *coagulation phase*.
31. The **vascular phase** is a period of local blood vessel constriction, or **vascular spasm,** at the injury site. *(Figure 19–12)*
32. The **platelet phase** follows as platelets are activated, aggregate at the site, and adhere to the damaged surfaces. *(Figure 19–12)*
33. The **coagulation phase** occurs as factors released by platelets and endothelial cells interact with **clotting factors** (through either the **extrinsic pathway,** the **intrinsic pathway,** or the **common pathway**) to form a **blood clot.** In this reaction sequence, suspended fibrinogen is converted to large, insoluble fibers of fibrin. *(Figure 19–12; Table 19–4)*
34. During **clot retraction,** platelets contract and pull the torn edges of the damaged vessel closer together. (*Figure 19–12*)
35. During **fibrinolysis,** the clot gradually dissolves through the action of **plasmin,** the activated form of circulating **plasminogen.**

Review Questions

See the blue Answers tab at the back of the book.

LEVEL 1 Reviewing Facts and Terms

1. Identify the five types of white blood cells in the following photographs.



   (a) _____
   (b) _____
   (c) _____
   (d) _____
   (e) _____
2. The formed elements of the blood include
   (a) plasma, fibrin, and serum.
   (b) albumins, globulins, and fibrinogen.
   (c) WBCs, RBCs, and platelets.
   (d) a, b, and c.
3. Blood temperature is approximately _____, and blood pH averages _____.
   (a) 36°C, 7.0
   (b) 39°C, 7.8
   (c) 38°C, 7.4
   (d) 37°C, 7.0
4. Plasma contributes approximately _____ percent of the volume of whole blood, and water accounts for _____ percent of the plasma volume.
   (a) 55, 92
   (b) 25, 55
   (c) 92, 55
   (d) 35, 72
5. Serum is
   (a) the same as blood plasma.
   (b) plasma minus the formed elements.
   (c) plasma minus the proteins.
   (d) plasma minus fibrinogen.
   (e) plasma minus the electrolytes.
6. A hemoglobin molecule is composed of
   (a) two protein chains.
   (b) three protein chains.
   (c) four protein chains and nothing else.
   (d) four protein chains and four heme groups.
   (e) four heme groups but no protein.

7. The following is a list of the steps involved in the process of hemostasis.
   (1) coagulation
   (2) fibrinolysis
   (3) vascular spasm
   (4) retraction
   (5) platelet phase

   The correct sequence of these steps is
   (a) 5, 1, 4, 2, 3.
   (b) 3, 5, 1, 4, 2.
   (c) 2, 3, 5, 1, 4.
   (d) 3, 5, 4, 1, 2.
   (e) 4, 3, 5, 2, 1.
8. Stem cells responsible for lymphopoiesis are located in
   (a) the thymus and spleen.
   (b) the lymph nodes.
   (c) the red bone marrow.
   (d) all of these structures.
9. _____ and _____ affect almost every aspect of the clotting process.
   (a) Calcium and vitamin K
   (b) Calcium and vitamin B_{12}
   (c) Sodium and vitamin K
   (d) Sodium and vitamin B_{12}
10. What five major functions are performed by blood?
11. Name the three major types of plasma proteins and identify their functions.
12. Which type of antibodies does plasma contain for each of the following blood types?
   (a) Type A
   (b) Type B
   (c) Type AB
   (d) Type O
13. What four characteristics of WBCs are important to their response to tissue invasion or injury?
14. Which kinds of WBCs contribute to the body's nonspecific defenses?
15. Name the three types of lymphocytes and identify their functions.
16. What is the difference between prothrombin and thrombin?
17. What four conditions cause the release of erythropoietin?
18. What contribution from the intrinsic and the extrinsic pathways is necessary for the common pathway to begin?

LEVEL 2 Reviewing Concepts

19. Dehydration would
   (a) cause an increase in the hematocrit.
   (b) cause a decrease in the hematocrit.
   (c) have no effect on the hematocrit.
   (d) cause an increase in plasma volume.
20. Erythropoietin directly stimulates RBC formation by
   (a) increasing rates of mitotic divisions in erythroblasts.
   (b) speeding up the maturation of red blood cells.
   (c) accelerating the rate of hemoglobin synthesis.
   (d) a, b, and c.
21. The waste product bilirubin is formed from
   (a) transferrin.
   (b) globin.
   (c) heme.
   (d) hemosiderin.
   (e) ferritin.
22. A difference between the A, B, and O blood types and the Rh factor is
   (a) Rh agglutinogens are not found on the surface of red blood cells.
   (b) Rh agglutinogens do not produce a cross-reaction.
   (c) individuals who are Rh^- do not carry agglutinins to Rh factor unless they have been previously sensitized.
   (d) Rh agglutinogens are found free in the plasma.
   (e) Rh agglutinogens are found bound to plasma proteins.
23. How do red blood cells differ from white blood cells in both form and function?
24. How do elements of blood defend against toxins and pathogens in the body?
25. What is the role of blood in the stabilization and maintenance of body temperature?
26. Relate the structure of hemoglobin to its function.
27. Why is aspirin sometimes prescribed for the prevention of vascular problems?

LEVEL 3 Critical Thinking and Clinical Applications

28. A test for prothrombin time is used to identify deficiencies in the extrinsic clotting pathway; prothrombin time is prolonged if any of the factors are deficient. A test for activated partial thromboplastin time is used in a similar fashion to detect deficiencies in the intrinsic clotting pathway. Which factor would be deficient if a person had a prolonged prothrombin time but a normal partial thromboplastin time?
29. In the disease mononucleosis ("mono"), the spleen enlarges because of increased numbers of phagocytes and other cells. Common signs and symptoms of this disease include pale complexion, a tired feeling, and a lack of energy sometimes to the point of not being able to get out of bed. What might cause these signs and symptoms?
30. Almost half of our vitamin K is synthesized by bacteria that inhabit the large intestine. Based on this information, how could taking a broad-spectrum antibiotic for a long time cause frequent nosebleeds?
31. After Randy was diagnosed with stomach cancer, nearly all of his stomach had to be removed. Postoperative treatment included regular injections of vitamin B_{12}. Why was this vitamin prescribed, and why were injections specified?