17

Blood

Blood is the river of life that surges within us, transporting nearly everything that must be carried from one place to another. Long before modern medicine, blood was viewed as magical—an elixir that held the mystical force of life—because when it drained from the body, life departed as well. Today, blood still has enormous importance in the practice of medicine. Clinicians examine it more often than any other tissue when trying to determine the cause of disease in their patients.

In this chapter, we describe the composition and functions of this life-sustaining fluid that serves as a transport "vehicle" for the organs of the cardiovascular system (*cardio* = heart, *vasc* = blood vessels). To get started, we need a brief overview of blood circulation, which is initiated by the pumping action of the heart. Blood exits the *heart* via *arteries*, which branch repeatedly until they become tiny *capillaries*. By diffusing across the capillary walls, oxygen and nutrients leave the blood and enter the body tissues, and carbon dioxide and wastes move from the tissues to the bloodstream. As oxygen-deficient blood leaves the capillary beds, it flows into *veins*, which return it to the heart. The returning

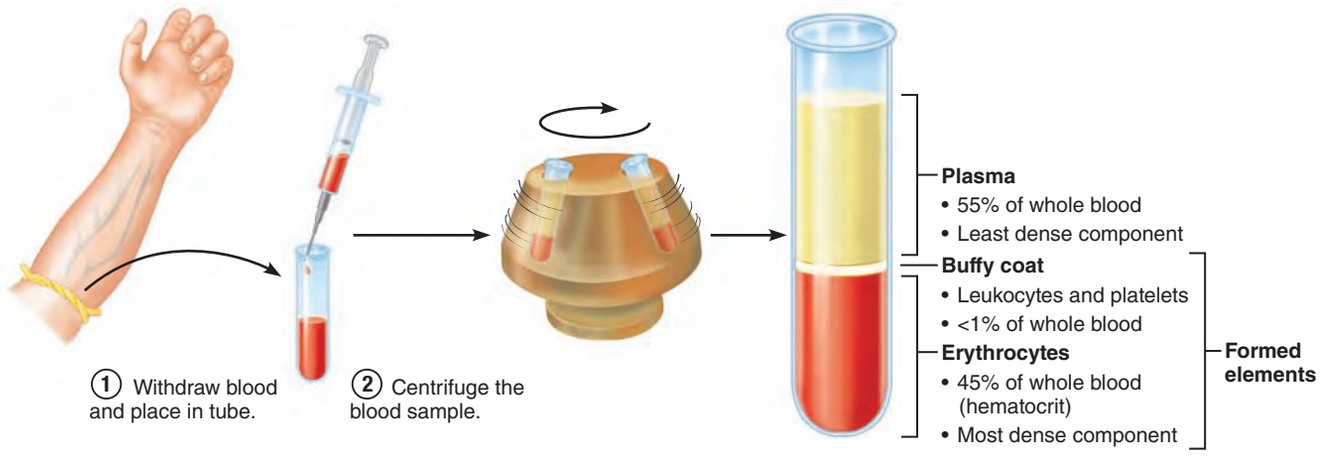


Figure 17.1 **The major components of whole blood.**

blood then flows from the heart to the lungs, where it picks up oxygen and then returns to the heart to be pumped throughout the body once again. Now let us look more closely at the nature of blood.

Overview: Blood Composition and Functions

- ✓ Describe the composition and physical characteristics of whole blood. Explain why it is classified as a connective tissue.
- ✓ List eight functions of blood.

Components

Blood is the only fluid tissue in the body. It appears to be a thick, homogeneous liquid, but the microscope reveals that it has both cellular and liquid components. Blood is a specialized connective tissue in which living blood cells, called the *formed elements*, are suspended in a nonliving fluid matrix called *plasma* (plaz′mah). Blood lacks the collagen and elastic fibers typical of other connective tissues, but dissolved fibrous proteins become visible as fibrin strands during blood clotting.

If we spin a sample of blood in a centrifuge, centrifugal force packs down the heavier formed elements and the less dense plasma remains at the top **(Figure 17.1)**. Most of the reddish mass at the bottom of the tube is *erythrocytes* (ĕ-rith′ro-sīts; *erythro* = red), the red blood cells that transport oxygen. A thin, whitish layer called the **buffy coat** is present at the erythrocyte-plasma junction. This layer contains *leukocytes* (*leuko* = white), the white blood cells that act in various ways to protect the body, and *platelets*, cell fragments that help stop bleeding.

Erythrocytes normally constitute about 45% of the total volume of a blood sample, a percentage known as the **hematocrit** (he-mat′o-krit; "blood fraction"). Normal hematocrit values vary. In healthy males the norm is 47% ± 5%; in females it is 42% ± 5%. Leukocytes and platelets contribute less than 1% of blood volume. Plasma makes up most of the remaining 55% of whole blood.

Physical Characteristics and Volume

Blood is a sticky, opaque fluid with a characteristic metallic taste. As children, we discover its saltiness the first time we stick a cut finger into our mouth. Depending on the amount of oxygen it is carrying, the color of blood varies from scarlet (oxygen rich) to dark red (oxygen poor). Blood is more dense than water and about five times more viscous, largely because of its formed elements. It is slightly alkaline, with a pH between 7.35 and 7.45.

Blood accounts for approximately 8% of body weight. Its average volume in healthy adult males is 5–6 L (about 1.5 gallons), somewhat greater than in healthy adult females (4–5 L).

Functions

Blood performs a number of functions, all concerned in one way or another with distributing substances, regulating blood levels of particular substances, or protecting the body.

Distribution

Distribution functions of blood include

- Delivering oxygen from the lungs and nutrients from the digestive tract to all body cells.
- Transporting metabolic waste products from cells to elimination sites (to the lungs to eliminate carbon dioxide, and to the kidneys to dispose of nitrogenous wastes in urine).
- Transporting hormones from the endocrine organs to their target organs.

Regulation

Regulatory functions of blood include

- Maintaining appropriate body temperature by absorbing and distributing heat throughout the body and to the skin surface to encourage heat loss.

- Maintaining normal pH in body tissues. Many blood proteins and other bloodborne solutes act as buffers to prevent excessive or abrupt changes in blood pH that could jeopardize normal cell activities. Additionally, blood acts as the reservoir for the body's "alkaline reserve" of bicarbonate ions.
- Maintaining adequate fluid volume in the circulatory system. Blood proteins prevent excessive fluid loss from the bloodstream into the tissue spaces. As a result, the fluid volume in the blood vessels remains ample to support efficient blood circulation to all parts of the body.

Protection

Protective functions of blood include

- Preventing blood loss. When a blood vessel is damaged, platelets and plasma proteins initiate clot formation, halting blood loss.
- Preventing infection. Drifting along in blood are antibodies, complement proteins, and white blood cells, all of which help defend the body against foreign invaders such as bacteria and viruses.

Blood Plasma

✓ Discuss the composition and functions of plasma.

Blood **plasma** is a straw-colored, sticky fluid (Figure 17.1). Although it is mostly water (about 90%), plasma contains over 100 different dissolved solutes, including nutrients, gases, hormones, wastes and products of cell activity, proteins, and inorganic ions (electrolytes). Electrolytes (Na^+, Cl^-, etc.) vastly outnumber the other solutes. Table 17.1 summarizes the major plasma components.

Although outnumbered by the lighter electrolytes, the heavier plasma proteins are the most abundant plasma solutes by weight, accounting for about 8% of plasma weight. Except for hormones and gamma globulins, most plasma proteins are produced by the liver. Plasma proteins serve a variety of functions, but they are *not* taken up by cells to be used as fuels or metabolic nutrients as are most other organic solutes, such as glucose, fatty acids, and amino acids.

Albumin (al-bu′min) accounts for some 60% of plasma protein. It acts as a carrier to shuttle certain molecules through the circulation, is an important blood buffer, and is the major blood protein contributing to the plasma osmotic pressure (the pressure that helps to keep water in the bloodstream).

The composition of plasma varies continuously as cells remove or add substances to the blood. However, assuming a healthy diet, plasma composition is kept relatively constant by various homeostatic mechanisms. For example, when blood protein levels drop undesirably, the liver makes more proteins. When the blood starts to become too acidic (acidosis), both the lungs and the kidneys are called into action to restore plasma's normal, slightly alkaline pH. Body organs make dozens of adjustments, day in and day out, to maintain the many plasma solutes at life-sustaining levels.

Table 17.1 Composition of Plasma

CONSTITUENT	DESCRIPTION AND IMPORTANCE
Water	90% of plasma volume; dissolving and suspending medium for solutes of blood; absorbs heat
Solutes	
Electrolytes	Most abundant solutes by number; cations include sodium, potassium, calcium, magnesium; anions include chloride, phosphate, sulfate, and bicarbonate; help to maintain plasma osmotic pressure and normal blood pH
Plasma proteins	8% (by weight) of plasma; all contribute to osmotic pressure and maintain water balance in blood and tissues; all have other functions (transport, enzymatic, etc.) as well
▪ Albumin	60% of plasma proteins; produced by liver; main contributor to osmotic pressure
▪ Globulins	36% of plasma proteins
alpha, beta	Produced by liver; most are transport proteins that bind to lipids, metal ions, and fat-soluble vitamins
gamma	Antibodies released by plasma cells during immune response
▪ Fibrinogen	4% of plasma proteins; produced by liver; forms fibrin threads of blood clot
Nonprotein nitrogenous substances	By-products of cellular metabolism, such as urea, uric acid, creatinine, and ammonium salts
Nutrients (organic)	Materials absorbed from digestive tract and transported for use throughout body; include glucose and other simple carbohydrates, amino acids (protein digestion products), fatty acids, glycerol and triglycerides (fat digestion products), cholesterol, and vitamins
Respiratory gases	Oxygen and carbon dioxide; oxygen mostly bound to hemoglobin inside RBCs; carbon dioxide transported dissolved as bicarbonate ion or CO_2, or bound to hemoglobin in RBCs
Hormones	Steroid and thyroid hormones carried by plasma proteins

☑ Check Your Understanding

1. What is the hematocrit? What is its normal value?
2. List two protective functions of blood.
3. Are plasma proteins used as fuel for body cells? Explain your answer.

For answers, see Appendix H.

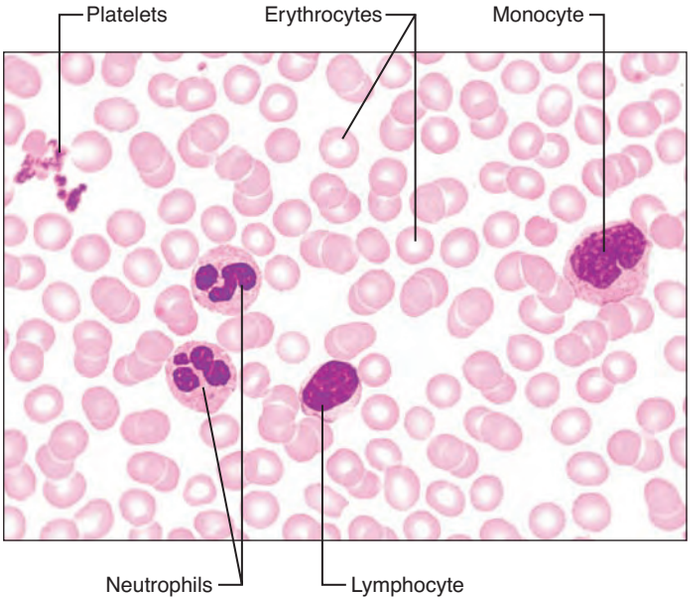


Figure 17.2 Photomicrograph of a human blood smear stained with Wright's stain. (640×)

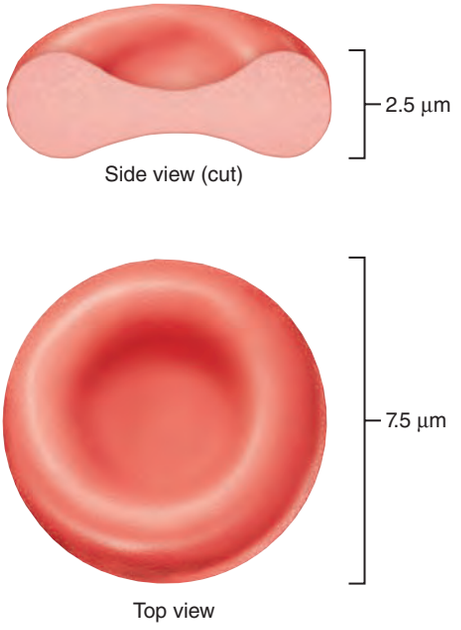


Figure 17.3 Structure of erythrocytes (red blood cells). Notice the distinctive biconcave shape.

Formed Elements

The **formed elements** of blood—*erythrocytes, leukocytes*, and *platelets*—have some unusual features.

- Two of the three are not even true cells: Erythrocytes have no nuclei or organelles, and platelets are cell fragments. Only leukocytes are complete cells.
- Most of the formed elements survive in the bloodstream for only a few days.
- Most blood cells do not divide. Instead, stem cells divide continuously in red bone marrow to replace them.

If you examine a stained smear of human blood under the light microscope, you will see disc-shaped red blood cells, a variety of gaudily stained spherical white blood cells, and some scattered platelets that look like debris **(Figure 17.2)**. Erythrocytes vastly outnumber the other types of formed elements. Table 17.2 on p. 644 summarizes the important characteristics of the formed elements.

Erythrocytes (Red Blood Cells)

- ✓ Describe the structure, function, and production of erythrocytes.
- ✓ Describe the chemical composition of hemoglobin.
- ✓ Give examples of disorders caused by abnormalities of erythrocytes. Explain what goes wrong in each disorder.

Structural Characteristics

Erythrocytes or **red blood cells (RBCs)** are small cells, about 7.5 µm in diameter **(Figure 17.3)**. Shaped like biconcave discs—flattened discs with depressed centers—they appear lighter in color at their thin centers than at their edges. Consequently, erythrocytes look like miniature doughnuts when viewed with a microscope.

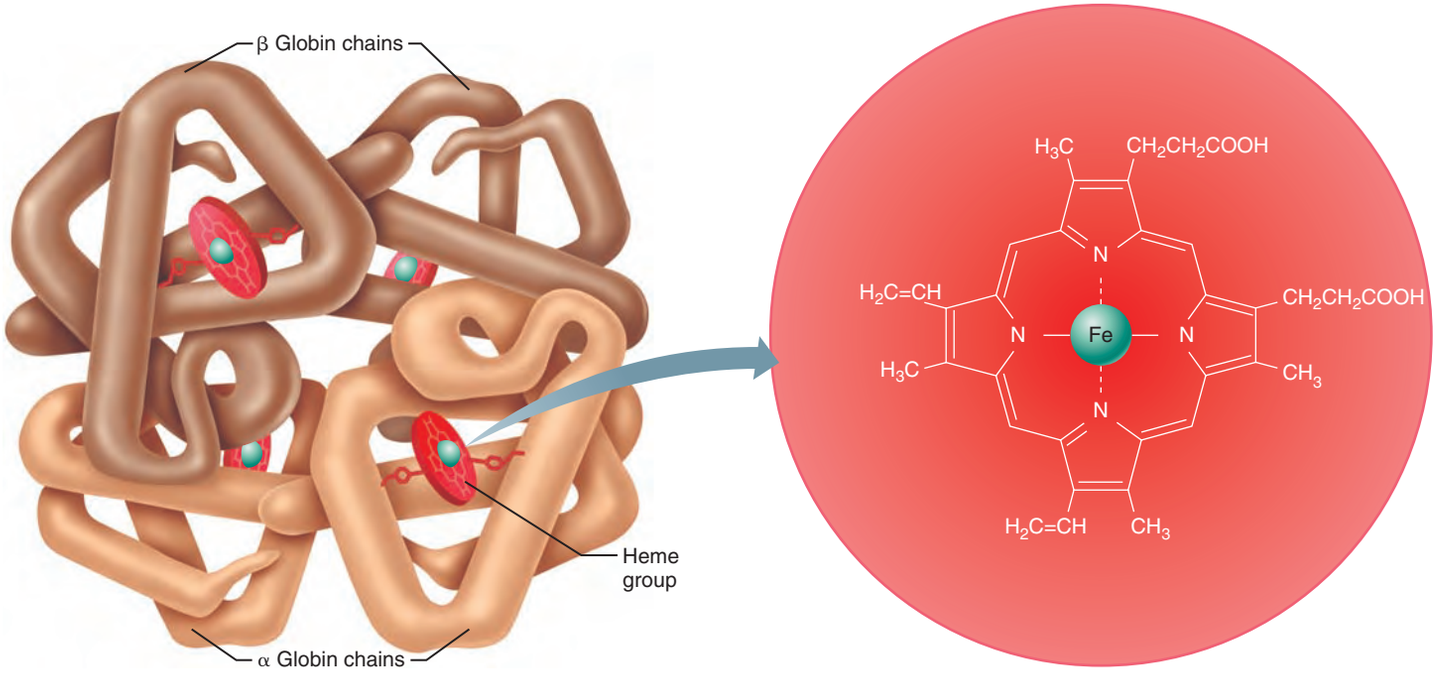
Mature erythrocytes are bound by a plasma membrane, but lack a nucleus (are *anucleate*) and have essentially no organelles. In fact, they are little more than "bags" of *hemoglobin* (*Hb*), the RBC protein that functions in gas transport. Other proteins are present, such as antioxidant enzymes that rid the body of harmful oxygen radicals, but most function as structural proteins, allowing the RBC to deform yet spring back into shape.

For example, a network of proteins, especially one called *spectrin*, attached to the cytoplasmic face of RBC plasma membranes maintains the biconcave shape of an erythrocyte. The spectrin net is deformable, allowing erythrocytes to change shape as necessary—to twist, turn, and become cup shaped as they are carried passively through capillaries with diameters smaller than themselves—and then to resume their biconcave shape.

The erythrocyte is a superb example of complementarity of structure and function. It picks up oxygen in the capillaries of the lungs and releases it to tissue cells across other capillaries throughout the body. It also transports some 20% of the carbon dioxide released by tissue cells back to the lungs. Three structural characteristics contribute to erythrocyte gas transport functions:

- Its small size and biconcave shape provide a huge surface area relative to volume (about 30% more surface area than comparable spherical cells). The biconcave disc shape is ideally suited for gas exchange because no point within the cytoplasm is far from the surface.
- Discounting water content, an erythrocyte is over 97% hemoglobin, the molecule that binds to and transports respiratory gases.

17



(a) Hemoglobin consists of globin (two alpha and two beta polypeptide chains) and four heme groups.

(b) Iron-containing heme pigment.

Figure 17.4 Structure of hemoglobin. Hemoglobin's structure makes it a highly efficient oxygen carrier.

- Because erythrocytes lack mitochondria and generate ATP by anaerobic mechanisms, they do not consume any of the oxygen they carry, making them very efficient oxygen transporters indeed.

Erythrocytes are the major factor contributing to blood viscosity. Women typically have a lower red blood cell count than men [4.2–5.4 million cells per microliter (1 μl = 1 mm^3) of blood versus 4.7–6.1 million cells/μl respectively]. When the number of red blood cells increases beyond the normal range, blood becomes more viscous and flows more slowly. Similarly, as the number of red blood cells drops below the lower end of the range, the blood thins and flows more rapidly.

Functions of Erythrocytes

Erythrocytes are completely dedicated to their job of transporting respiratory gases (oxygen and carbon dioxide). **Hemoglobin**, the protein that makes red blood cells red, binds easily and reversibly with oxygen, and most oxygen carried in blood is bound to hemoglobin. Normal values for hemoglobin are 13–18 grams per 100 milliliters of blood (g/100 ml) in adult males, and 12–16 g/100 ml in adult females.

Hemoglobin is made up of the red **heme** pigment bound to the protein **globin**. Globin consists of four polypeptide chains—two alpha (α) and two beta (β)—each binding a ringlike heme group **(Figure 17.4a)**. Each heme group bears an atom of iron set like a jewel in its center (Figure 17.4b). A hemoglobin molecule can transport four molecules of oxygen because each iron atom can combine reversibly with one molecule of oxygen. A single red blood cell contains about 250 million hemoglobin molecules, so each of these tiny cells can scoop up about 1 billion molecules of oxygen!

The fact that hemoglobin is contained in erythrocytes, rather than existing free in plasma, prevents it (1) from breaking into fragments that would leak out of the bloodstream (through porous capillary walls) and (2) from making blood more viscous and raising osmotic pressure.

Oxygen loading occurs in the lungs, and the direction of transport is from lungs to tissue cells. As oxygen-deficient blood moves through the lungs, oxygen diffuses from the air sacs of the lungs into the blood and then into the erythrocytes, where it binds to hemoglobin. When oxygen binds to iron, the hemoglobin, now called **oxyhemoglobin**, assumes a new three-dimensional shape and becomes ruby red.

In body tissues, the process is reversed. Oxygen detaches from iron, hemoglobin resumes its former shape, and the resulting **deoxyhemoglobin**, or *reduced hemoglobin*, becomes dark red. The released oxygen diffuses from the blood into the tissue fluid and then into tissue cells.

About 20% of the carbon dioxide transported in the blood combines with hemoglobin, but it binds to globin's amino acids rather than to the heme group. This formation of **carbaminohemoglobin** (kar-bam″ĭ-no-he″muh″glo′bin) occurs more readily when hemoglobin is in the reduced state (dissociated from oxygen). Carbon dioxide loading occurs in the tissues, and the direction of transport is from tissues to lungs, where carbon dioxide is eliminated from the body. We describe the loading and unloading of these respiratory gases in Chapter 22.

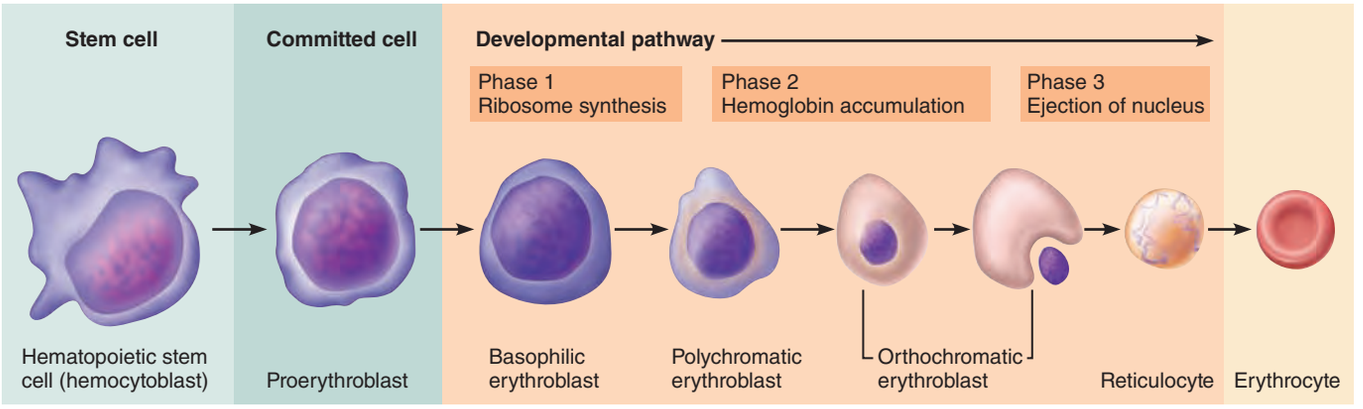


Figure 17.5 Erythropoiesis: formation of red blood cells. Reticulocytes are released into the bloodstream. The myeloid stem cell, the phase intermediate between the hematopoietic stem cell and the proerythroblast, is not illustrated.

Production of Erythrocytes

Blood cell formation is referred to as **hematopoiesis** (hem″ah-to-poi-e′sis; *hemato* = blood; *poiesis* = to make). Hematopoiesis occurs in the **red bone marrow**, which is composed largely of a soft network of reticular connective tissue bordering on wide blood capillaries called *blood sinusoids*. Within this network are immature blood cells, macrophages, fat cells, and *reticular cells* (which secrete the connective tissue fibers). In adults, red marrow is found chiefly in the bones of the axial skeleton and girdles, and in the proximal epiphyses of the humerus and femur.

The production of each type of blood cell varies in response to changing body needs and regulatory factors. As blood cells mature, they migrate through the thin walls of the sinusoids to enter the bloodstream. On average, the marrow turns out an ounce of new blood containing 100 billion new cells every day.

The various formed elements have different functions, but there are similarities in their life histories. All arise from the **hematopoietic stem cell**, sometimes called a *hemocytoblast* (*cyte* = cell, *blast* = bud). These undifferentiated precursor cells reside in the red bone marrow. However, the maturation pathways of the various formed elements differ, and once a cell is *committed* to a specific blood cell pathway, it cannot change. This commitment is signaled by the appearance of membrane surface receptors that respond to specific hormones or growth factors, which in turn "push" the cell toward further specialization.

Stages of Erythropoiesis Erythrocyte production, or **erythropoiesis** (ĕ-rith″ro-poi-e′sis), begins when a hematopoietic stem cell descendant called a **myeloid stem cell** transforms into a **proerythroblast (Figure 17.5)**. Proerythroblasts, in turn, give rise to **basophilic erythroblasts** that produce huge numbers of ribosomes. During these first two phases, the cells divide many times. Hemoglobin is synthesized and iron accumulates as the basophilic erythroblast transforms into a **polychromatic erythroblast** and then an **orthochromatic erythroblast**. The "color" of the cell cytoplasm changes as the blue-staining ribosomes become masked by the pink color of hemoglobin. When an orthochromatic erythroblast has accumulated almost all of its hemoglobin, it ejects most of its organelles. Additionally, its nucleus degenerates and is pinched off, allowing the cell to collapse inward and eventually assume the biconcave shape. The result is the **reticulocyte** (essentially a young erythrocyte), so named because it still contains a scant *reticulum* (network) of clumped ribosomes.

The entire process from hematopoietic stem cell to reticulocyte takes about 15 days. The reticulocytes, filled almost to bursting with hemoglobin, enter the bloodstream to begin their task of oxygen transport. Usually they become fully mature erythrocytes within two days of release as their ribosomes are degraded by intracellular enzymes.

Reticulocytes account for 1–2% of all erythrocytes in the blood of healthy people. **Reticulocyte counts** provide a rough index of the *rate* of RBC formation—reticulocyte counts below or above this range indicate abnormal rates of erythrocyte formation.

Regulation and Requirements for Erythropoiesis

The number of circulating erythrocytes in a given individual is remarkably constant and reflects a balance between red blood cell production and destruction. This balance is important because having too few erythrocytes leads to tissue hypoxia (oxygen deprivation), whereas having too many makes the blood undesirably viscous.

To ensure that the number of erythrocytes in blood remains within the homeostatic range, new cells are produced at the incredibly rapid rate of more than 2 million per second in healthy people. This process is controlled hormonally and depends on adequate supplies of iron, amino acids, and certain B vitamins.

Hormonal Controls **Erythropoietin (EPO)**, a glycoprotein hormone, stimulates the formation of erythrocytes **(Figure 17.6)**. Normally, a small amount of EPO circulates in the blood at all times and sustains red blood cell production at a basal rate. The kidneys play the major role in EPO production, although the liver also produces some. When certain kidney cells become

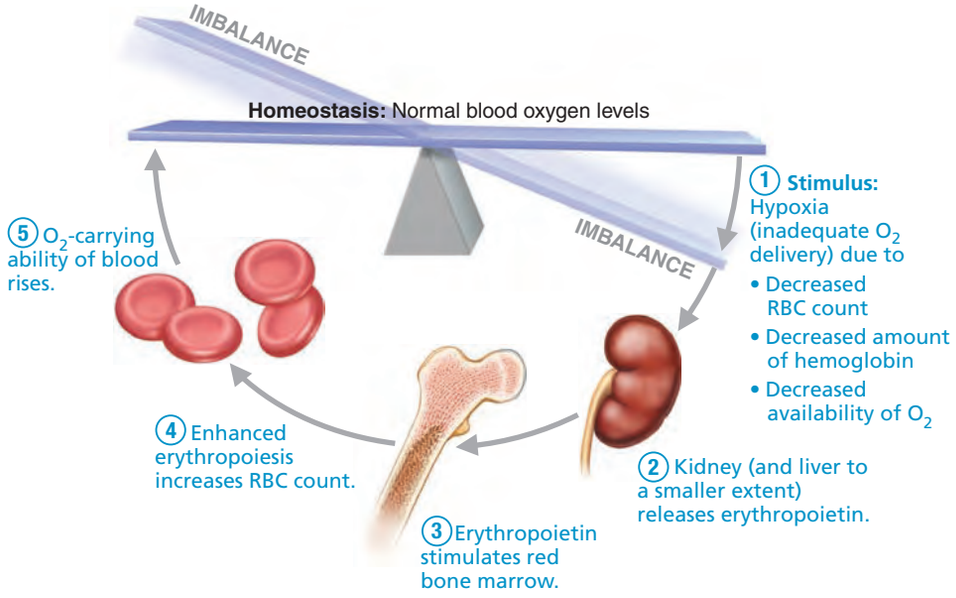


Figure 17.6 **Erythropoietin mechanism for regulating erythropoiesis.**

hypoxic (oxygen deficient), oxygen-sensitive enzymes are unable to carry out their normal functions of degrading an intracellular signaling molecule called hypoxia-inducible factor (HIF). As HIF accumulates, it accelerates the synthesis and release of erythropoietin.

The drop in normal blood oxygen levels that triggers EPO formation can result from

- Reduced numbers of red blood cells due to hemorrhage (bleeding) or excessive RBC destruction
- Insufficient hemoglobin per RBC (as in iron deficiency)
- Reduced availability of oxygen, as might occur at high altitudes or during pneumonia

Conversely, too many erythrocytes or excessive oxygen in the bloodstream depresses erythropoietin production. Note that it is not the number of erythrocytes in blood that controls the rate of erythropoiesis. Instead, control is based on their ability to transport enough oxygen to meet tissue demands.

Bloodborne erythropoietin stimulates red marrow cells that *are already committed* to becoming erythrocytes, causing them to mature more rapidly. One to two days after erythropoietin levels rise in the blood, the rate of reticulocyte release and the reticulocyte count rise markedly. Notice that hypoxia does not activate the bone marrow directly. Instead it stimulates the kidneys, which in turn provide the hormonal stimulus that activates the bone marrow.

Homeostatic Imbalance 17.1

Renal dialysis patients whose kidneys have failed produce too little EPO to support normal erythropoiesis. Consequently, they routinely have red blood cell counts less than half those of healthy individuals. Genetically engineered (recombinant) EPO has helped these patients immeasurably.

Unfortunately, some athletes abuse recombinant EPO—particularly professional bike racers and marathon runners seeking increased stamina and performance. However, the consequences can be deadly. By injecting EPO, healthy athletes increase their normal hematocrit from 45% to as much as 65%. Then, with the dehydration that occurs in a long race, the blood concentrates even further, becoming a thick, sticky "sludge" that can cause clotting, stroke, and heart failure. ✚

The male sex hormone *testosterone* also enhances the kidneys' production of EPO. Because female sex hormones do not have similar stimulatory effects, testosterone may be at least partially responsible for the higher RBC counts and hemoglobin levels seen in males. Also, a wide variety of chemicals released by leukocytes, platelets, and even reticular cells stimulates bursts of RBC production.

Dietary Requirements The raw materials required for erythropoiesis include the usual nutrients and structural materials—amino acids, lipids, and carbohydrates. Iron is essential for hemoglobin synthesis. Iron is available from the diet, and intestinal cells precisely control its absorption into the bloodstream in response to changing body stores of iron.

Approximately 65% of the body's iron supply (about 4000 mg) is in hemoglobin. Most of the remainder is stored in the liver, spleen, and (to a much lesser extent) bone marrow. Free iron ions (Fe^{2+}, Fe^{3+}) are toxic, so iron is stored inside cells as protein-iron complexes such as **ferritin** (fer′ĭ-tin) and **hemosiderin** (he″mo-sid′er-in). In blood, iron is transported loosely bound to a transport protein called **transferrin**, and developing erythrocytes take up iron as needed to form hemoglobin **(Figure 17.7)**. Small amounts of iron are lost each day in feces, urine, and perspiration. The average daily loss of iron is 1.7 mg in women and 0.9 mg in men. In women, the menstrual flow accounts for the additional losses.

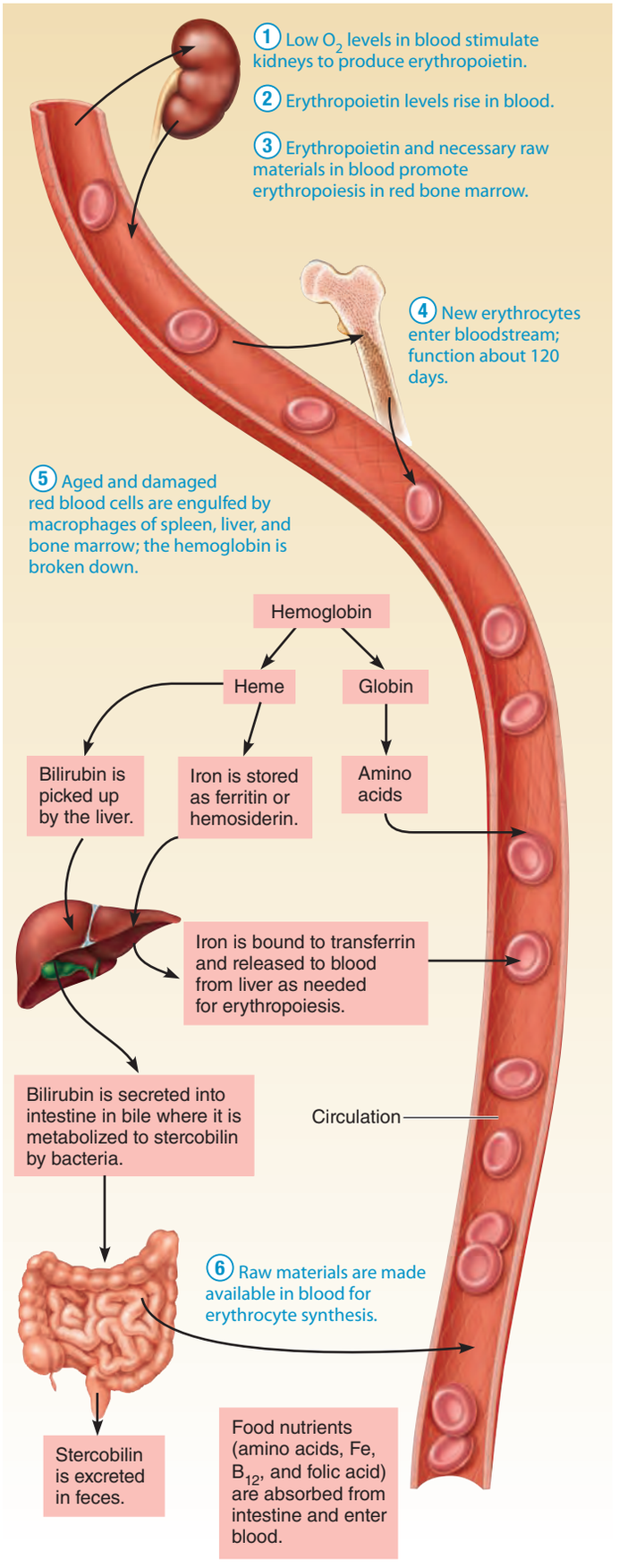


Figure 17.7 **Life cycle of red blood cells.**

Two B-complex vitamins—vitamin B_{12} and folic acid—are necessary for normal DNA synthesis. Even slight deficits jeopardize rapidly dividing cell populations, such as developing erythrocytes.

Fate and Destruction of Erythrocytes

Red blood cells have a useful life span of 100 to 120 days. Their anucleate condition carries with it some important limitations. Red blood cells are unable to synthesize new proteins, grow, or divide. Erythrocytes become "old" as they lose their flexibility, become increasingly rigid and fragile, and their hemoglobin begins to degenerate. They become trapped and fragment in smaller circulatory channels, particularly in those of the spleen. For this reason, the spleen is sometimes called the "red blood cell graveyard."

We will briefly describe the fate of aged and damaged erythrocytes here, but Figure 17.7 gives a more detailed account. Macrophages engulf and destroy dying erythrocytes. The heme of their hemoglobin is split off from globin. Its core of iron is salvaged, bound to protein (as ferritin or hemosiderin), and stored for reuse. The balance of the heme group is degraded to **bilirubin** (bil″ĭ-roo′bin), a yellow pigment that is released to the blood and binds to albumin for transport. Liver cells pick up bilirubin and in turn secrete it (in bile) into the intestine, where it is metabolized to *urobilinogen*. Most of this degraded pigment leaves the body in feces, as a brown pigment called *stercobilin*. The protein (globin) part of hemoglobin is metabolized or broken down to amino acids, which are released to the circulation.

Erythrocyte Disorders

Most erythrocyte disorders can be classified as anemia or polycythemia. We describe some of the many varieties and causes of these conditions next.

Anemia **Anemia** (ah-ne′me-ah; "lacking blood") is a condition in which the blood's oxygen-carrying capacity is too low to support normal metabolism. It is a *sign* of some disorder rather than a disease in itself. Its hallmark is blood oxygen levels that are inadequate to support normal metabolism. Anemic individuals are fatigued, often pale, short of breath, and chilled.

The causes of anemia can be divided into three groups: blood loss, not enough red blood cells produced, or too many of them destroyed.

- **Blood loss.** *Hemorrhagic anemia* (hem″o-raj′ik) is caused by blood loss. In acute hemorrhagic anemia, blood loss is rapid (as might follow a severe stab wound); it is treated by replacing the lost blood. Slight but persistent blood loss (due to hemorrhoids or an undiagnosed bleeding ulcer, for example) causes chronic hemorrhagic anemia. Once the primary problem is resolved, normal erythropoietic mechanisms replace the lost blood cells.
- **Not enough red blood cells produced.** A number of problems can decrease erythrocyte production. These problems range from lack of essential raw materials (such as iron) to complete and utter failure of the red bone marrow.

  Iron-deficiency anemia is generally a secondary result of hemorrhagic anemia, but it also results from inadequate

intake of iron-containing foods and impaired iron absorption. The erythrocytes produced, called **microcytes**, are small and pale because they cannot synthesize their normal complement of hemoglobin. The obvious treatment is to increase iron intake in diet or through iron supplements.

Pernicious anemia is an autoimmune disease that most often affects the elderly. The immune system of these individuals destroys cells of their own stomach mucosa. These cells produce a substance called **intrinsic factor** that must be present for vitamin B_{12} to be absorbed by intestinal cells. Without vitamin B_{12}, the developing erythrocytes grow but cannot divide, and large, pale cells called **macrocytes** result. Treatment involves regular intramuscular injections of vitamin B_{12} or application of a B_{12}-containing gel to the nasal lining once a week.

As you might expect, lack of vitamin B_{12} in the diet also leads to anemia. However, this is usually a problem only in strict vegetarians because meats, poultry, and fish provide ample vitamin B_{12} in the diet of nonvegetarians.

Renal anemia is caused by the lack of EPO, the hormone that controls red blood cell production. Renal anemia frequently accompanies renal disease because damaged or diseased kidneys cannot produce enough EPO. Fortunately, it can be treated with synthetic EPO.

Aplastic anemia may result from destruction or inhibition of the red marrow by certain drugs and chemicals, ionizing radiation, or viruses. In most cases, though, the cause is unknown. Because marrow destruction impairs formation of *all* formed elements, anemia is just one of its signs. Defects in blood clotting and immunity are also present. Blood transfusions provide a stopgap treatment until stem cells harvested from a donor's blood, bone marrow, or umbilical cord blood can be transplanted.

- **Too many red blood cells destroyed.** In *hemolytic anemias* (he″mo-lit′ik), erythrocytes rupture, or lyse, prematurely. Hemoglobin abnormalities, transfusion of mismatched blood, and certain bacterial and parasitic infections are possible causes. Here we focus on the hemoglobin abnormalities.

Production of abnormal hemoglobin usually has a genetic basis. Two such examples, thalassemia and sickle-cell anemia, can be serious, incurable, and sometimes fatal diseases. In both diseases the globin part of hemoglobin is abnormal and the erythrocytes produced are fragile and rupture prematurely.

Thalassemias (thal″ah-se′me-ahs; "sea blood") typically occur in people of Mediterranean ancestry, such as Greeks and Italians. One of the globin chains is absent or faulty, and the erythrocytes are thin, delicate, and deficient in hemoglobin. There are many subtypes of thalassemia, classified according to which hemoglobin chain is affected and where. They range in severity from mild to so severe that monthly blood transfusions are required.

In **sickle-cell anemia**, the havoc caused by the abnormal hemoglobin, *hemoglobin S* (*HbS*), results from a change in just one of the 146 amino acids in a beta chain of the globin molecule! (See **Figure 17.8**.) This alteration causes the beta chains to link together under low-oxygen conditions, forming

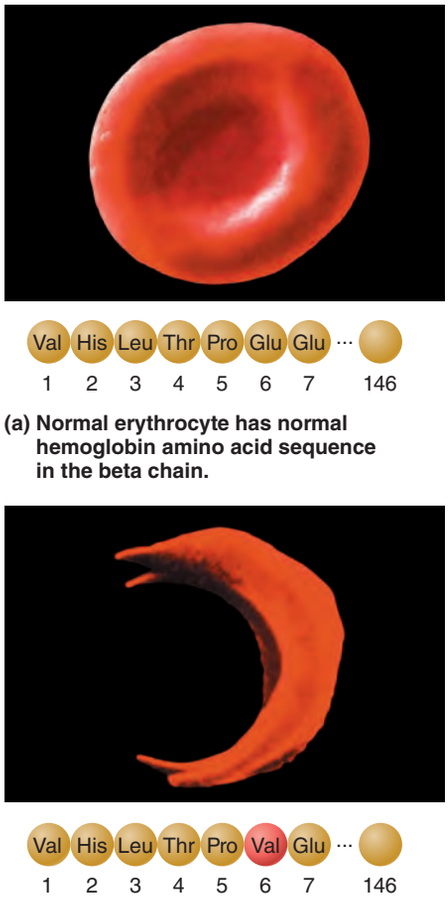


Figure 17.8 Sickle-cell anemia. Scanning electron micrographs (4950×).

stiff rods so that hemoglobin S becomes spiky and sharp. This, in turn, causes the red blood cells to become crescent shaped when they unload oxygen molecules or when the oxygen content of the blood is lower than normal, as during vigorous exercise and other activities that increase metabolic rate.

The stiff, deformed erythrocytes rupture easily and tend to dam up in small blood vessels. These events interfere with oxygen delivery, leaving the victims gasping for air and in extreme pain. Bone and chest pain are particularly severe, and infection and stroke are common sequels. Blood transfusion is still the standard treatment for an acute sickle-cell crisis, but preliminary results using inhaled nitric oxide to dilate blood vessels are promising.

Sickle-cell anemia occurs chiefly in black people who live in the malaria belt of Africa and among their descendants. It strikes nearly one of every 500 black newborns in the United States.

Why would such a dangerous genetic trait persist in a population? Globally, about 250 million people are infected with malaria and about a million die each year. While individuals with two copies of the sickle-cell gene have sickle-cell

anemia, individuals with only one copy of the gene (sickle-cell trait) have a better chance of surviving malaria. Their cells only sickle under abnormal circumstances, most importantly when they are infected with malaria. Sickling reduces the malaria parasites' ability to survive and enhances macrophages' ability to destroy infected RBCs and the parasites they contain.

Several treatment approaches focus on preventing RBCs from sickling. Fetal hemoglobin (HbF) does not "sickle," even in those destined to have sickle-cell anemia. *Hydroxyurea*, a drug used to treat chronic leukemia, switches the fetal hemoglobin gene back on. This drug dramatically reduces the excruciating pain and overall severity and complications of sickle-cell anemia (by 50%). Another class of drugs reduces sickling by blocking ion channels in the RBC membrane, keeping ions and water inside the cell. Other approaches being tested include oral arginine to stimulate nitric oxide production and dilate blood vessels, stem cell transplants, and gene therapy to deliver genes for synthesizing normal beta chains.

Polycythemia **Polycythemia** (pol″e-si-the′me-ah; "many blood cells") is an abnormal excess of erythrocytes that increases blood viscosity, causing it to sludge, or flow sluggishly. *Polycythemia vera*, a bone marrow cancer, is characterized by dizziness and an exceptionally high RBC count (8–11 million cells/μl). The hematocrit may be as high as 80% and blood volume may double, causing the vascular system to become engorged with blood and severely impairing circulation. Severe polycythemia is treated by diluting blood—removing some blood and replacing it with saline.

Secondary polycythemias result when less oxygen is available or EPO production increases. The secondary polycythemia that appears in individuals living at high altitudes is a normal physiological response to the reduced atmospheric pressure and lower oxygen content of the air in such areas. RBC counts of 6–8 million/μl are common in such people.

Blood doping, practiced by some athletes competing in aerobic events, is artificially induced polycythemia. Some of the athlete's red blood cells are drawn off and stored. The body quickly replaces these erythrocytes because removing blood triggers the erythropoietin mechanism. Then, when the stored blood is reinfused a few days before the athletic event, a temporary polycythemia results.

Since red blood cells carry oxygen, the additional infusion should translate into increased oxygen-carrying capacity due to a higher hematocrit, and hence greater endurance and speed. Other than the risk of stroke and heart failure due to high hematocrit and high blood viscosity described earlier, blood doping seems to work. However, the practice is considered unethical and has been banned from the Olympic Games.

☑ Check Your Understanding

4. How many molecules of oxygen can each hemoglobin molecule transport? What part of the hemoglobin binds the oxygen?
5. Patients with advanced kidney disease often have anemia. Explain the connection.

For answers, see Appendix H.

Leukocytes (White Blood Cells)

- ✓ List the classes, structural characteristics, and functions of leukocytes.
- ✓ Describe how leukocytes are produced.
- ✓ Give examples of leukocyte disorders, and explain what goes wrong in each disorder.

General Structural and Functional Characteristics

Leukocytes (*leuko* = white), or **white blood cells (WBCs)**, are the only formed elements that are complete cells, with nuclei and the usual organelles. Accounting for less than 1% of total blood volume, leukocytes are far less numerous than red blood cells. On average, there are 4800–10,800 WBCs/μl of blood.

Leukocytes are crucial to our defense against disease. They form a mobile army that helps protect the body from damage by bacteria, viruses, parasites, toxins, and tumor cells. As such, they have special functional characteristics. Red blood cells are confined to the bloodstream, and they carry out their functions in the blood. But white blood cells are able to slip out of the capillary blood vessels—a process called **diapedesis** (di″ah-pĕ-de′sis; "leaping across")—and the circulatory system is simply their means of transport to areas of the body (mostly loose connective tissues or lymphoid tissues) where they mount inflammatory or immune responses.

As we explain in more detail in Chapter 21, the signals that prompt WBCs to leave the bloodstream at specific locations are cell adhesion molecules displayed by endothelial cells forming the capillary walls at sites of inflammation. Once out of the bloodstream, leukocytes move through the tissue spaces by **amoeboid motion** (they form flowing cytoplasmic extensions that move them along). By following the chemical trail of molecules released by damaged cells or other leukocytes, a phenomenon called **positive chemotaxis**, they pinpoint areas of tissue damage and infection and gather there in large numbers to destroy foreign substances and dead cells.

Whenever white blood cells are mobilized for action, the body speeds up their production and their numbers may double within a few hours. A *white blood cell count* of over 11,000 cells/μl is **leukocytosis**. This condition is a normal homeostatic response to an infection in the body.

Leukocytes are grouped into two major categories on the basis of structural and chemical characteristics. *Granulocytes* contain obvious membrane-bound cytoplasmic granules, and *agranulocytes* lack obvious granules. We provide general information about the various leukocytes next. More details appear in **Figure 17.9** and **Table 17.2** on p. 644.

Students are often asked to list the leukocytes in order from most abundant to least abundant. The following phrase may help you with this task: **N**ever **l**et **m**onkeys **e**at **b**ananas (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

Granulocytes

Granulocytes (gran′u-lo-sīts), which include neutrophils, eosinophils, and basophils, are all roughly spherical in shape. They are larger and much shorter lived (in most cases) than

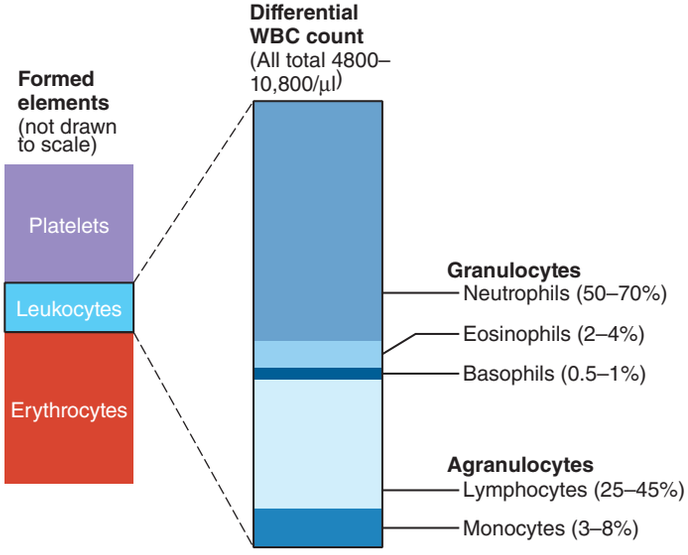


Figure 17.9 Types and relative percentages of leukocytes in normal blood. Erythrocytes comprise nearly 98% of the formed elements, and leukocytes and platelets together account for the remaining 2+%.

erythrocytes. They characteristically have lobed nuclei (rounded nuclear masses connected by thinner strands of nuclear material), and their membrane-bound cytoplasmic granules stain quite specifically with Wright's stain. Functionally, all granulocytes are phagocytes to some degree.

Neutrophils **Neutrophils** (nu′tro-filz), the most numerous white blood cells, account for 50–70% of the WBC population. Neutrophils are about twice as large as erythrocytes.

The neutrophil cytoplasm contains very fine granules (of two varieties) that are difficult to see (Table 17.2 and **Figure 17.10a**). Neutrophils get their name (literally, "neutral-loving") because their granules take up both *basic* (blue) and *acidic* (red) *dyes*. Together, the two types of granules give the cytoplasm a lilac color. Some of these granules contain hydrolytic enzymes, and are regarded as lysosomes. Others, especially the smaller granules, contain a potent "brew" of antimicrobial proteins, called **defensins**.

Neutrophil nuclei consist of three to six lobes. Because of this nuclear variability, they are often called **polymorphonuclear leukocytes** (*PMNs*) or simply *polys* (*polymorphonuclear* = many shapes of the nucleus).

Neutrophils are our body's bacteria slayers, and their numbers increase explosively during acute bacterial infections such as meningitis and appendicitis. Neutrophils are chemically attracted to sites of inflammation and are active phagocytes. They are especially partial to bacteria and some fungi, and bacterial killing is promoted by a process called a respiratory burst. In the **respiratory burst**, the cells metabolize oxygen to produce potent germ-killer oxidizing substances such as bleach and hydrogen peroxide. In addition, defensin-mediated lysis occurs when the granules containing defensins merge with a microbe-containing phagosome. The defensins form peptide "spears" that pierce holes in the membrane of the ingested "foe."

Eosinophils **Eosinophils** (e″o-sin′o-filz) account for 2–4% of all leukocytes and are approximately the size of neutrophils. Their nucleus usually resembles an old-fashioned telephone receiver—it has two lobes connected by a broad band of nuclear material (Table 17.2 and Figure 17.10b).

Large, coarse granules that stain from brick red to crimson with acid (eosin) dyes pack the cytoplasm. These granules are lysosome-like and filled with a unique variety of digestive

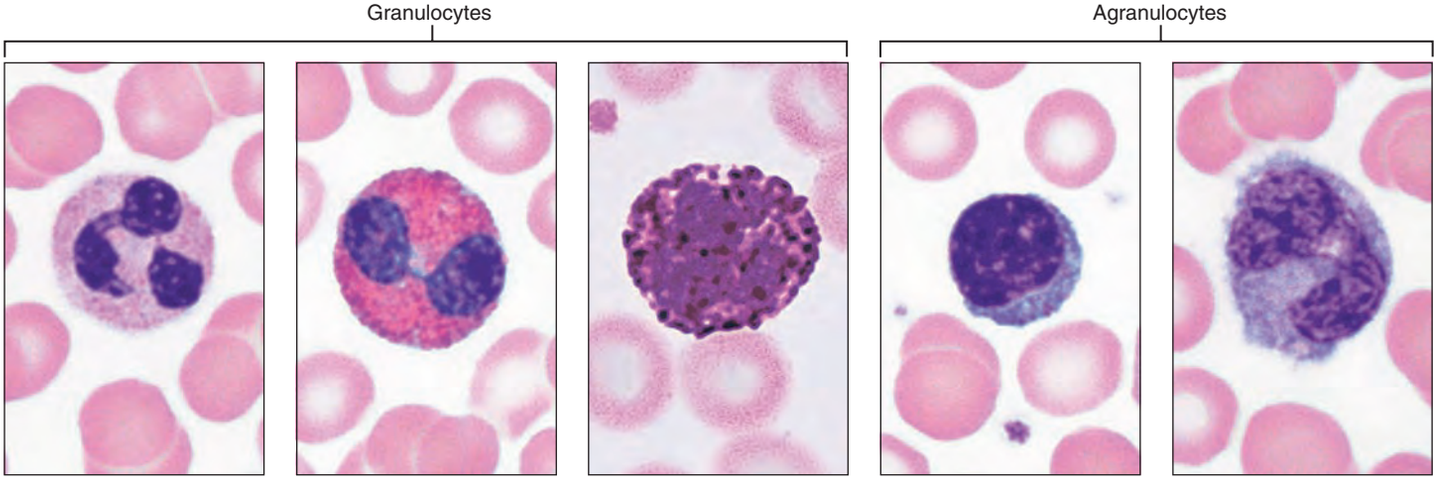


Figure 17.10 Leukocytes. In each case the leukocytes are surrounded by erythrocytes. Neutrophils, eosinophils, and basophils have visible cytoplasmic granules; lymphocytes and monocytes do not. (All 1750×, Wright's stain.)

enzymes. However, unlike typical lysosomes, they lack enzymes that specifically digest bacteria.

The most important role of eosinophils is to lead the counterattack against parasitic worms, such as flatworms (tapeworms and flukes) and roundworms (pinworms and hookworms) that are too large to be phagocytized. These worms are ingested in food (especially raw fish) or invade the body via the skin and then typically burrow into the intestinal or respiratory mucosae. Eosinophils reside in the loose connective tissues at the same body sites, and when they encounter a parasitic worm "prey," they gather around and release the enzymes from their cytoplasmic granules onto the parasite's surface, digesting it away.

Eosinophils have complex roles in many other diseases including allergies and asthma. While they contribute to the tissue damage that occurs in many immune processes, we are also beginning to recognize them as important modulators of the immune response.

Basophils **Basophils** are the rarest white blood cells, accounting for only 0.5–1% of the leukocyte population. Their cytoplasm contains large, coarse, histamine-containing granules that have an affinity for the basic dyes (*basophil* = base loving) and stain purplish-black (Figure 17.10c). *Histamine* is an inflammatory chemical that acts as a vasodilator (makes blood vessels dilate) and attracts other white blood cells to the inflamed site; drugs called antihistamines counter this effect. The deep purple nucleus is generally U or S shaped with one or two conspicuous constrictions.

Granulated cells similar to basophils, called *mast cells*, are found in connective tissues. Although mast cell nuclei tend to be more oval than lobed, the cells are similar microscopically, and both cell types bind to a particular antibody (immunoglobulin E) that causes the cells to release histamine. However, they arise from different cell lines.

Agranulocytes

The **agranulocytes** include lymphocytes and monocytes, WBCs that lack *visible* cytoplasmic granules. Although similar to each other structurally, they are functionally distinct and unrelated cell types. Their nuclei are typically spherical or kidney shaped.

Lymphocytes **Lymphocytes**, accounting for 25% or more of the WBC population, are the second most numerous leukocytes in the blood. When stained, a typical lymphocyte has a large, dark-purple nucleus that occupies most of the cell volume. The nucleus is usually spherical but may be slightly indented, and it is surrounded by a thin rim of pale-blue cytoplasm (Table 17.2 and Figure 17.10d). Lymphocyte diameter ranges from 5 to 17 μm, but they are often classified according to size as small (5–8 μm), medium (10–12 μm), and large (14–17 μm).

Large numbers of lymphocytes exist in the body, but relatively few (mostly the small lymphocytes) are found in the bloodstream. In fact, lymphocytes are so called because most are closely associated with lymphoid tissues (lymph nodes, spleen, etc.), where they play a crucial role in immunity. **T lymphocytes (T cells)** function in the immune response by acting directly against virus-infected cells and tumor cells. **B lymphocytes (B cells)** give rise to *plasma cells*, which produce **antibodies** (immunoglobulins) that are released to the blood. (We describe B and T lymphocyte functions in Chapter 21.)

Monocytes **Monocytes** account for 3–8% of WBCs. With an average diameter of 18 μm, they are the largest leukocytes. They have abundant pale-blue cytoplasm and a darkly staining purple nucleus, which is distinctively U or kidney shaped (Table 17.2 and Figure 17.10e).

When circulating monocytes leave the bloodstream and enter the tissues, they differentiate into highly mobile **macrophages** with prodigious appetites. Macrophages are actively phagocytic, and they are crucial in the body's defense against viruses, certain intracellular bacterial parasites, and *chronic* infections such as tuberculosis. As we explain in Chapter 21, macrophages are also important in activating lymphocytes to mount the immune response.

Production and Life Span of Leukocytes

Like erythropoiesis, **leukopoiesis**, or the production of white blood cells, is stimulated by chemical messengers. These messengers, which can act either as paracrines or hormones, are glycoproteins that fall into two families of hematopoietic factors, **interleukins** and **colony-stimulating factors**, or **CSFs**. The interleukins are numbered (e.g., IL-3, IL-5), but most CSFs are named for the leukocyte population they stimulate—for example, *granulocyte-CSF* (*G-CSF*) stimulates production of granulocytes. Hematopoietic factors, released by supporting cells of the red bone marrow and mature WBCs, not only prompt the white blood cell precursors to divide and mature, but also enhance the protective potency of mature leukocytes.

Homeostatic Imbalance 17.2

Many of the hematopoietic hormones (EPO and several of the CSFs) are used clinically. These hormones stimulate the bone marrow of cancer patients who are receiving chemotherapy (which suppresses the marrow) and of those who have received stem cell transplants, and to beef up the protective responses of AIDS patients. ✚

Figure 17.11 shows the pathways of leukocyte differentiation, starting with the hematopoietic stem cell that gives rise to all of the formed elements in the blood. An early branching of the pathway divides the **lymphoid stem cells**, which produce lymphocytes, from the **myeloid stem cells**, which give rise to all other formed elements. In each granulocyte line, the committed cells, called **myeloblasts** (mi′ĕ-lo-blasts″), accumulate lysosomes, becoming **promyelocytes**. The distinctive granules of each granulocyte type appear next in the **myelocyte** stage and then cell division stops. In the subsequent stage, the nuclei arc, producing the **band cell** stage. Just before granulocytes leave the marrow and enter the circulation, their nuclei constrict, beginning the process of nuclear segmentation.

The bone marrow stores mature granulocytes and usually contains about ten times more granulocytes than are found in the blood. The normal ratio of granulocytes to erythrocytes produced is about 3:1, which reflects granulocytes' much shorter life span (0.25 to 9.0 days). Most die combating invading microorganisms.

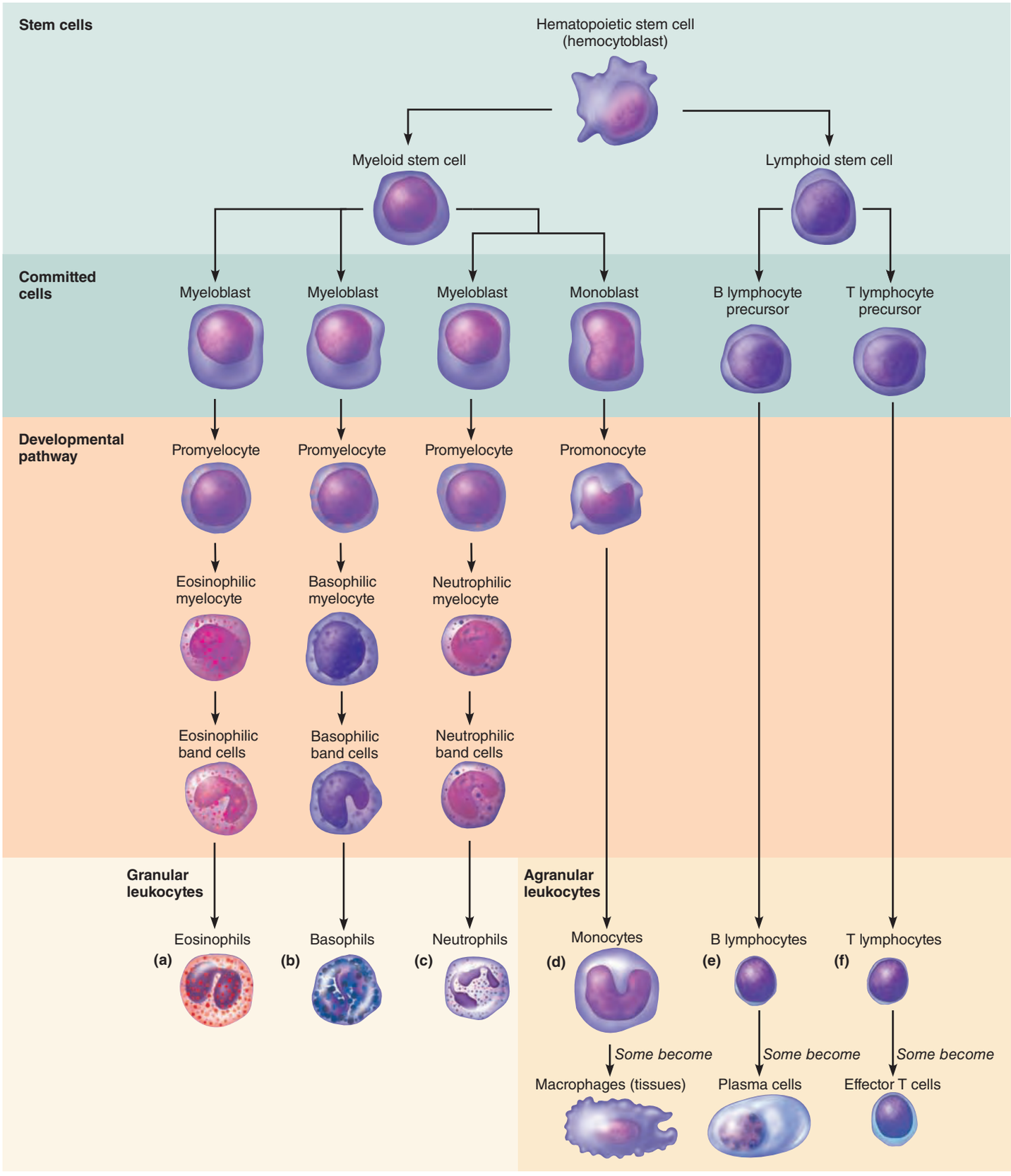
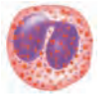
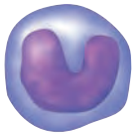
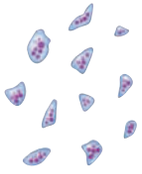


Figure 17.11 Leukocyte formation. Leukocytes arise from ancestral stem cells called hematopoietic stem cells. **(a–c)** Granular leukocytes develop via a sequence involving myeloblasts. **(d)** Monocytes, like granular leukocytes, are progeny of the myeloid stem cell and share a common precursor with neutrophils (not shown). **(e)** Only lymphocytes arise via the lymphoid stem cell line.

Table 17.2 Summary of Formed Elements of the Blood

CELL TYPE	ILLUSTRATION	DESCRIPTION*	CELLS/μL (mm^3) OF BLOOD	DURATION OF DEVELOPMENT (D) AND LIFE SPAN (LS)	FUNCTION
Erythrocytes (red blood cells, RBCs)		Biconcave, anucleate disc; salmon-colored; diameter 7–8 μm	4–6 million	D: about 15 days LS: 100–120 days	Transport oxygen and carbon dioxide
Leukocytes (white blood cells, WBCs)		Spherical, nucleated cells	4800–10,800		
Granulocytes					
▪ Neutrophil		Multilobed nucleus; inconspicuous cytoplasmic granules; diameter 10–12 μm	3000–7000	D: about 14 days LS: 6 hours to a few days	Phagocytize bacteria
▪ Eosinophil		Bilobed nucleus; red cytoplasmic granules; diameter 10–14 μm	100–400	D: about 14 days LS: about 5 days	Kill parasitic worms; complex role in allergy and asthma
▪ Basophil		Bilobed nucleus; large purplish-black cytoplasmic granules; diameter 10–14 μm	20–50	D: 1–7 days LS: a few hours to a few days	Release histamine and other mediators of inflammation; contain heparin, an anticoagulant
Agranulocytes					
▪ Lymphocyte		Spherical or indented nucleus; pale blue cytoplasm; diameter 5–17 μm	1500–3000	D: days to weeks LS: hours to years	Mount immune response by direct cell attack or via antibodies
▪ Monocyte		U- or kidney-shaped nucleus; gray-blue cytoplasm; diameter 14–24 μm	100–700	D: 2–3 days LS: months	Phagocytosis; develop into macrophages in the tissues
Platelets		Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 μm	150,000–400,000	D: 4–5 days LS: 5–10 days	Seal small tears in blood vessels; instrumental in blood clotting

*Appearance when stained with Wright's stain.

Despite their similar appearance, the two types of agranulocytes have very different lineages.

- Monocytes are derived from myeloid stem cells, and share a common precursor with neutrophils that is not shared with the other granulocytes. Cells following the monocyte line pass through the **monoblast** and **promonocyte** stages before leaving the bone marrow and becoming monocytes (Figure 17.11d).
- T and B lymphocytes are derived from **T** and **B lymphocyte precursors**, which arise from the lymphoid stem cell. The T lymphocyte precursors leave the bone marrow and travel to the thymus, where their further differentiation occurs (as we describe in Chapter 21). B lymphocyte precursors remain and mature in the bone marrow.

Monocytes may live for several months, whereas the life span of lymphocytes varies from a few hours to decades.

Leukocyte Disorders

Overproduction of abnormal leukocytes occurs in leukemia and infectious mononucleosis. At the opposite pole, **leukopenia** (loo″ko-pe′ne-ah) is an abnormally low white blood cell count (*penia* = poverty), commonly induced by drugs, particularly glucocorticoids and anticancer agents.

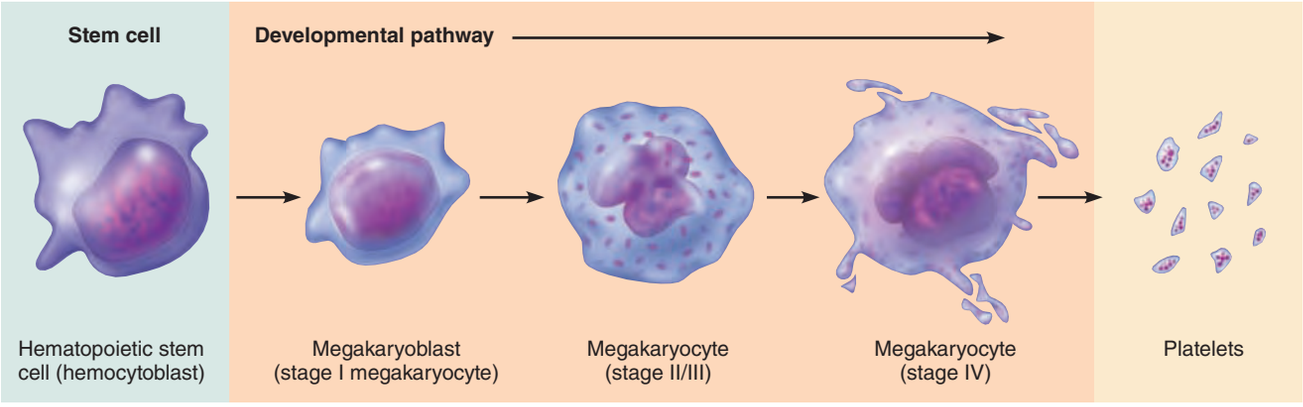


Figure 17.12 Formation of platelets. The hematopoietic stem cell gives rise to cells that undergo several mitotic divisions unaccompanied by cytoplasmic division to produce megakaryocytes. The plasma membrane of the megakaryocyte fragments, liberating the platelets. (Intermediate stages between the hematopoietic stem cell and megakaryoblast are not illustrated.)

Leukemias The term *leukemia*, literally "white blood," refers to a group of cancerous conditions involving overproduction of abnormal white blood cells. As a rule, the renegade leukocytes are members of a single *clone* (descendants of a single cell) that remain unspecialized and proliferate out of control, impairing normal red bone marrow function. The leukemias are named according to the cell type primarily involved. For example, *myeloid leukemia* involves myeloblast descendants, whereas *lymphocytic leukemia* involves the lymphocytes. Leukemia is *acute* (quickly advancing) if it derives from stem cells, and *chronic* (slowly advancing) if it involves proliferation of later cell stages.

The more serious acute forms primarily affect children. Chronic leukemia occurs more often in elderly people. Without therapy, all leukemias are fatal, and only the time course differs.

In all leukemias, cancerous leukocytes fill the red bone marrow and immature WBCs flood into the bloodstream. The other blood cell lines are crowded out, so severe anemia and bleeding problems result. Other symptoms include fever, weight loss, and bone pain. Although tremendous numbers of leukocytes are produced, they are nonfunctional and cannot defend the body in the usual way. The most common causes of death are internal hemorrhage and overwhelming infections.

Irradiation and antileukemic drugs can destroy the rapidly dividing cells and induce remissions (symptom-free periods) lasting from months to years. Stem cell transplants are used in selected patients when compatible donors are available.

Infectious Mononucleosis Sometimes called the "kissing disease," *infectious mononucleosis* is a highly contagious viral disease most often seen in young adults. Caused by the Epstein-Barr virus, its hallmark is excessive numbers of agranulocytes, many of which are atypical. The affected individual complains of being tired and achy, and has a chronic sore throat and a low-grade fever. There is no cure, but with rest the condition typically runs its course to recovery in a few weeks.

Platelets

✓ Describe the structure and function of platelets.

Platelets are not cells in the strict sense. About one-fourth the diameter of a lymphocyte, they are cytoplasmic fragments of extraordinarily large cells (up to 60 μm in diameter) called **megakaryocytes** (meg″ah-kar′e-o-sīts). In blood smears, each platelet exhibits a blue-staining outer region and an inner area containing granules that stain purple. The granules contain an impressive array of chemicals that act in the clotting process, including serotonin, Ca^{2+}, a variety of enzymes, ADP, and platelet-derived growth factor (PDGF).

Platelets are essential for the clotting process that occurs in plasma when blood vessels are ruptured or their lining is injured. By sticking to the damaged site, platelets form a temporary plug that helps seal the break. (We explain this process shortly.) Because they are anucleate, platelets age quickly and degenerate in about 10 days if they are not involved in clotting. In the meantime, they circulate freely, kept mobile but inactive by molecules (nitric oxide, prostacyclin) secreted by endothelial cells lining the blood vessels.

A hormone called **thrombopoietin** regulates the formation of platelets. Their immediate ancestral cells, the megakaryocytes, are progeny of the hematopoietic stem cell and the myeloid stem cell, but their formation is quite unusual **(Figure 17.12)**. In this line, repeated mitoses of the **megakaryoblast** (also called a stage I megakaryocyte) occur, but cytokinesis does not. The final result is the mature (stage IV) megakaryocyte (literally "big nucleus cell"), a bizarre cell with a huge, multilobed nucleus and a large cytoplasmic mass.

After it forms, the megakaryocyte presses against a sinusoid (the specialized type of capillary in the red marrow) and sends cytoplasmic extensions through the sinusoid wall into the bloodstream. These extensions rupture, releasing the platelet fragments like stamps being torn from a sheet of postage

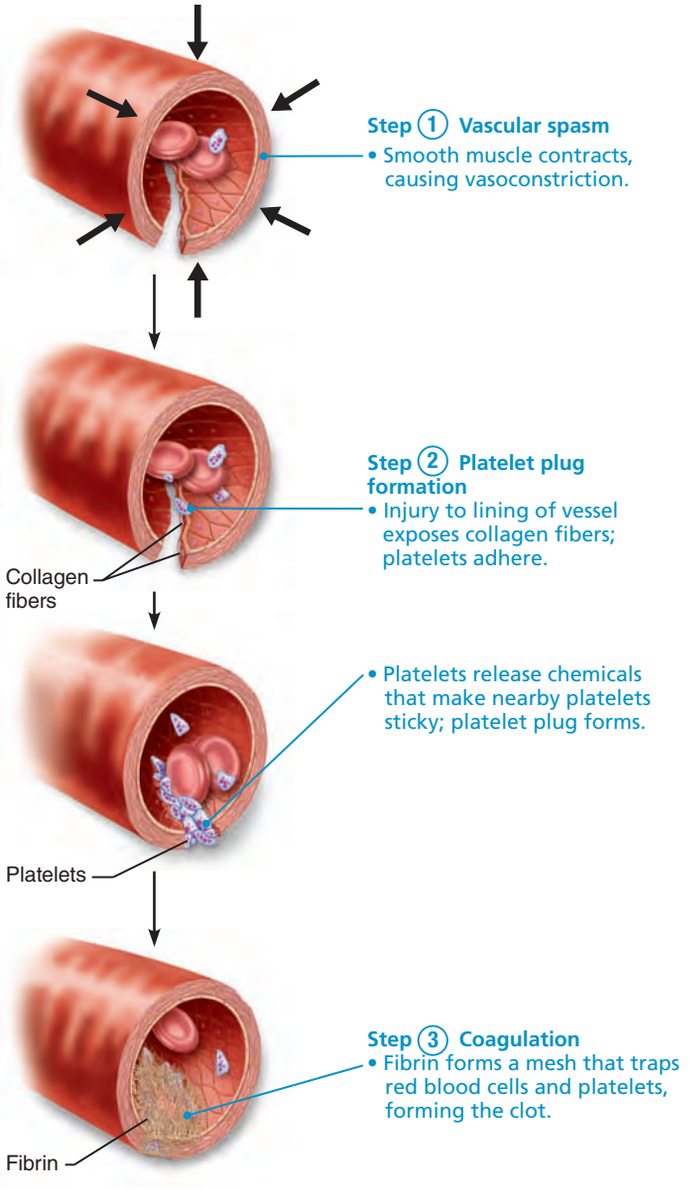


Figure 17.13 **Events of hemostasis.**

stamps and seeding the blood with platelets. The plasma membranes associated with each fragment quickly seal around the cytoplasm to form the grainy, roughly disc-shaped platelets (see Table 17.2), each with a diameter of 2–4 μm. Each microliter of blood contains 150,000 to 400,000 tiny platelets.

Check Your Understanding

6. Which WBCs turn into macrophages in tissues? Which other WBC is a voracious phagocyte?
7. Platelets are called "thrombocytes" in other animals. Which term that you've just learned relates to this name? What does this term mean?
8. Amos has leukemia. Even though his WBC count is abnormally high, Amos is prone to severe infections, bleeding, and anemia. Explain.

For answers, see Appendix H.

Hemostasis

- ✓ Describe the process of hemostasis. List factors that limit clot formation and prevent undesirable clotting.
- ✓ Give examples of hemostatic disorders. Indicate the cause of each condition.

Normally, blood flows smoothly past the intact blood vessel lining (endothelium). But if a blood vessel wall breaks, a whole series of reactions is set in motion to accomplish **hemostasis** (he″mo-sta′sis), which stops the bleeding (*stasis* = halting). Without this plug-the-hole defensive reaction, we would quickly bleed out our entire blood volume from even the smallest cuts.

The hemostasis response is fast, localized, and carefully controlled. It involves many *clotting factors* normally present in plasma as well as several substances that are released by platelets and injured tissue cells. During hemostasis, three steps occur in rapid sequence **(Figure 17.13)**: (1) vascular spasm, (2) platelet plug formation, and (3) coagulation (blood clotting). Following hemostasis, the clot retracts. It then dissolves as it is replaced by fibrous tissue that permanently prevents blood loss.

Step 1: Vascular Spasm

In the first step, the damaged blood vessels respond to injury by constricting (vasoconstriction) (Figure 17.13 (1)). Factors that trigger this **vascular spasm** include direct injury to vascular smooth muscle, chemicals released by endothelial cells and platelets, and reflexes initiated by local pain receptors. The spasm mechanism becomes more and more efficient as the amount of tissue damage increases, and is most effective in the smaller blood vessels. The spasm response is valuable because a strongly constricted artery can significantly reduce blood loss for 20–30 minutes, allowing time for the next two steps, platelet plug formation and blood clotting, to occur.

Step 2: Platelet Plug Formation

In the second step, platelets play a key role in hemostasis by aggregating (sticking together), forming a plug that temporarily seals the break in the vessel wall (Figure 17.13 (2)). They also help orchestrate subsequent events that form a blood clot.

As a rule, platelets do not stick to each other or to the smooth endothelial linings of blood vessels. Intact endothelial cells release nitric oxide and a prostaglandin called **prostacyclin** (or PGI_2). Both chemicals prevent platelet aggregation in undamaged tissue and restrict aggregation to the site of injury.

However, when the endothelium is damaged and the underlying collagen fibers are exposed, platelets adhere tenaciously to the collagen fibers. A large plasma protein called *von Willebrand factor* stabilizes bound platelets by forming a bridge between collagen and platelets. Platelets swell, form spiked processes, become stickier, and release chemical messengers including the following:

- **Adenosine diphosphate (ADP)**—a potent aggregating agent that causes more platelets to stick to the area and release their contents

Table 17.3 Blood Clotting Factors (Procoagulants)

FACTOR NUMBER	FACTOR NAME	NATURE	SOURCE	PATHWAY; FUNCTION
I	Fibrinogen	Plasma protein	Liver	Common pathway; converted to fibrin (insoluble weblike substance of clot)
II	Prothrombin	Plasma protein	Liver*	Common pathway; converted to thrombin (converts fibrinogen to fibrin)
III	Tissue factor (TF)	Plasma membrane glycoprotein	Tissue cells	Activates extrinsic pathway
IV	Calcium ions (Ca^{2+})	Inorganic ion	Plasma	Needed for essentially all stages of coagulation process; always present
V	Proaccelerin	Plasma protein	Liver, platelets	Common pathway
VI†				
VII	Proconvertin	Plasma protein	Liver*	Both extrinsic and intrinsic pathways
VIII	Antihemophilic factor (AHF)	Plasma protein	Liver, lung capillaries	Intrinsic pathway; deficiency results in hemophilia A
IX	Plasma thromboplastin component (PTC)	Plasma protein	Liver*	Intrinsic pathway; deficiency results in hemophilia B
X	Stuart factor	Plasma protein	Liver*	Common pathway
XI	Plasma thromboplastin antecedent (PTA)	Plasma protein	Liver	Intrinsic pathway; deficiency results in hemophilia C
XII	Hageman factor	Plasma protein; activated by negatively charged surfaces (e.g., glass)	Liver	Intrinsic pathway; activates plasmin; initiates clotting in vitro; activation initiates inflammation
XIII	Fibrin stabilizing factor (FSF)	Plasma protein	Liver, bone marrow	Cross-links fibrin, forming a strong, stable clot

*Synthesis requires vitamin K
†Number no longer used; substance now believed to be same as factor V

- **Serotonin** and **thromboxane A_2** (throm-boks′ān; a short-lived prostaglandin derivative)—messengers that enhance vascular spasm and platelet aggregation

As more platelets aggregate, they release more chemicals, aggregating more platelets, and so on, in a positive feedback cycle (see Figure 1.6 on p. 11). Within one minute, a platelet plug is built up, further reducing blood loss. Platelets alone are sufficient for sealing the thousands of minute rips and holes that occur unnoticed as part of the daily wear and tear in your smallest blood vessels. Because platelet plugs are loosely knit, larger breaks need additional reinforcement.

Step 3: Coagulation

The third step, **coagulation** or **blood clotting**, reinforces the platelet plug with fibrin threads that act as a "molecular glue" for the aggregated platelets (Figure 17.13 ③). The resulting blood clot (fibrin mesh) is quite effective in sealing larger breaks in a blood vessel. Blood is transformed from a liquid to a gel in a multistep process that involves a series of substances called **clotting factors**, or **procoagulants** (Table 17.3).

Most clotting factors are plasma proteins synthesized by the liver. They are numbered I to XIII according to the order of their discovery; hence, the numerical order does not reflect their reaction sequence. All (except tissue factor) normally circulate in blood in inactive form until mobilized. Although vitamin K is not directly involved in coagulation, this fat-soluble vitamin is required for synthesizing four of the clotting factors (Table 17.3).

Figure 17.14 illustrates the way clotting factors act together to form a clot. The coagulation sequence looks intimidating at first glance, but two things will help you cope with its complexity. First, realize that in most cases, *activation turns clotting factors into enzymes* by clipping off a piece of the protein, causing it to change shape. Once one clotting factor is activated, it activates the next in sequence, and so on, in a cascade. (In Figure 17.14, we use the subscript "a" to denote the activated clotting factor.) Two important exceptions to this generalization are fibrinogen and Ca^{2+}, as we will see below.

The second strategy that will help you cope is to recognize that coagulation occurs in three phases. Each phase has a specific end point, as we discuss next.

Phase 1: Two Pathways to Prothrombin Activator

Coagulation may be initiated by either the **intrinsic** or the **extrinsic pathway**. In the body, the same tissue-damaging events usually trigger both pathways. Outside the body (such as in a test tube), *only* the intrinsic pathway initiates blood clotting. Before we examine how these pathways are different, let's see what they have in common.

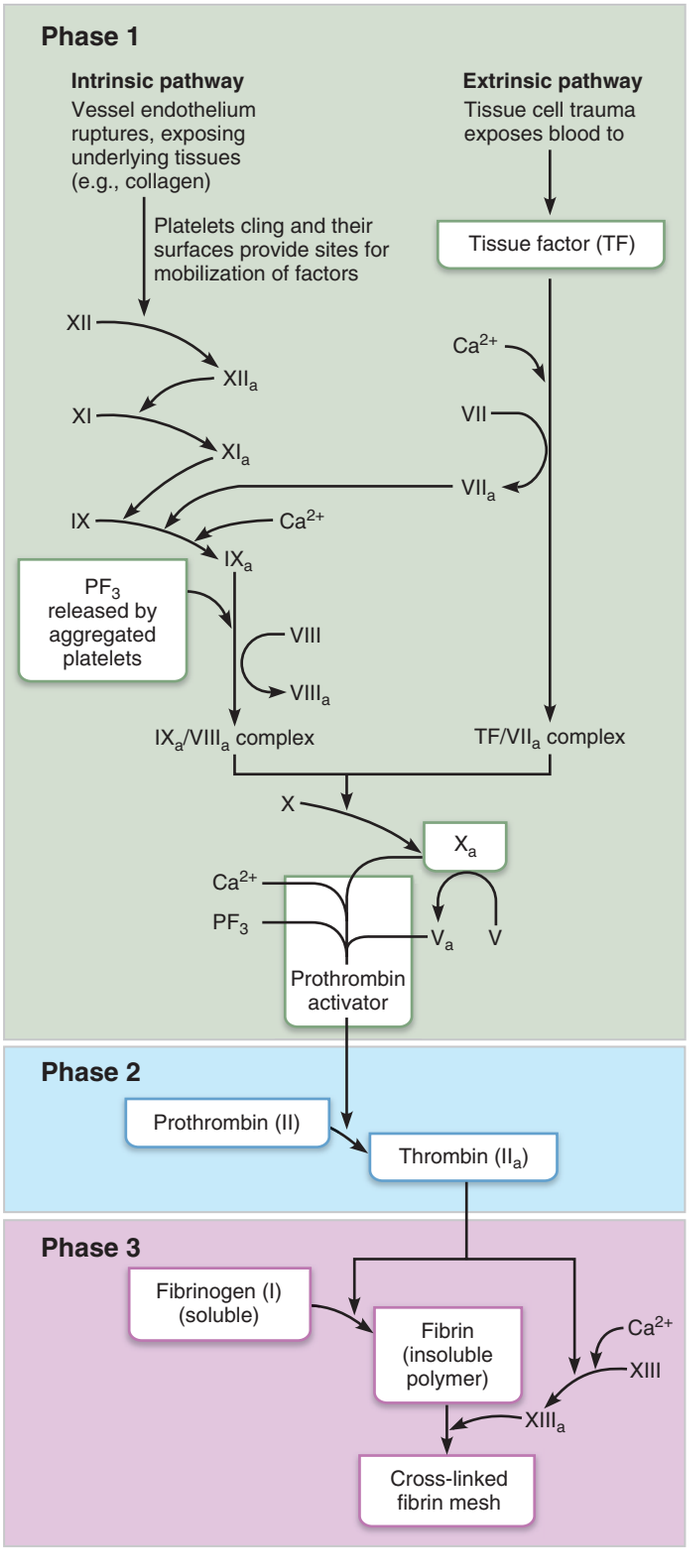


Figure 17.14 The intrinsic and extrinsic pathways of blood clotting (coagulation). The subscript "a" indicates the activated clotting factor (procoagulant).

Pivotal components in both pathways are negatively charged membranes, particularly those of platelets, that contain phosphatidylserine, also known as **PF_3** (platelet factor 3). Many intermediates of both pathways can be activated only in the presence of PF_3. The intermediate steps of each pathway *cascade* toward a common intermediate, factor X (Figure 17.14). Once factor X has been activated, it complexes with calcium ions, PF_3, and factor V to form **prothrombin activator**. This is usually the slowest step of the blood clotting process, but once prothrombin activator is present, the clot forms in 10 to 15 seconds.

The intrinsic and extrinsic pathways usually work together and are interconnected in many ways, but there are significant differences between them. The *intrinsic pathway* is

- Called *intrinsic* because the factors needed for clotting are present *within* (intrinsic to) the blood.
- Triggered by negatively charged surfaces such as activated platelets, collagen, or glass. (This is why this pathway can initiate clotting in a test tube.)
- Slower because it has many intermediate steps.

The *extrinsic pathway* is

- Called *extrinsic* because the tissue factor it requires is *outside* of blood.
- Triggered by exposing blood to a factor found in tissues underneath the damaged endothelium. This factor is called **tissue factor (TF)** or **factor III**.
- Faster because it bypasses several steps of the intrinsic pathway. In severe tissue trauma, it can form a clot in 15 seconds.

Phase 1 ends with the formation of a complex substance called *prothrombin activator*.

Phase 2: Common Pathway to Thrombin

Prothrombin activator catalyzes the conversion of a plasma protein called **prothrombin** into the active enzyme **thrombin**.

Phase 3: Common Pathway to the Fibrin Mesh

The end point of phase 3 is a *fibrin mesh* that traps blood cells and effectively seals the hole until the blood vessel can be permanently repaired. Thrombin catalyzes the transformation of the *soluble* clotting factor **fibrinogen** into **fibrin**. The fibrin molecules then polymerize (join together) to form long, hairlike, *insoluble* fibrin strands. (Notice that, unlike other clotting factors, activating fibrinogen does not convert it into an enzyme, but instead allows it to polymerize.) The fibrin strands glue the platelets together and make a web that forms the structural basis of the clot. Fibrin makes the liquid plasma become gel-like and traps formed elements that try to pass through it **(Figure 17.15)**.

In the presence of calcium ions, thrombin also activates **factor XIII (fibrin stabilizing factor)**, a cross-linking enzyme that binds the fibrin strands tightly together, forming a fibrin mesh. Cross-linking further strengthens and stabilizes the clot, effectively sealing the hole until the blood vessel can be permanently repaired.

Factors that inhibit clotting are called **anticoagulants**. Whether or not blood clots depends on a delicate balance between clotting factors and anticoagulants. Normally, anticoagulants dominate and prevent clotting, but when a vessel is ruptured, clotting factor activity in that area increases

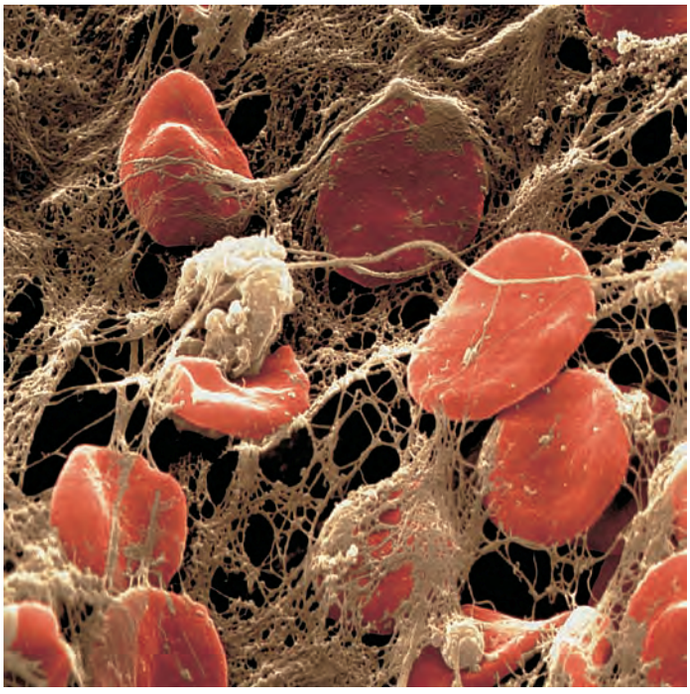


Figure 17.15 Scanning electron micrograph of erythrocytes trapped in a fibrin mesh. (2700×).

dramatically and a clot begins to form. Clot formation is normally complete within 3 to 6 minutes after blood vessel damage.

Clot Retraction and Fibrinolysis

Although the process of hemostasis is complete when the fibrin mesh is formed, there are still things that need to be done to stabilize the clot and then remove it when the injury is healed and the clot is no longer needed.

Clot Retraction

Within 30 to 60 minutes, a platelet-induced process called **clot retraction** further stabilizes the clot. Platelets contain contractile proteins (actin and myosin), and they contract in much the same manner as smooth muscle cells. As the platelets contract, they pull on the surrounding fibrin strands, squeezing **serum** (plasma minus the clotting proteins) from the mass, compacting the clot and drawing the ruptured edges of the blood vessel more closely together.

Even as clot retraction is occurring, the vessel is healing. **Platelet-derived growth factor (PDGF)** released by platelets stimulates smooth muscle cells and fibroblasts to divide and rebuild the vessel wall. As fibroblasts form a connective tissue patch in the injured area, endothelial cells, stimulated by vascular endothelial growth factor (VEGF), multiply and restore the endothelial lining.

Fibrinolysis

A clot is not a permanent solution to blood vessel injury, and a process called **fibrinolysis** removes unneeded clots when healing has occurred. This cleanup detail is crucial because small clots form continually in vessels throughout the body. Without fibrinolysis, blood vessels would gradually become completely blocked.

The critical natural "clot buster" is a fibrin-digesting enzyme called **plasmin**, which is produced when the plasma protein **plasminogen** is activated. Large amounts of plasminogen are incorporated into a forming clot, where it remains inactive until appropriate signals reach it. The presence of a clot in and around the blood vessel causes the endothelial cells to secrete **tissue plasminogen activator (tPA).** Activated factor XII and thrombin released during clotting also activate plasminogen. As a result, most plasmin activity is confined to the clot, and circulating enzymes quickly destroy any plasmin that strays into the plasma. Fibrinolysis begins within two days and continues slowly over several days until the clot finally dissolves.

Factors Limiting Clot Growth or Formation

Factors Limiting Normal Clot Growth

Once the clotting cascade has begun, it continues until a clot forms. Normally, two homeostatic mechanisms prevent clots from becoming unnecessarily large: (1) swift removal of clotting factors, and (2) inhibition of activated clotting factors. For clotting to occur in the first place, the concentration of activated clotting factors must reach certain critical levels. Clots do not usually form in rapidly moving blood because the activated clotting factors are diluted and washed away. For the same reasons, a clot stops growing when it contacts blood flowing normally.

Other mechanisms block the final step in which fibrinogen is polymerized into fibrin. They work by restricting thrombin to the clot or by inactivating it if it escapes into the general circulation. As a clot forms, almost all of the thrombin produced is bound onto the fibrin threads. This is an important safeguard because thrombin also exerts positive feedback effects on the coagulation process prior to the common pathway. Not only does it speed up the production of prothrombin activator by acting indirectly through factor V, but it also accelerates the earliest steps of the intrinsic pathway by activating platelets. By binding thrombin, fibrin effectively acts as an anticoagulant, preventing the clot from enlarging and thrombin from acting elsewhere.

Antithrombin III, a protein present in plasma, quickly inactivates any thrombin not bound to fibrin. Antithrombin III and **protein C**, another protein produced in the liver, also inhibit the activity of other intrinsic pathway clotting factors.

Heparin, the natural anticoagulant contained in basophil and mast cell granules, is also found on the surface of endothelial cells. It inhibits thrombin by enhancing the activity of antithrombin III. Like most other clotting inhibitors, heparin also inhibits the intrinsic pathway.

Factors Preventing Undesirable Clotting

As long as the endothelium is smooth and intact, platelets are prevented from clinging and piling up. Also, antithrombic substances—nitric oxide and prostacyclin—secreted by the endothelial cells normally prevent platelet adhesion. Additionally, vitamin E quinone, a molecule formed in the body when vitamin E reacts with oxygen, is a potent anticoagulant.

Disorders of Hemostasis

Blood clotting is one of nature's most elegant creations, but it sometimes goes awry. The two major disorders of hemostasis are at opposite poles. **Thromboembolic disorders** result from conditions that cause undesirable clot formation. **Bleeding disorders** arise from abnormalities that prevent normal clot formation. **Disseminated intravascular coagulation (DIC)**, which has characteristics of both types of disorder, involves both widespread clotting and severe bleeding.

Thromboembolic Disorders

Despite the body's many safeguards, undesirable intravascular clotting, called "hemostasis in the wrong place" by some, sometimes occurs.

Thrombi and Emboli A clot that develops and persists in an *unbroken* blood vessel is called a **thrombus**. If the thrombus is large enough, it may block circulation to the cells beyond the occlusion and lead to death of those tissues. For example, if the blockage occurs in the coronary circulation of the heart (coronary thrombosis), the consequences may be death of heart muscle and a fatal heart attack.

If the thrombus breaks away from the vessel wall and floats freely in the bloodstream, it becomes an **embolus** (plural: *emboli*). An embolus ("wedge") is usually no problem until it encounters a blood vessel too narrow for it to pass through. Then it becomes an **embolism**, obstructing the vessel. For example, emboli that become trapped in the lungs (pulmonary embolisms) dangerously impair the body's ability to obtain oxygen. A cerebral embolism may cause a stroke.

Conditions that roughen the vessel endothelium, such as atherosclerosis or inflammation, cause thromboembolic disease by allowing platelets to gain a foothold. Slowly flowing blood or blood stasis is another risk factor, particularly in bedridden patients and those taking a long flight without moving around. In this case, clotting factors are not washed away as usual and accumulate, allowing clots to form.

Anticoagulant Drugs A number of drugs—most importantly aspirin, heparin, and warfarin—are used clinically to prevent undesirable clotting. **Aspirin** is an antiprostaglandin drug that inhibits thromboxane A_2 formation (blocking platelet aggregation and platelet plug formation). Clinical studies of men taking low-dose aspirin (one aspirin every two days) over several years demonstrated a 50% reduction in incidence of heart attack.

Other medications that are prescribed as anticoagulants are heparin (see above) and warfarin, an ingredient in rat poison. Administered in injectable form, heparin is the anticoagulant most used in the hospital (for preoperative and postoperative heart patients and for those receiving blood transfusions). Taken orally, **warfarin** (Coumadin) is a mainstay of outpatient treatment to reduce the risk of stroke in those prone to atrial fibrillation, a condition in which blood pools in the heart. Warfarin works via a different mechanism than heparin—it interferes with the action of vitamin K in the production of some clotting factors (see Impaired Liver Function below). New on the scene is *dabigatran*, a direct inhibitor of thrombin that is a welcome alternative to warfarin.

The *Closer Look* box in Chapter 19 (pp. 700–701) describes other drugs that dissolve blood clots (such as tPA) and innovative medical techniques for treating clots.

Bleeding Disorders

Anything that interferes with the clotting mechanism can result in abnormal bleeding. The most common causes are platelet deficiency (thrombocytopenia) and deficits of some clotting factors, which can result from impaired liver function or genetic conditions such as hemophilia.

Thrombocytopenia A condition in which the number of circulating platelets is deficient, **thrombocytopenia** (throm″bo-si″to-pe′ne-ah) causes spontaneous bleeding from small blood vessels all over the body. Even normal movement leads to widespread hemorrhage, evidenced by many small purplish spots, called *petechiae* (pe-te′ke-e), on the skin.

Thrombocytopenia can arise from any condition that suppresses or destroys the red bone marrow, such as bone marrow malignancy, exposure to ionizing radiation, or certain drugs. A platelet count of under 50,000/μl of blood is usually diagnostic for this condition. Transfusions of concentrated platelets provide temporary relief from bleeding.

Impaired Liver Function When the liver is unable to synthesize its usual supply of clotting factors, abnormal and often severe bleeding occurs. The causes can range from an easily resolved vitamin K deficiency (common in newborns) to nearly total impairment of liver function (as in hepatitis or cirrhosis).

Liver cells require vitamin K to produce clotting factors. Although intestinal bacteria make some vitamin K, we obtain most of it from vegetables in our diet and dietary deficiencies are rarely a problem. However, vitamin K deficiency can occur if fat absorption is impaired, because vitamin K is a fat-soluble vitamin that is absorbed into the blood along with fats. In liver disease, the nonfunctional liver cells fail to produce not only the clotting factors, but also bile that is required to absorb fat and vitamin K.

Hemophilias The term **hemophilia** refers to several hereditary bleeding disorders that have similar signs and symptoms. *Hemophilia A* results from a deficiency of **factor VIII (antihemophilic factor)**. It accounts for 77% of cases. *Hemophilia B* results from a deficiency of factor IX. Both types are genetic conditions that occur primarily in males (X-linked conditions, discussed in Chapter 29). *Hemophilia C*, a less severe form seen in both sexes, is due to a lack of factor XI. The relative mildness of hemophilia C, compared to the A and B forms, reflects the fact that the clotting factor (factor IX) that the missing factor XI activates can also be activated by factor VII (see Figure 17.14).

Symptoms of hemophilia begin early in life. Even minor tissue trauma causes prolonged and potentially life-threatening bleeding into tissues. Commonly, the person's joints become seriously disabled and painful because of repeated bleeding into the joint cavities after exercise or trauma. Hemophilias are managed clinically by transfusions of fresh plasma or injections of the appropriate purified clotting factor. These therapies provide relief for several days but are expensive and inconvenient.

In addition, dependence on transfusions or injections has caused other problems. In the past, many hemophilia patients became

infected by the hepatitis virus and, beginning in the early 1980s, by HIV, a blood-transmitted virus that depresses the immune system and causes AIDS. (See Chapter 21.) New infections are now avoided as a result of new testing methods for HIV, availability of genetically engineered clotting factors, and hepatitis vaccines.

Disseminated Intravascular Coagulation (DIC)

DIC is a situation in which widespread clotting occurs in intact blood vessels and the residual blood becomes unable to clot. Blockage of blood flow accompanied by severe bleeding follows. DIC most commonly happens as a complication of pregnancy or a result of septicemia or incompatible blood transfusions.

Check Your Understanding

9. What are the three steps of hemostasis?
10. What is the key difference between fibrinogen and fibrin? Between prothrombin and thrombin? Between most factors before and after they are activated?
11. Which bleeding disorder results from not having enough platelets? From absence of clotting factor VIII?

For answers, see Appendix H.

Transfusion and Blood Replacement

- Describe the ABO and Rh blood groups. Explain the basis of transfusion reactions.
- Describe fluids used to replace blood volume and the circumstances for their use.

The human cardiovascular system minimizes the effects of blood loss by (1) reducing the volume of the affected blood vessels, and (2) stepping up the production of red blood cells. However, the body can compensate for only so much blood loss. Losing 15–30% causes pallor and weakness. Losing more than 30% of blood volume results in severe shock, which can be fatal.

Transfusing Red Blood Cells

Whole blood transfusions are routine when blood loss is rapid and substantial. In all other cases, infusions of **packed red cells** (whole blood from which most of the plasma and leukocytes have been removed) are preferred for restoring oxygen-carrying capacity. The usual blood bank procedure involves collecting blood from a donor and mixing it with an anticoagulant, such as certain citrate or oxalate salts, which prevents clotting by binding calcium ions. The shelf life of the collected blood at 4°C is about 35 days. Because blood is such a valuable commodity, it is most often separated into its component parts so that each component can be used when and where it is needed.

Human Blood Groups

People have different blood types, and transfusion of incompatible blood can be fatal. RBC plasma membranes, like those of all body cells, bear highly specific glycoproteins at their external surfaces, which identify each of us as unique from all others. These glycoprotein markers are called *antigens*. An antigen is anything the body perceives as foreign and that generates an immune response. Examples are toxins and molecules on the surfaces of bacteria, viruses, and cancer cells—and mismatched RBCs.

One person's RBC proteins may be recognized as foreign if transfused into someone with a different red blood cell type, and the transfused cells may be agglutinated (clumped together) and destroyed. Since these RBC antigens promote agglutination, they are more specifically called **agglutinogens** (ag″loo-tin′o-jenz).

At least 30 groups of naturally occurring RBC antigens (blood groups) are found in humans, and many variants occur in individual families ("private antigens") rather than in the general population. The presence or absence of various antigens allows a person's blood cells to be classified into each of these different blood groups. Antigens determining the ABO and Rh blood groups cause vigorous transfusion reactions (in which the foreign erythrocytes are destroyed) when they are improperly transfused. For this reason, blood typing for these antigens is always done before blood is transfused.

Other antigens (such as those in the MNS, Duffy, Kell, and Lewis groups) are mainly of legal or academic importance. Because these factors rarely cause transfusion reactions, blood is not specifically typed for them unless the person is expected to need several transfusions, in which case reactions are more likely to occur. Here we describe only the ABO and Rh blood groups.

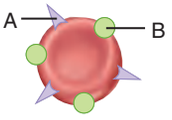
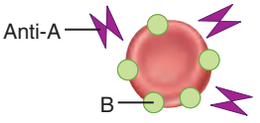
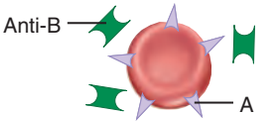
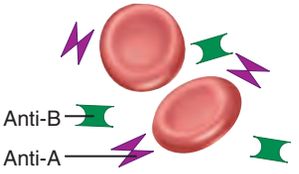
ABO Blood Groups The **ABO blood groups** are based on the presence or absence of two agglutinogens, type A and type B **(Table 17.4)**. Depending on which of these a person inherits, his or her ABO blood group will be one of the following: A, B, AB, or O. The O blood group, which has neither agglutinogen, is the most common ABO group in North America for whites, blacks, Asians, and Native Americans. AB, with both antigens, is least prevalent. The presence of either the A or the B agglutinogen results in group A or B, respectively.

Unique to the ABO blood groups is the presence in the plasma of *preformed antibodies* called **agglutinins**. The agglutinins act against RBCs carrying ABO antigens that are *not* present on a person's own red blood cells. A newborn lacks these antibodies, but they begin to appear in the plasma within two months and reach adult levels between 8 and 10 years of age. As indicated in Table 17.4, a person with neither the A nor the B antigen (group O) possesses both anti-A and anti-B antibodies, also called *a* and *b agglutinins* respectively. Those with group A blood have anti-B antibodies, while those with group B have anti-A antibodies. AB individuals have neither antibody.

Rh Blood Groups There are 52 named Rh agglutinogens, each of which is called an **Rh factor**. Only three of these, the C, D, and E antigens, are fairly common. The Rh blood typing system is so named because one Rh antigen (agglutinogen D) was originally identified in *rhesus* monkeys. Later, the same antigen was discovered in humans.

About 85% of Americans are Rh^+ (Rh positive), meaning that their RBCs carry the D antigen. As a rule, a person's ABO and Rh blood groups are reported together, for example, O^+, A^-, and so on.

Table 17.4 ABO Blood Groups

BLOOD GROUP	RBC ANTIGENS (AGGLUTINOGENS)	ILLUSTRATION	PLASMA ANTIBODIES (AGGLUTININS)	BLOOD THAT CAN BE RECEIVED	FREQUENCY (% OF U.S. POPULATION) WHITE	BLACK	ASIAN	NATIVE AMERICAN
AB	A B		None	A, B, AB, O "Universal recipient"	4	4	5	<1
B	B		Anti-A (a)	B, O	11	20	27	4
A	A		Anti-B (b)	A, O	40	27	28	16
O	None		Anti-A (a) Anti-B (b)	O "Universal donor"	45	49	40	79

Unlike the ABO system antibodies, anti-Rh antibodies do not spontaneously form in the blood of Rh^- (Rh negative) individuals. However, if an Rh^- person receives Rh^+ blood, the immune system becomes sensitized and begins producing anti-Rh antibodies against the foreign antigen soon after the transfusion. Hemolysis does not occur after the first such transfusion because it takes time for the body to react and start making antibodies. But the second time, and every time thereafter, a typical transfusion reaction occurs in which the recipient's antibodies attack and rupture the donor RBCs.

Homeostatic Imbalance 17.3

An important problem related to the Rh factor occurs in pregnant Rh^- women who are carrying Rh^+ babies. The first such pregnancy usually results in the delivery of a healthy baby. But, when bleeding occurs as the placenta detaches from the uterus, the mother may be sensitized by her baby's Rh^+ antigens that pass into her bloodstream. If so, she will form anti-Rh antibodies unless treated with RhoGAM before or shortly after she has given birth. (The same precautions are taken in women who have miscarried or aborted the fetus.) RhoGAM is a serum containing anti-Rh agglutinins. By agglutinating the Rh factor, it blocks the mother's immune response and prevents her sensitization.

If the mother is not treated and becomes pregnant again with an Rh^+ baby, her antibodies will cross through the placenta and destroy the baby's RBCs, producing a condition known as **hemolytic disease of the newborn**, or **erythroblastosis fetalis**. The baby becomes anemic and hypoxic. In severe cases, brain damage and even death may result unless transfusions are done *before* birth to provide the fetus with more erythrocytes for oxygen transport. Additionally, one or two *exchange transfusions* (see Related Clinical Terms, p. 657) are done after birth. The baby's Rh^+ blood is removed, and Rh^- blood is infused. Within six weeks, the transfused Rh^- erythrocytes have been broken down and replaced with the baby's own Rh^+ cells. ✚

Transfusion Reactions: Agglutination and Hemolysis

When mismatched blood is infused, a **transfusion reaction** occurs in which the recipient's plasma agglutinins attack the donor's red blood cells. (Note that the donor's plasma antibodies may also agglutinate the recipient's RBCs, but these antibodies are so diluted in the recipient's circulation that this does not usually present a problem.)

The initial event, agglutination of the foreign red blood cells, clogs small blood vessels throughout the body. During the next few hours, the clumped red blood cells begin to rupture or are destroyed by phagocytes, and their hemoglobin is released into the bloodstream. When the transfusion reaction is exceptionally severe, the RBCs are lysed almost immediately.

These events lead to two easily recognized problems: (1) The transfused blood cells cannot transport oxygen, and (2) the clumped red blood cells in small vessels hinder blood flow to tissues beyond those points. Less apparent, but more devastating, is the consequence of hemoglobin that escapes into the bloodstream. Circulating hemoglobin passes freely into the kidney tubules, causing cell death and renal shutdown. If shutdown is complete (acute renal failure), the recipient may die.

Transfusion reactions can also cause fever, chills, low blood pressure, rapid heartbeat, nausea, vomiting, and general toxicity, but in the absence of renal shutdown, these reactions are rarely lethal. Treatment of transfusion reactions focuses on preventing kidney damage by administering fluid and diuretics to increase urine output, diluting and washing out the hemoglobin.

As indicated in Table 17.4, group O red blood cells bear neither the A nor the B antigen, so theoretically group O is the **universal donor**. Indeed, some laboratories are developing methods to enzymatically convert other blood types to type O by clipping off the extra (A- or B-specific) sugar molecule. Since group AB plasma is devoid of antibodies to both A and B antigens, group AB people are theoretically **universal recipients** and can receive blood transfusions from any of the ABO groups. However, these classifications are misleading, because they do not take into account the other agglutinogens in blood that can trigger transfusion reactions.

The risk of transfusion reactions and transmission of life-threatening infections (particularly with HIV) from pooled blood transfusions has increased public interest in **autologous transfusions** (*auto* = self). In autologous transfusions, the patient *predonates* his or her own blood, and it is stored and immediately available if needed during an operation.

Blood Typing

It is crucial to determine the blood group of both the donor and the recipient *before* blood is transfused. **Figure 17.16** briefly outlines the general procedure for determining ABO blood type. Because it is so critical that blood groups be compatible, cross matching is also done. *Cross matching* tests whether the recipient's serum will agglutinate the donor's RBCs or the donor's serum will agglutinate the recipient's RBCs. Typing for Rh factors is done in the same manner as ABO blood typing.

Restoring Blood Volume

When a patient's blood volume is so low that death from shock is imminent, there may not be time to type blood, or appropriate whole blood may be unavailable. Such emergencies demand that blood *volume* be replaced immediately to restore adequate circulation.

Fundamentally, blood consists of proteins and cells suspended in a salt solution. Replacing lost blood volume essentially consists of replacing that isotonic salt solution. *Normal saline* or a *multiple electrolyte solution* that mimics the electrolyte composition of plasma (for example, *Ringer's solution*) are the preferred choices.

You might think that it would be important to add materials to mimic the osmotic properties of albumin in blood, and indeed this has been widely practiced. However, studies have shown that **plasma expanders** such as *purified human serum albumin, hetastarch*, and *dextran* provide no benefits over much cheaper electrolyte solutions and are actually associated with significant complications of their own. Volume replacement restores adequate circulation but cannot, of course, replace the oxygen-carrying capacity of the lost red blood cells. Research on ways to replace that capability by using artificial blood substitutes is ongoing.

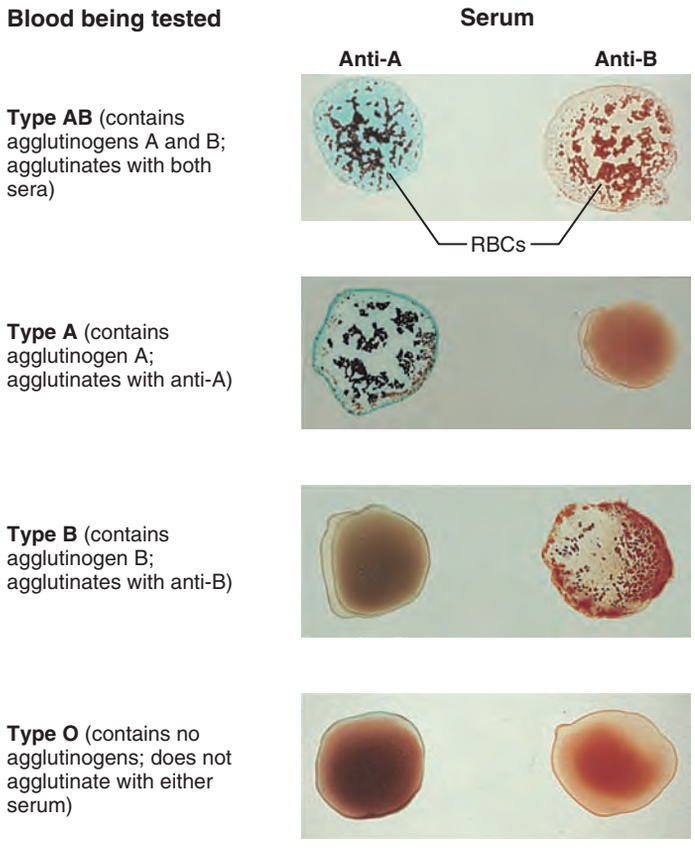


Figure 17.16 Blood typing of ABO blood types. When serum containing anti-A or anti-B agglutinins is added to a blood sample diluted with saline, agglutination will occur between the agglutinin and the corresponding agglutinogen (A or B).

☑ Check Your Understanding

12. Nigel is told he has type B blood. Which ABO antibodies does he have in his plasma? Which agglutinogens are on his RBCs? Could he donate blood to an AB recipient? Could he receive blood from an AB donor? Explain.

For answers, see Appendix H.

17

Diagnostic Blood Tests

✓ Explain the diagnostic importance of blood testing.

A laboratory examination of blood yields information that can be used to evaluate a person's health. For example, in some anemias, the blood is pale and has a low hematocrit. A high fat content (*lipidemia*) gives blood plasma a yellowish hue and forecasts problems in those with heart disease. Blood glucose tests indicate how well a diabetic is controlling diet and blood sugar levels. Leukocytosis signals infections; severe infections yield larger-than-normal buffy coats in the hematocrit.

Microscopic studies of blood can reveal variations in the size and shape of erythrocytes that indicate iron deficiency or pernicious anemia. A **differential white blood cell count**, which

determines the relative proportions of individual leukocyte types, is a valuable diagnostic tool. For example, a high eosinophil count may indicate a parasitic infection or an allergic response somewhere in the body.

A number of tests provide information on the status of the hemostasis system. For example, clinicians determine the **prothrombin time** to assess the ability of blood to clot, or do a **platelet count** when thrombocytopenia is suspected.

Two batteries of tests—a SMAC (SMA24, CHEM-20, or similar series) and a **complete blood count (CBC)**—are routinely ordered during physical examinations and before hospital admissions. SMAC is a blood *chemistry* profile that measures various electrolytes, glucose, and markers of liver and kidney disorders. The CBC includes counts of the different types of formed elements, the hematocrit, measurements of hemoglobin content, and size of RBCs. Together these tests provide a comprehensive picture of a person's general health in relation to normal blood values.

Appendix F lists normal values for selected blood tests.

Developmental Aspects of Blood

- ✓ Describe changes in the sites of blood production and in the type of hemoglobin produced after birth.
- ✓ Name some blood disorders that become more common with age.

Early in fetal development, blood cells form at many sites—the fetal yolk sac, liver, and spleen, among others—but by the seventh month, the red marrow has become the primary hematopoietic area and remains so (barring serious illness) throughout life. If there is a severe need for blood cell production, however, the liver and spleen may resume their fetal blood-forming roles. Additionally, inactive yellow bone marrow regions (essentially fatty tissue) may reconvert to active red marrow.

Blood cells develop from collections of mesenchymal cells, called *blood islands*, derived from the mesoderm germ layer. The fetus forms a unique hemoglobin, **hemoglobin F**, that has a higher affinity for oxygen than does adult hemoglobin (hemoglobin A). It contains two alpha and two gamma (γ) polypeptide chains per globin molecule, instead of the paired alpha and beta chains typical of hemoglobin A. After birth, the liver rapidly destroys fetal erythrocytes carrying hemoglobin F, and the baby's erythroblasts begin producing hemoglobin A.

The most common blood diseases that appear during aging are chronic leukemias, anemias, and clotting disorders. However, these and most other age-related blood disorders are usually precipitated by disorders of the heart, blood vessels, or immune system. For example, the increased incidence of leukemias in old age is believed to result from the waning efficiency of the immune system, and abnormal thrombus and embolus formation reflects atherosclerosis, which roughens the blood vessel walls.

Check Your Understanding

13. Emily Wong, 17, is brought to the ER with a fever, headache, and stiff neck. You suspect bacterial meningitis. Would you expect to see an elevated neutrophil count in a differential WBC count? Explain.
14. How is hemoglobin F different from adult hemoglobin?

For answers, see Appendix H.

Blood serves as the vehicle that the cardiovascular system uses to transport substances throughout the body, so it could be considered the servant of the cardiovascular system. On the other hand, without blood, the normal functions of the heart and blood vessels are impossible. So perhaps the organs of the cardiovascular system, described in Chapters 18 and 19, are subservient to blood. The point of this circular thinking is that blood and the cardiovascular system are vitally intertwined in their common functions: to ensure that nutrients, oxygen, and other vital substances reach all tissue cells of the body and to relieve the cells of their wastes.

17

Chapter Summary

MAP™ For more chapter study tools, go to the Study Area of MasteringA&P at **www.masteringaandp.com**.

There you will find:

- Interactive Physiology iP
- A&PFlix A&PFlix
- Practice Anatomy Lab PAL
- PhysioEx PEx
- Videos, Practice Quizzes and Tests, MP3 Tutor Sessions, Case Studies, and much more!

Overview: Blood Composition and Functions (pp. 632–633)

Components (p. 632)

1. Blood is composed of formed elements and plasma. The hematocrit is a measure of one formed element, erythrocytes, as a percentage of total blood volume.

Physical Characteristics and Volume (p. 632)

2. Blood is a viscous, slightly alkaline fluid representing about 8% of total body weight. Blood volume of a normal adult is about 5 L.

Functions (pp. 632–633)

3. Distribution functions include delivering oxygen and nutrients to body tissues, removing metabolic wastes, and transporting hormones.
4. Regulation functions include maintaining body temperature, constant blood pH, and adequate fluid volume.
5. Protective functions include hemostasis and prevention of infection.

Blood Plasma (p. 633)

1. Plasma is a straw-colored, viscous fluid and is 90% water. The remaining 10% is solutes, such as nutrients, respiratory gases, electrolytes, hormones, and proteins. Plasma makes up 55% of whole blood.

2. Plasma proteins, most made by the liver, include albumin, globulins, and fibrinogen. Albumin is an important blood buffer and contributes to the osmotic pressure of blood.

Formed Elements (pp. 634–646)

1. Formed elements, accounting for 45% of whole blood, are erythrocytes, leukocytes, and platelets. All formed elements arise from hematopoietic stem cells in red bone marrow.

Erythrocytes (Red Blood Cells) (pp. 634–640)

2. Erythrocytes (red blood cells, RBCs) are small, biconcave cells containing large amounts of hemoglobin. They have no nucleus and few organelles. Spectrin allows the cells to change shape as they pass through tiny capillaries.
3. Oxygen transport is the major function of erythrocytes. In the lungs, oxygen binds to iron atoms in hemoglobin molecules, producing oxyhemoglobin. In body tissues, oxygen dissociates from iron, producing deoxyhemoglobin.
4. Red blood cells begin as hematopoietic stem cells and, through erythropoiesis, proceed from the proerythroblast (committed cell) stage to the basophilic, polychromatic and orthochromatic erythroblast, and reticulocyte stages. During this process, hemoglobin accumulates and the organelles and nucleus are extruded. Differentiation of reticulocytes is completed in the bloodstream.
5. Erythropoietin and testosterone enhance erythropoiesis.
6. Iron, vitamin B_{12}, and folic acid are essential for production of hemoglobin.
7. Red blood cells have a life span of approximately 120 days. Macrophages of the spleen and liver remove old and damaged erythrocytes from the circulation. Released iron from hemoglobin is stored as ferritin or hemosiderin to be reused. The balance of the heme group is degraded to bilirubin and secreted in bile. Amino acids of globin are metabolized or recycled.

iP Respiratory System; Topic: Gas Transport, pp. 3–5, 11–17.

8. Erythrocyte disorders include anemia and polycythemia.

Leukocytes (White Blood Cells) (pp. 640–645)

9. Leukocytes are white blood cells (WBCs). All are nucleated, and all have crucial roles in defending against disease. Two main categories exist: granulocytes and agranulocytes.
10. Granulocytes include neutrophils, eosinophils, and basophils. Neutrophils are active phagocytes. Eosinophils attack parasitic worms, and their numbers increase during allergic reactions. Basophils contain histamine, which promotes vasodilation and enhances migration of leukocytes to inflammatory sites.
11. Agranulocytes have crucial roles in immunity. They include lymphocytes—the "immune cells"—and monocytes which differentiate into macrophages.
12. Leukopoiesis is directed by colony-stimulating factors and interleukins released by supporting cells of the red bone marrow and mature WBCs.
13. Leukocyte disorders include leukemias and infectious mononucleosis.

Platelets (pp. 645–646)

14. Platelets are fragments of large megakaryocytes formed in red marrow. When a blood vessel is damaged, platelets form a plug to help prevent blood loss and play a central role in the clotting cascade.

Hemostasis (pp. 646–651)

1. Hemostasis is prevention of blood loss. The three major steps of hemostasis are vascular spasm, platelet plug formation, and blood coagulation.

Vascular Spasm and Platelet Plug Formation (pp. 646–647)

2. Spasms of smooth muscle in blood vessel walls and accumulation of platelets (platelet plug) at the site of vessel injury stop or slow down blood loss temporarily until coagulation occurs.

Coagulation (pp. 647–649)

3. Coagulation of blood may be initiated by either the intrinsic or the extrinsic pathway. Platelet phospholipid (PF_3) is crucial to both pathways. Tissue factor (factor III) exposed by tissue injury allows the extrinsic pathway to bypass many steps of the intrinsic pathway. A series of activated clotting factors oversees the intermediate steps of each cascade. The pathways converge as prothrombin is converted to thrombin.

Clot Retraction and Fibrinolysis (p. 649)

4. After a clot is formed, clot retraction occurs. Serum is squeezed out and the ruptured vessel edges are drawn together. Smooth muscle, connective tissue, and endothelial cell proliferation and migration repair the injured blood vessel.
5. When healing is complete, clot digestion (fibrinolysis) occurs.

Factors Limiting Clot Growth or Formation (p. 649)

6. Abnormal expansion of clots is prevented by removal of coagulation factors in contact with rapidly flowing blood and by inhibition of activated blood factors. Prostacyclin (PGI_2) and nitric oxide secreted by the endothelial cells help prevent undesirable (unnecessary) clotting.

Disorders of Hemostasis (pp. 650–651)

7. Thromboembolic disorders involve undesirable clot formation, which can block vessels.
8. Thrombocytopenia, a deficit of platelets, causes spontaneous bleeding from small blood vessels. Hemophilia is caused by a genetic deficiency of certain coagulation factors. Liver disease can also cause bleeding disorders because many coagulation proteins are formed by the liver.
9. Disseminated intravascular coagulation (DIC) is a condition of bodywide clotting in undamaged blood vessels and subsequent hemorrhages.

Transfusion and Blood Replacement (pp. 651–653)

Transfusing Red Blood Cells (pp. 651–653)

1. Whole blood transfusions are given to replace severe and rapid blood loss. Packed RBCs are given to replace lost O_2-carrying capacity.
2. Blood group is based on agglutinogens (antigens) present on red blood cell membranes.
3. When mismatched blood is transfused, the recipient's agglutinins (plasma antibodies) clump the foreign RBCs. The clumped RBCs may block blood vessels temporarily and then are lysed. Released hemoglobin may cause renal shutdown.
4. Before whole blood can be transfused, it must be typed and cross matched to prevent transfusion reactions. The most important blood groups for which blood must be typed are the ABO and Rh groups.

Restoring Blood Volume (p. 653)

5. Plasma volume can be replaced with balanced electrolyte solutions, and these are generally preferred over plasma expanders.

Diagnostic Blood Tests (pp. 653–654)

1. Diagnostic blood tests can provide valuable information about the current status of the blood and of the body as a whole.

Developmental Aspects of Blood (p. 654)

1. Fetal hematopoietic sites include the yolk sac, liver, and spleen. By the seventh month of development, the red bone marrow is the primary blood-forming site.
2. Blood cells develop from blood islands derived from mesoderm. Fetal blood contains hemoglobin F. After birth, hemoglobin A is formed.
3. The major blood-related problems associated with aging are leukemia, anemia, and thromboembolic disease.

Review Questions

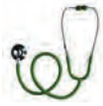
Multiple Choice/Matching

(Some questions have more than one correct answer. Select the best answer or answers from the choices given.)

1. The blood volume in an adult averages approximately **(a)** 1 L, **(b)** 3 L, **(c)** 5 L, **(d)** 7 L.
2. The hormonal stimulus that prompts red blood cell formation is **(a)** serotonin, **(b)** heparin, **(c)** erythropoietin, **(d)** thrombopoietin.
3. All of the following are true of RBCs except **(a)** biconcave disc shape, **(b)** life span of approximately 120 days, **(c)** contain hemoglobin, **(d)** contain nuclei.
4. The most numerous WBC is the **(a)** eosinophil, **(b)** neutrophil, **(c)** monocyte, **(d)** lymphocyte.
5. Blood proteins play an important part in **(a)** blood clotting, **(b)** immunity, **(c)** maintenance of blood volume, **(d)** all of the above.
6. The white blood cell that releases histamine and other inflammatory chemicals is the **(a)** basophil, **(b)** neutrophil, **(c)** monocyte, **(d)** eosinophil.
7. The blood cell that can become an antibody-secreting cell is the **(a)** lymphocyte, **(b)** megakaryocyte, **(c)** neutrophil, **(d)** basophil.
8. Which of the following does not promote multiple steps in the clotting pathway? **(a)** PF_3, **(b)** factor XI, **(c)** thrombin, **(d)** Ca^{2+}.
9. The normal pH of the blood is about **(a)** 8.4, **(b)** 7.8, **(c)** 7.4, **(d)** 4.7.
10. Suppose your blood is AB positive. This means that **(a)** agglutinogens A and B are present on your red blood cells, **(b)** there are no anti-A or anti-B antibodies in your plasma, **(c)** your blood is Rh^+, **(d)** all of the above.

Short Answer Essay Questions

11. (a) Define formed elements and list their three major categories. (b) Which is least numerous? (c) Which comprise(s) the buffy coat in a hematocrit tube?
12. Discuss hemoglobin relative to its chemical structure, its function, and the color changes it undergoes during loading and unloading of oxygen.
13. If you had a high hematocrit, would you expect your hemoglobin determination to be low or high? Why?
14. What nutrients are needed for erythropoiesis?
15. (a) Describe the process of erythropoiesis. (b) What name is given to the immature cell type released to the circulation? (c) How does it differ from a mature erythrocyte?
16. Besides the ability to move by amoeboid motion, what other physiological attributes contribute to the function of white blood cells in the body?
17. (a) If you had a severe infection, would you expect your WBC count to be closest to 5000, 10,000, or 15,000/μl? (b) What is this condition called?
18. (a) Describe the appearance of platelets and state their major function. (b) Why should platelets not be called "cells"?
19. (a) Define hemostasis. (b) List the three major phases of coagulation. Explain what initiates each phase and what the phase accomplishes. (c) In what general way do the intrinsic and extrinsic mechanisms of clotting differ? (d) Which ion is essential to virtually all stages of coagulation?
20. (a) Define fibrinolysis. (b) What is the importance of this process?
21. (a) How is clot overgrowth usually prevented? (b) List two conditions that may lead to unnecessary (and undesirable) clot formation.
22. How can liver dysfunction cause bleeding disorders?
23. (a) What is a transfusion reaction and why does it happen? (b) What are its possible consequences?
24. How can poor nutrition lead to anemia?
25. What blood-related problems are most common in the aged?



Critical Thinking and Clinical Application Questions

1. Cancer patients being treated with chemotherapeutic drugs designed to destroy rapidly dividing cells are monitored closely for changes in their red and white blood counts. Why so?
2. Mary Healy, a young woman with severe vaginal bleeding, is admitted to the emergency room. She is three months pregnant, and the physician is concerned about the volume of blood she is losing. (a) What type of transfusion will probably be given to this patient? (b) Which blood tests will be performed before starting the transfusion?
3. Alan Forsythe, a middle-aged college professor from Boston, is in the Swiss Alps studying astronomy during his sabbatical leave. He has been there for two days and plans to stay the entire year. However, he notices that he is short of breath when he walks up steps and tires easily with any physical activity. His symptoms gradually disappear, and after two months he feels fine. Upon returning to the United States, he has a complete physical exam and is told that his erythrocyte count is higher than normal. (a) Attempt to explain this finding. (b) Will his RBC count remain at this higher-than-normal level? Why or why not?
4. A young child is diagnosed as having acute lymphocytic leukemia. Her parents cannot understand why infection is a major problem for Janie when her WBC count is so high. Can you provide an explanation for Janie's parents?
5. Mrs. Ryan, a middle-aged woman, appears at the clinic complaining of multiple small hemorrhagic spots in her skin and severe nosebleeds. While taking her history, the nurse notes that Mrs. Ryan works as a rubber glue applicator at a local factory. Rubber glue contains benzene, which is known to be toxic to red marrow. Using your knowledge of physiology, explain the connection between the bleeding problems and benzene.
6. A reticulocyte count indicated that 5% of Tyler's red blood cells were reticulocytes. His blood test also indicated he had polycythemia and a hematocrit of 65%. Explain the connection between these three facts.

7. In 1998, the U.S. Food and Drug Administration approved the nation's first commercial surgical glue to control bleeding during certain surgeries. Called Tisseel, it forms a flexible mesh over an oozing blood vessel to help stem bleeding within five minutes. This sealant is made from two blood proteins that naturally cause blood to clot when they react together. Name these proteins.
8. Jenny, a healthy young woman, had a battery of tests during a physical for a new job. Her RBC count was at the higher end of the normal range at that time, but four weeks later it was substantially elevated beyond that. When asked if any circumstances had changed in her life, she admitted to taking up smoking. How might her new habit explain her higher RBC count?
9. Mr. Chu has been scheduled for surgery to have his arthritic hip replaced. His surgeon tells him he must switch from aspirin to acetaminophen for pain control before his surgery. Why?

AT THE CLINIC

Related Clinical Terms

Blood chemistry tests Chemical analysis of substances in the blood, e.g., glucose, iron, calcium, protein, bilirubin, and pH.

Blood fraction Any one of the components of whole blood that has been separated out from the other blood components, such as platelets or clotting factors.

Bone marrow biopsy A sample of red bone marrow is obtained by needle aspiration (typically from the anterior or posterior iliac crest), and examined to diagnose disorders of blood-cell formation, leukemia, various marrow infections, and anemias resulting from damage to or failure of the marrow.

Exchange transfusion A technique of removing the patient's blood and infusing donor blood until a large fraction of the patient's blood has been replaced; used to treat fetal blood incompatibilities and poisoning victims.

Hematology (hem″ah-tol′o-je) Study of blood.

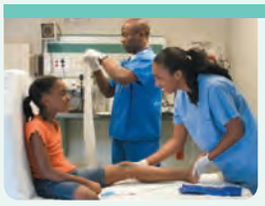
Hematoma (hem″ah-to′mah) Accumulated, clotted blood in the tissues usually resulting from injury; visible as "black and blue" marks or bruises; eventually absorbed naturally unless infections develop.

Hemochromatosis (he″mo-kro″mah-to′sis) An inherited disorder of iron overload in which the intestine absorbs too much iron from the diet. The iron builds up in body tissues, where it oxidizes to form compounds that poison those organs (especially joints, liver, and pancreas).

Myeloproliferative disorder All-inclusive term for a group of proliferative disorders (disorders in which normal cell division controls are lost) including leukoerythroblastic anemia involving fibrosis of the bone marrow, polycythemia vera, and leukemia.

Plasmapheresis (plaz″mah-fĕ-re′sis) A process in which blood is removed, its plasma is separated from formed elements, and the formed elements are returned to the patient or donor. The most important application is removal of antibodies or immune complexes from the blood of individuals with autoimmune disorders (multiple sclerosis, myasthenia gravis, and others). Also used by blood banks to collect plasma for burn victims and to obtain plasma components for therapeutic use.

Septicemia (sep″tĭ-se′me-ah; *septos* = rotten) Excessive and harmful levels of bacteria or their toxins in the blood. Also called blood poisoning.



Case Study Blood

Earl Malone is a 20-year-old passenger on the bus that crashed on Route 91. Upon arrival at the scene, paramedics make the following observations:

- Right upper quadrant (abdominal) pain
- Cyanotic
- Cool and clammy skin
- Blood pressure 100/60 and falling, pulse 100

Paramedics start an IV to rapidly infuse a 0.9% sodium chloride solution (normal saline). They transport him to a small rural hospital where Mr. Malone's blood pressure continues to fall and his cyanosis worsens. The local physician begins infusing O negative packed red blood cells (PRBCs) and arranges transport by helicopter to a trauma center. She sends additional PRBC units in the helicopter for transfusion en route. After arrival at the trauma center, the following notes were added to Mr. Malone's chart:

- Abdomen firm and distended
- Blood drawn for typing and cross matching; packed A positive blood cells infused
- Emergency FAST (Focused Assessment with Sonography for Trauma) ultrasound is positive for intraperitoneal fluid

A positive FAST scan indicates intra-abdominal bleeding. Mr. Malone's condition continues to deteriorate, so he is prepared for surgery, which reveals a lacerated liver. The laceration is repaired, and Mr. Malone's vital signs stabilize.

1. Mr. Malone was going into shock because of blood loss, so paramedics infused a saline solution. Why would this help?
2. Mr. Malone was switched from saline to PRBCs. What problem does infusion of PRBCs address that the saline solution could not?
3. Why was the physician able to use O negative blood before the results of the blood type tests were obtained?
4. Mr. Malone's blood type was determined to be A positive. What plasma antibodies (agglutinins) does he have, and what type of blood can he receive?
5. What would happen if doctors had infused type B PRBCs into Mr. Malone's circulation?

(Answers in Appendix H)